CLINICAL REVIEW

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Reviewer Name(s)	Amy Kao, MD
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Established/Proper Name	Fenfluramine
Trade Name	Fintepla
Applicant	Zogenix, Inc
Dosage Form(s)	Oral solution (2.2 mg/mL)
Applicant Proposed Dosing Regimen(s)	• Initial starting and maintenance dosage 0.1 mg/kg twice daily • Patients not on concomitant stiripentol: maximum daily maintenance dosage 0.35 mg/kg twice daily (maximum daily dosage 26 mg) • Patients taking concomitant stiripentol plus clobazam: maximum daily maintenance dosage 0.2 mg/kg twice daily (maximum daily dosage 17 mg)
Applicant Proposed Indication(s)/Population(s)	Treatment of seizures associated with Dravet syndrome and Lennox-Gastaut 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 and Lennox-Gastaut syndrome in patients 2 years of age and older

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Glossary

AC	advisory committee
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	aortic regurgitation
AS	atonic seizure
ASM	antiseizure medication
AST	aspartate aminotransferase
BID	twice a day
BRF	Benefit Risk Framework
BRIEF	Behavior Rating Inventory of Executive Function
CBD	cannabidiol
CGI-I	Clinical Global Impression – Improvement scale
CLB	clobazam
CNS	central nervous system
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
DCR	data change request
DEE	developmental and/or epileptic encephalopathy
DMC	data monitoring committee
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DRM	Division of Risk Management
DS	Dravet syndrome
DSF	frequency of seizures that result in drops (drop seizure frequency)
ECHO	echocardiogram
ECG	electrocardiogram
eCRF	electronic case report form
eCTD	electronic common technical document
eDiary	electronic seizure diary
EEG	electroencephalogram
EMA	European Medicines Agency
EOS	end of study
ET	early termination
ETASU	elements to assure safe use
ESC	Epilepsy Study Consortium
EU	European Union

FBM	felbamate
FEN	fenfluramine
FDA	Food and Drug Administration
GCP	good clinical practice
GTC	generalized tonic clonic
HADS	Hospital Anxiety and Depression Scale
ICAB	International Cardiology Advisory Board
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
IR	information request
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IWRS	Interactive web response system
LFTs	liver function tests
LGS	Lennox-Gastaut syndrome
LEV	levetiracetam
MCSF	mean convulsive seizure frequency
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MR	mitral regurgitation
NDA	new drug application
norFEN	norfenfluramine
OCP	Office of Clinical Pharmacology
OLE	open-label extension
OND	Office of New Drugs
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAH	pulmonary arterial hypertension
PASP	pulmonary artery systolic pressure
PI	prescribing information or package insert
PK	pharmacokinetics
PMR	postmarketing requirement
PP	per protocol
PR	pulmonic (or pulmonary) regurgitation
PRO	patient reported outcome
PV	pharmacovigilance
QOLCE	Quality of Life in Childhood Epilepsy

RCT	randomized controlled trial
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
sGTC	secondarily generalized-tonic-clonic
sNDA	supplemental new drug application
SOC	standard of care
SJS	Stevens-Johnson syndrome
STP	stiripentol
SUDEP	sudden unexpected death in epilepsy patients
T+M	titration and maintenance periods
TEAE	treatment emergent adverse event
TEN	toxic epidermal necrosis
THC	tetrahydrocannabinol
TID	three times a day
TPM	topiramate
TR	tricuspid regurgitation
TS	tonic seizure
TA	tonic atonic seizure
UK	United Kingdom
ULN	upper limit of normal
US	United States (of America)
VABS	Vineland Adaptive Behavior Scale
VHD	valvular heart disease
VPA	valproic acid or valproate
WRO	written responses only

1. Executive Summary

1.1. Product Introduction

Fenfluramine (FEN), an amphetamine analogue, is currently approved for the treatment of seizures associated with Dravet syndrome (DS) in patients 2 years of age and older. Although the mechanism of action remains unclear and may depend on multiple factors, it is theorized that fenfluramine reduces seizures by increasing extrasynaptic levels of 5-hydroxytryptamine (5-HT, serotonin) 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.

In this supplemental application, the Applicant proposes a new indication for FEN (tradename Fintepla) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older.

The marketed and proposed formulation of fenfluramine is an oral solution of 2.2 mg/mL fenfluramine, equivalent to 2.5 mg/mL of the hydrochloride salt. The dosing regimen in the prescribing information is based on the fenfluramine base but is comparable to the dosing of the 2.5 mg/ml solution of the hydrochloride salt used in the clinical trials (i.e., 0.2 mg/kg of the salt is roughly equivalent to 0.2 mg/kg of the base [rounded]; 0.5 mg/kg of the salt is roughly equivalent to 0.4 mg/kg of the base; 0.8 mg/kg of the salt is roughly equivalent to 0.7 mg/kg of the base).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Evidence of effectiveness for FEN for the treatment of seizures associated with LGS in patients 2 years of age and older is based on positive results from a single adequate and well controlled trial, a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, Phase 3 study (ZX008-1601 Part 1).

The level of evidence provided is adequate to support the conclusion that FEN is effective for the treatment of seizures in the population studied, given that there is confirmatory evidence from trials which supported the approval of FEN for the indication of the treatment of seizures in DS in patients 2 years and older.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Fenfluramine (FEN), 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 (VHD) and pulmonary arterial hypertension (PAH) and was determined to have been withdrawn from the U.S. market due to safety in 2015. It was approved for the treatment of seizures associated with Dravet syndrome (DS) in patients 2 years and older in June 2020, based upon the demonstration of efficacy, specifically the reduction of monthly convulsive seizure frequency, and safety in 2 randomized clinical trials. Fenfluramine is an oral solution given twice daily by mouth, and is prescribed and dispensed through a Risk Evaluation and Mitigation System (REMS) to moderate the risk of VHD and PAH.

Lennox-Gastaut syndrome (LGS) is a severe epilepsy syndrome which is characterized by multiple seizure types and cognitive impairment which may be due at least in part to the seizures. The seizures are frequent and often refractory to multiple medications and other treatments. Characteristic seizure types are tonic seizures and other types which cause the patient to drop suddenly, placing the patient at risk for physical injury and further limiting independent functioning. Patients with LGS have increased risk of status epilepticus and mortality. The seizures and cognitive impairment contribute to significant disability. Seizures often persist despite use of the 7 approved seizure treatments for patients with LGS (cannabidiol, clobazam, rufinamide, lamotrigine, topiramate, felbamate, and clonazepam), which are moderately effective.

The efficacy of FEN in LGS was demonstrated in one randomized clinical trial, in which FEN and standard of care was compared to standard of care treatment alone. There is evidence of clinical benefit based on reduction of monthly drop seizure frequency with FEN at 0.8 mg/kg/day. The key secondary outcome measure of patients who had at least a 50% reduction in drop seizure frequency showed a greater proportion of responders in the 0.8 mg/kg/day group than in the placebo group and was supportive.

Risks identified in the clinical safety data were similar to those identified in the trials in DS and include decreased appetite; fatigue, malaise, and asthenia; and somnolence, sedation, and lethargy. Fatigue and somnolence is observable. Decreased appetite may also be observed and, particularly in growing children, can be combined with monitoring of weight. When necessary, FEN dose reduction or discontinuation can take place.

The most concerning risks associated with FEN are VHD (particularly aortic and/or mitral regurgitation) and PAH, neither of which have thus far been observed in the DS and LGS development programs. These fenfluramine-related adverse effects were reported in the 1990's and considered to be due to FEN and the closely-related drug dexfenfluramine, based on case report studies, meta-analyses, and retrospective reports. Duration of treatment of FEN appears to be a risk factor for development of either VHD or PAH, 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 VHD or PAH 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.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• LGS is a severe form of childhood epilepsy characterized by refractory seizures of multiple types, including seizures which cause drops, and intellectual impairment. The cognitive impairment may be, in part, exacerbated by the seizures. • Seizures in patients with LGS are generally refractory to antiseizure medications (ASMs). Seizure-freedom almost never occurs. • Patients with LGS are at risk for Sudden unexplained death in epilepsy (SUDEP) and status epilepticus.	LGS is a severe epilepsy syndrome that has significant morbidity due to refractory seizures, many of which cause drops and secondary injury, and cognitive impairment. Mortality is higher in pediatric patients with LGS than the general pediatric population. Seizures and seizure-related events are frequent causes of death.
Current Treatment Options	• A primary objective of treatment of seizures in patients with LGS is reduction in frequency of the most incapacitating and injurious seizures (e.g., tonic-clonic seizures, tonic seizures). • Seven drugs are approved by FDA for reduction of seizures in patients with LGS, and several other drugs are used to treat seizures in patients with LGS, but seizures in LGS continue to generally be resistant to ASMs (even when used as polytherapy) and complete seizure control with resolution of intellectual and psychosocial dysfunction is almost never achieved. • Significant adverse drug reactions are reported for many of the approved and/or frequently used drugs to treat seizures	Seven drugs are approved for the treatment of seizures in LGS, and other drugs are used off-label. However, seizures in patients with LGS continue to be refractory with significant impact on function, independence, and physical safety. Severe adverse drug effects have been reported with both approved drugs and the drugs frequently used off-label and must be considered when choosing an ASM treatment, especially in children and adolescents. The treatment armamentarium in LGS would benefit

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	in LGS, such as drug induced liver injury (cannabidiol), hepatic failure (valproate, felbamate), aplastic anemia or other hematologic abnormalities (felbamate, valproate), Stevens-Johnson syndrome (lamotrigine), somnolence and sedation (cannabidiol), tolerance (clobazam, clonazepam), decreased appetite (topiramate)	from more therapeutic options that are efficacious and well-tolerated.
Benefit	• There is one pivotal trial that demonstrates the efficacy of FEN given orally in patients with LGS. The primary endpoint was the percent change from baseline in the frequency of seizures that result in drops (DSF) in the FEN 0.8 mg/kg/day group compared with placebo. There was a statistically significant (p = 0.0013) decrease from baseline in DSF (-26.5% median percent change) compared to the placebo group (-7.59% median percent change). The analysis results were generally consistent across subgroups. • The key secondary endpoint of proportion of patients in the FEN 0.8 mg/kg/day group who were 50% responders compared to placebo was statistically significant and was consistent with the findings of the primary endpoint. • Data integrity was a concern due to the retrospective entering or modification of seizure diary data and the lack of immediate access to some source documents. Therefore the primary and secondary endpoint analyses were performed on the "pre-DCR [pre-data	A pivotal clinical trial identified clinically meaningful and statistically significant reduction in median drop seizure frequency from baseline in FEN 0.8 mg/kg/day compared to placebo. FEN expands the treatment options expected to provide benefit in the treatment of seizures associated with LGS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	change request]" dataset which retained seizure classification changes adjudicated by the Epilepsy Study Consortium (ESC), an organization of academic research investigators that provides consultation services to sponsors with a goal being the optimization of clinical study methodology, including consistency of seizure classification across drug trials.	
Risk and Risk Management	• Decreased appetite - Most frequently reported treatment emergent adverse event (TEAE) in the double-blind through open-label treatment periods for the controlled safety population - 2 patients had a serious adverse event (SAE) of decreased appetite - 4 patients discontinued treatment due to decreased appetite • Weight loss - 24.8% of patients in the double-blind through open-label treatment periods for the controlled safety population had ≥7% weight loss - 2 patients had weight decreased as an SAE - By their last visit in the OLE study, 11.3% of patients had a ≥7% weight loss from baseline—weight loss slowed down during the OLE study • Somnolence, Sedation, and Lethargy - Second most frequently reported TEAE in the double-blind through open-label treatment periods	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 (AR) may be monitored. Neither VHD nor PAH have been observed to date in the Fintepla development program, although both were associated with FEN when previously approved as an anorectic agent. VHD or PAH may be identified by regular monitoring via ECHO, 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 to determine if the drug should be discontinued. Because ECHO monitoring is necessary for identifying VHD or PAH, a REMS with elements to assure safe

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	for the controlled safety population - 5 patients had SAEs of somnolence - Somnolence led to discontinuation • No strong dose-response for AEs • VHD and PAH - Reported with use of FEN and dexfenfluramine when used as anorectic agents in the 1990's - Monitoring via echocardiograms (ECHO) during the controlled and OLE studies revealed no clinically-confirmed VHD or structural valve abnormalities - 2 patients, one 11 years-old, one 23-years-old had FDA-defined VHD of mild aortic regurgitation but have not had progression on ECHO or symptoms through almost 2 ½ and 3 years of exposure	use (ETASU) continues to be necessary, as is a box warning.

1.4. Patient Experience Data

The primary endpoint for the pivotal trial was based on seizure counts, which were recorded by patients and/or caregivers in an electronic diary. 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

LGS is a severe form of epilepsy which presents during childhood. An epileptic encephalopathy and electroclinical syndrome with a childhood onset, diffuse slow spike-wave complexes, and several types of seizures was first described by Lennox and Davis in 1950[1], and the syndrome was further defined by Gastaut et al in 1966[2]. It is characterized by a triad of electro-clinical findings: multiple refractory seizure types, developmental delay and an interictal electroencephalogram (EEG) pattern of diffuse, slow spike-wave complexes[3,4]. LGS is considered a developmental and/or epileptic encephalopathy (DEE), in which the seizures and the epileptic activity contribute to the developmental delay and behavioral abnormalities[5].

The etiology of LGS is often divided into two groups: recognizable (primarily genetic or structural) or unknown. Etiologies can be identified in 60-75% of patients and include a wide variety of causes, such as hypoxic-ischemic insults (most common), tuberous sclerosis complex,

[1] Arzimanoglou A, French J, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol 2009; 8: 82–93
[2] Gastaut H, Roger J, et al. Childhood epileptic encephalopathy with diffuse slow spike-waves (otherwise known as "petit mal variant") or Lennox syndrome. Epilepsia. 1966 Jun;7(2):139-79.
[3] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for Revised Classification of Epilepsies and Epileptic Syndromes. Epilepsia. 30(4):38%399, 1989
[4] Hancock EC, Cross JH. Treatment of Lennox-Gastaut syndrome. Cochrane Database Syst Rev. 2013 Feb 28;(2):
[5] Camfield PR. Definition and natural history of Lennox-Gastaut syndrome. Epilepsia, 52(Suppl. 5):3–9, 2011

brain malformations, and traumatic brain injuries[1,5,6]. Seizures associated with LGS might occur de novo or might follow severe infantile seizure disorders, such as infantile spasms. A variety of genetic anomalies have been reported in patients with the diagnosis of LGS, including variants or mutations in the SCN1A, FOXG1, DNM1, and CHD2 genes. SCN1A mutations underly the majority of cases of DS.

LGS has been estimated to account for 1-10% of childhood epilepsies; this wide range is likely due to the potential for clinicians to identify many young pediatric patients with multiple seizure types and developmental delay as having LGS. Trevathan et. al. assessed the epidemiology of patients with LGS using data captured in study of pediatric patients with developmental disabilities. The authors found the prevalence of epilepsy to be 6 per 1,000 children, with 4% of those patients classified as LGS[7]. In their evaluation, LGS was defined by onset of multiple seizure types prior to age 11 years and an EEG with slow spike-wave complexes (<2.5 Hz) but developmental delay was not used as a diagnostic criterion. Children and adolescents with LGS have a higher mortality rate than the age-matched cohorts, with an up to 14 times increased risk of death during childhood and adolescence[8]. Common reported proximate causes of death in patients with LGS are SUDEP, status epilepticus, or seizures[8].

Onset of LGS typically occurs before 8 years of age, with peak presentation occurring between ages 3 and 5 years[1,5]. Because all clinical and EEG features may not be present at onset of the disorder, the diagnosis of LGS may be delayed. Some patients (20-60%)[1] have evidence of delayed intellectual development at the time of diagnosis, especially those who present later. Cognitive impairment becomes more obvious over time, with intellectual dysfunction in 75-95% of patients within 5 years of initial diagnosis[9]. Severity of patients' cognitive and behavior impairments vary from minimally affected (rare) to profoundly impaired.

Drop attacks occur in more than 50% of patients with LGS and are the most disabling of the seizure types[1]. The most basic definition of a drop attack is a seizure that leads to a fall or would have caused a fall. In patients with LGS, drop attacks are often but not always preceded by a myoclonic jerk but occur too quickly for intervention, thus frequently leading to injury. Other seizure types seen in patients with LGS include non-convulsive status epilepticus in 50-70% of patients[1], myoclonic seizures, focal seizures with or without secondary generalization, generalized tonic-clonic seizures, and hemiclonic seizures. Tonic seizures are the most characteristic type of seizure in LGS and are characterized by "a sustained increase in muscle

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[6] Asadi-Pooya AA. Lennox-Gastaut syndrome: a comprehensive review. *Neurol Sci* 2018; 39:403-414.
[7] Trevathan E, Murphy CC, Yeargin-Allsopp M. Prevalence and descriptive epidemiology of Lennox-Gastaut syndrome among Atlanta children. *Epilepsia* 1997; 38:1283–1288.
[8] Autry AR, Trevathan E, et al. Increased Risk of Death Among Children With Lennox-Gastaut Syndrome and Infantile Spasms. *J Child Neuro* 2010; 25(4):441-447.
[9] Hancock EC, Cross HJ. Treatment of Lennox-Gastaut syndrome. *Cochrane Database Syst Rev* 2013 Feb 28; (2):CD003277.

contraction lasting a few seconds to minutes"[10]. Tonic seizures may range in severity from a brief flexion of the head and trunk to affecting muscles of the trunk and extremities leading to falls and injuries. Atypical absence seizures are also frequently seen in patients with LGS and present with a brief loss or impairment of consciousness (without the typical EEG pattern of 3 per second spike-wave activity)[5].

2.2. Analysis of Current Treatment Options

Seizures in LGS are usually resistant to ASMs and complete seizure control with resolution of intellectual and psychosocial dysfunction is almost never achieved. The primary objective of treatment of seizures in patients with LGS is reduction in frequency of the most incapacitating and injurious seizures (e.g., drop attacks and tonic-clonic seizures)[11].

Seven drugs are approved by the US Food and Drug Administration (FDA) for reduction of seizures in patients with LGS: cannabidiol, clobazam, rufinamide, lamotrigine, topiramate, felbamate, and clonazepam (Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication). Cannabidiol, clobazam, felbamate, lamotrigine, rufinamide, and topiramate were studied in patients with LGS in randomized controlled trials.

In controlled clinical trials, the frequency of drop attacks decreased significantly with adjunctive use of lamotrigine[13], topiramate[12], or clobazam[13]. Valproic acid (VPA), although not approved for use in patients with LGS, is considered a first line treatment, along with lamotrigine and topiramate. Non-pharmacologic treatments for patients with LGS include corpus callosotomy as palliative treatment for drop attacks[1], vagus nerve stimulation[1], and ketogenic diet[14].

In 2013, Hancock and Cross conducted a review of pharmacologic therapies used to treat LGS in terms of control of seizures and adverse effects[9]. They searched various databases (Cochrane Epilepsy Group, MEDLINE, EMBASE) for randomized controlled trials (RCTs) of drug treatment in patients with LGS and identified 9 RCTs. In their analysis, the authors note that they were unable to perform meta-analyses or comparative analyses, "because each trial looked at

[10] Blume WT, Luders HO, Mizrahi E, et al. ILAE Commission Report. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. *Epilepsia* 2001; 42:1212–18.
[11] Michoulas A, Farrell K (2010) Medical management of Lennox-Gastaut syndrome. *CNS Drugs* 24(5):363–374.
[12] Sachdeo RC, Glauser TA, Ritter F, et al. A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. *Neurology* 1999; 52:1882–87.
[13] Ng YT, Conry JA, Drummond R, et al. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. *Neurology* 2011 Oct 11;77(15):1473-81.
[14] Freeman JM, Vining EP. Seizures decrease rapidly after fasting: preliminary studies with the ketogenic diet. *Arch Pediatr Adoles Med* 1999; 53:946–49.

different populations, different therapies and considered different outcomes." They concluded that "The optimum treatment for LGS remains uncertain and no study to date has shown any one drug to be highly efficacious…" and "clinicians will need to continue to consider each patient individually, taking into account the potential benefit of each therapy weighed against the risk of adverse effects." An updated Cochrane Review was performed in 2020 and identified 11 RCTs using adjunctive ASMs for LGS. The authors noted a lack of RCTs of monotherapy and head-to-head comparisons of adjunctive ASMs[15].

[15] Brigo F, Jones K, Eltze C, and Matricardi S. Anti-seizure medications for Lennox-Gastaut syndrome. *Cochrane Database Syst Rev* 2021 Apr 7; 4(4):CD003277.

- Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments for Lennox-Gastaut Syndrome					
Cannabidiol (CBD)	Treatment of seizures associated with LGS in patients 2 years of age and older	2018	10-20 mg/kg/day daily (divided BID)	Statistically significant median percentage change in drop seizure frequency (per 28 days) from baseline in CBD treatment groups compared to placebo in 2 studies: • Study 1414—42%, 37%, and 17% reductions in the CBD 20 mg/kg (p=0.0016), CBD 10 mg/kg (p=0.0047), and PBO groups, respectively • Study 1423—44% reduction in the CBD 20 mg/kg/day group (p=0.0135).[16]	Hepatocellular injury, somnolence and sedation, hypersensitivity reactions, decreased appetite and weight loss, diarrhea, decreased hemoglobin and hematocrit, and rash
Clobazam (CLB)	Adjunctive treatment of seizures associated with LGS in patients 2 years of age and older	2011	Patients ≤30 kg: 5-20 mg daily (divided BID) Patients >30 kg: 20-40 mg daily (divided BID)	Statistically significant reduction in mean percent reduction from baseline in weekly drop seizure frequency: Low dose (0.25 mg/kg/day): p<0.05 Med dose (0.5 mg/kg/day): (p<0.01) High dose (1 mg/kg/day): (p<0.01)	Somnolence/sedation, withdrawal symptoms, skin reactions (Stevens-Johnson Syndrome [SJS], toxic epidermal necrolysis [TEN])
Rufinamide	Adjunctive treatment of seizures associated with LGS in pediatric patients 1 year	2008	45 mg/kg daily, divided BID, maximum 3200 mg per day	• Median percent change in total seizure frequency per 28 days (p=0.0015) • Median percent change in tonic-atonic seizure frequency per 28 days (p<0.0001)	Shortening of the QT interval (unknown clinical risk); somnolence or fatigue, and coordination abnormalities, dizziness, gait disturbances, and ataxia; Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); leukopenia

[16] NDA 210365 Epidiolex clinical review (Natalie Getzoff, MD), dated 6/14/2018

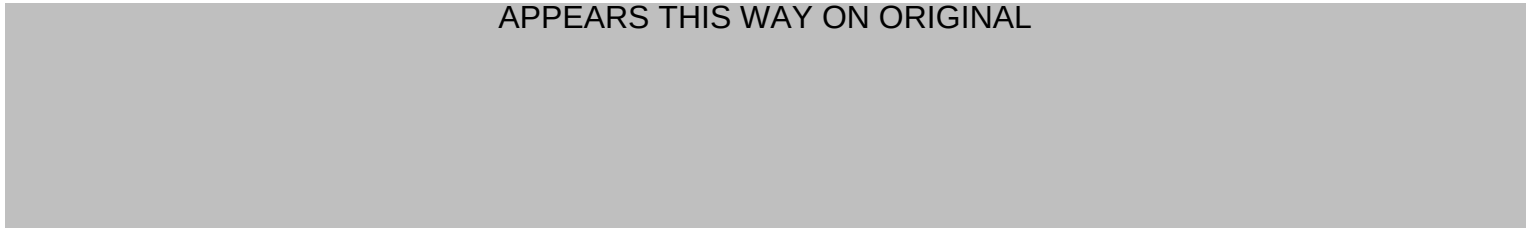
Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments for Lennox-Gastaut Syndrome					
	of age and older, and in adults			• Improvement in Seizure Severity Rating from Global Evaluation (p=0.0041)	
Lamotrigine	Adjunctive therapy for generalized seizures of LGS in patients aged 2 years and older	Initial: 1994 LGS: 1998	> 12 years: 100-500 mg divided BID (depending on concomitant ASMs especially VPA) ≤12 years: 1-15 mg/kg/day, divided BID depending on concomitant ASMs (especially VPA)	• A decrease in the frequency of all seizures compared with placebo (–32% vs –9%; p=0.02)[17] • Median percentage reduction from baseline in major motor seizures (p<0.05) • Drop attacks and tonic-clonic seizures were "significantly reduced" by lamotrigine	Serious skin rashes (including SJS), greater in pediatric than adult patients; DRESS; hepatic failure; blood dyscrasias: neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia; aseptic meningitis; SUDEP; status epilepticus
Topiramate (TPM)	Adjunctive therapy for seizures associated with LGS in patients 2 years of age and older	Initial: 1996 LGS: 2001	Adults: 200-400 mg daily divided BID Pediatrics: 5 to 9 mg/kg daily divided BID	• Median percent reduction in drop attacks (p<0.05) • Parental global rating of seizure severity (p<0.05)	Acute myopia and secondary angle closure glaucoma; visual field defects; metabolic acidosis; cognitive-related dysfunction; depression or mood problems; fetal anomalies (cleft lip and/or cleft palate and small for gestational age); hyperammonemia with or without encephalopathy; nephrolithiasis

[17] Motte J, Trevathan E, Arvidsson JF, et al. Lamotrigine for generalized seizures associated with Lennox-Gastaut Syndrome. *N Engl J Med* 1997; 337:1807–12.

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments for Lennox-Gastaut Syndrome					
Felbamate (FBM)	Adjunctive therapy in treatment of partial and generalized seizures associated with LGS	1993	45 mg/kg daily divided TID to QID	• A decrease in the frequency of all seizures compared with placebo (–19% vs +4%; p=0.002)[18] • Statistically significant reductions in total, atonic, and tonic-clonic seizures	Aplastic anemia; hepatic failure
Clonazepam	Useful alone or as an adjunct in the treatment of the LGS (petit mal variant)	Initial: 1975	Adults: maintenance dose dependent on response, max 20 mg daily (divided TID) Pediatric: infants/children (≤10 years or 30 kg) maintenance dose of 0.1 to 0.2 mg/kg daily divided TID	• Not available	central nervous system (CNS) depression, withdrawal symptoms; Worsening of seizures especially in patients with multiple seizure types

Abbreviations: BID = twice a day, TID = three times a day

[18] The Felbamate Study Group in Lennox-Gastaut Syndrome. Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome). *N Engl J Med* 1993; 328:29–33.



3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Fenfluramine (FEN) 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. FEN 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.[19,20] On March 8, 1999, FEN 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.[21] In September 2015, the FDA determined that Pondimin® and Ponderex® specifically were withdrawn from the U.S. market due to reasons of safety or effectiveness.[22]

The initial approval of FEN 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%).

On June 25, 2020, FEN was approved by the FDA as Fintepla for the treatment of seizures associated with DS in patients 2 years of age and older. The approval was based on data from seven studies, including two randomized, double-blind, placebo-controlled trials, a long-term open-label safety study, and an open-label pharmacokinetics (PK) study in patients with DS age 2 to 18 years. The 2 randomized trials demonstrated that FEN at doses of 0.2 and 0.8 mg/kg/day in the absence of concomitant stiripentol (STP) and 0.5 mg/kg/day in patients taking concomitant STP, as compared to placebo, reduced the frequency of convulsive seizures in patients with DS. The most common reported AEs included decreased appetite (37% of patients in the pooled FEN treatment group versus 8% of patients in the pooled placebo group); somnolence, sedation, lethargy (25% of patients in the pooled FEN treatment group versus 11%

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

of patients in the pooled placebo group); and weight loss (in 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 baseline weight by the final visit of the controlled studies). Measured weight loss appeared to slow down during the open label extension study. ECHO assessments, which included a primary assessment of the number of subjects who developed FDA-defined VHD or PAH (mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation), and a secondary analysis of summary of findings on valve structure and morphology, did not demonstrate VHD or PAH[23].

Of note, the original NDA for Fintepla for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older was submitted on February 5, 2019. A refuse-to-file letter was issued on April 5, 2019 due to the submission of incorrect datasets and the need to "conduct an extensive data quality assessment to ensure the accuracy of trial results" prior to resubmitting the NDA. An incomplete nonclinical package was also cited, although this was later determined to be a review issue rather than a filing issue. The NDA was resubmitted on September 25, 2019. The FDA site inspections during the review cycle (b) (4) identified substantial data integrity issues, which included extensive new seizure data entries and modifications of previously entered seizure data which were retrospectively performed as long as a year after the original event date, with source data which was not reliably retained by study sites or which demonstrated discrepancies when compared to the seizure dataset. These issues were caused by poor caregiver compliance of completing electronic seizure diaries (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 issues; and inadequate centralized and on-site monitoring efforts to proactively identify and follow-up on missing data. Retrospective data were collected in 96% of randomized patients and involved 8.6% of total seizure frequency in one pivotal study; retrospective data were collected in 90% of randomized patients and involved 9.2% of total seizure frequency in the other pivotal study. However, despite these significant data integrity concerns, reanalysis of the primary and key secondary efficacy endpoints for both pivotal studies using "pre-edited" datasets (which reverted data to values prior to retrospective modifications), demonstrated that outcomes remained statistically significant in favor of the FEN treatment groups.

At the time of original NDA approval, the following postmarketing requirements (PMRs) were issued:

- 3887-1: A fertility and early embryonic development study of FEN in rat
- 3887-2: An embryofetal development study of FEN in rat
- 3887-3: An embryofetal development study of FEN in rabbit
- 3887-4: A pre- and postnatal development study of FEN in rat
- 3887-5: A 6-month carcinogenicity study of FEN in transgenic mice

[23] NDA 212102 Fintepla clinical review (Natalie Getzoff, MD), dated 6/25/2020

- 3887-6: A 2-year carcinogenicity study of FEN in rat
- 3887-7: A single-arm pregnancy safety study for a minimum of 10 years, to assess pregnancy complications and birth outcomes in women exposed to FEN during pregnancy
- 3887-8: A prospective observational registry study in epilepsy patients taking Fintepla to characterize the risks of the development of symptomatic or asymptomatic VHD and/or PAH, including assessment of echocardiograms (ECHOs) at baseline and every 6 months for 5 years or until the last ECHO following interruption of FEN treatment
- 3887-9: A PK study to determine an appropriate dose of FEN to minimize toxicity in patients with varying degrees of hepatic impairment.

In addition to PMRs, a REMS requirement was issued. In June 2020, the Fintepla REMS was approved, to ensure the benefit of Fintepla outweighs the risk of VHD and PAH. The Fintepla REMS program requires that prescribing healthcare providers and dispensing pharmacies are certified, that patients are enrolled and counseled on the risks and the requirements for echocardiogram monitoring, that procedures and policies are established by wholesalers to ensure that distribution is only to certified pharmacies, and that certified pharmacies have procedures and policies in place to ensure that Fintepla is only dispensed to patients based on prescriptions from certified prescribers. Requirements also include an implementation system and a timetable for submission of assessments (6 months, 12 months and annually thereafter). On June 23, 2021, the Applicant submitted its 12-month REMS assessment report; consultation between the Office of Surveillance and Epidemiology (OSE) and the Office of New Drugs (OND) determined that the REMS was meeting the goal of mitigating the risk of VHD and PAH associated with Fintepla, and no modifications were necessary.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 132604 was submitted to FDA on March 16, 2017, for Study ZX008-1601, a study of the safety and efficacy of FEN in the treatment of seizures associated with LGS.

Significant clinical interactions between FDA and the Applicant include the following:

- Pre-IND meeting Written Responses Only (WRO; issued January 31, 2017)
- May Proceed Letter (issued April 24, 2017)
- Orphan designation granted to FEN for treatment of LGS (June 19, 2017)
- Request for Fast Track designation for the adjunctive treatment of seizures associated with LGS (September 25, 2017); denied due to lack of demonstration of the potential to address an unmet medical need for an indication for which, at the time, there were 5 approved drugs (November 8, 2017)
- Type C meeting request for feedback on support for the planned supplemental NDA (sNDA; WRO issued September 15, 2020).
    - The feedback included submission requirements to prevent the data issues which were experienced with the original NDA submission, including the need to

provide the final study report for the 2-year rat carcinogenicity study, the pre-edited efficacy datasets if retrospective adjustments occurred, and integrated analyses of results of the blinded and open-label extension phases of Study 1601 and interim results from long-term Study 1900.

- Type B pre-sNDA meeting (teleconference held June 22, 2021; minutes sent to the Applicant July 22, 2021)
    - The Applicant reviewed its process for determining and documenting seizure classification and drop seizure designation and explained the potential reasons for and timeframe allowed for retrospective data changes or additions in Study 1601.
    - The Applicant noted that it planned to submit a "post-data change request (post-DCR)" dataset and a "pre-DCR" dataset in which all data changes are reverted except for changes to seizure classification as determined by the ESC, and to perform analyses on both datasets.
    - The Applicant also explained the process of manual reconciliation of seizure classifications and drop seizure designations.
    - The Division recommended conducting a population PK and exposure-response analysis.
    - The Division noted that a REMS for Fintepla integrating the LGS indication should be submitted.

3.3. Foreign Regulatory Actions and Marketing History

The marketing application for FEN (as Fintepla) for the indication of treatment of seizures associated with DS in patients 2 years of age and older was authorized as in the European Union (EU) and United Kingdom (UK) in December 2020. The Applicant has submitted its Type II Variation Market Authorization Application to the EMA for Fintepla for the treatment of seizures associated with LGS.

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

4.1. Office of Scientific Investigations (OSI)

Please see Study ZX008-1601 Part 1 for a detailed discussion of eDiary entry and data changes. Please also see Dr. Alfaro's review for a complete discussion of OSI's findings. Her conclusion was as follows:

"There was no access to the source documentation to support retrospective proxy data entry, and therefore the reliability of proxy data entries was not able to be determined. OSI recommended that the FDA statisticians perform a sensitivity analysis to assess the robustness of the results reported by the Sponsor. Some protocol deviations were noted in particular at one site, however OSI concluded that the study appears to have been conducted adequately and the data generated by the sites appear acceptable in supportive of the respective indication."

The choice of the three domestic clinical sites for inspection was primarily based on risk ranking in the site selection tool, numbers of enrolled subjects, impact on efficacy endpoint, and prior inspection history (or lack thereof). Note that inspections did not verify whether a seizure was a drop seizure based on eDiary data, because whether a seizure was considered a drop seizure was determined by the ESC. The sites included:

1) Site 121 (PI Ronald Davis MD; Orlando, Florida): No discrepancies in eDiary data (including data of seizure, seizure type, and number of seizures) were noted. There was no evidence of underreporting of AEs except with 1 of the 8 total randomized patients.
2) Site 104 (PI Ann Hyslop Segeren MD; Miami, Florida): Ten patients were randomized at this site.
    a. One subject's reason for study discontinuation was inaccurately recorded as "physician decision," and not lack of efficacy.
    b. One eligibility violation of fewer than the required drop seizures was noted, however potential impact would not favor the investigational drug.
    c. One subject was not re-consented after an abnormal ECHO result until the subject's last day of the study; the Independent Data and Safety Monitoring Committee (IDSMC) had requested that the appropriate informed consent form be signed prior to continuation in the study.
    d. One subject had a delay in performance of a repeat ECHO after an incomplete ECHO study.
    e. One AE (of upper respiratory infection) was not transcribed from the source documents to the AE log or electronic Case Report Form (eCRF); however this

would not have likely impacted the safety analysis conclusion.

f. Clinician rated Clinical Global Impression – Improvement (CGI-I) scores, a key secondary efficacy endpoint, were missing for the end-of-study visit for 4 subjects, and were characterized as minor protocol deviations.

3) Site 126 (PI Michael Scott Perry, MD; Fort Worth, Texas): 6 patients were randomized. One subject's reason for study discontinuation was inaccurately recorded as "withdrawal by subject," and not lack of efficacy. There were otherwise no discrepancies in eDiary data (including data of seizure, seizure type, and number of seizures) were noted. There was no evidence of underreporting of AEs.

Reviewer's comment: The Division had concerns relating to data integrity, similar to those related to retrospective data entry in the trials which supported the original NDA for the treatment of seizures associated with Dravet syndrome. However, the site inspections which were performed for this sNDA did not reveal as significant issues as those found during site inspections for the original NDA. Efficacy analysis performed on the dataset in which retrospective data changes (other than those related to seizure classification and drop seizure designation which were adjudicated by the ESC) were reverted, demonstrated statistically significant results which were similar to the results from analysis of the dataset with all data changes retained. The outcome of the efficacy analysis did not appear to be impacted by data issues.

4.2. Product Quality

Fintepla is an already approved product.

4.3. Clinical Microbiology

No new clinical microbiology studies were included in this sNDA.

4.4. Nonclinical Pharmacology/Toxicology

Please see Dr. Fisher's review for discussion of the nonclinical studies submitted in this sNDA.

4.5. Clinical Pharmacology

The proposed doses are the same as the already approved doses for treatment of seizures associated with DS. 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

- 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							
ZX008-1601 Part 1 Cohort A* NCT03355209 *Cohort A is comprised of patients in NA, EUR, and AUS (Cohort B is comprised of patients from Japan)	Randomized, double blind, placebo-controlled, efficacy and safety study (completed)	FEN oral solution 0.2 or 0.8 mg/kg/day (maximum 30 mg/day) divided BID vs placebo	Primary: Change from baseline in DSF per 28 days during T+M periods for the 0.8 mg/kg/day group compared with the placebo group. Key secondary endpoints: • The proportion of patients in each FEN group who achieved a ≥ 50% reduction from baseline in DSF vs placebo • Percentage of patients in each FEN group who were rated on the CGI-I by the Investigator as improved vs placebo • The 3 endpoints above for the 0.2 mg/kg/day group	Baseline: 4 wks Titration: 2 wks Maintenance: 12 wks Taper or Transition: 2 wks	335 screened 263 randomized FEN 0.8 mg/kg/day: 87 FEN 0.2 mg/kg/day: 89 PBO: 87	2-35 years with a clinical diagnosis of LGS and refractory drop seizures, ≥ 8 drop seizures in the 4 wks prior to screening, on 1 to 4 ASMs Concomitant STP was not excluded but no patients were on it	65 sites: US (31), CAN (2), MEX (1), SWE (1), DEN (1), BEL (3), DEU (6), FRA (6), ESP (4), ITA (5), NLD (1), POL (2), AUS (2)
Studies to Support Safety							
ZX008-1601 Part 2 Cohort A NCT03355209	Open-label, uncontrolled, long-term extension study (ongoing)	FEN oral solution 0.2 mg/kg/day for 1 month, then flexible dosing to max 0.8 mg/kg/day (max 30 mg/day), divided BID	Primary: Assess the long-term safety and tolerability of FEN, including effects on ECHO and electrocardiograms (ECG) Secondary: to assess the efficacy of FEN relative to pre-FEN baseline	54 weeks (12-month treatment period and 2-week post-dosing period)	247	Patients who completed Study 1601 Part 1 Cohort A	63 sites in North America (32), Europe (29), and Australia (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
ZX008-1900 NCT03936777	Open-label, uncontrolled, long-term extension study (ongoing)	Starting dose as prescribed at the last visit in Study 1601 Part 2, adjusted according to recent weight, and flexibly adjusted to 0.8 mg/kg/day (max 30 mg)	Primary: Assess the long-term safety and tolerability of FEN	Up to 36 months (24 months in DEN)	131 patients with LGS at interim analysis (cutoff date Oct 19, 2020)	Patients with rare seizure disorders e.g. epileptic encephalopathies including DS and LGS, who completed Study 1601 Part 2 Cohort A, DS Study ZX008-1503 or other Zogenix-sponsored trial with FEN	46 sites in North America (20), Europe (24), and Australia (2)
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
ZX008-1505	Part 1: 2-part, randomized, open-label, single-dose, 3-way crossover DDI study Part 2: 2-way crossover food effect study (completed)	Part 1: Regimen A: FEN 0.8 mg/kg B: STP 3500 mg, CLB 20 mg, VPA 25 mg/kg C: FEN 0.8 mg/kg + STP 3500 mg, CLB 20 mg, VPA 25 mg/kg Part 2: D: FEN 0.8 mg/kg after fast E: FEN 0.8 mg/kg dose after high-fat breakfast	Primary: Assess the PK profile of FEN (single oral dose) with and without STP regimen (STP/CB/VPA) Secondary objectives included: Evaluate the safety and tolerability of FEN (single oral dose) in the fed and fasted state	Part 1: 3 days Part 2: 2 days	Part 1: 26 Part 2: 14	Healthy adults	Single center (Quotient Sciences, Nottingham, UK)
ZX008-1603	Randomized, double-blind, double-dummy,	Cohort 1 (C1) Treatment A: FEN 15 mg BID Days 1-6, single dose Day 7; moxifloxacin matching	Primary: Evaluate effects of multiple oral administrations of a therapeutic and supratherapeutic dose of FEN on the QT interval	8 days	180	Healthy adults	Single center (Celerion, Arizona, US)

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
	placebo- and positive-controlled, thorough QT study (completed)	placebo single dose Days 1 and 8 Cohort 2 Treatment B: FEN 60 mg BID, same schedule and placebo as C1 Cohort 3 Treatment C: FEN matching placebo BID D1-6, single dose D7, moxifloxacin single dose D1, moxifloxacin matching placebo single dose D8 Cohort 3 Treatment D: FEN matching placebo BID D1-6, single dose D7, moxifloxacin matching placebo single dose D1, moxifloxacin single dose D8	corrected by Fridericia's formula (QTcF)				
ZX008-1604	Open-label DDI study (completed)	Single oral dose FEN 0.4 mg/kg Days 1 and 22; CBD titrated up to 700 mg BID+THC titrated up to 35 mg Days 14-31	Primary: Assess the PK profiles of FEN and norfenfluramine after a single FEN dose administered with a meal, with and without CBD at steady state	31 days	32	Healthy adult recreational drug users	Single center (INC Research Toronto, Inc, Ontario, CAN)
ZX008-1902	Open-label, adaptive, renal impairment study (completed)	Single oral dose FEN 0.4 mg/kg	Primary: Compare the PK of a single dose of FEN in patients with varying degrees of renal impairment with that of healthy matched control patients Secondary: Assess the safety and tolerability	1 day	16	8 adults with severe renal impairment, 8 with normal renal function	3 centers (Orlando, Florida, Miami, Florida, Saint Paul, Minnesota, US)
ZX008-1904	Open-label, crossover DDI study	Treatment Period 1: All cohorts: single dose FEN 0.4 mg/kg	Primary: Compare the PK profile of fenfluramine and norfenfluramine following a single oral dose of	25 or 26 days	Cohort 1: 18 Cohort 2: 18 Cohort 3: 19	Healthy adults	Single center (PPD Development,

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
	(completed)	Treatment Period 2: Cohort 1: fluvoxamine 50 mg QD D9-12, 50 mg BID D13-23, 50 mg QD D24-25, single dose FEN 0.4 mg/kg D17 Cohort 2: paroxetine 20 mg QD D9-12, 30 mg QD D13-24, 20 mg QD D25, 10 mg QD D26, FEN 0.4 mg/kg D18 Cohort 3: rifampin 600 mg QD D9-25, FEN 0.4 mg/kg D19	ZX008 with and without steady-state CYP1A2 inhibitor (fluvoxamine), CYP2D6 inhibitor (paroxetine), and CYP2B6 inducer (rifampin) Secondary: Assess the safety and tolerability				LP, Texas, USA)

Abbreviations: ASM = Antiseizure medication; AUS = Australia; BEL = Belgium; BID = twice daily; CAN = Canada; CBD = cannabidiol; CGI-I = Clinical Global Impression-Improvement; CLB = clobazam; DDI = drug-drug interaction; DEN = Denmark; DEU = Germany; DS = Dravet syndrome; DSF = drop seizure frequency; ECG = electrocardiogram; ECHO = echocardiogram; ESP = Spain; EUR = Europe; FEN = fenfluramine; FRA = France; GBR = Great Britain; ITA = Italy; LGS = Lennox-Gastaut Syndrome; MEX = Mexico; NA = North America; NLD = Netherlands; PK = pharmacokinetic; POL = Poland; QD = once daily; STP = stiripentol; SWE = Sweden; T+M = Titration and Maintenance; THC = tetrahydrocannabinol; wks = weeks; UK = United Kingdom; US = USA; VPA = valproate

5.2. Review Strategy

This clinical review primarily examines Study ZX008-1601 Part 1 Cohort A, a multicenter, randomized, double-blind, placebo-controlled efficacy and safety evaluation in children and adults with LGS [Cohort A is comprised of patients from North America, Europe, and Australia, whereas Cohort B consists of patients from Japan]. This single study was considered potentially sufficient to demonstrate evidence of effectiveness in the indication of LGS, given the prior approval with demonstration of effectiveness in the treatment of children with DS, a DEE which has features in common with LGS and.

Statistical analysis of the data was performed and reported by Dr. Xiangmin Zhang and is used as the basis of the clinical efficacy analyses in this clinical review. Study ZX008-1601 Part 2 reported uncontrolled efficacy data, and therefore will not be included in the discussion of efficacy. The clinical relevance of the efficacy analyses will be discussed in this review.

This reviewer performed safety analyses on data provided by the Applicant from pivotal study ZX008-1601 Part 1, and interim data from ongoing studies 1601 Part 2 Cohort A and 1900 (LGS participants only). Study 1601 Part 2 Cohort A is an open-label long-term extension study in patients from Study 1601 Part 1 Cohort A. Study 1900 is an open-label long-term extension study in patients with epileptic encephalopathies, including LGS and DS, who completed Study 1601 Part 2 Cohort A, Study ZX008-1503 (in DS), or another Zogenix-sponsored trial with FEN.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study ZX008-1601 Part 1 (Cohort A)

6.1.1. Study Design

Title

A Two-Part Study of ZX008 in Children and Adults with Lennox-Gastaut Syndrome (LGS); Part 1: A Randomized, Double-blind, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as Adjunctive Therapy for Seizures in Children and Young Adults with LGS, Followed by Part 2: An Open-Label Extension to Assess Long-Term Safety of ZX008 in Children and Adults with LGS

Overview and Objective

Study ZX008-1601 Part 1 was a Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical trial of 2 doses of fenfluramine (company designation ZX008) in children and adults with seizures associated with LGS.

The primary objective of Part 1 and of the entire study was to evaluate the effect of FEN 0.8 mg/kg/day versus placebo as adjunctive therapy for the treatment of uncontrolled seizures in children and adults with LGS based on the change in frequency of seizures that result in drops ("drop seizures") between baseline and the combined Titration and Maintenance (T+M) periods.

The key secondary objectives of Part 1 were:

- To evaluate the effect of FEN 0.2 mg/kg/day versus placebo based on the change in frequency of drop seizures (DSF) between baseline and T+M
- To evaluate the effect of FEN 0.2 and 0.8 mg/kg/day (independently) versus placebo on the proportion of subjects who achieve a ≥ 50% reduction from baseline in DSF
- To evaluate the effect of FEN 0.2 and 0.8 mg/kg/day (independently) versus placebo on the CGI-I rating, as assessed by the Principal Investigator.

There were a number of other secondary objectives, which included evaluating the effect of the FEN 0.2 and 0.8 mg/kg/day on change in frequency of all seizures that typically result in drops (not just those confirmed by the ESC), on change in frequency of all countable motor seizures, on change in frequency of all countable nonmotor seizures, and on change in frequency of all countable (motor and nonmotor) seizures, as well as evaluating the proportion of subjects who achieve a worsening, >0 to <25%, ≥25%, ≥50%, ≥75%, 100% reduction, and "near seizure freedom" (0 or 1 seizures). Change in frequency of non-drop seizures was performed as a post hoc analysis.

The safety objectives of ZX008-1601 Part 1 included evaluating for the safety and tolerability of FEN 0.2 and 0.8 mg/kg/day versus placebo with various assessments including ECGs and ECHOs. The primary ECHO and ECG objectives were specified in the Statistical Analysis Plan (SAP) for Cardiovascular Endpoints. The primary ECHO objective was to evaluate the effect of FEN 0.8 mg/kg/day on the mitral and aortic valves, and for the development of VHD and PAH.

The PK objective of ZX008-1601 Part 1 was to evaluate the PK of FEN 0.2 and 0.8 mg/kg/day at steady state and obtain exposure data for population PK analysis.

Trial Design

- Basic Study Design
  Study ZX008-1601 Part 1 was a Phase 3, multicenter, double-blind, randomized, placebo-controlled, 2-cohort study to assess the efficacy of 2 doses of oral FEN for drop seizures in patients with LGS. The study also assessed the safety, tolerability, and PK of FEN use in this population. The analysis for this review includes data from only Cohort A, which consists of patients in North America, Europe, and Australia. Cohort B consists of patients enrolled in Japan only. This efficacy section of this review discusses only Part 1 of Study ZX008-1601.

The study consisted of a 4-week Baseline period, a 14-week Treatment period (including a 2-week Titration and 12-week Maintenance period), and a 2-week Taper period (if patients exited the study) or Transition period (if patients enrolled in Study ZX008-1601 Part 2, the OLE). This general design is similar to other pivotal trials evaluating efficacy of ASM treatments.

- Trial location
  The study enrolled patients across 65 sites in North America, Europe, and Australia. 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)[24]. The use of placebo was the appropriate choice for a control group for this indication and in this patient population which has refractory epilepsy and is typically on several concomitant ASMs. Comparison to a placebo arm is felt to be necessary to fulfill the scientific objectives and regulatory requirements to demonstrate both efficacy and safety in this population, as a comparator is required to reliably assess the impact on seizure frequency, given the variability amongst patients at baseline in terms of seizure frequency, severity, type, and variable time between seizures.

- Diagnostic criteria
  Patients were enrolled if they had a diagnosis of LGS and/or fulfilled 4 clinical criteria for a diagnosis of LGS with seizures that resulted in drops. Patients must have had a minimum number of drop seizures in the 4 weeks prior to screening.

- Key inclusion/exclusion criteria
  Inclusion Criteria:
  1. Age 2 to 35 years, inclusive
  2. Females of childbearing potential must not have been pregnant or breast-feeding and must have had a negative urine or serum pregnancy test. Patients must have been willing to use medically acceptable forms of birth control, which included abstinence, while being treated in this study and for 90 days after the last dose of study drug.
  3. Must have had a diagnosis of LGS with seizures resulting in drops which were not controlled by current antiseizure treatments. Patients without a formal LGS diagnosis could still be enrolled if all other criteria were met.

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

4. Must have met all of the following:
    a. Onset of seizures at ≤11 years of age
    b. Multiple seizure types (must have included tonic or tonic-atonic seizures), including countable motor seizures that result in drops (eligible seizure types being generalized-tonic-clonic, tonic, clonic, atonic, focal with observable motor signs, and myoclonic)
    c. Abnormal cognitive development
    d. Evidence of EEG which showed abnormal background activity and slow spike-and-wave pattern <2.5 Hz (EEG report, copy of the EEG trace, or physician note that described the EEG findings)
5. Must have had ≥8 drop seizures in the 4 weeks prior to screening (at least 4 drop seizures in the first 2 weeks and 4 in the last 2 weeks)
6. Must be taking 1 to 4 ASMs (not counting rescue medications for seizures)
7. All medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation) must have been stable for 4 weeks prior to screening and were expected to remain stable throughout the study.
8. Informed consent (and assent if possible) were obtained
9. Parent/caregiver was willing and able to comply with diary completion, visits, and drug accountability.

Exclusion Criteria:

1. Known hypersensitivity to FEN or any of the excipients
2. A neurodegenerative disease
3. History of hemiclonic seizures in the first year of life
4. Only drop seizure clusters, in which individual seizures could not be reliably counted
5. Pulmonary arterial hypertension
6. Current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction, or stroke, or clinically significant structural cardiac abnormality
7. Current or recent history of anorexia nervosa, bulimia, or depression within the prior year that required medical or psychological treatment for a duration > 1 month
8. Current or past history of glaucoma
9. 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 enrolled after review and approval by the Medical Monitor and the Sponsor, with consideration of comorbidities and concomitant medications.
10. Concomitant therapy with: centrally-acting anorectic agents; monoamine-oxidase inhibitors; 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
11. Taking FBM for less than a year prior to screening, or did not have stable liver

function and hematology tests, or dose not stable for at least 60 days prior to screening

12. At imminent risk of self-harm or harm to others based on clinical interview and/or responses provided on the Columbia-Suicide Severity Rating Scale (C-SSRS). Patients 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.
13. Positive result on urine or serum tetrahydrocannabinol (THC) panel or whole blood cannabidiol (CBD) at screening

Randomization Inclusion Criteria

1. Approved for study inclusion by the ESC, an organization of academic research investigators that provides consultation services to sponsors with a goal being the optimization of clinical study methodology, including consistency of seizure classification across drug trials
2. No exclusionary cardiovascular or cardiopulmonary abnormality on screening ECHO, ECG, or physical examination and approved for entry by the central cardiac reader (including but not limited to trace or greater mitral or aortic valve regurgitation in a patient ≤18 years of age, mild or greater mitral or aortic valve regurgitation in a subject >18 years of age, possible signs of pulmonary hypertension, evidence of left ventricular systolic or diastolic dysfunction)
3. Stable baseline with ≥ 2 seizures resulting in drops per week during the 4-week baseline
4. Parent/caregiver had been compliant with eDiary completion during the baseline period, in the opinion of the investigator and sponsor.

Reviewer's comment: The eligibility criteria for Study ZX008-1601 Part 1 are reasonable.

- Dose selection

The 0.2 and 0.8 mg/kg/day doses of FEN used in Study ZX008-1601 Part 1 are the approved doses of FEN in the current PI. These doses were originally based on open-label safety and efficacy data from a published single-center, dose-finding study of add-on FEN in patients with LGS ages 3 to 17 years (n=13) in Belgium (Study S58545), and were studied in the pivotal studies which supported approval for the indication in DS.

The 0.5 mg/kg/day dose of FEN selected for concomitant administration with STP is the approved dosing for the indication of DS when given with STP, and was originally based on

the predicted effects of STP on FEN and the dose that matched the exposure for the reference dose of 0.8 mg/kg/day in the absence of STP in DS Study 1504 Cohort 1. The dose of 0.5 mg/kg/day was studied in patients on concomitant STP in DS Study 1504 Cohort 2. Although concomitant STP was not excluded from Study ZX008-1601, no participants were on concomitant STP during the LGS development program.

The VHD which was previously observed in obese adult patients appeared to be dose-dependent with greater severity above 40 to 60 mg/day. In the DS and LGS development programs, a maximum dose of 30 mg/day (20 mg/day if on concomitant STP) was chosen to minimize potential exposure overlap with those doses.

- Study treatments
  Patients randomized to a 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, to a maximum of 30 mg/day. 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 1601 Part 1

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

- Assignment to treatment
  Patients were randomly allocated in a double-blind manner to FEN 0.2 mg/kg/day, FEN 0.8 mg/kg/day, or placebo using a central interactive web response system (IWRS). Randomization was stratified by weight (<37.5 kg, ≥37.5 kg) with a target of at least 25% of patients in each weight group, to ensure balance across treatment arms.

  Reviewer's comment: A patient was eligible for enrollment in the Baseline period if the inclusion and exclusion criteria were met. At the conclusion of the Baseline period, these criteria were reapplied, along with the randomization criteria discussed above. Randomization occurred once those randomization criteria were fulfilled. 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 trials.

- Blinding
  Once a randomization number was assigned to a patient, the site recorded the patient's initials on the corresponding study drug labels. Patients were randomly assigned different concentrations of the oral solution by the IWRS in order to ensure that the volume of study

drug could not be associated with the dose group, and the IWRS instructed site personnel as to the volume to be administered based on the subject's weight. The identity of the IMP assigned to patients was held by the IWRS. The blind was to be broken only if assignment was needed for treatment decision-making; patients were to be discontinued upon breaking the blind. The transition period to Study ZX008-1601 Part 2 was also performed in a blinded fashion, as will be discussed later in this review.

Reviewer's comment: The described methods of blinding appear adequate. The primary endpoint of change in 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 ASM treatment trials.

The potential for reporting bias is potentially increased by retrospective reporting of seizures; however, the Division determined that any potential bias did not impact the efficacy outcome. This is further discussed below.

- Dose modification, dose discontinuation
  After the titration period, patients were to continue on their randomized dose through the maintenance period.

  See 8.5.1. Valvular Heart Disease and Pulmonary Arterial Hypertension below for discussion of the process of the Independent Data and Safety Monitoring Committee (IDSMC) assessment of patients based on ECHO criteria and determination of steps including potential reduction or discontinuation of study drug. Thresholds based on ECHO criteria were discussed extensively with the Agency for the DS pivotal trials and were described in Dr. Getzoff's clinical review[25].

- Administrative structure
  The ESC is an independent organization of academic research investigators that provides consultation services to sponsors with a goal being the optimization of clinical study methodology; the ESC evaluated all patients for the diagnosis of LGS for study inclusion and verified the seizure types of screened patients.

  Safety data were reviewed periodically by the Applicant's Medical Monitor and by an IDSMC. The International Cardiac Advisory Board (ICAB) was an advisory body to the

[25] NDA 212102 Fintepla clinical review (Natalie Getzoff, MD), dated 6/25/2020

Applicant, composed of board-certified pediatric cardiologists with specialization in ECHO, that monitored cardiac safety and provided advice to the IDSMC.

- Procedures and schedule
  See the following schedule of key assessments, adapted from the Schedule of Assessments from the Applicant.

- Table 4: Schedule of Key Assessments, Study ZX008-1601

Visit Number	Baseline Period			Titration + Maintenance Period								EOS/ ET	Post-Dosing	Cardiac Follow-up
	Screening	2 (Phone)	Randomization	Titration Period			Maintenance Period							
	1		3		4, 5 (Phone)	6	7 (Phone)	8	9 (Phone)	10	11 (Phone)	12	13	14
Study Day	**-28**	**-15**	**-1**	**1**	**4, 8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**197**
Informed Consent	X											X		
Inclusion/Exclusion Criteria	X		X											
Vital signs, Weight	X		X			X		X		X		X		
Height	X											X		
12-lead ECG	X		X					X				X		X
Doppler ECHO	X							X				X		X
Urine or serum pregnancy test	X		X					X				X		
Clinical laboratory evaluation	X		X					X				X		
Plasma sample for FEN PK								X						
Background ASMs PK			X			X		X		X		X		
Tanner Staging (>7 to 18 years)			X									X		
Subject Diary	D	R	C/R/D		R	C/R/D	R	C/R/D	R	C/R/D	R	C/R/D	C/R	
Study Medication			D		R	C/R/D	R	C/R/D	R	C/R/D	R	C/R/D	C/R	
C-SSRS	X		X			X		X		X		X		
CGI-I (parent/caregiver, PI)						X		X		X		X		
BRIEF, HADS (parent/caregiver), QOLCE			X									X		
VABS			X					X				X		
Adverse events				X										
AESI				X										X

Abbreviations: ASM=antiseizure medication; AESI=Adverse events of special interest; BRIEF=Behavior Rating Inventory of Executive Function; C=Collect; C-SSRS=Columbia-Suicide Severity Rating Scale; D=Dispense; ECG=electrocardiogram; EOS=end of study; ET=early termination; HADS=Hospital Anxiety and Depression Scale; PI=Investigator; PK=pharmacokinetics; QOLCE=Quality of Life in Childhood Epilepsy; R=Review; VABS=Vineland Adaptive Behavior Scale

The seizure diary and data entry process was reviewed at length at the pre-sNDA meeting, in the study report, and through several information requests (IRs) and responses sent during the review cycle.

An eDiary through a home-based handheld device was provided to each subject; this included a seizure module which was designed to model the paper seizure diary form provided by the ESC for use in clinical trials since 2009. During the screening visit, the Investigator assigned a clinical classification to each seizure type which the caregiver described. Study site personnel entered the caregiver's seizure descriptions and names of rescue medications into the eDiary for selection from a drop-down list. The Investigator would also assign a drop designation to each seizure description which would be entered, along with seizure type designations, into a form for review by the ESC as well as into the eCRF. The ESC would then approve or change seizure classifications and drop designations, and the eDiary would be updated if needed.

The process of ESC review occurred in parallel to initiation of the Baseline period and eDiary use by the parent/caregiver, so as to minimize the duration of time necessary for patients to participate in a placebo-controlled trial. The parent/caregiver was to complete the eDiary daily to capture seizure events, rescue medication use, and administrations of study medication. In addition to type, number, duration, and time of seizure, caregivers also indicated whether each seizure resulted in a fall or would have depending on the subject's body position. This field was ultimately not analyzed due to a large number of DCRs relating to this field (7.6% of seizure event records), suggesting that there was confusion amongst caregivers as to how to answer this question. There was no field in the eDiary that documented ESC classification of drop designation.

Because information about seizures is often provided to caregivers by other observers (e.g., teacher or grandparent), the eDiary was programmed to allow entry and/or editing of seizure information for up to 7 days past the date of the event. After 7 days, site personnel could enter seizure data which was not previously entered by the caregiver, "if acceptable source documentation was provided," per the protocol, when the device was next accessible to the study site (i.e., at the next study visit). Site personnel were also able to make changes to the seizure classifications and seizure descriptions, based on ESC determination. Other changes to previously-entered data would require a DCR which would be implemented by Signant Health, the manager of the electronic diaries and associated internet-based data portal. If a new seizure type occurred after the initial set-up of the eDiary, the caregiver could enter a new description in the eDiary, and the process of sending information to the ESC to confirm seizure classification would occur, with potential need for site personnel to update the eDiary after ESC review.

The Applicant noted that a total of 1659 seizures were entered de novo via proxy entry by site personnel for 80 of 263 (30%) patients, accounting for 1.2% of seizures. In addition, retrospective changes were reportedly made to 16,089 (12%) seizures for 174 of 263 (66%) of patients, not counting data that was not analyzed in primary and secondary efficacy endpoints (i.e., not counting the large number of DCRs made to the field relating to falling). The majority of changes made were due to ESC determinations regarding seizure type identification fields (including seizure descriptions and classifications). The Applicant reports that other data fields were changed in only 0.7% of seizures.

Reviewer's comment: As discussed in Office of Scientific Investigations (OSI)*, the Division has concerns relating to data integrity, specifically due to the inability to access and review source documentation for retrospective proxy data entered by study site personnel. However, these proxy data changes entered by site personnel affected a relatively low amount of data in this submission. Although there were a significant number of retrospective changes made based on ESC determinations of seizure classifications, risk of bias is less in that situation because classifications were originally assigned by Investigators, were reviewed by the ESC by a blinded process, and were supported by source documentation. Efficacy analysis performed on the dataset in which retrospective data changes (other than those related to seizure classification and drop seizure designation which were adjudicated by the ESC) were reverted, demonstrated statistically significant results which were similar to the results from analysis of the dataset with all data changes retained.*

The Applicant notes that the eDiary has been redesigned for future trials, such that the seizure classification will be programmed into an index table rather than attached to individual seizure records; therefore, a change to an ESC-approved classification will result in a single change regardless of the number of seizures experienced. Other challenges which need to be addressed for future trials relate to the lack of capture of drop designation in the eDiary and to the lack of source documentation for proxy data entry by study site personnel.

- Concurrent medications
  Patients had to be on at least one ASM at a stable dose during the trial. All non-pharmacological therapies for epilepsy (e.g., ketogenic diet, vagus nerve stimuation) 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 study drug, taken during the study was to be recorded on the eCRF and the Medical Monitor was to be informed. Concomitant STP was not excluded but no subjects were on STP.

  Prohibited concomitant therapies included:

- Felbamate (FBM), unless the patient had been on FBM for ≥12 months prior to screening, with a stable dose for ≥60 days before screening and stable liver function and hematology laboratory tests
- Drugs that interact with central serotonin, including imipramine, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin- or norepinephrine-reuptake inhibitors, vortioxetine
- Drugs that increase cardiovascular risk e.g., atomoxetine and those with noradrenergic reuptake properties
- Drugs intended to facilitate weight loss
- Products that contain cannabis or cannabinoids

- Treatment compliance
  Caregivers recorded administration of study drug in the eDiary as "Yes, the full dose," "Yes, a partial dose," or "No." Participants were asked to bring used, partially-used, and unused bottles of study drug to every study visit.

  Caregivers were to enter seizure data in the eDiary daily; on a day with no seizures, they would need to answer the question, "Do you have a seizure to report for [date]?" as "No, this day has been seizure free."

- Rescue medications
  The use of rescue medication was allowed and was captured in the eCRF and in the eDiary in association with the seizure for which it was given.

- Subject completion, discontinuation, or withdrawal
  Patients who completed the treatment period were invited to participate in Study ZX008-1601 Part 2, the open-label extension study. Patients underwent a blinded 2-week transition or taper period, depending on whether they enrolled in Part 2. Patients who did not enroll in Part 2 underwent a taper of the study drug, receiving product from a new bottle at each step in order to preserve the blind. Patients who were randomized to FEN 0.2 mg/kg/day would receive placebo for Days 1-4 after maintenance or early termination, and placebo for Days 5-8 after maintenance or early termination. Patients who were randomized to 0.8 mg/kg/day received FEN 0.4 mg/kg/day for Days 1-4 and FEN 0.2 mg/kg/day for Days 5-8. Patients who were randomized to placebo would receive bottles of placebo for each step.

  Patients who enrolled in Part 2 underwent a transition period in which they transitioned from their blinded daily dose to a 0.2 mg/kg dose over 2 weeks.

  Patients were required to discontinue from the study for:
  - Development of signs or symptoms indicative of cardiac valvulopathy or regurgitation, or pulmonary hypertension for which IDSMC, in consultation with

cardiac readers and the investigator, believed the benefit of continued participation did not outweigh the risk
- Entering the clinical investigation in violation of the protocol
- Requiring or starting the use of an unacceptable or contraindicated concomitant medication or chronic daily seizure therapy was changed
- Condition changing so that the subject no longer met the inclusion criteria or developed any of the exclusion criteria
- Noncompliance with protocol procedures in an ongoing or repeated manner
- Experiencing an AE that warrants withdrawal
- Clinically significant worsening of seizures, judged by investigator or subject/ caregiver such that treatment outside of the protocol and other than FEN was assumed to be in the subject's best interest; frequent or increased use of rescue medication could be considered indicative of worsening
- An "actual suicide attempt" as classified by the C-SSRS
- Investigator's opinion that it is not in the subject's best interest to continue
- Being found to be pregnant while on study.

For missing values due to discontinuation/withdrawal, 2 different methods for imputation were incorporated into the efficacy analysis. One method was "worst value substituted," i.e., if the DSF during T+M was lower than baseline, the baseline value would be substituted from the point of withdrawal to the end of the planned duration of T+M, but if the DSF was higher than baseline, there would be no substitution. The other method was a differential imputation method, in which dropouts due to AE, noncompliance, loss to follow-up or participant withdrawal would have the DSF values substituted with the "worst value" as described above; dropouts due to other reasons such as lack of efficacy would have the observed DSF imputed for the remainder of the time between dropout and end of planned duration of T+M. With both methods, the DSF for the planned duration of T+M would then be computed as a weighted mean of the value before dropout and the imputed value after dropout.

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 the percent change from baseline in the frequency of seizures that result in drops (i.e., drop seizure frequency [DSF]) in the treatment period (titration and maintenance periods [T+M]) in the FEN 0.8 mg/kg/day group compared with the placebo group. Seizures that result in drops were defined as those of generalized-tonic-clonic (GTC), secondarily generalized-tonic-clonic (SGTC), tonic (TS), atonic (AS), and tonic/atonic (TA)

seizure types which resulted in a drop for the subject and were confirmed as such by the ESC.

The frequency of drop seizures per 28 days was derived as follows:

$$\frac{28 \times \text{Total number of drop seizures during the (Baseline or T+M) period}}{\text{Total number of days in the (Baseline or T+M) period with nonmissing diary data.}}$$

Reviewer's comment: The primary efficacy endpoint was evaluated based on seizure diary entries, as is typical for other similar trials in patients with epilepsy. Efficacy of FEN in LGS was measured by reduction in drop seizure frequency because drop seizures are disabling and reliably observed by caregivers. 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

The key secondary endpoints were assessed in a testing hierarchy in the following order, i.e., once a p-value of >0.05 was obtained for an endpoint, formal statistical testing of remaining endpoints would stop or be considered exploratory:

1) Proportion of patients considered treatment responders, defined as those who achieved a ≥50% reduction from baseline in DSF, in the FEN 0.8 mg/kg/day group compared to placebo
2) Proportion of patients who achieved improvement (minimally, much, or very much improved) in the CGI-I as assessed by the Principal Investigator at Visit 12 (End of Study or Early Termination) in the FEN 0.8 mg/kg/day group compared to placebo. This is a 7-point on which a subject's condition is rated: "Very Much Improved" (1); "Much Improved"; "Slightly Improved"; "No Change"; "Slightly Worse"; "Much Worse"; "Very Much Worse" (7).
3) Change from baseline in DSF in T+M in the FEN 0.2 mg/kg/day group compared to placebo
4) Proportion of patients who achieved a ≥50% reduction from baseline in DSF, in the FEN 0.2 mg/kg/day group compared to placebo
5) Proportion of patients who achieved improvement (minimally, much, or very much improved) in the CGI-I as assessed by the PI at End of Study or Early Termination in the FEN 0.2 mg/kg/day group compared to placebo.

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

Other Secondary Efficacy Endpoints

- The following were assessed in the FEN 0.8 mg/kg/day and 0.2 mg/kg/day groups, each during T+M and Maintenance alone, and compared independently to placebo:
  - Change in frequency of all seizures that typically result in drops (GTC, SGTC, TS, AS, TA), whether ESC-confirmed as drop seizures or not
  - Change in frequency of all countable motor seizures (GTC, SGTC, TS, AS, TA, clonic seizures [CS], focal seizures with clearly observable motor signs, and hemiclonic seizures)
  - Change in frequency of all countable nonmotor seizures (absence, myoclonic, focal without clear observable motor signs, infantile spasms, and epileptic spasms)
  - Change in frequency of all countable seizures, motor and nonmotor
- The proportion of subjects who achieve a worsening from Baseline (ie, ≤0% reduction), or >0%, ≥25%, ≥50%, ≥75%, or 100% reduction between Baseline and T+M, and Baseline and Maintenance, in seizures that result in drops, seizures that typically result in drops, all countable motor seizures, all countable nonmotor seizures, and all countable seizures was tabulated.
- Number of seizure-free days, defined as days with no seizures that result in drops and days with no countable motor seizures
- Duration of longest interval (in days) between seizures resulting in drops
- CGI-I as assessed by the caregiver

Reviewer's comment: The frequency of each drop seizure subtype was also analyzed. Because it is possible that a drug might reduce some seizures while increasing other seizures in patients with multiple seizure types, it is important to assess the frequency of all seizure types which are typically observed in patients with LGS. Although the longest interval between seizures resulting in drops is not an outcome measure used often in ASM trials and is not independent of the primary efficacy outcome, it may provide clinically meaningful information on the duration of time between disabling seizures in patients with LGS.

Safety Endpoints

The safety and tolerability of FEN was assessed through evaluation of AEs. Safety measurements also included physical and neurological examinations, vital signs, body weight and body mass index, laboratory safety parameters, C-SSRS, cognitive function as assessed by the Behavior Rating Index for Executive Function Scale (BRIEF), and 12-lead ECGs and Doppler ECHOs.

The main endpoint of the ECHO analysis was the number of subjects who developed

VHD at any time during the program. Additional ECHO endpoints included:

- Number of subjects who met the FDA case definition of drug-associated VHD (i.e., moderate or greater mitral regurgitation [MR] and/or mild or greater aortic regurgitation [AR])
- Number of subjects <18 years with trace or greater MR and/or AR at each visit and overall
- Number of subjects 18 years or older with moderate or greater MR and/or mild or greater AR at each visit and overall
- Pulmonary arterial systolic pressure (PASP): number of patients with any PASP >35 mmHg post-baseline; mean change from baseline to EOS or last visit on or before data cutoff date; mean maximum change from baseline at any time; number of subjects with change from baseline at any time of >10 mmHg, >15 mmHg, and >20 mmHg
- Number of subjects with moderate or greater tricuspid regurgitation (TR) or pulmonic regurgitation (PR)
- Number of subjects with baseline normal, trace, or mild TR or PR and moderate or greater TR or PR at end of study or last visit on or before data cutoff
- Number of subjects less than 18 years with trace or greater MR, stratified by days of exposure
- Number of subjects 18 years or older with moderate or greater MR, stratified by days of exposure.

The main endpoint of the ECG analysis was the mean change between measurements of QT interval corrected (QTcF) after baseline adjustment. Other endpoints include change in mean QRS duration, change in mean PR interval measurement, change in mean heart rate from baseline. Further endpoints and analysis are discussed in the Applicant's Statistical Analysis Plan (SAP) for Cardiovascular Endpoints.

Reviewer's comment: The planned safety assessments are acceptable. The FDA criteria for VHD was described in a Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report[20] published in 1997 on cardiac valvopathy associated with exposure to FEN or dexfenfluramine. At that time, the data suggested that prevalence of valvopathy may be higher among patients exposed to drug for at least 6 months. Based on available data on development of VHD and PAH in adults treated with fenfluramine, it is unclear if the risk is related more so to duration of therapy versus drug exposure, and/or whether risk may increase with increasing age. Due to the potential extended exposure from chronic administration in patients with LGS and the greater number of adults with LGS as compared to those with the currently-approved indication, DS, ECHO monitoring is appropriate.

Statistical Analysis Plan

The original SAP was dated January 8, 2020. An addendum was dated June 31, 2021, which documented post-hoc analyses for Study ZX008-1601 Part 1 Cohort A.

Analysis populations

- Safety (SAF) Population: all randomized patients who received 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 received 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.
- Per Protocol (PP) Population: all randomized patients who met the inclusion criteria for baseline drop seizure count, received at least one dose of FEN or placebo, completed at least 4 weeks of diary data in the maintenance period, and who had no major protocol deviations.

Primary efficacy analysis

The primary endpoint, the percent change from baseline in DSF in T+M in the FEN 0.8 mg/kg/day group compared with placebo, was planned to be analyzed using a non-parametric analysis of covariance (ANCOVA) model with treatment group and weight strata group (< 37.5 kg, ≥ 37.5 kg) as factors, with rank of baseline DSF as a covariate, and rank of percent change in DSF in T+M as response. The primary analysis compared the FEN 0.8 mg/kg/day group to the placebo group using a two-sided test at the α =0.05 level of significance. The FEN 0.8 mg/kg/day group was planned to be tested on the primary and key secondary endpoints first, then the FEN 0.2 mg/kg/day group on the primary and key secondary endpoints, in a sequential fashion. A serial gatekeeping strategy was to be used to maintain the Type 1 error rate at α =0.05 across the analyses of primary and key secondary objectives.

Sensitivity analyses on the mITT population on the primary efficacy endpoint that were planned included:

- Wilcoxon rank-sum in place of the nonparametric ANCOVA
- Repeat primary analysis on the PP population
- Repeat primary analysis with exclusion of seizure clusters
- Repeat primary analysis with exclusion of extreme outliers
- Analysis using 2 different methods for imputation of missing values due to subject drop out (worst value and differential imputation method)
- Analyses using datasets which revert data changes which were made by DCR or by proxy entry by study site personnel.

Key Secondary Efficacy Analyses

The percentage of subjects with ≥50% decrease in DSF from baseline between treatment

groups was planned to be compared using a logistic regression model that incorporated treatment group, weight strata (<37.5 kg, ≥ 37.5 kg), and baseline seizure frequency as covariates. Separate models were fit for ZX008 0.2 mg/kg/day vs. placebo and ZX008 0.8 mg/kg/day vs. placebo. The number and percentage of subjects who had a worsening, ≥0% reduction, ≥25% reduction, ≥50% reduction, ≥75% reduction, 100% reduction, and near seizure-freedom were tabulated for each treatment. Near seizure-freedom was defined as having 0 or 1 seizures leading to a drop in the T+M period.

The second key secondary endpoint, mean CGI-I score, and the number and percentage of subjects who showed improvement (i.e., had a score of 3 or lower), and the number and percentage who did not improve (i.e., had a score of 4 or higher) were to be presented for each treatment group at each assessment time point, including a comparison between each active treatment and the placebo group using the Cochran-Mantel-Haenszel test stratified by weight strata.

Safety Analyses

- All safety summaries were based on the SAF Population.
- An integrated summary of cardiovascular safety was presented in a separate safety analysis which was conducted with a separate cardiovascular SAP.
- AESI included elevated prolactin level ≥2x above ULN, hypoglycemia of <3.0mmol/L or 54 mg/dL with or without symptoms, and suicidal thoughts, ideation, or gestures.

Protocol Amendments

There were 2 protocol amendments for Study 1601 Part 1. Table 5 summarizes important modifications to the protocol.

- Table 5: Summary of Major Protocol Amendments, Study 1601 Part 1

Amendment Number	Date	Major Changes
1.0	Jan 10 2018	• Added myoclonic seizures that result in a drop to the types of seizures assessed in secondary endpoints • Clarified inclusion and exclusion criteria (including inclusion of patients without a formal LGS diagnosis but fulfilling all other criteria; exclusion of pulmonary disease; deletion of prohibition of carbamazepine, phenobarbital, phenytoin) • Clarified information to be recorded for AE reporting (including that relating to status epilepticus; deletion of AESIs of chest pain, dyspnea, persistent cough, increased blood pressure, new heart murmur, tachycardia, bradycardia, signs of right heart failure, signs of prolactinemia, serotonin syndrome, due to these AESIs being nonspecific, capturing common signs and symptoms rather than a relevant diagnosis). • Clarified that if there are findings on ECG or ECHO at the 6-month follow-up, further follow-ups will be scheduled every 3 months until resolved or stabilized • Added clinical data from completed randomized, double-blind study of FEN in DS (Study 1)

Amendment Number	Date	Major Changes
2.1	JUL 20 2019	• Updated information about ECHO alert levels for trace regurgitation • Updated objectives/endpoints (including primary efficacy endpoint being percent change in DSF as opposed to mean change in number of drop seizures; move of CGI-I from exploratory to key secondary endpoint; addition of change in frequency of all countable motor seizures to secondary endpoint; addition of "near seizure freedom to secondary objectives; move of rescue medication, status epilepticus from secondary to exploratory) • Updated statistical analyses (including that primary analysis performed after last subject in Cohort A completed last study visit of Part 1, secondary analysis after last Cohort B subject completed last study visit of Part 2, and compared) • Clarified reason for initial dose of 0.2 mg/kg/day in Part 2 (to determine minimally effective dose) • Increased enrollment number (b) (4) to 250 in Cohort A • Clarified visit window allowances during transition between Part 1 and 2 • Clarified prohibited medications • Updated phone visit options for Visits 13 and 23 • Updated parameters regarding repeat lab sample collection in Baseline

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that Study 1601 Part 1 was conducted in in compliance with International Conference on Harmonisation Good Clinical Practice 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, protocol, and amendments for this trial were submitted to and approved by the institutional review board or independent ethics committee at each participating trial site.

Financial Disclosure

In the financial disclosure summary, the Applicant identified 2 investigators with disclosable financial interests. (b) (6) declared proprietary interest in FEN, receipt of honoraria for consulting in an advisory board, and receipt of a research grant. (b) (6) holds equity in the sponsor company in excess of $50,000. The Applicant states "To minimize any potential bias, Study 1601 was conducted as a randomized, double-blind, placebo-controlled trial. Additionally, a separate Independent Data Safety Monitoring Committee (IDSMC) was utilized to oversee subject safety and review study data. Both Study 1601 and Study 1900 were conducted as multi-center trials to reduce the impact of data from a single site on the overall study outcome."

Reviewer's comment: The methods used to mitigate potential bias of these investigators are

Patient Disposition

The first subject was enrolled in Study 1601 Cohort A on (b) (6) and the date of the last patient's last visit was October 25, 2019. A total of 335 patients were screened for participation, 72 of whom were screen failures; 263 were randomized in a 1:1:1 ratio to placebo (n=87), FEN 0.2 mg/kg/day (n=89), and FEN 0.8 mg/kg/day (n=87). The mITT population and safety population were comprised of these 263 patients.

A Part 1 completer was defined by the Applicant as a randomized patient who either completed Part 1 through Visit 12 or who completed at least through Visit 8 (on maintenance dosing for at least 1 month) and then enrolled in the Part 2 OLE.

As seen in Table 6 below, the majority of patients completed the study (245/263, 93.2%). 97.7% of patients in the placebo group completed the study, while 92.1% and 89.7% of patients in the FEN 0.2 mg/kg/day and FEN 0.8 mg/kg/day groups, respectively, completed the study. None of the placebo patients terminated from the study early because of AEs; a roughly equal number of patients discontinued the study early between the FEN 0.2 and 0.8 mg/kg/day groups (4.5% and 4.6% respectively). One patient in each of the 0.2 mg/kg/day and the 0.8 mg/kg/day groups discontinued during the titration period; the remainder discontinued during the maintenance period.

No patients exited the study due to lack of efficacy, per the Applicant; however, 2 patients, both randomized to the 0.8 mg/kg/day group, were noted to have transitioned to the open-label phase early. Subject (b) (6) was "allowed to enroll into the open-label extension early as per the Sponsor and Medical Monitor." Subject (b) (6) was a 19-year-old male who had been in the maintenance period of Study 1601 Part 1 for 18 days; the "Sponsor instructed site to immediately transition the subject to the OL phase and skip the rest of the blinded phase."

In addition to these 2 patients, there were another 3 patients (two randomized to the placebo group and one to the 0.8 mg/kg/day group) who exited early but after Visit 8, who then entered Study 1601 Part 2, and therefore were considered study completers. Subject (b) (6) (placebo) had "lots of seizures and entered Part 2 earlier" as the reason for discontinuation of Part 1. Subject (b) (6) (placebo) discontinued on study day 50 due to "ADVERSE EVENT: increased seizures," and started Part 2 on study day 64. Subject (b) (6) (0.8 mg/kg/day), discontinued due to truncal dystonia on study day 104 and started Part 2 immediately.

- Table 6: Disposition Events by Arm for Exposed Patients, Study 1601 Part 1 Cohort A

Disposition Event	Placebo (N=87)	FEN 0.2 mg/kg/day (N=89)	FEN 0.8 mg/kg/day (N=87)	Total (N=263)
Completed	85 (97.7%)	82 (92.1%)	78 (89.7%)	245 (93.2%)
Adverse Event	0	4 (4.5%)	4 (4.6%)	8 (3.0%)
Lack of Efficacy (presumed)	0	0	2 (2.3%)	2 (0.76%)
Protocol Deviation	0	1 (1.1%)	0	1 (0.38%)
Physician Decision	1 (1.1%)	1 (1.1%)	0	2 (0.76%)
Withdrawal by Subject	1 (1.1%)	1 (1.1%)	2 (2.3%)	4 (1.5%)
Death	0	0	1 (1.1%)	1 (0.38%)

Source: review of ADSL and ADAE datasets and narratives

Protocol Violations/Deviations

The Applicant reported at least one major protocol deviation for 138 (52.5%) patients. The number of patients with at least 1 major protocol deviation was similar across the treatment groups: 41 (47.1%) of placebo patients, 49 (55.1%) of patients in the 0.2 mg/kg/day arm, and 48 (55.2%) of patients in the 0.8 mg/kg/day arm.

Patients were excluded from the PP population if a major protocol deviation could result in a change in the outcome of the primary efficacy analysis. For instance, patients with less than 8 seizures that resulted in drops during Baseline did not meet inclusion/exclusion criteria and were excluded from the PP population; 3 were omitted from the placebo arm, 1 from the 0.2 mg/kg/day arm, and 1 from the 0.8 mg/kg/day arm. A total of 54 patients were excluded from the PP population, divided similarly across the treatment groups: 18 (20.7%) from the placebo arm, 18 (20.2%) from the 0.2 mg/kg/day arm, and 18 (20.7%) from the 0.8 mg/kg/day.

Reviewer's comment: Given that the protocol violations were equally balanced between the treatment arms, the impact on the primary endpoint was not felt to be significant.

Demographic Characteristics

- Table 7: Baseline Demographics of the Randomized Population (mITT and Safety Population), Study 1601 Part 1 Cohort A

Subgroup	Placebo (N = 87) n (%)	FEN 0.2 mg/kg/day (N = 89) n (%)	FEN 0.8 mg/kg/day (N = 87) n (%)	Total (N = 263) n (%)
Sex				
Female	41 (47.1)	43 (48.3)	33 (37.9)	117 (44.5)
Male	46 (52.9)	46 (51.7)	54 (62.1)	146 (55.5)
Age				

Subgroup	Placebo (N = 87) n (%)	FEN 0.2 mg/kg/day (N = 89) n (%)	FEN 0.8 mg/kg/day (N = 87) n (%)	Total (N = 263) n (%)
Mean	14.4	13.4	13.4	13.7
SD	7.71	7.79	7.28	7.59
Min, Max	2, 35	3, 35	2, 35	2, 35
Age Group				
<6 years	9 (10.3)	17 (19.1)	12 (13.8)	38 (14.4)
≥6 to <18 years	52 (59.8)	47 (52.8)	50 (57.5)	149 (56.7)
18 to 35 years	26 (29.9)	25 (28.1)	25 (28.7)	76 (28.9)
Race				
Native American	0	0	0	0
Native Hawaiian/Pacific Islander	0	1 (1.1)	0	1 (0.4)
Asian	2 (2.3)	3 (3.4)	4 (4.6)	9 (3.4)
Multiple	2 (2.3)	0	1 (1.1)	3 (1.1)
Black or African American	4 (4.6)	5 (5.6)	3 (3.4)	12 (4.6)
White	71 (81.6)	67 (75.3)	70 (80.5)	208 (79.1)
Not Reported/Unknown	8 (9.2)	13 (14.6)	9 (10.3)	30
Ethnicity				
Hispanic or Latino	16 (18.4)	21 (23.6)	14 (16.1)	51 (19.4)
Missing	6 (6.9)	10 (11.2)	7 (8.0)	23 (8.7)
Not Hispanic or Latino	65 (74.7)	58 (65.2)	66 (75.9)	189 (71.9)
Region				
Canada	2 (2.3)	1(1.1)	4(4.6)	7 (2.7)
Mexico	1 (1.1)	2 (2.2)	0	3 (1.1)
Australia	2 (2.3)	1 (1.1)	6 (6.9)	9 (3.4)
Europe	41 (47.1)	43 (48.3)	38 (43.7)	122 (46.4)
United States	41 (47.1)	42 (47.2)	39 (44.8)	122 (46.4)
Baseline Height (m)				
Mean	1.448	1.417	1.417	1.428
SD	0.2170	0.2453	0.2480	0.2368
Median	1.5	1.475	1.470	1.480
Baseline Weight (kg)				
Mean	43.85	42.36	42.24	42.81
SD	20.673	20.979	21.399	20.951
Median	38.70	41.00	39.00	39.00
Baseline weight, n(%)				
<37.5 kg	42 (48.3)	42 (47.2)	40 (46)	124 (47.1)
≥37.5 kg	45 (51.7)	47 (52.8)	47 (54)	139 (52.9)
Baseline BMI (kg/m2)				
Mean	19.74	19.60	19.71	19.68
SD	4.995	5.229	5.075	5.082
Median	18.40	18.90	18.50	18.60

Source: adapted from 1601 Part 1 CSR, Tables 10 and 11; verified through ADSL.xpt

Reviewer's comment: The baseline demographics of the patients randomized in Study 1601 Part 1 Cohort A were generally similar between groups, although there were a higher percentage of male patients in the 0.8 mg/kg/day arm. The majority of patients were non-Hispanic or Latino white patients. Approximately 28 to 30% of each arm was comprised of adult patients.

Other Baseline Characteristics

- Table 8: Other baseline characteristics (e.g., disease characteristics, concomitant ASMs), Study 1601 Part 1 Cohort A

	Placebo (N = 87) n (%)	FEN 0.2 mg/kg (N = 89) n (%)	FEN 0.8 mg/kg (N = 87) n (%)	Total (N = 263) n (%)
Baseline drop seizure frequency (per 28 days)				
Mean	164.37	223.00	194.99	
SD	309.801	435.498	308.894	
Median	53	85	83	
Min, Max	(2, 1761)	(4.1, 2943)	(6.5, 1803)	
Number of patients experiencing seizure types at baseline, n (%)				
Generalized-tonic-clonic	40 (46)	38 (42.7)	39 (44.8)	117 (44.5)
SGTC	8 (9.2)	6 (6.7)	9 (10.3)	23 (8.7)
Tonic	68 (78.2)	67 (75.3)	67 (79.3)	202 (76.8)
Atonic	31 (35.6)	34 (38.2)	36 (41.4)	101 (38.4)
Tonic/atonic	21 (24.1)	21 (23.6)	16 (18.4)	58 (22.1)
Number of concomitant ASMs, n (%)				
Patients with ≥1	86 (98.9)*	89 (100)	86 (98.9)*	261 (99.2)
1	12 (13.8)	11 (12.4)	4 (4.6)	27 (10.3)
2	19 (21.8)	24 (27)	24 (27.6)	67 (25.5)
3	34 (39.1)	30 (33.7)	32 (36.8)	96 (36.5)
4	21 (24.1)	23 (25.8)	26 (29.9)	70 (26.6)
5	0	1 (1.1)	0	1 (0.4)
Concomitant AEDs				
n (%)	86 (98.9)*	89 (100)	86 (98.9)*	261 (99.2)
Acetazolamide	0	3 93.4)	1 (1.1)	4 (1.5)
Brivaracetam	3 (3.4)	4 (4.5)	5 (5.7)	12 (4.6)
Carbamazepine	5 (5.7)	3 (3.4)	2 (2.3)	10 (3.8)
Clobazam	38 (43.7)	36 (40.4)	45 (51.7)	119 (45.2)
Clonazepam	9 (10.3)	12 (13.5)	8 (9.2)	29 (11)
Diazepam	1 (1.1)	1 (1.1)	2 (2.3)	4 (1.5)
Eslicarbazepine	1 (1.1)	2 (2.3)	2 (2.3)	5 (1.9)
Ethosuximide	3 (3.4)	3 (3.4)	8 (9.2)	14 (5.3)

	Placebo (N = 87) n (%)	FEN 0.2 mg/kg (N = 89) n (%)	FEN 0.8 mg/kg (N = 87) n (%)	Total (N = 263) n (%)
Felbamate	9 (10.3)	14 (15.7)	13 (14.9)	36 (13.7)
Gabapentin	1 (1.1)	2 (2.2)	0	3 (1.1)
Lacosamide	7 (8.0)	10 (11.2)	9 (10.3)	26 (9.9)
Lamotrigine	29 (33.3)	30 (33.7)	29 (33.3)	88 (33.5)
Levetiracetam	20 (23.0)	17 (19.1)	23 (26.4)	60 (22.8)
Lorazepam	2 (2.3)	0	1 (1.1)	3 (1.1)
Oxcarbazepine	2 (2.3)	5 (5.6)	3 (3.4)	10 (3.8)
Perampanel	7 (8)	5 (5.6)	6 (6.9)	18 (6.8)
Phenobarbital	5 (5.7)	2 (2.2)	4 (4.6)	11 (4.2)
Phenytoin	3 (3.4)	1 (1.1)	3 (3.4)	7 (2.7)
Rufinamide	18 (20.7)	17 (19.1)	18 (20.7)	53 (20.2)
Sultiame	0	2 (2.2)	2 (2.3)	4 (1.5)
Tiagabine	0	1 (1.1)	0	1 (0.4)
Valproate, all forms	49 (56.3)	52 (58.4)	46 (52.9)	147 (55.9)
Vigabatrin	5 (5.7)	3 (3.4)	7 (8)	15 (5.7)
Zonisamide	7 (8.0)	6 (6.7)	7 (8)	20 (7.6)

* One patient in the placebo group was only on potassium bromide. One patient in the 0.8 mg/kg/day did not report concomitant ASMs and was excluded from the PP population.
Source: Adapted from Tables 12, 13, 16, and 17, Study 1601 Part 1 CSR Table 16; verified by ADCM

Reviewer's comment: In general, the baseline characteristics of the patients' seizures in the three treatment groups were reasonably similar. All patients in all of the groups experienced drop seizures at baseline. The mean DSF at baseline was lowest in the placebo group (164) and 223 and 195 in the 0.2 mg/kg/day and 0.8 mg/kg/day groups, respectively. Median baseline DSF, which may be less sensitive to outliers, was lowest in the placebo group (53) and comparable in the 0.2 mg/kg/day and 0.8 mg/kg/day groups (85 and 83, respectively). Regarding seizure types that typically cause drop seizures, they were fairly equally distributed across treatment arms; those with highest incidence were tonic seizures (affecting 75 to 79% of patients across treatment arms) and generalized-tonic-clonic seizures (affecting 43 to 46% of patients across treatment arms).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was assessed by input into the eDiary and measurement of the weight of residual study drug solution at each study visit. When compliance was measured as a percentage of assigned dose taken, most patients had ≥90% compliance in all groups (94.2%, 92.1%, and 91.9% in the placebo, 0.2, and 0.8 mg/kg/day groups, respectively).

As seen in Table 9, the most commonly used concomitant ASMs were VPA [all forms] (55.9% of

total population), CLB (45.2%); lamotrigine (33.5%); and LEV (22.8%). The only ASM in which a difference of ≥ 10% between any of the treatment groups occurred was CLB, for which use was highest in the 0.8 mg/kg/day arm (43.7%, 40.4%, 51.7% of patients in placebo, 0.2 mg/kg/day, 0.8 mg/kg/day groups, respectively). No subjects received STP.

During the treatment period (T+M), the mean number of days on which rescue medication was used per 28 days was numerically higher in the placebo and 0.8 mg/kg/day groups (1.4 and 1.5 days, respectively) compared to the 0.2 mg/kg/day group (0.8 days). The number of patients who received rescue medication was 29 (33.3%), 25 (28.1%), and 34 (39.1%) in the placebo, 0.2 mg/kg/day, and 0.8 mg/kg/day groups, respectively.

Reviewer's comment: It Is unclear that the degree of difference in the number of days on which rescue medication was administered and in the number of patients who received rescue medication would cause a significant imbalance in the arms.

Efficacy Results – Primary Endpoint

All randomized patients who received at least one dose of FEN or placebo and for whom at least one week of diary data were available were included in the mITT population. The primary efficacy analysis, as well as key secondary analyses, were performed on the 263 patients in the mITT population, according to the treatment group to which patients were randomized (87 [33%] in the placebo group, 89 [33.8%] in the 0.2 mg/kg/day group, and 87 [33%] in the 0.8 mg/kg/day group).

As noted above, the primary efficacy endpoint was the percent change from baseline in DSF in T+M periods in the FEN 0.8 mg/kg/day group compared with the placebo group. Key secondary endpoints included percentage of subjects with ≥50% reduction from baseline in DSF during T+M and proportion of patients who achieved improvement in the CGI-I as assessed by the PI at Visit 12 (Day 99 end of study or early termination).

As discussed in Study Design (Procedures and Schedule section), the Division had concerns regarding data integrity. The addition of de novo seizure data and modification of previously-entered seizure data could take place at any time after the date of the actual occurrence of the seizure. Retrospective data entry or modification to the data in the eDiary could occur in 3 ways: 1) By the caregiver until 7 days after the seizure event; 2) By study site personnel at any time (when the device was accessible, typically at the next in-person visit), limited to data which had not previously been entered (missing data) or to data in the seizure classifications and seizure descriptions fields, which would be based on corrections from the ESC; or 3) By a DCR sent by study site personnel to Signant Health, the manager of the eDiaries and associated internet-based data portal. Changes made by DCR might include entry errors of any data point,

such as seizure type, number, time, clustering, or rescue medication. Some "pending" tags in the seizure classification field for a new seizure type which emerged during the trial also would need to be updated via a DCR after approval by the ESC. Note that if it were determined that a new seizure type which was entered by the caregiver was actually not a new seizure, study site personnel could manually deny that seizure type, and "denied" data points would not be included in the efficacy analyses.

The Applicant conducted sensitivity analyses on the primary efficacy endpoint and key secondary endpoints for 2 datasets which reverted datapoints to their original values, prior to the addition or modification of data. One dataset, which the Applicant named "Pre-DCR version 2," removed all datapoints which were entered or modified by study site personnel ("proxy entries") and datapoints which were entered or modified by DCR. The other dataset, which the Applicant named "Pre-DCR version 3," removed proxy entries and changes made by DCR, except changes made to the seizure classification field. The rationale for the retention of changes to the classification field included: classifications were originally assigned by investigators and not patients/caregivers; classifications were reviewed by the ESC by a blinded process; seizures which emerged during the trial would be undercounted if classifications were reverted; and source documentation for these changes are retained by the Applicant and the ESC. The Applicant's sensitivity analyses demonstrated statistically significant results which were similar to the results from analysis of the dataset with all data changes retained.

In principle, the role of the ESC in confirmation of eligibility of participants, standardization of the classification of seizure types, and the determination of what seizures are considered drop seizures, should improve the accuracy of data and consistency of seizure classification across study sites and across trials. The integrity of proxy entries was of greater concern, because the study sites were relied upon to ensure that source documentation was solicited and retained. For the reasons discussed, the Division determined that "Pre-DCR version 3," which removed retrospective proxy entries and changes made by DCR but retained changes made to the seizure classification field, should be used for efficacy analysis.

As verified by Dr. Xiangmin Zhang's Statistical Review and Evaluation, when the datasets that included all data changes were analyzed and all randomized patients (the mITT population) were included, the FEN 0.8 mg/kg/day group had a statistically significant ($p = 0.0013$) decrease from baseline in DSF (-26.5% median percent change) compared to the placebo group (-7.59% median percent change). The difference between the FEN 0.2 mg/kg/day group (-14.16% median percent change) and placebo was not statistically significant ($p = 0.0939$). When "Pre-DCR version 3," the dataset with all proxy entries removed and DCR changes, except for seizure classifications, reverted to original values, was analyzed, the findings were consistent. The difference between the FEN 0.8 mg/kg/day and placebo groups was statistically significant ($p=0.0037$). The difference between the FEN 0.2 mg/kg/day and placebo groups was not statistically significant ($p=0.1917$). However the endpoint of change from baseline in DSF in T+M in the 0.2 mg/kg/day group was the third key secondary endpoint.

Reviewer's comment: Compared with the placebo group, the FEN 0.8 mg/kg/day dose group demonstrated a statistically significant reduction in drop seizures from baseline to the treatment period. As noted above, this is the same primary efficacy endpoint used in most ASM treatment trials, although the seizure types counted toward the primary endpoint may differ based on the underlying disease. The findings are both statistically significant and clinically meaningful.

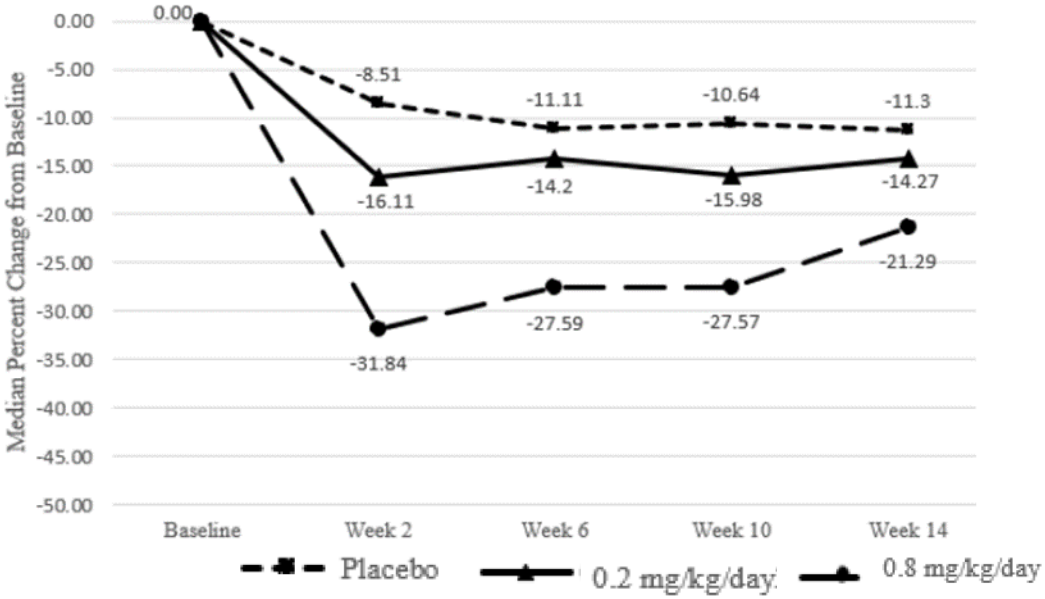
- Table 9: Primary Efficacy Endpoint Results based on dataset with data changes reverted except for seizure classifications, Study 1601 Part 1 Cohort A

Drop Seizure Frequency per 28 days	Placebo	FEN 0.2 [a] mg/kg/day	FEN 0.8 mg/kg/day
Baseline Summary Statistics			
N	85*	86*	83*
Mean (SD)	162.93 (312.679)	219.33 (441.246)	189.42 (300.275)
Median	54.96	77.78	80
Min, Max	(3.0, 1761)	(1, 2984.6)	(6.5, 1803)
T+M Period Summary Statistics			
Mean (SD)	145.85 (267.929)	246.01 (618.251)	166.96 (295.45)
Median	45.71	61.83	54.57
Min, Max	(0, 1701.3)	(0, 5110.9)	(0.3, 1562)
Percent Change from Baseline			
Mean (SD)	-1.74 (48.909)	53.98 (399.272)	-19.19 (60.095)
Median	-8.69	-13.22	-23.69
Min, Max	(-100, 244.8)	(-100, 3307.3)	(-95.2, 402.1)
Nonparametric Model			
p-value for comparison with Placebo		0.1917	0.0037
HL Estimate for median difference (95% CI)		-8.65 (-24.04, 6.73)	-18.41 (-29.41, -7.40)

Source: adapted from ZX008-1601 Part 1 Cohort A Summary of Posthoc Pre-DCR Sensitivity Analyses, Table 3
[a] Change from baseline in DSF in T+M in the FEN 0.2 mg/kg/day group compared to placebo was not a primary efficacy endpoint; it was the third key secondary endpoint. It is presented here for comparison.
*Reversions to original values eliminated Baseline seizure records for 2 patients in the placebo group, 3 patients in the 0.2 mg/kg/day group, and 4 patients in the 0.8 mg/kg/day group, therefore change from Baseline could not be determined
Abbreviations: HL = Hodge-Lehmann; SD = standard deviation

Consistent results were seen for analysis of the absolute changes from Baseline in DSF at the timepoints of the end of Titration (Week 2) and each subsequent 4-week period of the Maintenance period (Weeks 6, 10, and 14), as seen in Figure 1.

- Figure 1: Median Percent Change in Drop Seizure Frequency based on dataset with data changes reverted except for seizure classifications, Study 1601 Part 1 Cohort A



Source: Figure 2, ZX008-1601 Part 1 Cohort A Summary of Posthoc Pre-DCR Sensitivity Analyses, based on Table 14.2.1.1.1.1c

The Applicant performed subgroup analyses on the primary efficacy endpoint which included age group, weight, sex, race, region (US versus non-US), number of prior ASMs, number of concomitant ASMs, and baseline frequency of drop seizures. The results of pertinent subgroup analyses are summarized in Table 10 below.

- Table 10: Subgroup Analyses of the Primary Efficacy Endpoint based on the "original" dataset which retained all data changes, Study 1601 Part 1 Cohort A

Subgroup Item	Treatment	N	Treatment Mean	Treatment Median	Min, Max
2 to <18 years	Placebo	61	14.45	-4.85	-100, 557.1
	0.2 mg/kg	64	58.60	-7.19	-100, 3307.3
	0.8 mg/kg	62	-15.51	-20.30	-95.2, 402.1
≥ 18 years	Placebo	26	-18.59	-17.76	-80.8, 55.7
	0.2 mg/kg	25	-30.07	-33.13	-77.8, 74.3
	0.8 mg/kg	25	-35.01	-36.34	-84.1, 93.8
< 37.5 kg	Placebo	42	14.03	-6.49	-77.4, 557.1
	0.2 mg/kg	42	16.40	-13.95	-100.0, 700.9
	0.8 mg/kg	40	-16.91	-16.32	-95.2, 71.8
≥ 37.5 kg	Placebo	45	-4.25	-11.21	-100, 400.2
	0.2 mg/kg	47	49.15	-14.16	-94.7, 3307.3
	0.8 mg/kg	47	-24.69	-35.29	-91.9, 402.1
Male	Placebo	46	4.64	-7.84	-100, 557.1
	0.2 mg/kg	46	78.91	-10.45	-94.7, 3307.3
	0.8 mg/kg	54	-26.11	-25.31	-89.5, 71.8
Female	Placebo	41	4.50	-7.59	-80.8, 400.2
	0.2 mg/kg	43	-14.68	-30.48	-100, 121.6
	0.8 mg/kg	33	-12.94	-30.08	-95.2, 402.1
White	Placebo	71	3.92	-7.59	-80.8, 557.1
	0.2 mg/kg	67	3.27	-14.16	-89, 700.9
	0.8 mg/kg	70	-18.96	-25.31	-95.2, 402.1
Non-white	Placebo	8	-10.39	-6.54	-47.7, 33.1
	0.2 mg/kg	9	-46.54	-55.67	-100, 78.3
	0.8 mg/kg	8	-22.70	-18.41	-74.6, 32.7
Unknown/Not Reported	Placebo	8	25.37	-7.03	-100, 400.2
	0.2 mg/kg	13	246.03	-10.05	-94.7, 3307.3
	0.8 mg/kg	9	-36.43	-37.8	-91.9, 16.5
U.S.	Placebo	41	18.93	-5.73	-100, 557.1
	0.2 mg/kg	42	65.19	-17.71	-100, 3307.3
	0.8 mg/kg	39	-24.56	-26.59	-95.2, 65.5
Non-U.S.	Placebo	46	-8.22	-10.51	-77.4, 62.4
	0.2 mg/kg	47	5.55	-10.85	-94.7, 700.9
	0.8 mg/kg	48	-18.31	-26.75	-91.9, 402.1

Source: From Table 14.2.1.6.8.1 of Applicant's response to IR, dated Feb 14, 2022, and Tables 27, 28, 29, 31 of CSR Study ZX008-1601 Part 1

Reviewer's comment: As per Dr. Zhang's review, some extreme values were observed, which affected the mean percent change from Baseline in DSF. In addition, the study was not powered to detect statistical significance within the subgroup analyses, and therefore the

*sample size for many of the subgroup categories was relatively small. However, it appears that the median percent change in DSF with FEN, in particular the 0.8 mg/kg/day group, was generally greater than placebo in the subgroups studied. Because the pivotal trials which supported approval of FEN for the indication of DS were in children 2 to 18 years of age, of particular note is that the results also favored FEN in the **≥18** year age group.*

Data Quality and Integrity

See Section 4.1 and Study Design (Procedures and Schedule section) for further discussion of the data integrity concerns in Study 1601 Part 1.

Reviewer's comment: As discussed in previous sections, although the Division has concerns relating to data integrity, those concerns in relation to seizure classification changes based on ESC determinations are less significant. The Division determined that it was acceptable to base efficacy analyses on the dataset in which retrospective data changes other than those related to seizure classification and drop seizure designation which were adjudicated by the ESC were reverted. Sensitivity analyses demonstrated consistent results, verified by our Statistical Reviewer.

Efficacy Results – Secondary and other relevant endpoints

The prespecified key secondary endpoints for Study 1601 Part 1 were the 50% responder rate and the proportion of patients who achieved improvement in the CGI-I as assessed by the PI in the FEN 0.8 mg/kg/day group and in the FEN 0.2 mg/kg/day group, independently and in the order of the testing hierarchy discussed in Section 6 above. These are summarized in Table 11 below.

- Proportion of patients with ≥50% reduction in drop seizure frequency
  Based on the dataset with data changes reverted except for seizure classifications, the proportion of patients with a reduction of 50% or more during the treatment period from their baseline DSF was greater in the 0.8 mg/kg/day and 0.2 mg/kg/day FEN groups (24.1% and 27.9% respectively), compared with the placebo group (8.2%). Both the 0.8 and 0.2 groups were statistically better than placebo (p=0.0084 and p=0.0022, respectively). This endpoint in the 0.8 mg/kg/day group was the first key secondary endpoint. The 50% responder rate for the 0.2 mg/kg/day group was the fourth key secondary endpoint and was considered nominal due to lack of significance for the second key secondary endpoint which will be discussed next.

- Proportion of patients who achieved improvement in the CGI-I as assessed by the PI
  The number of patients in the 0.8 mg/kg/day group who were rated by the PI as improved (i.e., "minimally improved" [score of 3], "much improved" [score of 2], or "very much improved" [score of 1]) on the CGI-I at the EOS Visit (Week 12, Day 99) was greater than the number in the placebo group (39 [48.8%] in the 0.8 mg/kg/day group compared to 27 [33.8%] in the placebo group), but the difference was not statistically significant (p=0.0567). Dr. Zhang's review included re-analysis with imputation of missing CGI-I scores as no improvement; the p-value was still greater than 0.05. This was the second key secondary endpoint, and therefore subsequent endpoint analyses were considered nominal or exploratory. A pre-specified exploratory analysis assessed the percentages of patients rated as showing "clinically meaningful" improvement (i.e., as "much improved" or "very much improved") at EOS, and showed a significant difference in both the FEN 0.8 (21 patients [26.3%], p=0.0007) and 0.2 mg/kg/day (17 patients [20%], p=0.010) groups compared to placebo (5 patients [6.3%]).

- Change from baseline in DSF in T+M in the FEN 0.2 mg/kg/day group compared to placebo
  This third key secondary endpoint was presented in Table 9: Primary Efficacy Endpoint Results based on dataset with data changes reverted except for seizure classifications, Study 1601 Part 1 Cohort A and outcome did not meet statistical significance.

- Table 11: Key Secondary Endpoints Results, Study 1601 Part 1 Cohort A

	Statistic	Placebo	FEN 0.2 mg/kg/day	FEN 0.8 mg/kg/day
Proportion of **≥50%** Responders during T+M	N	85	86	83
	Patients experienced, n(%)	7 (8.2)	24 (27.9)	20 (24.1)
	OR (95%CI)		4.15 (1.67, 10.32)	3.48 (1.38, 8.80)
	p-value		0.0022	0.0084
Patients rated as improved (score 1, 2, 3) on CGI-I by investigator	N	80	85	80
	n(%)	27 (33.8)	38 (44.7)	39 (48.8)
	p-value		0.1565	0.0567

Source: adapted from Table 6, ZX008-1601 Part 1 Cohort A Summary of Posthoc Pre-DCR Sensitivity Analyses, and from Table 34, CSR ZX008-1601 Part 1

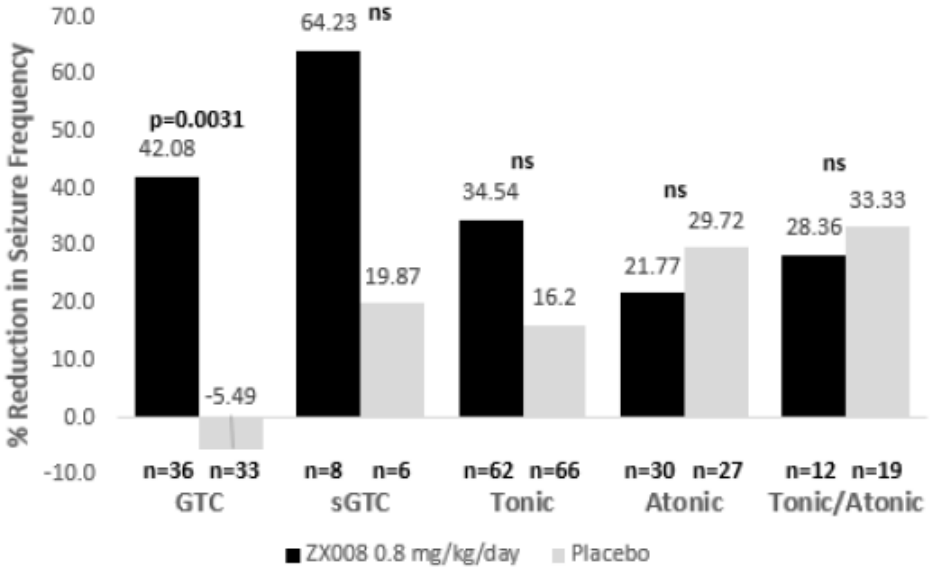
Reviewer's comment: The result of the analysis of the first key secondary endpoint, the proportion of patients with a reduction of 50% or more from their baseline DSF in the 0.8 mg/kg/day group compared to placebo, was statistically significant and supportive of the primary efficacy endpoint. However, the 50% responder rate is not independent of the primary efficacy endpoint and does not provide information separate from the primary efficacy endpoint.

The result of the analysis of the second key secondary endpoint, the proportion of patients who were rated by the PI as being minimally, much, or very much improved on the CGI-I at the end of the treatment period in the 0.8 mg/kg/day group compared to placebo was not statistically significant, and therefore subsequent secondary endpoints were considered nominal or exploratory. The CGI scales were developed to provide the clinician's assessment of the patient's global functioning, and it may indeed be that "minimal" improvement is perceived as not as meaningful; the percentages of patients rated as much or very much improved at EOS were statistically significant for both treatment arms compared to placebo. However, the next secondary endpoint in the testing hierarchy, change from baseline in DSF in the FEN 0.2 mg/kg/day group compared to placebo did not meet statistical significance, nor did the secondary endpoint of patients in the 0.2 mg/kg/day group rated as improved on CGI-I by investigator. (b) (6)

Other Secondary Endpoints of Clinical Interest

- Analysis by typical drop seizure type
  Changes from Baseline during T+M in the frequency of each of the types of seizures which typically result in drops (GTC, sGTC, tonic, atonic, and tonic/atonic) were evaluated. Based on the dataset with data changes reverted except for seizure classifications, the greatest median percentage decreases relative to placebo were seen for GTC both in the 0.8 mg/kg/day group (p=0.0031) and the 0.2 mg/kg/day group (p=0.0012). The results for the different seizure types in the 0.8 mg/kg/day group are depicted in Figure 2. A numeric decrease in secondarily generalized-tonic-clonic and tonic seizures as compared to placebo was seen, which did not reach statistical significance.

- Figure 2 Median Percent Decrease from Baseline in Frequency per 28 days of Each Type of Drop Seizure during T+M, based on dataset with data changes reverted except for seizure classifications, Study 1601 Part 1 Cohort A



Source: Figure 3, ZX008-1601 Part 1 Cohort A Summary of Posthoc Pre-DCR Sensitivity Analyses

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Reviewer's comment: As reflected in Table 8: Other baseline characteristics (e.g., disease characteristics, concomitant ASMs), Study 1601 Part 1 Cohort A*above, the incidence of drop seizure types in the study participants from highest to lowest was: tonic (76.8% of study participants), GTC (44.5%), atonic (38.4%), tonic/atonic (22.1%), and secondarily GTC (8.7%). Note that the classification of a GTC seizure as secondarily generalized may be difficult to determine based on clinical history alone, so a pragmatic approach may be to consider GTC and secondarily GTC seizures together. All seizure types which cause drops have the potential to cause physical injury, including head trauma, tooth injury, lacerations, and fractures. Although a definitive conclusion cannot be drawn, it is notable that the reduction in GTC seizures was statistically significant, because they are the second-most frequent seizure type that caused drops in the study participants and may suggest the potential for broader use in other epilepsy disorders which involve GTC seizures.*

- Change from baseline in frequency of all countable motor seizures

All countable motor seizures included the 5 drop seizure types, as well as clonic seizures, hemiclonic seizures, and focal seizures with clearly observable motor signs. The findings were consistent with the primary efficacy endpoint; the comparison between the 0.8 mg/kg/day and placebo groups was statistically significant while the comparison between the 0.2 mg/kg/day and placebo groups was not statistically significant. This endpoint may

not add much additional meaningful information, because drop seizures are the most disabling in LGS.

- Change from baseline in frequency of countable nonmotor seizures

  Countable nonmotor seizures, which include absence, atypical absence, myoclonic, focal without clear observable motor signs, infantile spasms, epileptic spasms, were analyzed. The comparisons between both treatment groups (independently) and the placebo group were not significant. However the median percentage change from baseline was in the direction of a reduction in seizures for all 3 arms (-27.18%, -46.89%, and -19.05% in the placebo, 0.2, and 0.8 mg/kg/day groups, respectively). Non-drop seizures, which included all countable seizure types that did not meet the criteria for drop seizures, were also analyzed post hoc. Change in non-drop seizure frequency was not statistically significant for either FEN group; the percentages of patients who had no change or worsening from Baseline in the FEN groups were similar compared to placebo.

Reviewer's comment: Change in nonmotor 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. Nonmotor seizures, while not as physically disabling as convulsive seizures, still cause significant morbidity for patients with LGS, although they are generally more difficult to quantify reliably in a trial setting due to less observable signs and tendency for some to occur in clusters. The analysis of median change in countable nonmotor seizure frequency, and analysis by countable nonmotor seizure type, did not show worsening of particular seizure types.

- Percentages of subjects with ≤0%, >0%, ≥25%, ≥75%, and 100% reduction from baseline in drop seizure frequency

  The percentage of participants with a ≥25% reduction was statistically significant in both the 0.8 and 0.2 mg/kg/day groups compared with placebo. Statistical significance was not reached at the ≥75% reduction level for either treatment arm. One patient in the placebo group, 1 patient in the 0.2 mg/kg/day group, and 0 patients in the 0.8 mg/kg/day group were drop seizure-free. Few participants achieved near-seizure freedom (0 or 1 observed seizure), with 1, 2, and 1 subject in the placebo, 0.2 mg/kg/day, and 0.8 mg/kg/day groups, respectively. Fewer participants in the 0.8 mg/kg/day group had an increase in or no change compared with placebo. Overall, 39/263 (14.8%) of participants had a worsening of up to a 25% increase from baseline in DSF (18.4%, 14.6%, and 11.5% in the placebo, 0.2, and 0.8 mg/kg/day groups, respectively). A >25% increase in DSF was seen in 44/263 (16.7%) of participants (19.5%, 20.2%, and 10.3% of placebo, 0.2, and 0.8 mg/kg/day groups, respectively). Responder analyses were also performed for the frequency of seizures that typically result in drops,

countable motor seizures, countable nonmotor seizures, all countable, and non-drop seizures.

Clinical reviewer's comment: Because of the relatively small numbers of patients in all of these responder analyses, it is difficult to draw any meaningful clinical conclusions from the individual analyses. Of note, the occurrence of some patients with worsening or relative lack of response, and the rarity of seizure freedom is not unusual in an epileptic encephalopathy such as LGS.

Dose/Dose Response

As reflected in Table 9 and Figure 1, there was a trend suggestive of dose response, with numerical but not statistically significant reduction in DSF in the 0.2 mg/kg/day group.

Although based on uncontrolled data, there was also a suggestion of dose response from Study ZX008-1601 Part 2, the OLE for participants of Study ZX008-1601 Part 1, in which seizure diaries continued to be maintained. In Study ZX008-1601 Part 2, all participants started on 0.2 mg/kg/day after a blinded Transition period. After the initial month, dosing could be increased from 0.2 mg/kg/day to a maximum of 0.8 mg/kg/day (not to exceed 30 mg/day), based on effect and tolerability. The Applicant analyzed seizure frequency data by mean daily dose (calculated as the sum of each day's dosage divided by duration of dosing) and found increased reduction of DSF with increased dosing (median 11.71% decrease in participants on >0 to <0.4 mg/kg/day; median 27.47% decrease in participants on 0.4 to <0.6 mg/kg/day; and median 36.17% decrease in participants on ≥0.6 mg/kg/day). This analysis is complicated, however, by the maximum dose of 30 mg/day, which could be reached by a patient weighing more than 50 kg at lower than 0.6 mg/kg/day.

Durability of Response and Persistence of Effect

Analyses of the primary endpoint were performed on the maintenance period alone and on each 4-week period of the maintenance period, as depicted in Figure 1 above. Consistent results were seen.

247 participants of Study ZX008-1601 Part 1 Cohort A enrolled in the ongoing, open-label, 12-month long-term extension Study ZX008-1601 Part 2. Seizure diaries were maintained during Study ZX008-1601 Part 2. The Applicant reports that the median percentage decrease of ESC-confirmed drop seizure frequency from Baseline (of Part 1) for the overall open-label treatment period was 27.93%; and 29.3% of participants achieved a 50% or greater reduction in DSF. The interpretation of that data is limited due to the uncontrolled nature of the data; however, there appears to be sustained efficacy.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

There is only a single efficacy study included in this review and therefore this section is not applicable. Study ZX008-1601 Part 2 reported uncontrolled efficacy data, and therefore was not analyzed.

7.1.1. Primary Endpoints

There is only a single efficacy study included in this review.

7.1.2. Secondary and Other Endpoints

There is only a single efficacy study included in this review.

7.1.3. Subpopulations

There is only a single efficacy study included in this review.

7.1.4. Dose and Dose-Response

There is only a single efficacy study included in this review.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

There is only a single efficacy study included in this review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Benefit-risk assessment will need to continue in the postmarket setting, particularly in relation to the risk of VHD and PAH, as patients have an increasing duration of exposure with continued use, and as a greater number of adults (patients with LGS or patients with DS who age into adulthood or are recognized as having DS in adulthood) are exposed. In addition, as mentioned above in the discussion of LGS, the underlying causes of LGS are heterogeneous, contributed to by the potential for clinicians to identify many patients with multiple seizure types and intellectual disability as having LGS. Some patients with LGS have been found to have genetic anomalies. FEN may be increasingly used in patients who have a genetically-based epileptic encephalopathy and phenotype of LGS.

7.2.2. Other Relevant Benefits

7.3. Integrated Assessment of Effectiveness

Overall the data in this submission from a single randomized, double-blind, placebo-controlled study supports evidence of effectiveness of FEN in the treatment of seizures associated with LGS at a dose of 0.8 mg/kg/day.

Study ZX008-1601 Part 1 Cohort A demonstrated statistical and clinical significance of its primary efficacy endpoint, the percent change from baseline in the frequency of seizures that result in drops (GTC, sGTC, tonic, atonic, and tonic/atonic seizures) in the treatment period in the FEN 0.8 mg/kg/day group compared with the placebo group. This was supported by a key secondary endpoint of 50% responder rate in this higher-dose group. A key secondary endpoint of the same efficacy measure in the FEN 0.2 mg/kg/day group was not statistically significant [redacted] (b) (6) However there was a numerical decrease in seizures and suggestion of a potential dose-response.

The approval of FEN for the treatment of seizures associated with DS provides confirmatory evidence, specifically a finding of efficacy based on change from baseline in the frequency of convulsive seizures in 2 double-blind, randomized, placebo-controlled trials. There is overlap in the seizures assessed in the primary efficacy endpoint in the pivotal DS trials with the seizures assessed in the primary efficacy endpoint in the pivotal LGS trial. Convulsive seizures in the DS trials were defined as GTC, sGTC, tonic, tonic/atonic, clonic, hemiclonic, and focal with observable motor signs. In the LGS trial, the most significant reduction was seen in GTC seizures. Both "convulsive" and drop seizures are highly disabling seizures.

There are also shared characteristics between the syndromes of LGS and DS. They are both severe DEEs which are characterized by mixed seizure types, intellectual disability, and increased risk of mortality. LGS is a relatively broad clinical diagnosis and phenotype; some patients with a diagnosis of LGS have been found to have genetic anomalies, such as SCN1A mutations which underly the clinical diagnosis of DS.

8. Review of Safety

8.1. Safety Review Approach

The studies that evaluated safety for this submission included:

- Study ZX008-1601
    - Part 1 Cohort A: A completed, randomized, double-blind, placebo-controlled, Phase 3 efficacy and safety evaluation in patients in North America, Europe, and Australia with LGS

- Part 2 Cohort A: An open-label, 12-month long-term extension study with a 2-week post-dosing/taper, in patients with LGS from Part 1 (ongoing)

- Study ZX008-1900 "An Open-Label Extension Trial to Assess the Long-term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy for Seizures in Patients with Rare Seizure Disorders such as Epileptic Encephalopathies Including Dravet Syndrome and Lennox-Gastaut Syndrome" (ongoing).

As reflected in Table 12 below, the primary safety analyses were performed on the controlled population (referred to as ISS-SAF) of randomized subjects in Study 1601 Cohort A who received 1 or more doses of FEN during their participation in Study 1601 Part 1, Part 2, or Study 1900 and was based on the combined T+M periods.

The open-label safety population (referred to as ISS-OLE-SAF) consisted of all subjects who received at least 1 dose in Study 1601 Part 2, regardless of whether they entered Study 1900. Patients in Study ZX008-1601 Part 1 who enrolled in Part 2 underwent a blinded 2-week Transition Period, such that all participants in Part 2 were on FEN 0.2 mg/kg/day for Month 1 of Part 2; the Applicant's goal was to assess effectiveness of this dose in all study subjects. After Month 1, based on effectiveness and tolerability, the dose could be adjusted in maximum increments of 0.2 mg/kg/day to a maximum of 0.8 mg/kg/day, not to exceed 30 mg/day.

Data from Study 1900 was also reviewed as part of the complete Integrated Summary of Safety (ISS) review. Subjects entering Study 1900 had participated in DS Study 1503 or LGS Study 1601 Part 2, but only those patients with LGS were included in the ISS. At entry into Study 1900, patients received FEN at the dose prescribed at the last visit in those previous studies but had volume adjusted for body weight. Subsequently, if warranted, increases could occur in 0.2 mg/kg/day increments, no more frequently than every 7 days, to a maximum of 0.8 mg/kg/day, not to exceed 30 mg/day, or doses could be decreased for tolerability or safety concerns. Dosage of concomitant ASMs could be changed and concomitant ASMs could be withdrawn, as long as the participants remained on a minimum of 1 concomitant ASM in addition to FEN. At data cutoff, 131 patients with LGS were enrolled in this study.

120-Day Safety Update:
The data cutoff for the interim analysis of Study 1601 Part 2 Cohort A and Study 1900 was October 19, 2020. A 120-day safety update was submitted on January 24, 2022, and included cumulative safety information through the data cutoff date of August 2, 2021, which included an additional 12 subjects enrolled in Study 1900 (total 143 in Study 1900).

- Table 12: Number of Patients in Analysis Populations

	from 1601 Part 1 Cohort A
Total Study Participants	335
Total Randomized (mITT population)	263
Total Randomized and Received ≥ 1 dose of FEN during DB or OLE studies (ISS-SAF)	262
Total Enrolled in OLE 1601 Part 2	247
Total Enrolled in OLE 1601 Part 2 – Received ≥ 1 dose of FEN by interim cutoff date (October 19, 2020) [ISS-OLE-SAF]	247
Total Completed OLE 1601 Part 2 by cutoff date of 120-day safety update (August 2, 2021)[a]	161
Total Enrolled in OLE 1900 (LGS only)	131
Total Enrolled in OLE 1900 – Received ≥ 1 dose of FEN by interim cutoff date (October 19, 2020) [LGS only]	131
Total Enrolled in OLE 1900 – Received ≥ 1 dose of FEN by cutoff date of 120-day safety update (August 2, 2021) [LGS only]	143

Source: ADSL
Abbreviations: DB=double-blind; OLE=open-label extension.
[a] Study 1601 Part 2 Cohort A is ongoing; all participants have either completed the study or discontinued

8.2. Review of the Safety Database

8.2.1. Overall Exposure

- 263 patients were randomized in Study ZX008-1601 Part 1 Cohort A. One patient who had been randomized to placebo for Study ZX008-1601 Part 1 Cohort A did not enroll in Part 2, so there were 262 participants in the controlled safety population who received at least 1 dose of FEN. Because dosing in Study ZX008-1601 Part 2 and Study 1900 was flexible, duration of exposure by dose was assessed in dose groups based on mean daily dose and is summarized in Table 13. The longest duration of exposure was 42 months.
- Study ZX008-1601 Part 2 Cohort A began enrolling on April 18, 2018. Patients who were in a FEN arm during Study 1601 Part 1 and who enrolled in Study 1601 Part 2 could have had a total duration of FEN exposure of 70 weeks during the entirety of Study ZX008-1601. This uncontrolled safety population was comprised of 247 patients who enrolled in Study ZX008-1601 Part 2 and received at least 1 dose of FEN. The first subject enrolled in Study 1900 on (b) (6). By the data cutoff date for the 120-day safety update, a total of 143 patients had enrolled in Study 1900.

- Table 13: Duration of Exposure According to Mean Daily Dose, ISS-SAF Population

Duration (Months)	>0 to <0.4 mg/kg/day (n)	0.4 to <0.6 mg/kg/day (n)	≥0.6 mg/kg/day (n)	Total n (%)
Total n (%)	82 (31%)	101 (39%)	79 (30%)	262 (100%)
1 to < 6	21	10	6	37 (14%)
6 to < 12	22	21	4	47 (18%)
12 to < 18	7	13	8	28 (11%)
18 to < 24	6	5	6	17 (6%)
24 to <36	19	44	40	103 (39%)
≥ 36	3	6	15	24 (9%)

a: Mean daily dose was calculated as the sum of each day's dosage divided by duration of dosing, calculated over patient's treatment period in Study 1601 Parts 1 and 2 and Study 1900
Source: adapted from 120 day safety update, Table 3

8.2.2. Relevant characteristics of the safety population

See Table 7 in Section 6.1.2 above for a summary of demographic characteristics. The baseline demographics were generally similar amongst the treatment groups. Of note, 186 patients in the safety population were between 2 and <18 years of age; 76 patients were 18 to 35 years of age. Patients younger than 18 years of age had a mean exposure of 595.17 days (approximately 19 ½ months); patients 18 years and older had a mean exposure of 611.05 days (approximately 20 months).

8.2.3. Adequacy of the safety database

Based on the characteristics in Table 7, the development program provides generally adequate representation across the LGS population; however, the majority of patients were non-Hispanic white patients. The course of LGS is not known to differ importantly in minority populations. It is unclear if race or ethnicity are factors that would predispose to fenfluramine-induced VHD or PAH; however, neither have been reported as factors in published studies. Given the rarity of these diseases, the patient demographic exposure seems adequately diverse and generalizable to the to-be-marketed U.S. patient population.

8.3 Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no concerns regarding the integrity of the data submitted for the safety review. The datasets provided by the Applicant were complete, and I was sufficiently able to reproduce the safety analyses of the Applicant and perform my own analyses when necessary.

8.3.2. Categorization of Adverse Events

For Study ZX008-1601 Part 1 and Part 2, MedDRA version 20.1 was used to code AEs. For Study 1900, MedDRA version 21.2 was used to code AEs.

The Applicant used standard procedures to collect and analyze AE data. Investigators were asked to decide on causality and to provide their opinion on intensity (mild, moderate, severe) of each AE. The standard definitions of SAE and TEAE were used in the development program. Status epilepticus lasting less than 30 minutes was entered as an AE. Status epilepticus was entered as an SAE if SAE criteria (e.g., hospitalization) were met or if the status epilepticus persisted for 30 minutes or longer, regardless of administration of rescue medication, and was either diagnosed by a medical professional or occurred more than once in a day. Clinically significant abnormalities in clinical laboratory tests were to be documented as AEs.

AEs of Special Interest (AESI) were listed as:

- Elevated prolactin level ≥2 times above the ULN
- Hypoglycemia <30.0 mmol/L or 54 mg/dL with or without symptoms
- Suicidal thoughts, ideation, or gestures.

Overall, the Applicant's coding of AE terms was sufficient. I reviewed the ADAE.xpt datafile for accuracy of translation from verbatim to preferred term through manual review. A few similar terms were grouped together during my review to avoid underestimating any potential safety signals/risks. Terms were recoded as noted in Table 14.

- Table 14: Recoded AE Codes

Original Coded Preferred Term(s)	Recoded Term
Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased	Elevated transaminase
Prolactinemia, Blood prolactin elevated	Blood prolactin elevated
Platelet count decreased, Thrombocytopenia	Thrombocytopenia
Otitis media acute, Otitis media, Otitis Externa	Ear infection
Viral gastroenteritis, Gastrointestinal disorder, Gastrointestinal infection, Gastroenteritis sapovirus, Rotavirus	Gastroenteritis
Initial insomnia, Insomnia	Insomnia
Atonic seizures, Change in seizure presentation, Clonic convulsion, Epilepsy, Generalised tonic-clonic seizure, Myoclonic epilepsy, Myoclonic seizure, Partial seizures, Petit mal epilepsy, Seizure cluster, Tonic convulsion	Seizure
Upper respiratory tract infection viral, rhinovirus, rhinitis	Upper Respiratory Tract Infection
Pneumonia, pneumonia mycoplasma, pneumonia viral	Pneumonia
Ataxia, balance disorder	Gait disorder

As seen in Table 15 below, a few seizures were omitted through incomplete translation from the verbatim term to the preferred term. These events were added to the dataset.

- Table 15: Additional Seizures Identified in AE Dataset, ISS

Dictionary-Derived Term	Reported Term for the Adverse Event	Add
Cellulitis	CELLULITIS TO HEAD S/P FALL FROM SEIZURE	Seizure
Laceration	HEAD LACERATION DUE TO SEIZURE	Seizure
Fall	FALL (SECONDARY TO SEIZURE)	Seizure
Fall	FALL (SEIZURE-RELATED)	Seizure
Tooth loss	LOST TOOTH IN DROP	Seizure
Nasal injury	CUT ON NOSE (DUE TO SEIZURE-RELATED FALL)	Seizure
Eye disorder	INCREASED EYE ROLLS	Seizure
Respiratory infection	STATUS (RESPIRATORY INFECTION RELATED)	Status epilepticus

Reviewer's comment: Overall, the categorization and coding of TEAEs was appropriate and sufficient, especially given the consistency of the safety findings with those seen in the trials which supported the indication in DS. With recoding of the above terms, my analysis yielded safety outcomes which were essentially the same as the Applicant's although exact numbers may be slightly different.

8.3.3. Routine Clinical Tests

Refer to the Schedule of Key Assessments (Table 4: Schedule of Key Assessments, Study ZX008-1601) and discussion of Safety Endpoints in Study Design above for a summary of the performed clinical examinations. Routine clinical tests were performed including laboratory assessments which included liver function tests and routine hematology tests, coagulation tests, urinalysis, vital signs, physical and neurologic exams, as well as cognitive assessment through the BRIEF. Related to AESIs, tests of growth, precocious puberty and thyroid function, and the C-SSRS were performed. Cardiac monitoring will be discussed later in this review.

8.4 Safety Results

8.4.1. Deaths

Two deaths have been reported during this development program, one of which occurred during the controlled trial. One patient death (Subject (b) (6)) occurred on Study Day 87 in Study ZX008-1601 Part 1 in a 7-year-old patient who had been randomized to FEN 0.8 mg/kg/day, and was attributed to SUDEP. The second patient death (Subject (b) (6)) occurred during Study ZX008-1601 Part 2 in a 31-year-old patient and was attributed to respiratory failure due to severe aspiration pneumonia associated with severe convulsive status

epilepticus. This patient had been randomized to FEN 0.2 mg/kg/day during Study ZX008-1601 Part 1, and began Part 2 on Day 127 of overall study participation. The dose was titrated up per protocol to 0.6 mg/kg/day on Study Day 246. She was reported to have been COVID-19 positive (mild severity) between approximately Study Days 328 and 347. On Study Day 350, convulsive status epilepticus resulted in hospitalization and was noted to have resolved after treatment by Study Day 351. Death occurred on Study Day 353.

Reviewer's comment: As discussed, patients with LGS are at higher risk for mortality due to SUDEP and complications of status epilepticus, which often include aspiration pneumonia related to poor oral motor coordination and axial hypotonia that are characteristic of epileptic encephalopathies. The narratives of these 2 patients describe different clinical circumstances around their deaths, suggesting different causes of death. It would not seem appropriate to attribute these deaths to the investigational drug.

8.4.2. Serious Adverse Events

A total of 31 serious TEAEs occurred in 18 patients during the titration and maintenance periods of double-blind Study ZX008-1601 Part 1 Cohort A (Table 16 below). The incidence of serious TEAEs was similar in patients in the 0.2 mg/kg/day group and the placebo group. The incidence was higher in the FEN 0.8 mg/kg/day group; however, the majority of the serious TEAEs had low likelihood of being related to the drug (e.g., infection/subcutaneous abscess, dehydration, rash), although the small numbers make this difficult to definitively determine. The serious TEAEs which occurred at highest incidence (3 patients each) in the 0.8 mg/kg/day group were status epilepticus and pneumonia. The serious TEAE which occurred with highest incidence (3 patients) in the placebo group was seizure/change in seizure presentation (frequently described as increased seizures), which suggests that status epilepticus in the 0.8 mg/kg/day group was not related to FEN. One patient in the 0.8 mg/kg/day group who had somnolence was withdrawn from the drug.

Reviewer's Comments: The types and frequencies of TEAEs reported in the controlled safety population are similar to those seen in other ASM trials of refractory epilepsy.

- Table 16: Serious Treatment-Emergent Adverse Events during Double-Blind Study 1601 Part 1 Cohort A, Controlled Safety Population

	Placebo (N=87)		FEN 0.2 mg/kg (N=89)		FEN 0.8 mg/kg (N=87)		Overall (N=263)	
	n	%	n	%	n	%	n	%
Subject with any SAE	4	4.6	4	4.5	10	11.5	18	6.8
SUDEP	0		0		1	1.1	1	0.3
Seizure/Change in seizure presentation	3	3.4	2	2.2	0		5	1.9

	Placebo (N=87)		FEN 0.2 mg/kg (N=89)		FEN 0.8 mg/kg (N=87)		Overall (N=263)	
	n	%	n	%	n	%	n	%
(includes "increased eye roll")								
Status epilepticus	1	1.1	0		3	3.4	4	1.5
Pneumonia (includes "lung disorder")	0		1	1.1	3	3.4	4	1.5
Infection/subcutaneous abscess	0		0		2	2.2	2	0.7
Vomiting (includes "gastritis")	0		1	1.1	1	1.1	2	0.7
Constipation	0		1	1.1	0		1	0.3
Dehydration	0		0		1	1.1	1	0.3
Diarrhea	0		0		1	1.1	1	0.3
Humerus fracture	0		0		1	1.1	1	0.3
Irritability	0		1	1.1	0		1	0.3
Rash	0		0		1	1.1	1	0.3
Somnolence	0		0		1	1.1	1	0.3
Stereotypy	0		0		1	1.1	1	0.3
Thyroid mass	1	1.1	0		0		1	0.3

Source: Study ZX008-1601 Part 1 ADAE.xpt (analyzed in JMP)

Based on my analysis, a total of 176 serious TEAEs occurred in 69 patients in the controlled safety population, during the double-blind through open-label treatment periods (Table 17: Serious Treatment-Emergent Adverse Events during Double-Blind through Open-Label Treatment Periods, Controlled Safety Population). Nervous system and infectious serious TEAEs occurred most frequently (45% and 27%, respectively). The most frequently reported serious TEAE in this population was seizures, which occurred in 22 (8.4%) of patients. Other frequently reported serious TEAEs were status epilepticus (5.3%), pneumonia (3.8%), gastritis/vomiting (2.2%), somnolence (1.9%), dehydration (1.5%), and humerus/upper limb fracture (1.1%). All other serious TEAEs occurred in <1% of this population during the double-blind and open-label treatment periods.

Reviewer's Comments: The most frequently reported serious TEAEs in the controlled safety population, during the double-blind through open-label treatment periods, were seizures of any type, status epilepticus, and pneumonia, which are frequently reported in this population and are likely related to the underlying diagnosis and morbidity of LGS.

- Table 17: Serious Treatment-Emergent Adverse Events during Double-Blind through Open-Label Treatment Periods, Controlled Safety Population

MeDRA System Organ Class and Preferred Term	>0 to <0.4 mg/kg/day (N=82)		0.4 to <0.6 mg/kg/day (N=101)		**≥0.6** mg/kg/day (N=79)		Overall (N=262)	
	n	%	n	%	n	%	n	%
Subjects with any SAE	17	20.7	27	26.7	25	31.6	69	26.3

Blood/lymphatic system disorder: HUS	0		0		1	1.3	1	0.4
Congenital, familial, genetic disorders: pyloric stenosis	0		0		1	1.3	1	0.4
Eye disorders: keratoconus	0		1	1.0	0		1	0.4
Gastrointestinal disorders	1	1.2	4	4.0	5	6.3	10	3.8
Gastritis/Vomiting	1	1.2	3	3.0	2	2.5	6	2.2
Constipation	0		0		1	1.2	1	0.4
Diarrhea	0		0		1	1.2	1	0.4
Diverticulitis	0		1	1.0	0		1	0.4
Intestinal obstruction	0		0		1	1.2	1	0.4
General Disorders and Administration Site Conditions	3	3.7	5	5.0	6	7.6	14	5.3
Asthenia	0		2	2.0	0		2	0.8
Complication of device insertion	0		0		1	1.2	1	0.4
Gait disturbance/Gait inability	0		1		1	1.2	2	0.8
Pyrexia	0		0		1	1.2	1	0.4
SUDEP	0		0		1	1.2	1	0.4
Distributive shock	0		1	1.0	0		1	0.4
Dehydration	1	1.2	1	1.0	2	2.5	4	1.5
Hypothermia	1	1.2	0		0		1	0.4
Thyroid mass	1	1.2	0		0		1	0.4
Hepatobiliary disorders: cholelithiasis	0		1	1.0	0		1	0.4
Infections and Infestations	4	4.9	11	11	12	15.2	27	10.3
Pneumonia/pneumonia myocoplasmal	2	2.4	4	4	4	5.0	10	3.8
Coronavirus infection	0		1	1	1	1.2	2	0.8
Influenza	0		1	1	1	1.2	2	0.8
Urinary tract infection	0		1	1	1	1.2	2	0.8
Cellulitis of male external genital organ	0		1	1	0		1	0.4
Clostridium difficile colitis	0		1	1	0		1	0.4
Dengue fever	1	1.2	0		0		1	0.4
Gastroenteritis/gastroenteritis viral	0		0		2	2.5	2	0.8
Infection	0		1	1	0		1	0.4
Legionella infection	1	1.2	0		0		1	0.4
Respiratory syncytial virus bronchiolitis	0		0		1	1.2	1	0.4
Sepsis	0		0		2	2.5	2	0.8
Subcutaneous abscess	0		1	1	0		1	0.4
Injury, Poisoning and Procedural Complications	0		3	3.0	2	2.5	5	2.0
Humerus fracture/upper limb fracture	0		2	2.0	1	1.2	3	1.1
Foreign body in respiratory tract	0		0		1	1.2	1	0.4
Tooth loss	0		1	1	0		1	0.4
Investigations	0		1	1	2	2.5	3	1.1
Weight decreased	0		1	1	1	1.2	2	0.8
Blood prolactin increased	0		0		1	1.2	1	0.4

Metabolism and Nutrition Disorders	2	2.4	2	2.0	2	2.5	6	2.3
Decreased appetite	1	1.2	1	1.0	0		2	0.8
Diabetic ketoacidosis	1	1.2	0		0		1	0.4
Failure to thrive	0		0		1	1.2	1	0.4
Hypoalbuminemia	0		1	1.0	0		1	0.4
Nervous System Disorders	12	14.6	19	19.0	14	17.7	45	17.2
Status epilepticus	3	3.7	6	6.0	5	6.3	14	5.3
Seizure/change in seizure presentation/seizure clusters/GTC/increased eye rolls	7	8.5	8	8.0	7	8.9	22	8.4
Somnolence/depressed consciousness	1	1.2	3	3.0	1	1.2	5	1.9
Cerebral hemorrhage	0		0		1	1.2	1	0.4
Tremor	0		1	1.0	0		1	0.4
Dyskinesia	1	1.2	0		0		1	0.4
Headache	0		1	1.0	0		1	0.4
Psychiatric Disorders	0		0		5	6.3	5	1.9
Agitation	0		0		1	1.2	1	0.4
Breath holding	0		0		1	1.2	1	0.4
Hallucination	0		0		1	1.2	1	0.4
Irritability	0		0		1	1.2	1	0.4
Stereotypy	0		0		1	1.2	1	0.4
Respiratory, Thoracic and Mediastinal Disorders	0		0		4	5.1	4	1.5
Pneumonia aspiration	0		0		2	2.5	2	0.8
Pleurisy	0		0		1	1.2	1	0.4
Pneumonitis	0		0		1	1.2	1	0.4
Skin/Subcutaneous Tissue Disorder	0		1	1.0	0		1	0.4
Rash	0		1	1.0	0		1	0.4

Source: ISS 120-day safety update ADAE.xpt (JMP)
Abbreviation: HUS = hemolytic uremic syndrome

Two AESIs were reported (Table 18 Adverse Events of Special Interest during Double-Blind through Open-Label Treatment Periods, Controlled Safety Population. Elevated blood prolactin was seen in 3.4% of patients. Prolactin release has been associated with seizures, particularly generalized-tonic-clonic seizures. Of the 9 patients in which elevated prolactin was reported, 7 patients had had seizures within the prior 2 days, and 8 patients had a single isolated elevated prolactin level.

Reviewer's Comments: Prolactin has previously been speculated as being a measure of serotonergic activity. The clinical significance of asymptomatic elevated prolactin levels in the context of fenfluramine administration and frequent seizure activity is unclear. It is not clear that prolactin monitoring would be useful in identifying endocrine dysfunction.

- Table 18 Adverse Events of Special Interest during Double-Blind through Open-Label Treatment Periods, Controlled Safety Population

MedDRA System Organ Class and Preferred Term	Actual ZX008 Mean Daily Dose (mg/kg/day)			Overall (N = 262)
	> 0 to < 0.4 (N = 82)	0.4 to < 0.6 (N = 101)	≥ 0.6 (N = 79)	
Subjects with any AESI	1 (1.2%)	3 (3.0%)	5 (6.3%)	9 (3.4%)
Hyperprolactinemia/blood prolactin increased	1 (1.2%)	3 (3.0%)	5 (6.3%)	9 (3.4%)
Hypoglycemia	0	1 (1.0%)	0	1 (0.4%)

Source: ISS 120-day safety update ADAE.xpt (JMP)

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Twenty-six patients (9%) of the controlled safety population discontinued from the study and/or study drug during the double-blind through open-label treatment periods due to TEAEs. TEAEs which led to discontinuation in more than 1 patient included all seizures (including change in seizure presentation; 4.6% of the total controlled safety population), vomiting or gastritis (1.9%), decreased appetite (1.5%), somnolence (1.5%), fatigue (1.1%), and abnormal echocardiogram (0.8%). Patients who received the lowest mean daily dose of >0 to 0.4 mg/kg/day had the highest incidence of discontinuation due to seizures (8.5% of patients who received that dose versus 3% who received 0.4 to <0.6 mg/kg/day and 2.5% who received ≥0.6 mg/kg/day). Three (3.7%) patients who received >0 to 0.4 mg/kg/day discontinued due to decreased appetite, versus 1 (1.3%) patient who received ≥0.6 mg/kg/day.

Reviewer's Comments: A greater number of patients who received the low mean daily dose range of >0 to 0.4 mg/kg/day discontinued due to seizures or decreased appetite. An association between dose and AE was otherwise not clearly suggested for other AEs. In general, the TEAEs leading to discontinuation were consistent with AEs seen in similar circumstances in other ASM studies. Abnormal echocardiograms will be discussed later in the review.

8.4.4. Significant Adverse Events

A total of 36 patients in the controlled safety population experienced 59 TEAEs during the double-blind through open-label periods which were determined to be severe. Nine patients had status epilepticus which was rated as severe. Five patients had seizures which were rated as severe. Three patients had pneumonia and 2 patients had aspiration pneumonia which were rated as severe but were felt not to be related to the drug. Four patients had somnolence which

was rated as severe; the dose was not changed in 2 patients and was interrupted or reduced in the other two. Asthenia was rated as severe in 2 patients; the dose was reduced or interrupted in both patients and led to study withdrawal in one. Decreased appetite was rated as severe in 2 patients; the dose was not changed in one patient, but led to study withdrawal of the other patient.

Five patients in total withdrew from the study due to AEs which were rated as severe. In addition to the patients who discontinued due to asthenia and decreased appetite as mentioned above, one patient each withdrew because of weight loss, tremor, and walking instability.

Reviewer's Comments: The occurrence of severe AEs appears to be similar to that seen in other ASM studies, some of which (seizures, status epilepticus, pneumonia) are likely complications of the underlying condition of LGS. In general, the TEAEs leading to discontinuation were not clearly dose-dependent, but appear consistent with AEs seen in similar circumstances in other ASM studies. Based on previous findings with FEN, somnolence, asthenia, and decreased appetite will need to observed.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

During the titration and maintenance periods of the double-blind Study ZX008-1601 Part 1 Cohort A (i.e., not counting the titration/transition period into the subsequent OLE Study ZX008-1601 Part 2), a total of 827 TEAEs occurred in 212/263 patients (80.6%).

TEAEs were overall slightly more common in patients taking FEN 0.8 mg/kg/day (89.7%) than FEN 0.2 mg/kg/day (77.5%), which in turn experienced TEAEs slightly more commonly than patients in the placebo group (74.7%). Certain TEAEs appeared to occur at higher frequency in either or both FEN 0.2 and 0.8 mg/kg/day groups than in placebo. There was often no clear suggestion of dose-dependency except for possibly those AEs which relate to CNS depression; there was a similar incidence between patients in the placebo group and the FEN 0.2 mg/kg/day group, with a higher occurrence in the FEN 0.8 mg/kg/day group. Those TEAEs which occurred at ≥10% included diarrhea (12.6% in the FEN 0.8 mg/kg/day group, 11.2% in the FEN 0.2 mg/kg/day group, 4.6% in the placebo group), vomiting (8% in the 0.8 group, 13.5% in the 0.2 group, 5.7% in the placebo group), decreased appetite (35.6% in the 0.8 group, 20.2% in the 0.2 group, 11.5% in the placebo group), combined somnolence/lethargy (22.9% in the 0.8 group, 12.3% in the 0.2 group, 12.6% in the placebo group), and combined fatigue/asthenia (24.1% in the 0.8 group, 13.5% in the 0.2 group, 13.7% in the placebo group).

Reviewer's comment: In general, TEAEs were slightly more frequently seen in patients in the FEN groups than in the placebo group, without strong suggestion of dose-response except in

the situation of AEs related to central nervous system depression (e.g., somnolence/lethargy and fatigue/asthenia).

In the controlled population during the double-blind through open-label treatment periods, a total of 1981 treatment emergent adverse events (TEAEs) occurred in 245/262 (94.5%) patients in the controlled population during double-blind through open-label treatment periods.

Dose-dependence was, in general, not reflected in the overall percentages of patients who had TEAEs (89% of patients on a mean daily dose of >0 to <0.4 mg/kg/day, 97% of patients on a mean daily dose of 0.4 to <0.6 mg/kg/day, and 93.7% of patients on a mean daily dose of ≥0.6 mg/kg/day). TEAEs which occurred in ≥10% of patients included decreased appetite in 33.6% of the entire ISS-SAF population (26.8% of patients who received a mean daily dose of >0 to <0.4 mg/kg/day, 41.6% of patients who received a mean daily dose of 0.4 to <0.6 mg/kg/day, and 30.4% of patients who received a mean daily dose of ≥ 0.6 mg/kg/day), seizure/change in seizure presentation in 32.8% overall (26.8%, 31.7%, and 40.5%, respectively), fatigue in 21% overall (19.5%, 28.7%, 12.7, respectively), somnolence in 19.5% overall (15.9%, 24.8%, and 16.5% respectively), nasopharyngitis in 16.4% overall (13.4%, 13.9%, and 22.8%, respectively), pyrexia in 15.6% overall (12.2%, 15.8%, and 19%, respectively), diarrhea in 13.7% (11%, 15.8%, and 13.9%, respectively), vomiting in 13.7% overall (12.2%, 14.9%, and 13.9%, respectively), upper respiratory tract infection in 13.0% overall (7.3%, 15.8%, and 15.2%, respectively), constipation in 11.5% overall (6.1%, 11.9%, and 16.5%, respectively), and decreased weight in 11.1% overall (6.1%, 13.9%, and 12.7%, respectively).

Reviewer's comment: In general, the TEAEs during the combined blinded and open-label treatment periods were similar to those which occurred during the blinded period. The frequent TEAEs of nasopharyngitis and upper respiratory tract infection occur frequently in a pediatric population and may be particularly frequent in a population of patients with LGS who are more vulnerable systemically, and therefore are less likely to be adverse reactions to the drug. The TEAE of seizure is unlikely to be an adverse reaction, in light of the lack of consistent exacerbation of a particular seizure type shown in the subgroup analysis described in the efficacy review above, as well as the characteristic occurrence of intermittent increases in seizures in the natural history of LGS. Based on previous experience with FEN, the AEs of decreased appetite and weight, fatigue, and somnolence are likely to be adverse reactions. The gastrointestinal AEs of diarrhea, vomiting, and constipation, may be adverse reactions, particularly with the suggestion of dose dependence with constipation.

8.4.6. Laboratory Findings

In the blinded study, changes in laboratory values including hematology, chemistry, and urinalysis parameters from baseline over time were not clinically notable. The number of patients reporting TEAEs related to abnormal chemistry values was generally low and similar

between FEN and placebo groups, including liver function tests (2 patients in placebo group, 1 patient in FEN 0.2 mg/kg/day group).

The percentage of patients who had shifts from baseline compared to placebo was evaluated for platelet count, among patients who were or were not using valproate, and for prolactin levels. At baseline, similar percentages of patients in the placebo, FEN 0.2 mg/kg/day, and FEN 0.8 mg/kg/day groups who were using valproate had a normal platelet count (88.9%, 92.9%, and 92%, respectively). At Visit 8 (one month after titration to assigned dose was reached), more patients who were using valproate and had a normal baseline platelet count in the FEN 0.8 mg/kg/day group had a ≥25% decrease from baseline in platelet count (12.5% compared to 6.5% in the 0.2 mg/kg/day group and 6.8% in the placebo group). At Visit 12, more patients in both FEN groups had a ≥25% decrease from baseline in platelet count (4.7% of placebo, 11.8% of FEN 0.2 mg/kg/day, and 11.9% of FEN 0.8 mg/kg/day groups). Patients who were not on concomitant valproate and who had a normal baseline platelet count did not demonstrate increased percentages with significant decrease in platelet count over time.

Adverse events of elevated prolactin were discussed previously in this review, as it was identified as an AESI. The number of subjects with ≥25% increases from baseline in T+M was also evaluated. At Visit 8, among patients who had a normal baseline prolactin level, more subjects in the FEN 0.8 mg/kg/day group had a ≥25% increase from baseline compared to the other groups (42.5% of the placebo, 27.9% of the FEN 0.2, and 58.1% of the FEN 0.8mg/kg/day groups). At Visit 12, more patients in both FEN groups had a ≥25% increase from baseline compared to placebo (25.4% placebo, 39.1% of the FEN 0.2, 55.4% of the FEN 0.8 mg/kg/day groups. As discussed previously, the majority of patients with samples with increased prolactin had a seizure within the previous 48 hours.

In the double-blind through open-label treatment periods, 3 patients who had a normal baseline glucose had abnormally low glucose (two at OLE Month 3, one at OLE Month 6). A total of 32 patients had elevations in liver function tests (including gamma- glutamyl transaminase [GGT], alanine aminotransferase[ALT], aspartate aminotransferase [AST], and alkaline phosphatase [ALP]) and/or creatine kinase. Twenty-four of those patients had baseline hepatic enzyme elevations and either had normal values at some visits or were consistently but stably elevated throughout the study. Twenty-five patients had elevations in a single liver function panel (one with ALT elevation, 24 with GGT elevation). Brief lab summaries were reviewed for the patients who had elevations of several liver function tests:

- Subject (b) (6) (mean daily dose ≥0.6 mg/kg/day): On Study Day 671, ALT 624 U/L (5-30 U/L), AST 301 U/L (0-69 U/L), GGT 107 U/L (2-24 U/L). ALT and AST values decreased by Day 682 (9 days later) and resolved to normal by Day 689, while GGT increased to a maximum of 124 U/L by Day 682 and trended downwards through Day 710.
- Subject (b) (6) (≥0.6 mg/kg/day): GGT was elevated at 42 U/L (2-24 U/L) at baseline, increased to 820 U/L (2-24 U/L) on Day 1008, almost returning to normal by Day 1093

(32 U/L). ALT was within the reference range at baseline, and increased to 100 U/L (5-30 U/L) on Day 1008, returning to normal by Day 1093.

- (b) (6) (≥0.6 mg/kg/day): Baseline GGT 36 (2-24 U/L), maximum value of 100 U/L on Day 48, variable between 42 U/L on Day 111 and 91 U/L on Day 863. ALT 114 U/L on Day 48, normal by Day 111.
- (b) (6) (0.4 to <0.6 mg/kg/day): increased AST and CK in setting of reported TEAE of myositis beginning on Study Day 173; resolved by Day 178.
- (b) (6) (0.4 to <0.6): on Day 467, AST 126 U/L (9-34 U/L) and CK 10306 U/L. No TEAEs were reported. Values were within normal limits by Day 544.
- (b) (6) (0.4 to <0.6): On Day 210, GGT maximum was 151 U/L (7-38 U/L) however it had been above normal from Day 42 (45 U/L); decreased to 67 U/L by Day 836. ALP elevated at baseline (138 U/L with reference range 37-116 U/L), peak of 369 U/L on Day 836).
- (b) (6) (>0 to <0.4 mg/kg/day): On Day 216, GGT 434 (2-24 U/L) and ALT 153 U/L (5-30 U/L). GGT normal by Day 307 and ALT by Day 236.

Reviewer's comment: Absolute thrombocytopenia was not frequently seen; however, the decrease in platelet counts, which seems to be dose-dependent and time-dependent, suggests the need for platelet monitoring on concomitant valproate. Valproate is known to be associated with dose-dependent thrombocytopenia and its PI recommends platelet monitoring. The decrease in prolactin levels which also seems to be dose-dependent and time-dependent suggests a contribution of FEN beyond the prolactin elevation seen with seizures. However it is unclear what clinical significance this would have in the setting of asymptomatic elevation. Regarding liver function tests (LFTs), no clear pattern was seen in the patients with elevated LFTs; interpretation is difficult in the setting of concomitant ASMs which may contribute to LFT elevations and, in some cases, in the setting of intercurrent infection or inflammatory disease. No patients demonstrated drug-induced liver injury or met Hy's law criteria.

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. In the double-blind treatment period, TEAEs related to vital signs, other than pyrexia, were reported for only 1 subject each (hypertension and hypotension). No clinically significant changes were identified during the open-label treatment periods.

8.4.8. Electrocardiograms (ECGs)

No clinically significant findings in the analysis of ECGs were seen.

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.

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 protocol for monitoring for echocardiographic evidence of VHD and PAH was similar to that performed during the trials which supported the indication in DS. An extensive discussion of the background and details of the prospective monitoring program was included in Dr. Getzoff's clinical review of the trials which supported the indication in DS and in Dr. Walker's consultation from the Division of Cardiovascular and Renal Products for that original submission.

In brief, the main ECHO endpoint as delineated in the Statistical Analysis Plan for Cardiovascular Endpoints (for the Integrated Summary of Safety for Lennox-Gastaut Syndrome Subjects in Studies ZX008-1601 and ZX008-1900) was the number (%) of patients who developed clinically confirmed VHD at any time during the program. Additional endpoints for ECHO analysis included the number of patients who met the FDA case definition of drug-associated valvulopathy (mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation) at any time, the number of patients less than 18 years old with ≥trace mitral and/or aortic regurgitation, the number of patients ≥18 years old with ≥moderate mitral and/or mild aortic regurgitation, the number of patients with pulmonary artery systolic pressure (PASP) >35 mmHg after baseline, number of patients with change from baseline of >10mmHg, >15mmHg, >20 mmHg PASP.

Board-certified cardiologists who were blinded as to patients' treatment groups read the ECHOs for valve function and indices of pulmonary hypertension; a third cardiologist adjudicated in the event of a discrepancy between the 2 readings. Findings related to PAH or VHD on any of the 4 valves were reported to the Investigator with grades of absent, trace, mild, moderate, or severe. If the grade of regurgitation met the FDA case definition of VHD, adjudication would be performed by the International Cardiac Advisory Board, who advised the Applicant and provided advice to the IDSMC. The IDSMC would then determine the appropriate path for the participant, including discontinuation of the study drug, reduction of the study drug, or increased frequency of ECHO and ECG monitoring or other additional monitoring measures.

Specific guidelines based on increasing severity of regurgitation were delineated and were similar to those used in the DS studies. If it was determined that the drug should be tapered off, the patient was to be followed for a minimum of 6 months from discontinuation of the drug, until the condition had resolved or stabilized.

During the blinded study, no patients met the FDA case definition of VHD. One 18-year-old patient in the FEN 0.8 mg/kg/day group showed mild mitral regurgitation (MR) at Visit 12, however mild MR is seen commonly and is considered non-pathologic. One 11-year-old patient in the FEN 0.2 mg/kg/day group showed mild aortic regurgitation (AR) at Visit 12, however a subsequent transesophageal ECHO found no regurgitation. Other reported findings included trace mitral or trace aortic regurgitation, which are considered normal. When trace regurgitation was seen, the finding was often limited to a visit and not seen at the next visit. No significant findings related to right ventricular systolic pressure (RVSP), which provides an estimate of PASP.

Over the course of the blinded through open-label periods, there were 2 subjects (an 11-year-old child and a 23-year-old adult) who met the FDA case definition of VHD (mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation) based on the presence of mild AR, but have not had structural abnormalities of the valve, symptoms, or progression of echocardiographic findings with continued FEN use, and therefore no subject has had clinically-confirmed VHD. The 11-year-old had mild AR on an ECHO at the end of the double-blind treatment period after 14 weeks of exposure. A transesophageal ECHO (TEE) subsequently showed no AR and no structural abnormality of the valve. Subsequent transthoracic ECHOs through Study Day 1019 reported mild or trace AR and another TEE showed trace AR with a normal aortic valve. The 23-year-old has had several transthoracic ECHOs which have shown mild AR with no changes through Study Day 850.

As noted in the discussion of discontinuations due to TEAEs, there were 2 patients who discontinued FEN and the study due to an abnormal ECHO. Both had trace MR which was felt to be "possibly" related to FEN, but, in the general population, is not considered pathologic.

Reviewer's comment: There were no findings of clinically-confirmed VHD or PAH in the development program as of the cutoff date for the 120-day safety update (August 2, 2021). However, due to the need for chronic administration in the setting of epileptic encephalopathies and the unknown but potential contribution of duration of exposure, cumulative dose-exposure, and age to the risk of VHD and/or PAH, continued monitoring is necessary. 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.

In addition, the PMR issued at the time of the approval for the indication in DS and enhanced pharmacovigilance will provide further information on risk factors (e.g., demographics, concomitant drugs, underlying illnesses) and presentation of VHD and/or PAH in this population.

8.5.2. Effects on Appetite and Weight

Because FEN was previously marketed as an anorectic, albeit at higher doses of 60 to 120 mg, decreased appetite is not unexpected. However, the impact on weight gain and growth in a predominantly pediatric patient population is of concern. Therefore body weight loss of ≥7% and ≥10%, based on study visit measurements, was analyzed.

In the double-blind treatment period, 14 of the total randomized 263 patients (4.9%) had a weight loss of ≥7% at any study visit compared to baseline weight. None of these patients were in the placebo group; 6 (6.7% of the total patients in the 0.2 arm) were in the FEN 0.2 mg/kg/day group; and 8 of these patients (9.2% of the total number of patients in the 0.8 arm) were in the FEN 0.8 mg/kg/day group. Nine of these 14 patients had a weight loss of ≥10% at any visit (4 patients [4.5%] of the 0.2 mg/kg/day group and 5 patients [5.7%] of the 0.8 mg/kg/day group). Four of the 14 patients were 2 to 5 years old; 7 patients were 6 to 17 years old; and 3 patients were 18 years or older. Of the 14 patients, 7 showed evidence of weight increases over the course of the OLE. A patient's weight was considered "recovered" if they had a subsequent weight recorded that was within 1% of the baseline body weight. One of the 14 subjects (in the 0.2 mg/kg/day group) recovered the lost weight by 88 days, without change in the dose.

In the controlled safety population in the double-blind through open-label treatment periods, 65 patients (24.8%) had a ≥7% weight loss, 42 (16%) of whom had a ≥10% weight loss at any visit after baseline. There was a higher percentage of adult patients with significant weight loss; 27 of the 65 patients with a ≥7% weight loss were 18 years or older (35.5% of the population ≥18 years), while 38 of the 65 patients with a ≥7% weight loss were less than 18 years of age (20.3% of the population <18 years). The OLE data suggests that this weight loss decreases with longer time on FEN. Of the 247 patients in the open-label safety population, the proportion of patients who had a ≥7% weight loss by their last study visit was 11.3% (16 of these 28 patients were <18 years old, 12 of these 28 patients were ≥18 years old). Over time in the OLE study, the proportion of patients who had a ≥7% weight gain increased. This was particularly noted in children 2 to 17 years of age; at OLE Month 12, 12 of the remaining 97 children in the study (12.4%) had a ≥7% weight loss, but 43 (44.3%) had a ≥7% weight gain.

Reviewer's comment: The significance of the uncontrolled data suggesting recovery of weight loss is uncertain but reassuring. The clear finding is the FEN-associated weight loss seen in the double-blind treatment period. It was noted that 8 of the patients with ***≥7%*** *weight loss had experienced events which may have contributed to the weight loss, e.g., vomiting, gastroenteritis, or diarrhea. These events may indeed occur frequently in a pediatric population of patients with LGS, but they would likely serve as additional risk factors on top of the action of fenfluramine.*

8.6. Safety Analyses by Demographic Subgroups

Of particular interest in this submission is the inclusion of adults 18 years and older. The trials which supported the approval of FEN for the treatment of seizures associated with DS studied children 2 to 19 years of age. There is a higher number of adults who have the diagnosis of LGS, related to the longstanding recognition of the clinical syndrome and to the relatively broad clinical characteristics. Overall, the incidence of TEAEs was similar between children 2 to 17 years of age and adults 18 years and older. The most common TEAEs in adults included diarrhea, fatigue, irritability, and upper respiratory infection.

Comparing females and males, the overall incidence of TEAEs was also similar. For females, the most common TEAEs included decreased weight, in addition to the most common TEAEs for the overall controlled safety population. For males, the most common TEAEs included change in seizure presentation, in addition to the most common TEAEs for the general controlled safety population.

Regarding analysis based on ethnic subgroups, note that the patients in the "not reported" group was a small size (N=23), and that the majority of patients were not Hispanic or Latino (N=189) compared to Hispanic or Latino (N=50). The overall incidence of TEAEs was higher in the "not reported" ethnicity group (100%) than in the Hispanic/Latino (90%) and not Hispanic/Latino (93.7%) groups. Overall, the most common TEAEs were similar across the groups. Regarding analysis based on racial subgroups, note that the number of patients in non-White groups (33 in Other, 12 in Black or African American, 9 in Asian) were small compared to the number of patients in the White group (N=208). The overall incidence of TEAEs was similar across groups.

8.7. Specific Safety Studies/Clinical Trials

AESIs included suicidal thoughts, ideation, or gestures. None were reported. This is as expected for a patient population which typically has significant intellectual impairment.

The C-SSRS was used in the clinical studies. There was no significant change from baseline in patients' responses, and no patients' results indicated emergence of suicidality.

The BRIEF was an instrument which measures executive functioning which was included as a safety outcome to measure negative impact on cognitive functioning. No statistically significant differences were reported in any of the 5 domain scores, however data were available for only up to 34 patients.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable.

8.8.2. Human Reproduction and Pregnancy

No pregnancies were reported during the development program. PMR 3887-7 was issued at the time of approval for the indication of DS for a single-arm pregnancy safety study to collect and analyze information for a minimum of 10 years of pregnancy complications and birth outcomes in women exposed to FEN during pregnancy. The Applicant submitted a final protocol on August 27, 2021.

8.8.3. Pediatrics and Assessment of Effects on Growth

See section 8.5.2 above for discussion of weight loss. Laboratory assessments also included tests of growth and endocrine function, including growth hormone, insulin-like growth factor-1, luteinizing hormone, follicle-stimulating hormone, testosterone, and estradiol. Tanner staging was performed. Overall, there were no significant findings.

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

No overdoses of FEN have been reported during the development program; however, overdoses of FEN have been reported in the published literature, some of which have been fatal. Discussion of associated symptoms and signs was included in the labeling approved for the indication of treatment of seizures associated with DS, and have been retained in the Applicant's current proposed labeling.

Of note, brief periods of minor over-dosing errors occurred during the LGS studies. These included one patient that received doses of ≥1 mg/kg/day for 1 day, and one patient who received a dose over the maximum of 30 mg/day (40 mg/day, which was equal to 0.77 mg/kg/day) for 3 months. No related TEAEs were reported for these patients. Protocol deviations included 3 patients being prescribed 1.0 mg/kg/day; one patient received 20 mg/day for 3 weeks, one received 23.5 mg/day for 3 months, and one received 31.9 mg/day for 6 months. No related TEAEs were reported for these patients.

Regarding potential withdrawal or rebound, 4 subjects who did not continue treatment in Study 1900 experienced TEAEs, some serious, during the Study 1601 Part 2 open-label taper period. These consisted of status epilepticus occurring 4 days after the last dose of FEN, seizure occurring 8 days after the taper started, insomnia and change in seizure during the taper period, and vomiting during the taper period.

Reviewer's comment: The potential for overdosage and withdrawal seizures are appropriately addressed in Sections 10 Overdosage and 17 Patient Counseling Information of the proposed label. The observations that suggest a risk for withdrawal seizures are consistent with those that may be seen with discontinuation of other ASMs in patients with refractory epilepsy. There is no concern for abuse potential.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Postmarketing surveillance through the FDA Adverse Event Reporting System (FAERS) has not identified cases of VHD or PAH with Fintepla. The REMS and pharmacovigilance continue to facilitate the safe use of FEN.

On September 16, 2021, FAERS received an initial report of a 7-year-old with Dravet syndrome with echocardiogram reporting mild tricuspid regurgitation and estimated RVSP of 35-40 mmHg, approximately 56 months after onset of treatment. A repeat ECHO a month after the first ECHO reported a lower and normal RVSP. Both ECHOs were re-read by (b) (4) ECHO lab (contracted by the company to adjudicate cardiovascular AEs), who concluded that no signs of pulmonary artery hypertension were present in either ECHO. The next patient status form should be submitted to the FDA by April 2022.

8.9.2. Expectations on Safety in the Postmarket Setting

Adverse events are expected to be similar to those that have been seen in the DS development program, in patients who have received FEN in the postmarket setting since approval for the DS indication approximately 1 ½ years ago, and in the LGS clinical studies. Additional experience will be obtained from commercial use in a larger number of individuals with LGS who are somewhat older than the DS population. Additional understanding of the risk of VHD and PAH will be obtained from the REMS and PMRs.

8.9.3 Additional Safety Issues From Other Disciplines

Not applicable.

8.10. Integrated Assessment of Safety

Overall, the most frequently reported TEAEs in Study ZX008-1601 Part 1 Cohort A and in the interim analyses of ongoing Studies ZX008-1601 Part 2 Cohort A and 1900 were consistent with what was demonstrated in the DS development program. The most commonly reported adverse reactions (≥10%) seen with FEN in patients with LGS were diarrhea, decreased appetite, fatigue, somnolence, and vomiting. Thus far, 2 patients with LGS, one pediatric and one young adult, have had ECHOs which fulfill criteria for the FDA case definition of fenfluramine-associated VHD which was developed to screen for cases when originally recognized in the 1990s with higher doses (60-120 mg) administered to obese adults. However these 2 patients are not felt to have clinically-confirmed VHD as assessed by cardiologists and have had stable ECHOs while remaining on FEN for approximately 2 ¼ years in the child's case and for approximately 2 ¾ years in the young adult's case (at the time of data cutoff for the 120-day safety update for this submission). Additional long-term data will be helpful.

9. Advisory Committee Meeting and Other External Consultations

An AC 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.

Of significance is that the Applicant proposed dosing recommendations which are identical to those for the indication of DS, including an initial starting and maintenance dosage of 0.1 mg/kg twice daily. Because the total daily dosage of 0.2 mg/kg/day was not demonstrated to be effective in the randomized, double-blind, placebo-controlled trial submitted in this application, the dose of 0.1 mg/kg twice daily should be noted to be an initial starting dosage and should be titrated to the maintenance dosage of 0.35 mg/kg BID for which effectiveness was demonstrated.

Of note, the doses of FEN in the label differ from those used in the clinical studies, because the Applicant implemented the USP Salt Policy. The dose of 0.8 mg/kg/day (maximum 30 mg/day) used in the clinical studies is roughly equivalent to the 0.7 mg/kg/day (maximum 26 mg/day) in

the proposed label. With rounding, the 0.2 mg/kg dose in the label is the same as that used in the studies.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

At the time of the approval of Fintepla for the treatment of seizures associated with DS, a REMS with Elements to Assure Safe Use (ETASU) was also approved, to ensure that the benefit of FEN outweighs the risk of VHD and PAH. Implementation of the program began July 6, 2020, with the enabling of enrollment and certification on the website, with subsequent commercial drug distribution beginning July 13, 2020. A one-year REMS assessment report was submitted in June 2021 for the cumulative reporting period of June 25, 2020 through April 24, 2021. Review by Division of Risk Management (DRM) determined that the REMS was meeting its goal of mitigating the risk of VHD and PAH associated with Fintepla, and was meeting its objectives.

Please see the DRM's review of this sNDA for a complete discussion of edits to the REMS materials. No clinically-confirmed VHD or PAH has been observed thus far. However, due to the need for chronic administration in the setting of epileptic encephalopathies and the unknown but potential contribution of duration of exposure, cumulative dose-exposure, and age to the risk of VHD and/or PAH, continued echocardiographic monitoring and pharmacovigilance are necessary.

12. Postmarketing Requirements and Commitments

PMRs were issued at the time of approval for the indication of DS for the following clinical studies:

- PMR 3887-7: 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 FEN during pregnancy. The final protocol was submitted August 27, 2021.
- PMR 3887-8: a prospective observational registry study in epilepsy patients taking FEN using data from the REMS Registry and additional data beyond what is collected in the REMS registry, with primary objectives to characterize the risks of the development of symptomatic or asymptomatic VHD and/or PAH. This study was to include 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, and the assessment of ECHO data at baseline and every six months for five years, or until the last ECHO following interruption of FEN treatment. Final protocol was submitted August 27, 2021.

- PMR 3887-9: a clinical pharmacokinetic trial to determine an appropriate dose of FEN to minimize toxicity in patients with varying degrees of hepatic impairment.

13. Appendices

13.1. References

See footnotes throughout document.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 1601 (Part 1 and Part 2), 1900

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1601: 69; 1900: 73		
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): 2		
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: 1		
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)

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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