CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212102Orig1s000

SUMMARY REVIEW

Summary Review

Date	June 25, 2020
From	Philip H. Sheridan, MD Nick Kozauer, MD
Subject	Summary Review
NDA/BLA # and Supplement#	NDA 212102
Applicant	Zogenix, Inc.
Dates of Submission	September 25, 2019 September 25, 2019
PDUFA Goal Dates	June 25, 2020
Proprietary Name	Fintepla
Established or Proper Name	Fenfluramine
Dosage Form(s)	Oral solution (2.2 mg/mL)
Applicant Proposed Indication(s)/Population(s)	Treatment of seizures associated with Dravet syndrome in patients 2 years of age and older
Applicant Proposed Dosing Regimen(s)	0.2-0.7 mg/kg/day, maximum 26 mg/day, in patients not taking concomitant stiripentol; maximum 0.4 mg/kg/day or 17 mg/day in patients taking concomitant stiripentol. All doses are divided twice daily.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Fintepla is indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older.
Recommended Dosing Regimen(s) (if applicable)	The starting dose is 0.1 mg/kg twice daily which can be increased based on efficacy and tolerability. The maximum daily maintenance dose of Fintepla is 0.35 mg/kg twice daily, not to exceed a total daily dose of 26 mg. The maximum daily maintenance dose of Fintepla for patients taking concomitant stiripentol is 0.2 mg/kg twice daily not to exceed a total daily dose of 17 mg.

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

This application provides data to support the effectiveness and safety of fenfluramine (FEN), proprietary name Fintepla, for the treatment of seizures associated with Dravet syndrome (DS) in patients 2 years of age and older. FEN was previously approved as Pondimin for weight management in adults, but it was withdrawn from marketing for reasons of safety in 1997 due to an association with valvular heart disease (VHD) and pulmonary arterial hypertension (PAH).

FEN is structurally unrelated to other drugs approved for the treatment of seizures. FEN is a substituted amphetamine analog postulated to exert anti-seizure properties by stimulating multiple 5-HT receptor sub-types.

DS is a rare, severe, refractory epilepsy syndrome with onset in early childhood. DS is categorized as a developmental and epileptic encephalopathy, in which the epileptic activity is thought to contribute to developmental delay and behavioral abnormalities beyond the pathology of the underlying disease. DS is characterized by multiple seizure types that are generally refractory to the drugs typically used for the treatment of seizures. DS is associated with higher rates of mortality than those seen in the general epilepsy population, primarily because of a greater risk of status epilepticus and sudden unexpected death in epilepsy patients (SUDEP).

The applicant conducted two randomized, double-blind, placebo-controlled trials in DS patients 2 to 18 years of age with refractory seizures (Studies 1 and 1504-C2). Study 1 (N=117) compared 0.7 mg/kg/day and 0.2 mg/kg/day doses of FEN divided twice daily with placebo in patients who were not receiving stiripentol. Study 1504-C2 (N=85) compared a 0.4 mg/kg/day dose of FEN divided twice daily with placebo in patients who were receiving stiripentol and either clobazam, valproate, or both. The dose of FEN in Study 1504-C2 was based on the known ability of stiripentol to increase exposure to FEN when used concomitantly. The primary efficacy endpoint in both studies was the change from baseline in the frequency of convulsive seizures per 28 days during the combined 14-week (Study 1) or 15-week (Study 1504-C2) titration and maintenance periods (i.e., treatment period). The median longest interval between convulsive seizures was also assessed.

In Study 1 and Study 1504-C2, the reduction in convulsive seizure frequency per 28 days was statistically significantly greater for all dose groups of FEN compared to placebo. In Study 1, patients taking 0.2 and 0.7 mg/kg/day doses of FEN had 32% and 70% reductions in mean convulsive seizure frequency compared to placebo, respectively. In Study 1504-C2, patients taking a 0.4 mg/kg/day dose of FEN had a 60% reduction in mean convulsive seizure frequency compared to placebo. In both Study 1 and Study 1504-C2, FEN was also associated with a statistically significantly longer interval between convulsive seizures compared to placebo.

The most commonly observed adverse reactions in the two controlled trials that occurred with a greater incidence in FEN-treated patients than in placebo-

treated patients were in the central nervous system (e.g., somnolence and sedation, ataxia, falling) and gastrointestinal (e.g., decreased appetite, diarrhea, constipation, vomiting, decreased weight). The adverse event profile of FEN was largely consistent with many approved anti-epileptic drugs (AEDs).

VHD and PAH were not observed in the current development program in the setting of comprehensive monitoring for these risks; however, these risks (seen in the adult population treated with FEN when it was marketed for weight management) still remain significant. The risks of VHD and PAH will be managed by a REMS program (including baseline and periodic echocardiograms), addressed in labeling with a boxed warning, and characterized by a required postmarketing study. Additionally, the Warnings and Precautions section of labeling will describe the risks of decreased appetite and weight, somnolence and lethargy, suicidal behavior and ideation, withdrawal of seizure medications, serotonin syndrome, increased blood pressure, and glaucoma.

The risks associated with FEN treatment are acceptable, particularly given the strength of the findings of clinical efficacy in DS, which is a serious, debilitating, and life-threatening disorder.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Dravet syndrome (DS) is a severe form of childhood epilepsy that is characterized by early onset of refractory seizures of multiple types, frequent episodes of status epilepticus, and developmental arrest or regression. Patients typically present prior to 2 years of age (although the diagnosis may not be recognized until about age 2 years) with a variety of disabling seizure types and developmental delay. Cognitive impairment is regularly seen and may be partly caused by the seizures. Although the diagnosis of DS is made by clinical criteria, most patients with DS (about 80%) have mutations in the SCN1A gene, but the individual mutations vary widely. Seizures in patients with DS are generally refractory to anticonvulsant drugs, and freedom from seizures almost never occurs. Many patients experience fewer seizures in late adolescence and adulthood. Sudden unexplained death in epilepsy (SUDEP) and status epilepticus are more common in patients with DS than in most other childhood epilepsy syndromes, and increased mortality in DS patients (compared to the general population) is, in part, related to these events.	DS is a severe epilepsy syndrome that causes refractory seizures, cognitive impairment, and an increased risk of mortality related to seizures.

Current Treatment Options	In addition to the drugs commonly used off-label for the treatment of DS (clobazam, valproate, and topiramate), two drugs (cannabidiol and stiripentol) have been recently approved (June 2018 and August 2018, respectively) specifically for the treatment of seizures associated with DS.	There are only two other drugs approved for the treatment of seizures associated with DS.
Benefit	Two adequate and well-controlled efficacy trials were conducted in refractory DS patients with refractory seizures: Study 1 and Study 1504-2. The two studies were randomized, double-blind, placebo-controlled, parallel-group studies similar in design and consisted of Baseline, Titration, and Maintenance periods. Study 1 (N=117) compared 0.7 mg/kg/day and 0.2 mg/kg/day doses of FEN divided twice daily with placebo in patients who were not receiving stiripentol. Study 1504-C2 (N=85) compared a 0.4 mg/kg/day dose of FEN divided twice daily with placebo in patients who were receiving stiripentol and either clobazam, valproate, or both. The dose of FEN in Study 1504-C2 was based on the known ability of stiripentol to increase exposure to FEN when used concomitantly. Both studies used the change in the convulsive seizure frequency per 28 days during the Titration and Maintenance periods compared with the Baseline period as the primary efficacy endpoint. The proportion of patients with a 50% or greater reduction from Baseline in convulsive seizure frequency, and the longest interval between convulsive seizures, were the key secondary efficacy endpoints. In both trials, the reduction in convulsive seizure frequency per 28 days was statistically significantly greater for all dose groups of FEN compared to placebo. In Study 1, patients taking 0.2 and 0.7 mg/kg/day doses of FEN had 32% and 70% reductions in mean convulsive seizure frequency compared to placebo, respectively. In Study 1504-C2, patients taking a 0.4 mg/kg/day dose of FEN had a 60% reduction in mean convulsive seizure frequency compared to placebo. In both trials, greater percentages of FEN-treated patients had a 50% or greater reduction in seizures, and FEN was also associated with a statistically significantly longer interval between convulsive seizures compared to placebo.	This application has established that FEN is effective for the treatment of seizures associated with DS for patients age 2 years and above based on two adequate and well-controlled efficacy trials.

Risk and Risk Management	The most commonly observed adverse reactions in the two controlled trials that occurred with a greater incidence in FEN-treated patients than in placebo-treated patients were in the central nervous system (e.g., somnolence and sedation, ataxia, falling) and gastrointestinal (e.g., decreased appetite, diarrhea, constipation, vomiting, decreased weight). There was a dose-response for measured weight loss during the controlled trials with 2.4%, 12.8%, 18.6%, and 26.3% of patients in the placebo, and 0.2 mg, 0.4 mg, and 0.7 mg/kg/day FEN groups, respectively, having lost at least 7% of their baseline weight by the final visit of the controlled studies. Weight loss did appear to slow down significantly during an open-label safety study, suggesting that this effect waned over time or could be mitigated by increased feeding, change in diet, or even supplemental tube feedings. VHD and PAH were not observed in the current development program in the setting of comprehensive monitoring for these risks. Published literature, along with findings from the current safety database, suggest a potential for increased blood pressure with FEN use. Reports of hypertensive crises associated with FEN use have been published, but no such cases were observed in the current development program.	The common adverse event profile of FEN is largely consistent with many approved anti-epileptic drugs (AEDs). The risks of VHD and PAH (seen in the adult population treated with FEN when it was marketed for weight management) still remain significant. The risks of VHD and PAH will be managed by a REMS program with elements to ensure safe use (ETASU) (including baseline and periodic echocardiograms, and required patient education and caregiver and pharmacy certification), addressed in labeling with a boxed warning, and characterized by a required postmarketing study. The Warnings and Precautions section of labeling will describe the risks of decreased appetite and weight, somnolence and lethargy, suicidal behavior and ideation, withdrawal of seizure medications, serotonin syndrome, increased blood pressure, and glaucoma. The risks associated with FEN treatment are acceptable, particularly given the strength of the findings of clinical efficacy in DS, which is a serious, debilitating, and life-threatening disorder.

2. Background

This application provides data intended to support the effectiveness and safety of fenfluramine (FEN) for the treatment of seizures associated with Dravet syndrome (DS) in patients 2 years of age and older.

Fenfluramine

FEN is a substituted amphetamine analog that was approved in 1973, as Pondimin (fenfluramine HCl) tablets, for the treatment of obesity in adults (NDA 16618). It was withdrawn from the market for reasons of safety in 1997 due to an association with valvular heart valve disease (VHD) in patients who used the drug. Pulmonary arterial hypertension (PAH) has also been associated with FEN.

FEN is structurally unrelated to other antiepileptic drugs (AEDs). The precise mechanism by which FEN exerts its anticonvulsant effect in humans is unknown, but it is thought to act by stimulating multiple 5-HT receptor sub-types (i.e., 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C) resulting in the release of serotonin.

Epidiolex (cannabidiol) and Diacomit (stiripentol) are the only approved drugs for the treatment of seizures associated with DS. Epidiolex was approved in July 2018, and Diacomit was approved in August 2018. Most DS patients are not expected to have complete seizure control on these drugs, even in combination with other drugs commonly used off-label for DS (e.g., valproate, clobazam, and topiramate).

Dravet Syndrome

DS (previously known as severe myoclonic epilepsy of infancy) is characterized by refractory epilepsy with multiple seizure types, febrile seizures, frequent episodes of status epilepticus, and developmental arrest or regression. Onset of DS is typically before 2 years of age, with an initial presentation of seizures and developmental delay. Most, but not all, patients with the clinical syndrome have a mutation in the SCN1A gene affecting the α-subunit of the voltage-gated sodium channel.

DS is rare disorder categorized as a developmental and epileptic encephalopathy in which the epileptic activity is thought to contribute to developmental delay and behavioral abnormalities beyond the pathology of the underlying disease. The multiple seizure types that

are observed in DS are generally refractory to the drugs typically used for the treatment of seizures. DS is associated with higher rates of mortality than occur in the general epilepsy population, primarily related to a greater risk of status epilepticus and sudden unexpected death in epilepsy (SUDEP).

NDA 212102

This application provides efficacy and safety data from two randomized, double-blind, placebo-controlled trials in patients with DS patients (Studies 1 and 1504C2, discussed in Section 7 of this summary review).

In addition to the controlled safety data from these two trials, safety data were also provided from 2 other studies with DS patients (Studies 1503 and 1504C1, discussed in Section 8 of this summary review).

It was determined that information from published literature was necessary to inform the review of the hypertension risk associated with FEN (essential to support an approval action), leading to the review of this application under the 505(b)(2) pathway.

Significant Regulatory History Events for NDA 212102

A detailed regulatory history for the FEN drug development program is provided in the clinical review by Dr. Natalie Getzoff. The initial submission of NDA 212102 on February 5, 2019, resulted in the issuance of a refuse to file (RTF) letter (April 5, 2019) because of the applicant's failure to submit chronic nonclinical toxicity studies, the submission of incorrect SAS efficacy datasets, and the need to conduct an extensive data quality assessment to ensure the accuracy of trial results. During a subsequent Type A meeting (June 7, 2019), the applicant provided what appeared on face to be an acceptable quality assessment of how incorrect SAS efficacy datasets were inadvertently submitted. Additionally, it was determined that the lack of chronic nonclinical toxicity studies would be a review issue rather than an RTF issue for the planned resubmission. The applicant resubmitted the application on September 25, 2019.

As discussed in Section 7 of this summary review, the Office of Scientific Integrity (OSI) identified significant data reliability concerns in both the pivotal controlled trials related to the use of electronic seizure diaries (e-diaries), including extensive retrospective new seizure data entries and modifications of previously entered seizure data. One of the applicant's substantial submissions addressing these data reliability issues was accepted as a Major Amendment on February 25, 2020, which extended the PDUFA Action Date to June 25, 2020.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha R. Heimann. Dr. Heimann's review lists the entire OPQ team that was involved with the review of this application. Refer to the OPQ review for details of the product quality assessment.

The proposed product (an oral solution containing FEN) is a colorless, cherry-flavored solution containing 2.2 mg/mL FEN, as 2.5 mg/mL of fenfluramine hydrochloride.

Key review issues included stability of the drug during long-term storage and in use, qualification of a specified degradation product, adequacy of preservatives, palatability, and compatibility of product with dosing devices and feeding tubes. These were found to be acceptable. The microbial quality of the active pharmaceutical ingredient (API) and drug product were found to be adequate. The data were found to support a 36-month shelf-life for product stored at controlled room temperature and an in-use period of 95 days from bottle opening,

There were no outstanding issues identified in the OPQ review, and all manufacturing facilities for this product were found to be acceptable.

OPQ recommends approval.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. Ed Fisher, with Dr. Lois Freed performing the secondary review. The main findings and conclusions from the nonclinical reviews are discussed below.

FEN is a racemic compound, containing dexfenfluramine (d-FEN) and levofenfluramine (l-FEN), that is structurally different from other known AEDs. The mechanism of the anticonvulsant activity of FEN is not well-understood. FEN and its active metabolite, norfenfluramine may reduce seizures by acting as an agonist at specific serotonin receptors in the brain, including the 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C receptors, and also by acting on the sigma-1 receptor. From a safety standpoint, concern has focused on activity at 5-HT2B receptors, since that receptor subtype seems to be most important for the VHD associated with FEN that resulted in

its being taken off the market as a treatment for obesity for adults. The 5-HT1D and 5-HT2C were thought to be most important with respect to efficacy. 5-HT2B receptors are primarily expressed in the periphery, although there are some in the central nervous system (CNS), while 5-HT2C receptors are found primarily in the CNS. FEN demonstrated independent anticonvulsant activity in several animal models

In his review, Dr. Fisher notes that the applicant submitted published literature to address the chronic toxicity of FEN; however, none of these publications provided adequate information to support the application. Dr. Fisher further observes that the clinical review recommends approval based on the adequacy of the available human safety data along with appropriate safety warnings in labeling (including a boxed warning related to the risk of VHD and PAH) and the restrictions of a REMS program. Therefore, Dr. Fisher does not object to the approval of this NDA. The ongoing chronic toxicity studies will be submitted when the final study reports are available.

In her supervisory memo, Dr. Freed concurs with Dr. Fisher's assessment and recommendation. She also notes that the applicant submitted a standard battery of reproductive and developmental toxicology studies to the NDA on March 24, 2020.
Since this late submission did not allow sufficient time for a thorough review of these studies, she recommends that these reproductive and developmental toxicology be included as postmarketing requirements (PMRs) in the action letter in addition to PMRs for carcinogenicity studies in two species.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Jagan Parepally (clinical pharmacology reviewer), Dr. Angela Men (clinical pharmacology team lead), Dr. Jianghong Fan (physiologically-based pharmacokinetics reviewer), Dr. Xinyuan Zhang (physiologically-based pharmacokinetics team lead), Dr. Michael Bewernitz (pharmacometrics reviewer), and Dr. Atul Bhattaram (pharmacometrics team lead).

The following is a summary of the clinical pharmacology of FEN and review issues based on the OCP review.

Formulation: The to-be-marketed (TBM) 2.2 mg/mL oral solution formulation is identical to clinical trial formulation.

Active Moieties: The known active moieties in plasma are FEN and its metabolite norfenfluramine.

Absorption: FEN is well absorbed (the absolute bioavailability was 68% to 74%) following administration of the oral solution. The median FEN Tmax is 4 to 5 hours after multiple-dose administration. Co-administration with a high-fat meal showed no significant effect on the rate and the extent of absorption.

Distribution: Plasma protein binding of FEN is moderate (50%). The estimated volume of distribution (Vz/F) of FEN is 11.9 L/kg following oral administration in healthy subjects.

Metabolism: FEN is extensively metabolized in liver. More than 75% of FEN is metabolized to norfenfluramine prior to elimination, primarily by CYP1A2 (32%), CYP2B6 (42%), and CYP2D6 (46%). Other CYP enzymes involved to a minor extent are CYP2C9, CYP2C19, and CYP3A4/5. Norfenfluramine is then deaminated and oxidized to form inactive metabolites.

Elimination: The mean elimination half-life was 20 hours. Following oral administration radiolabeled dose, FEN (>90%) was eliminated in the urine as unchanged FEN, norfenfluramine, or other metabolites. FEN and norfenfluramine accounted for less than 25% of the total in urine and less than 5% is found in feces.

Dosage:

The OCP review concludes that FEN may be taken with or without food.

The recommended starting dose is 0.1 mg/kg twice daily (b) (4). The dose may be increased based on clinical efficacy and tolerability not less than every 4 days, to a maximum of 0.35 mg/kg twice daily (0.7 mg/kg/day) not to exceed a total daily dose of 26 mg.

Pharmacokinetic (PK) interactions have been observed when FEN is co-administered with stiripentol plus clobazam. The starting dose is 0.1 mg/kg twice daily, which can be increased based on efficacy and tolerability. The maximum daily maintenance dose of FEN for patients taking these medications is 0.2 mg/kg twice daily not to exceed a total daily dose of 17 mg.

The OCP review provides a detailed discussion regarding the fact that although, the applicant intended the dosing in Study 1504-C2 with concomitant stiripentol to approximate the exposures at the high-dose in Study 1, ultimately, exposures in Study 1504-C2 were higher. The data from Study 1 (0.7 mg/kg/day, with a maximum of 27 mg/day) and Study 1504-C2 (0.4 mg/kg/day, with a maximum of 17 mg/day), suggest that the concomitant use of stiripentol, with or without clobazam and valproate, resulted in an increase of FEN AUC by approximately 130% and a decrease in norfenfluramine exposure approximately 60%. The OCP review also discusses the fact that that these dose comparisons are not equivalent and the applicant's approach to modeling the impact of concomitant stiripentol and clobazam on FEN exposures at the same doses was inadequate. However, as the doses in Study 1504-C2 were determined to be safe and effective for the proposed indication by the clinical review, the OCP review agrees with the recommendation of dosing regimens as empirically evaluated in the development program, with a description of the known interactions in labeling.

Additional Drug-Drug Interactions: Concomitant administration of FEN did not significantly affect the PK of cannabidiol, stiripentol, clobazam, or valproate.

Renal Impairment: Few subjects with mild renal impairment were included in Phase 3 clinical trials. The OCP recommends that FEN not be used in patients with moderate and severe renal impairment and in patients undergoing hemodialysis.

Hepatic Impairment: FEN is extensively metabolized by the liver. Plasma drug concentrations may be affected in patients with significant hepatic impairment. No studies on the effect of hepatic impairment on the PK of FEN in adults or children were provided. Subjects with hepatic impairment were excluded from the Phase 3 clinical trials. Therefore, the OCP review recommends that FEN not be used in patients with hepatic impairment. A PMR will address the clinical PK of FEN in patients with varying degrees of hepatic impairment to determine appropriate dosing.

OCP recommends approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Xiangmin Zhang was the biometrics reviewer for this application, and Dr. Kun Jin was the biometrics team lead. Dr. Natalie Getzoff was the clinical reviewer for this application.

Study 1 and Study 1504-C2

The application contains data from two double-blind, randomized, placebo-controlled trials in support of the effectiveness of FEN for the treatment of seizures associated with DS; Study 1 and Study 1504-C2. Study 1 comprised data from two similarly designed trials; Study 1501 conducted in North America, and Study 1502, conducted in Europe and Australia. Due to slow recruitment during these respective trials, the Division agreed to the applicant's proposal that the first 120 consecutive randomized patients from both trials would constitute a combined analysis population referred to as Study 1.

Study 1 compared 0.7 mg/kg/day and 0.2 mg/kg/day doses of FEN divided twice daily (maximum dose of 26 mg/kg/day) with placebo in DS patients 2 to 18 years of age who were not receiving stiripentol. Study 1504-C2 compared a 0.4 mg/kg/day dose of FEN divided twice daily (maximum dose of 17 mg/kg/day) with placebo in DS patients 2 to 18 years of age who were receiving stiripentol and either clobazam, valproate, or both. The dose in Study 1504-C2 was based on a PK interaction with stiripentol, which increases the exposure to FEN. Note that the doses of FEN discussed in this summary review are expressed with respect to the fenfluramine dose, and not fenfluramine hydrochloride, which is referenced in some of the clinical reviews.

In both studies patients had to have a clinical diagnosis of DS and were inadequately controlled on at least one AED or other antiseizure treatment, including vagal nerve stimulation or a ketogenic diet. Both trials had a 6-week baseline period, during which patients were required to have a minimum of 6 convulsive seizures while on stable AED therapy. Convulsive seizures were defined as tonic, clonic, generalized tonic-clonic, tonic-atonic, secondarily generalized tonic-clonic, hemiclonic, and focal with observable motor signs. The baseline period was followed by randomization into a 2-week (Study 1) or 3-week (Study 1504-C2) titration period and a subsequent 12-week maintenance period, where the dose of FEN remained stable.

The primary efficacy endpoint in both studies was the change from baseline in the frequency of convulsive seizures per 28 days during the combined 14-week (Study 1) or 15-week (Study 1504-C2) titration and maintenance periods (i.e., treatment period). The primary efficacy analyses were conducted using the modified intent-to-treat (mITT) population, defined as all randomized patients who received at least one dose of study drug and for whom at least one week of seizure diary data were available. The primary endpoint was analyzed using an analysis of covariance (ANCOVA) model with treatment and age-group as factors, and log-transformed baseline convulsive seizure frequency as the covariate.

Efficacy Results

Studies 1 and 1504-C2 included 117 and 85 patients in the mITT populations, respectively. Demographic and baseline characteristics in both studies were balanced between treatment arms, with the average age of patients being approximately 9 years, a slight majority (52%) of patients being male, and 74% of patients being White. In Study 1, 98% of patients were taking between 1 and 4 concomitant AEDs. The most frequently used concomitant AEDs (in at least 25% of patients), were valproate (61%), clobazam (59%), and topiramate (25%). In Study 1504-C2, 100% of patients were taking between 2 and 4 concomitant AEDs. The most frequently used concomitant AEDs (in at least 25% of patients), were stiripentol (100%) (required by the protocol), clobazam (94%), and valproate (89%).

As demonstrated in Table 1, reproduced based on the biometrics review, in Study 1 and Study 1504-C2, the reduction in convulsive seizure frequency per 28 days was statistically significantly greater for all dose groups of FEN compared to placebo.

Table 1: Change in Convulsive Seizure Frequency During the Treatment Period in Patients with Dravet Syndrome (Study 1 and Study 1504-C2)

Convulsive Seizure Frequency (per 28 days)	**Placebo**	**FEN 0.2 mg/kg/day**	**FEN 0.7 mg/kg/day**	**FEN 0.4 mg/kg/day ±**
Study 1	**N=39**	**N=38**	**N=40**	**NA**
Baseline Period Median	29.4	18.1	18.7	NA
% Difference Relative to Placebo*		-37.1%	-70.0%	NA
p-value compared to placebo		0.043	<0.001	
Study 1504-C2	**N=42**	**NA**	**NA**	**N=43**
Baseline Period Median	11.5	NA	NA	15.0
% Difference Relative to Placebo*		NA	NA	-59.5%
p-value compared to placeb2				<0.001

*Derived from the primary analysis model
±All 0.4 mg/kg/day patients were also taking concomitant stiripentol, which increases the exposure of FEN.

Error! Reference source not found. and 2 display the percentage of patients by category of seizure response from baseline in convulsive seizure frequency (per 28 days) during the treatment period in Study 1 and Study 1504-C2, respectively.

Figure 1: Proportion of Patients by Category of Seizure Response for FEN and Placebo in Patients with Dravet Syndrome (Study 1)

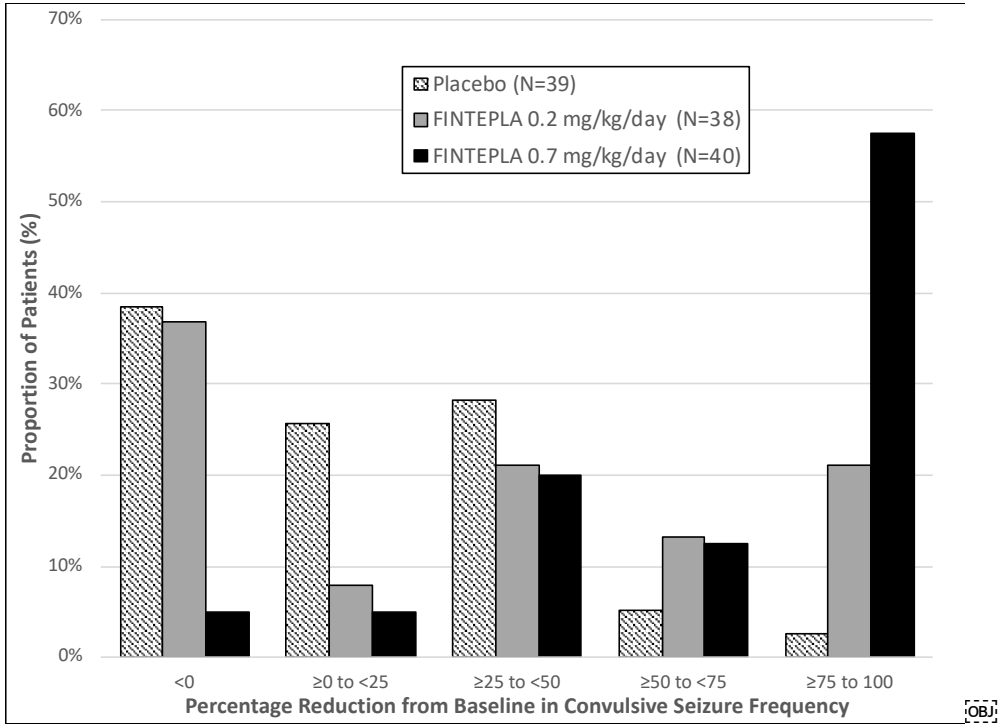
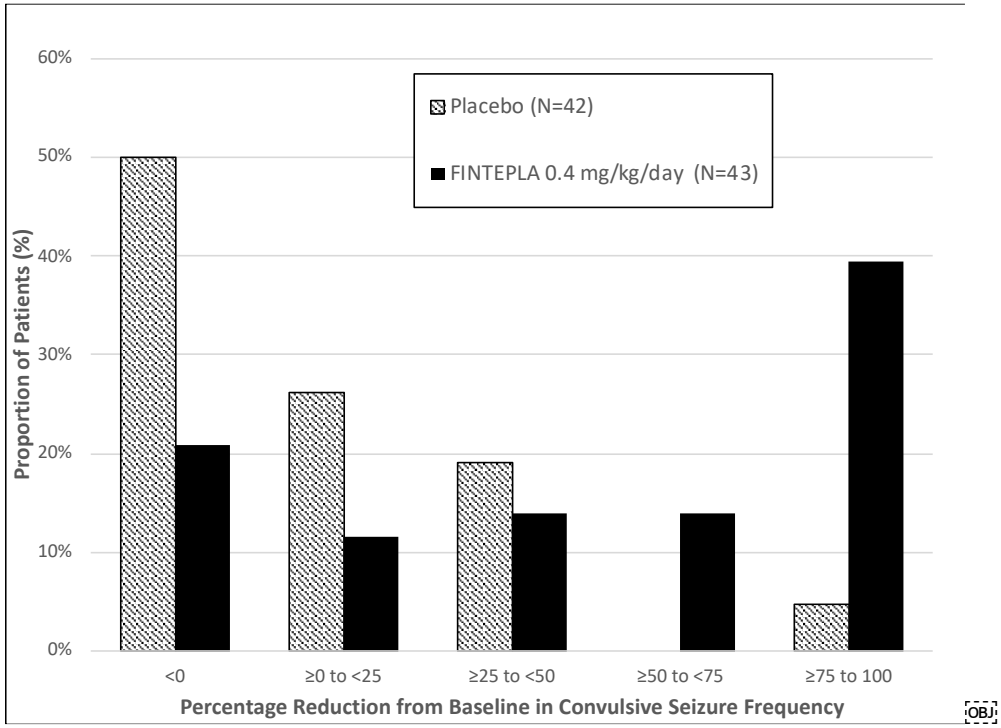


Figure 2: Proportion of Patients by Category of Seizure Response for FEN and Placebo in Patients with Dravet Syndrome (Study 1504-C2)



In Study 1, 3 of 40 (8%) patients in the FEN 0.7 mg/kg/day group and 3 of 38 (8%) patients in the FEN 0.2 mg/kg/day group reported no convulsive seizures during the 14-week treatment period, compared to 0 patients in the placebo group. In Study 1504-C2, 1 of 43

(2%) patients in the FEN 0.4 mg/kg/day group reported no convulsive seizures during the 15-week treatment period, compared to 0 patients in the placebo group.

Both Study 1 and Study 1504-C2 utilized electronic seizure diaries (e-diaries), which are relatively novel in AED efficacy trials, for the analysis of the efficacy endpoint data. Inspections conducted by the Office of Scientific Investigations (OSI) and the European Medicines Agency (EMA) (shared under a memorandum of understanding) identified significant potential data reliability concerns related to the e-diary data. These included extensive retrospective new seizure data entries and modifications of previously entered seizure data. The source data used by the sites in the retrospective data collection (e.g., paper diaries, calendars, capture forms) were either unavailable for review during the inspection or, if available, often demonstrated discrepancies when compared to the seizure dataset. These issues are likely a function of the novelty of use of e-diaries in trials (as opposed to any intentional trial misconduct); however, it was critical to understand the impact of these findings on the efficacy results.

Dr. Zhang reanalyzed the primary and key secondary efficacy endpoints using "pre-edited" datasets in which the seizure and end-of-day diary data were reverted to values consistent with what they would have been prior to the retrospective edits (additions and modifications). These datasets were obtained after multiple rounds of information requests (IRs) with the applicant, leading to a 3-month extension of the review timeline to allow for sufficient time to evaluate. Following these conservative re-analyses, Dr. Zhang concluded that the efficacy findings were essentially unchanged and remained highly statistically in favor of treatment with FEN.

Key Secondary Endpoints

As. Dr. Zhang notes in her review, Studies 1 and 1504-C2 prespecified a hierarchical examination of the same two key secondary endpoints, listed below.

- Proportion of patients with a 50% or greater reduction in seizures
  During the treatment period in Study 1, the proportion of patients with a reduction of 50% or more in their baseline convulsive seizure frequency was greater in the 0.7 mg/kg/day and 0.2 mg/kg/day FEN groups, compared with the placebo group. The odds ratios (ORs) were statistically significant for both the 0.7 mg/kg/day group (OR = 29.2; $p < 0.001$) and the 0.2 mg/kg/day group (OR =6.9; p=0.007). In Study 1504-C2, the proportion of patients with a reduction of 50% or more in their baseline convulsive seizure frequency was also greater in the FEN 0.4 mg/kg/day group, compared with the placebo group (OR = 25.4; $p < 0.001$).

- Median longest interval between convulsive seizures
  The longest interval between convulsive seizures measured the maximum of the number of days between consecutive convulsive seizures. In Study 1, the median longest intervals between convulsive seizures were 20.5 days and 13.0 days for the FEN 0.7 mg/kg/day and 0.2 mg/kg/day groups, respectively, compared to placebo (8.0 days). These results were statistically significant in favor of FEN ($p<0.001$ and 0.043, respectively). In Study 1504-C2, the median longest intervals between convulsive seizures were 12.0 days and 17.0 days for the placebo group and FEN 0.4 mg/kg/day group, respectively; this difference was statistically significant ($p<0.001$).

  Dr. Zhang's review discusses the impact of missing data on this endpoint as well as the results of a more conservative imputation approach than was used by the applicant. Her review concludes that even with this more conservative approach, the results of the analyses of this endpoint remain highly statistically significant in favor of FEN.

Efficacy Conclusion:

Both Study 1 and Study 1504C2 are adequate and well-controlled trials. There were concerns regarding the data generated by the e-diaries to capture seizure data in both trials. Specifically, there was very limited access to source data, and a significant number of entries were revised retrospectively. These issues were likely the result of inexperience in terms of the use of e-diaries in AED efficacy trials. The impact of these results was evaluated by a conservative re-analysis using datasets based on the original seizure entries. The results of the original efficacy analyses, and these conservative re-analyses, yield similarly strong findings that support the conclusion that FEN is highly effective for the treatment of seizures associated with DS 2 years of age and older.

8. Clinical - Safety

Dr. Natalie Getzoff performed the clinical safety review of this application. Dr. Shetarra Walker, from the Division of Cardiology and Nephrology (DCN), provided a consultative review of the cardiovascular safety data in this application.

To support the safety of FEN in the treatment of seizures associated with DS in patients 2 years of age and older, the applicant has provided safety data primarily from the two controlled efficacy trials (Study 1 and Study 1504C2) and one long-term open-label extension (OLE) safety study (Study 1503), as well as from a small open-label PK study (Study 1504C1).

(b) (4)

Table 2 summarizes the completed clinical studies that contributed to the safety review of this application. Studies 1 and 1504-C2 were pooled and served as the primary basis of the safety evaluation. Three early-phase studies that enrolled healthy volunteer subjects could not be pooled with the safety data derived from DS patients and did not provide any additional findings necessary for the conduct of this safety review.

Table 2 Completed Clinical Studies Contributing to the Safety Evaluation

Trial Identity	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 Safety							
Study 1 / Study 1501 Study 1502	Randomized, double blind, placebo-controlled	FEN oral solution 0.2 or 0.8 mg/kg/day (divided twice daily) vs equal volume of placebo. Titration: Initial dose for both FEN groups: FEN 0.2 mg/kg/day. For 0.8 mg/kg/day group increased to 0.4 mg/kg/day on day 5 and to 0.8 mg/kg/day on day 9.	Primary: Change in the mean convulsive seizure frequency (MCSF) per 28 days during the titration + maintenance (T+M) periods compared with the baseline period for the 0.8 mg/kg/day group. Key secondary endpoints: • Change in the MCSF per 28 days during treatment (T+M) compared with the baseline period for the 0.2 mg/kg/day group. • The proportion of subjects who achieve a ≥ 50% reduction from	Baseline: 6 weeks Titration: 2 wks Maintenance: 12 wks Taper/ Transition: 2 weeks	173 screened 119 randomized FEN 0.8 mg/kg/day: 40 FEN 0.2 mg/kg/day: 39 PBO: 40 Screen failures: 54	2-18 years with a clinical diagnosis of DS and refractory seizures, ≥ 6 convulsive seizures during baseline period while on ≥ 1 AED at a stable dose for ≥ 4 weeks. No patients taking concomitant STP	38 centers in 10 countries: USA (16), GBR (5), DEU (7), ITA (4), AUS, (2), BEL (1), DEN (1), CAN (1), ESP (1)

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			Baseline in convulsive seizure frequency (both dose groups). • Comparison between treatment and placebo groups in the longest convulsive seizure-free interval during T+M.				
Study 1504c2	Randomized, double blind, placebo-controlled	FEN oral solution 0.5 mg/kg/day (divided BID) vs equal volume of placebo. Titration: Initial dose FEN 0.2 mg/kg/day, increased to 0.4 mg/kg/day on day 8 and to 0.5 mg/kg/day on day 15.	Primary: Change in the mean convulsive seizure frequency (MCSF) per 28 days during T+M periods compared with the baseline period. Key secondary endpoints: • The proportion of subjects who achieve a ≥ 50% reduction from Baseline in convulsive seizure frequency (both dose groups). • Comparison between treatment and placebo groups in the longest convulsive seizure-free interval during T+M.	Baseline: 6 weeks Titration: 2 wks Maintenance: 12 wks Taper/ Transition: 2 weeks	115 screened 87 randomized FEN 0.5 mg/kg/day: 43 PBO: 44 Screen failures: 28	2-18 years with a clinical diagnosis of DS and refractory seizures, ≥ 6 convulsive seizures during baseline period while on ≥ 1 AED at a stable dose for ≥ 4 weeks. All patients taking concomitant STP	25 centers in 7 countries: USA (5), GBR (4), DEU (2), FRA (7), NLD, (2), CAN (2), ESP (3)*
Study to Support Safety							
Study 1503	Open-label, uncontrolled, long-term safety	FEN oral solution Flexible dosing 0.2-0.8 mg/kg/day (divided BID)	Primary: Assess the long-term safety and tolerability of FEN.	3 years	232 enrolled	2-18 years with a clinical diagnosis of DS and refractory seizures, enrolled into Studies 1, 1504-C1, or 1504-C2.	54 centers in 11 countries: USA (19), GBR (6), DEU (7), FRA (5), NLD, (2), CAN (2), ESP (3), ITA (6), BEL (1), AUS (3), DEN

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
							(1)*
Other Studies Pertinent to the Review of Safety							
Study 1504c1	Multicenter, open-label, partially randomized, multiple dose, PK study	1) Regimen 1: CLB + VPA + FEN 0.2 mg/kg; 2) Regimen 2: CLB + VPA + FEN 0.4 mg/kg; 3) Regimen 3: CLB + VPA + STP + FEN 0.2 mg/kg.	• Assess the PK profile of FEN (single oral dose) with CLB + VPA or with CLB + VPA + STP in subjects ages 2 to 18 years of age with Dravet syndrome, via the use of summary statistics • Model PK of FEN in single-dose regimens using FEN/norFEN concentration-time data	Transition: 2 weeks OLE: 6 months	20 screened 18 randomized Regimen 1: 3 Regimen 2: 5 Regimen 10	2-18 years with a clinical diagnosis of DS and refractory seizures, CLB, VPA, and STP at a stable dose for ≥ 4 weeks.	

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

Overall Patient Exposure:

The total number of unique DS patients who were exposed to FEN during the current development program prior to the cutoff date for the 120-day safety update was 341, including 312 patients treated for more than 6 months, 284 patients treated for more than 1 year, and 138 patients treated for more than 2 years.

In placebo-controlled trials of patients with DS, 122 patients were treated with FEN. The duration of treatment in these trials was 16 weeks (Study 1) or 17 weeks (Study 1504-C2).

In the context of a rare disease such as DS, these exposures are adequate to allow for a clinical safety review of the application.

Deaths:

Four deaths were reported during the development program, all attributed to SUDEP. One death occurred during the blinded phase of

(b) (4) and the treatment allocation for that patient remains blinded. The other three deaths occurred during Study 1503 (open-label, long-term safety). SUDEP is more commonly observed in patients with DS than in childhood epilepsy in general. It is not possible to attribute the deaths to FEN.

We agree with Dr. Getzoff's conclusion that the incidences of death (and SUDEP) observed are consistent with the expected rates in patients with DS.

Serious Adverse Events:

The overall incidence of treatment-emergent SAEs was 10.7% in the controlled safety population with similar incidences in the pooled FEN group (9%) as compared to the placebo group (12%). The most-frequently reported SAEs in the pooled FEN group were status epilepticus (4, 3.3%) and somnolence (3, 2.5%). In the placebo patients, seizure (6, 7.1%) was the most frequently seen SAE. Each remaining SAE was reported by only 1 or 2 patients.

The nature and frequency of the observed SAEs are similar to those reported in other trials in pediatric patients with refractory epilepsy.

Discontinuations Due to Adverse Events:

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

Treatment-Emergent Adverse Events (TEAEs) of All Severities:

Table 3 lists the adverse reactions that were reported in 5% or more of patients treated with FEN and at a rate greater than those on

placebo during the titration and maintenance phases of Study 1 and Study 1504-C2.

Table 3: Adverse Reactions in 5% or More of Patients Treated with FEN and Greater Than Placebo in Placebo-Controlled Trials

	FEN Dose Group			
	Study 1		Study 1504-C2	
	0.2 mg/kg/day	0.7 mg/kg/day	0.4 mg/kg/day	Combined Placebo Group
	N=39 %	N=40 %	N=43 %	N=84 %
Decreased appetite	23	38	49	8
Somnolence, sedation, lethargy	26	25	23	11
Diarrhea	31	15	23	6
Constipation	3	10	7	0
Abnormal echocardiogram[(1)]	18	23	9	6
Fatigue, malaise, asthenia	15	10	30	5
Ataxia, balance disorder, gait disturbance	10	10	7	1
Abnormal behavior	0	8	9	0
Blood pressure increased	13	8	0	5
Drooling, salivary hypersecretion	13	8	2	0
Hypotonia	0	8	0	0
Rash	8	8	5	4
Blood prolactin increased	0	5	0	0
Chills	0	5	2	0
Decreased activity	0	5	0	1
Dehydration	0	5	0	0
Insomnia	0	5	5	2
Pyrexia	15	5	21	14
Stereotypy	0	5	0	0
Upper respiratory tract infection	21	5	7	10
Vomiting	10	5	5	8
Weight decreased	13	5	7	1
Croup	5	3	0	1
Ear infection	8	3	9	5
Gastroenteritis	8	3	2	0

Increased heart rate	5	3	0	2
Irritability	0	3	9	2
Rhinitis	8	3	7	2
Tremor	3	3	9	0
Urinary incontinence	5	3	0	0
Decreased blood glucose	0	0	9	1
Bronchitis	3	0	9	1
Contusion	5	0	0	0
Eczema	0	0	5	0
Enuresis	5	0	0	0
Fall	10	0	0	4
Headache	8	0	0	2
Laryngitis	0	0	5	0
Negativism	5	0	0	0
Status epilepticus	3	0	12	2
Urinary tract infection	5	0	5	0
Viral infection	0	0	5	1

(1) Consisted of trace and mild mitral regurgitation, and trace aortic regurgitation, which are considered physiologic and often observed in normal healthy children and adults.

This pattern of TEAEs is largely consistent with those observed with many approved AEDs.

As discussed in Section 5 of this review, although the exposures to FEN in Study 1504-C2, in the setting of concomitant stiripentol use, were intended to approximate those at the 0.7 mg/kg/day dose in Study 1 without such use, the data from the development program suggested that the exposures were approximately 130% higher in Study 1504-C2. As Table 3 indicates, the incidences of some TEAEs were notably higher in Study 1504-C2 (e.g., fatigue, malaise, asthenia); however, the overall pattern of TEAEs remains acceptable and generally similar between these doses. In addition, the dosing recommendation in labeling will be based on efficacy and tolerability. Therefore, despite these differences in exposures, dosing instructions in labeling should empirically reflect those used in the development program.

Two patients were reported as exhibiting suicidality during the development program. One patient in the FEN 0.4 mg/kg/day group in Study 1504-C2 was reported to be exhibiting self-injurious behavior without suicidal intent at baseline and all visits through OLE Month 18. One patient reported suicidal ideation during (b) (4) (treatment allocation remains blinded) which persisted (reported as "mildly") into the OLE study. These particular findings do not raise clinical concerns with respect to a relationship with FEN exposure.

Safety Concerns of Special Interest:

Cardiovascular risk and decreases in weight and appetite were specifically evaluated as safety concerns of special interest.

Cardiovascular Risk

Cardiovascular risk was of special interest due to the FEN-associated VHD and PAH observed when FEN was marketed for treatment of obesity. Both Dr. Shetarra Walker's DCN consultative review and Dr. Getzoff' s clinical safety review provide detailed discussions of the history of cardiovascular findings associated with FEN.

Dr. Walker's review discusses the prospective cardiovascular safety monitoring (i.e., based on echocardiogram [ECHO] and ECG monitoring) that was conducted in the current development program. ECHOs and ECGs were read by two blinded central board-certified cardiologists with adjudication by a third in the event of a discrepancy. The focus of the ECHO evaluations was the change from baseline in the regurgitation "score" for the mitral and aortic valves at each time-point and the development of clinically meaningful changes in valve regurgitation or PAH (the details of which are provided in Dr. Walker's review). The following table, reproduced from Dr. Walker's review, summarizes the schedule of ECH and ECHO assessments in the development program.

Table 4: Schedule of ECG and ECHO Assessments

Study 1		(b) (4)	Study 1503		Study 1504 C1		Study 1504 C2	
ECHO	ECG		ECHO	ECG	ECHO	ECG	ECHO	ECG
Screening			Screening		Screening		Screening	
			Month 1	Month 1				Day -1
	Day 1		Month 3	Month 3				
Week 6	Week 6		Month 6	Month 6	Week 6	Week 6	Week 6	Week 6
Week 14	Week 14		Month 9	Month 9	Week 12	Week 12	Week 12	Week 12
			Month 12	Month 12	Week 26	Week 26		
			Month 15	Month 15				
			Month 18	Month 18				
			Month 21	Month 21				
Post- treatment follow-up 3 months								
Post-treatment follow-up 6 months								

Source: Adapted from Sponsor Table 1, CV ISS SAP, p17 of 34

Dr. Walker comments that FDA criteria for VHD, moderate or worse mitral regurgitation and mild or worse aortic regurgitation, were described in a Centers for Disease Control and Prevention Morbidity and Mortality Report published in 1997 on cardiac valvulopathy associated with exposure to FEN or dexfenfluramine.

ECG Findings

A thorough QT (tQT) trial was conducted in healthy volunteer subjects and evaluated exposures at 4-times the maximum recommended dose for the current indication. Dr. Walker's review concludes that this trial suggests no abnormal effect of FEN on cardiac rhythm; a finding consistent with the ECG data derived from the trials in DS patients.

ECHO Findings

Valvular Heart Disease (VHD)

Dr. Walker notes that 1648 ECHOs reported in this application were performed in 280 unique patients, with a mean number of 5.9 ECHOs per patient and a range of study duration between 63 to 823 days. Dr. Walker concludes that no patient developed VHD of any cardiac valve at any timepoint during the trials. She comments that all but one patient with MR had a trace finding, with the other having mild MR. AR was rare, and no more severe than trace. Dr. Walker comments that as trace to mild MR and trace AR are not clinically significant, as described in the FDA-definition of VHD, she has no clinical concern about these findings.

Longer duration of treatment appeared to be a risk factor for development of FEN-associated VHD when FEN and dexfenfluramine were used to treat obesity. The impact of drug exposure on development of VHD was not as clear when they were used as anorectic agents, although at least one study did suggest a correlation; however, there are inadequate drug-exposure data between adults and children to allow for an understanding of how exposures in pediatric patients would compare to those in obese adults.

Pulmonary Arterial Hypertension (PAH)

Pulmonary arterial systemic pressure (PASP) is an ECHO parameter used to screen for PAH. PASP can only be estimated from patients with measurable tricuspid regurgitation (TR) velocity jets. Dr. Walker agrees with the applicant's assertion that there was no evidence of PAH in the DS patients based on evaluable PASP estimates. She also concludes that the inability to estimate PASP in roughly half of the patients because of an absent or inadequate TR jet velocity is not surprising and not clinically concerning.

As with VHD, Dr. Walker notes that it is unclear how prolonged treatment duration or drug exposure relate to the overall risk of PAH, or if other predisposing factors also may play a role.

Cardiovascular Risk Conclusions

Although neither VHD nor PAH have been observed to date in the current development program, both of these disorders have been associated with FEN and thus patients with DS who are prescribed FEN are at risk of developing FEN-associated VHD or PAH. Many of the previously documented cases of FEN-associated VHD or PAH were asymptomatic and only 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.

Regular ECHO monitoring for VHD and PAH will be required to ensure the safe use of FEN in clinical practice. An ECHO must be performed prior to starting FEN, at 6-month intervals during treatment, and 3- to 6-months following the discontinuation of treatment, regardless of the presence of symptoms. Because ECHO monitoring is necessary for identifying VHD or PAH, a REMS with elements to ensure safe use (ETASU) will be necessary, as is a boxed warning. Section 14 of this review contains further details on the REMS components.

A postmarketing study based on patients enrolled in a REMS registry to better understand any association of VHD and PAH associated with treatment will also be required. Additionally, enhanced pharmacovigilance will also be requested to ensure closer postmarketing surveillance of cases of VHD and PAH. See Section 14 of this review for additional details.

Decreased Weight and Appetite

Decreases in appetite and weight were observed more frequently in the pooled FEN group (37% and 8%, respectively) than in the placebo group (8% and 1%, respectively). There was no clear dose-response for these findings, with a greater frequency of reports of decreased weight in the 0.2 mg/kg/day FEN group compared to the 0.4 and 0.7 mg/kg/day FEN groups, and the greatest frequency of decreased appetite in the 0.4 mg/kg/day FEN group (however, as noted previously, this dose resulted in exposures similar to the 0.7 mg/kg/day dose in the absence of concomitant stiripentol). Decreased appetite is especially notable because of the overall frequency of the event and the high-risk difference (28.6%). There was a dose-response for measured weight loss during the controlled trials with 2.4%, 12.8%, 18.6%, and 26.3% of patients in the placebo, and 0.2 mg, 0.4 mg, and 0.7 mg/kg/day FEN groups, respectively, having lost at least 7% of their baseline weight by the final visit of the controlled studies. Weight loss did appear to slow down significantly during the OLE study, suggesting that this effect waned over time or could be mitigated by increased feeding, change in diet, or even supplemental tube feedings. There appeared to be a potentially synergistic effect of stiripentol and FEN on appetite, as the incidence of decreased appetite in the 0.4 mg/kg/day FEN group (49%) was notably greater than that in the 0.2 mg/kg/day (23%) and 0.7 mg/kg/day (38%) FEN groups. Five of the seven patients in the placebo group who experienced decreased appetite were on concomitant stiripentol.

Laboratory Findings:

Examination of adverse events and clinical chemistry laboratory values reveals no evidence of a hepatotoxicity signal. There were no cases of drug-induced liver injury. No patient met Hy's law criteria. No patients discontinued treatment due to liver function test

(LFT) abnormalities or liver dysfunction.

Examination of hematology parameters revealed small decreases in the mean and median platelet counts from baseline in all FEN groups compared to placebo, although the mean and median values remained within the normal reference ranges. There was no dose response seen during the controlled trials with change from baseline of platelet counts. Rare TEAEs for thrombocytopenia or decreased platelet counts were reported but no changes to drug dosing occurred as a result of these TEAEs or laboratory findings.

Vital Signs:

There were no clinically significant differences in heart rate or body temperature between the FEN arm and placebo-arms of the two controlled studies.

Blood Pressure

As Dr. Getzoff details in her review, there have been reports in published literature of hypertension, including hypertensive crisis, in patients taking FEN, as well as literature describing the mechanism by which FEN and its active metabolite, norfenfluramine, may cause elevated blood pressure. During the controlled clinical studies, there was a greater incidence of hypertension or elevated blood pressure in patients in the pooled FEN group (8.2%) compared to that in the pooled placebo group (4.8%), although there was no dose-effect. Because of the plausible mechanism, reports of hypertensive crisis (including one positive rechallenge) in the published literature, and higher rates of hypertension in the pooled FEN group compared to placebo, this adverse effect will be described as a warning in labeling.

Overdosage:

There were no reports of FEN overdose during the FEN clinical trials, however, there have been a number of reports of overdose of FEN in the published literature, 10 of which were fatal. Because of the severity of some of the cases, the number of fatal cases, the high percentage of overdose in pediatric patients, and the short time to death in some cases, the Overdosage section of the prescribing information will reflect this information.

Safety Conclusion:

The adverse event profile of FEN is consistent with that of many approved AEDs.

FEN's most serious safety concern is the risk of developing VHD and/or PAH based on an association with these findings when FEN was marketed in adults for weight management. Although no cases of VHD or PAH have been reported to date in the current development program, FEN-associated VHD and PAH remain known risks to DS patients. It is uncertain the impact that longer durations of treatment may have on these risks. Additionally, the comparability of exposures in pediatric patients with those in obese adults with respect to these risks in also unknown.

In order to be prescribed FEN, all patients will be required to enroll in a REMS with ETASU. All patients must have a baseline ECHO prior to starting the drug, follow-up ECHOs every 6-months during treatment, and an ECHO 3- to 6-months following treatment discontinuation. As part of the REMS program, all patients will also be enrolled in a registry to gather additional information regarding any incident cases of either VHD or PAH. The REMS will also include mandatory patient education and prescriber and pharmacy certification.

Labeling will include a boxed warning regarding the risks of VHD and PAH. Additionally, the Warnings and Precautions section of labeling will describe the risks of decreased appetite and weight, somnolence and lethargy, suicidal behavior and ideation, withdrawal of seizure medications, serotonin syndrome, increased blood pressure, and glaucoma.

We agree with Dr. Getzoff that the risks associated with FEN are acceptable, given the demonstrated benefit of significantly improved seizure control for the DS patient population.

9. Advisory Committee Meeting

This application was not referred to an Advisory Committee for review because the clinical trial designs were acceptable, the efficacy findings were clear, and the safety profile was acceptable in light of the serious nature of the disease being treated. Labeling (and a REMS program focused on the VHD and PAH risks) will make prescribers fully aware of the risks associated with treatment, allowing them to inform patients and decide whether to use the drug.

10. Pediatrics

The studies for DS were conducted in a pediatric population down to two years of age. Because the product has orphan designation for DS, the Pediatric Research Equity Act (PREA) is not triggered.

11. Office of Scientific Integrity (OSI) Review

Dr. Cheryl Grandinetti's was the OSI reviewer. Her review provides a complete discussion of OSI's findings. Please see Section 7 of this summary review for a discussion of the inspection findings related to the use of e-diaries in the development program. Other inspection-related issues included non-reporting of protocol deviations, misclassification of major protocol deviations as minor, and inadequate drug accountability records.

12. Other Relevant Regulatory Issues

- No Good Clinical Practice (GCP) issues were identified in Dr. Getzoff' s clinical review.
- Dr. Getzoff concludes in her clinical review that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.
- The Controlled Substance Staff review (Reviewers Edward Hawkins, PhD and Shallian Bansil, PhD) determined that FEN does not have demonstrable abuse potential but will remain controlled in Schedule IV at the time of the NDA approval because of its previous regulatory history when it was marketed for the treatment of obesity. Section 9 of labeling will therefore indicate that FEN is a Schedule IV substance under the Controlled Substance Act.
- The Division of Pharmacovigilance I (DPV I) (Reviewer Karen Long, PharmD and Team Leader Allen Brinker, MD, MS) reviewed the published literature and identified 55 reported cases of overdose with FEN. As discussed in Section 8 of this summary review, this information informed the Overdosage section in labeling.
- DMEPA (Safety Evaluator Beverly Weitzman, PhD and Team Leader Briana Rider, PharmD, CPPS) reviewed labels and labeling including the Instructions for Use (IFU) making recommendations to reduce potential medication errors.

13. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

14. Postmarketing Recommendations

Risk Evaluation and Management Strategy (REMS)

The Division of Risk Management (DRM) review (Reviewers Carlisha Gentles, PharmD; Anahita Tavakoli, MA; and Charlotte Jones, MD, PhD, MDPH and Team Leader Laura Zendel, PharmD) concluded that a REMS is necessary for FEN due to the risk of VHD and PAH. The review indicates that the REMS requirements should include prescriber certification (ETASU A), pharmacy certification (ETASU B), safe use conditions to include patient counseling and enrollment (ETASU D), monitoring (ETASU E), a REMS registry (ETASU F), and a communication plan.

The REMS program is referred to as the REMS and includes the following components.

- Prescribers must be certified by enrolling in the FINTEPLA REMS program.
- Prescribers must counsel patients about the risk of VHD and PAH, how to recognize signs and symptoms of VHD and PAH, the need for baseline (pretreatment) and periodic cardiac monitoring via echocardiogram during treatment (every 6 months and 3 to 6 months following the discontinuation of treatment), and cardiac monitoring after treatment.
- Patients must enroll in the REMS program and comply with ongoing monitoring requirements
- The pharmacy must be certified by enrolling in the REMS program and must only dispense to patients who are authorized to receive treatment.
- Wholesalers and distributers must only distribute to certified pharmacies.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following studies are recommended as PMRs:

1. A fertility and early embryonic development study of fenfluramine in rat.

2. An embryofetal development study of fenfluramine in rat.

3. An embryofetal development study of fenfluramine in rabbit.

4. A pre- and postnatal development study of fenfluramine in rat.

5. A (b) (4) carcinogenicity study of fenfluramine in mouse.

6. A 2-year carcinogenicity study of fenfluramine in rat.

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 Fintepla (fenfluramine) during pregnancy. Provide a complete protocol that includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (b) (4) (b) (4) measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring as well as plans for comprehensive data analysis and yearly reporting.

8. A prospective observational registry study in epilepsy patients taking Fintepla using data from the REMS Registry and additional data beyond what is collected in the REMS Registry. The primary objectives are to characterize the risks of the development of symptomatic or asymptomatic VHD and/or PAH. This includes recruiting an adequate number of patients to assess the incidence of VHD and PAH, to identify risk factors for VHD and PAH, and to evaluate the impact of duration, dose-exposure, and cumulative exposure on the development of VHD and PAH. Evaluation should include the assessment of echocardiographic data; patients in the study should be evaluated with echocardiograms at baseline and every six months for five years, or until the last echocardiogram following interruption of Fintepla treatment.

9. A clinical pharmacokinetic trial to determine an appropriate dose of Fintepla (fenfluramine) to minimize toxicity in patients with varying degrees of hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

The timetables for draft protocol submission, final protocol submission, study completion, and final report submission for each of the PMRs are specified in the action letter.

Enhanced pharmacovigilance for cases of VHD and PAH will should include the following:

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

15. Recommended Comments to the Applicant

See action letter.

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/

PHILIP H SHERIDAN
06/25/2020 12:27:14 PM

NICHOLAS A KOZAUER
06/25/2020 06:12:36 PM