CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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<u>OTHER REVIEW(S)</u>

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	June 29, 2020
Reviewer:	Silvia Perez-Vilar, PharmD, PhD Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Fenfluramine-associated Valvular Heart Disease and Pulmonary Arterial Hypertension
Drug Name(s):	FINTEPLA (Fenfluramine hydrochloride, ZX008)
Application Type/Number:	NDA 212102
Submission Number:	212102/01
Applicant/sponsor:	Zogenix, Inc.
OSE RCM #:	2020-953

The original ARIA memo was dated June 23, 2020. This version, dated June 29, 2020, was amended to include "Assess a known serious risk" as FDAAA purpose (per Section 505(o)(3)(B)) to make it consistent with the approved labeling. The PMR development template refers to the original memo, dated June 23, 2020.

Reference ID: 4630019

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type		
-Initial		
-Interim		
-Final	X	X
Source of safety concern		
-Peri-approval	X	X
-Post-approval		
Is ARIA sufficient to help characterize the safety concern?		
Safety outcome	Valvular heart disease (VHD)	Pulmonary arterial hypertension (PAH)
-Yes		
-No	X	X
If "No", please identify the area(s) of concern.		
-Surveillance or Study Population	X	X
-Exposure		
-Outcome(s) of Interest	X	X
-Covariate(s) of Interest	X	X
-Surveillance Design/Analytic Tools		

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1. BACKGROUND INFORMATION

1.1. Medical Product

Fenfluramine hydrochloride[1] (FINTEPLA, Zogenix, Inc.) is an amphetamine analogue that increases the extracellular levels of serotonin (5-HT) in nervous tissue.[2] FINTEPLA, an oral solution containing 2.2 mg/mL fenfluramine equivalent to 2.5 mg/mL of the hydrochloride salt, is a new formulation of a previously approved product for the treatment of obesity, which was initially voluntarily withdrawn from the U.S. market in 1997 due to an association with valvular heart disease (VHD), then subsequently removed by the U.S. Food and Drug Administration (FDA) in 2015 (Food and Drug Administration 2015). Risk of pulmonary arterial hypertension (PAH) was the second reason for fenfluramine's withdrawal from the market (Abenhaim, Moride et al. 1996).[3] Fenfluramine is not currently marketed in any country.[4] It is a racemic compound of two stereoisomers, (+)-fenfluramine (dexfenfluramine) and (-)-fenfluramine (levofenfluramine), which are N-de-ethylated in the liver to form the main metabolites, (+)- and (-)-norfenfluramine (Rothman and Baumann 2009).

The new proposed indication is the treatment of seizures associated with Dravet syndrome (DS) in patients two years of age and older. DS, previously known as severe myoclonic epilepsy of infancy, is a severe developmental and epileptic encephalopathy characterized by the onset of prolonged febrile and afebrile seizures in infancy, and evolving to drug-resistant epilepsy with accompanying cognitive, behavioral, and motor impairment. It occurs in 1 in 15,700 births in the United States (Wu, Sullivan et al. 2015). Most cases are known to be caused by pathogenic variants in the sodium channel gene SCN1A (Steel, Symonds et al. 2017). Mortality during childhood and adolescence in patients with DS is about 15% (5–20%), primarily due to status epilepticus in the early years and sudden unexpected death in epilepsy patients in adolescence and adulthood (Akiyama, Kobayashi et al. 2010, Cooper, McIntosh et al. 2016). Older children and adults with DS tend to have improved seizure control, but moderate to severe intellectual disability and motor system abnormalities (Connolly 2016). Although FINTEPLA's mechanism of action is unclear and likely depends on multiple factors, it is theorized that it reduces seizures by increasing extrasynaptic serotonin levels through modulation of serotonin receptors (primarily 5-HT_{1A} receptors); however, there is some evidence that the fenfluramine molecule (and possibly its metabolites) reduce seizures by binding at specific receptors.[5] The proposed dosing regimen is initiation of dosing at 0.2 mg/kg/day and increase to 0.4 mg/kg/day on day 7 and 0.7 mg/kg/day (maximum) on day 14 in patients who are not on concomitant stiripentol. For patients taking concomitant stiripentol, the starting dose is 0.2 mg/kg/day with an increase to 0.4 mg/kg/day. The maximum daily dose for patients not on stiripentol is 26 mg and 17 mg for those on concomitant stiripentol.[6] The half-life is 20 hours following oral administration of FINTEPLA in healthy subjects.[7]

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[1] N-ethyl-α-methyl-3-(trifluoromethyl)phenethylamine hydrochloride.
[2] FINTEPLA (fenfluramine hydrochloride). Draft clinical review dated May 26, 2020. Division of Neurology 2. U.S. Food and Drug Administration
[3] Ibid.
[4] Ibid.
[5] Ibid.
[6] Ibid.
[7] Proposed FINTEPLA labeling dated June 25, 2020

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Prior to 2018, there were no approved treatments of seizures associated with DS in the United States. In June 2018, FDA approved cannabidiol (EPIDIOLEX, GW Research Ltd) for the treatment of seizures associated with Lennox-Gastaut syndrome or DS in patients two years of age and older.[8] In August 2018, FDA approved stiripentol (DIACOMIT, Biocodex SA) for the treatment of seizures associated with DS in patients two years of age and older taking clobazam.[9] There are also number of drugs used off-label as part of standard of care, including clobazam, valproic acid, topiramate, and levetiracetam. The ketogenic diet is typically used as an adjunct to pharmacologic treatment(s).[10]

1.2. Describe the Safety Concern

Summary of Historical Evidence for an Association of Fenfluramine and Dexfenfluramine with PAH and VHD at Higher Dosage Strengths When Used for Weight Loss

FDA approved PONDIMIN (fenfluramine hydrochloride) tablets 20 mg and PONDEREX (fenfluramine hydrochloride) capsules 20 mg in 1973, PONDIMIN sustained release tablets 60 mg in 1982, and REDUX (dexfenfluramine hydrochloride) capsules 15 mg in 1996, as prescription appetite suppressants for the treatment of obesity (Food and Drug Administration 2015). Both fenfluramine and dexfenfluramine appeared to act by affecting the metabolism of the neurotransmitter serotonin in the brain (Centers for Disease and Prevention 1997). Although FDA did not approve the combination with phentermine, another appetite suppressant approved in 1959, the "fen-phen" combination became very popular; in 1996 the total number of prescriptions for fenfluramine and phentermine in the United States exceeded 18 million (Connolly, Crary et al. 1997). In 1993, French investigators reported a cluster of cases of PAH among patients who had used derivatives of fenfluramine (Brenot, Herve et al. 1993). In a case-control study conducted in Europe and published in 1996, the use of anorexic drugs, mainly derivates of fenfluramine, was associated with an increased risk of PAH (Abenhaim, Moride et al. 1996). In 1997, U.S. cardiac ultrasonographers and clinicians described VHD in 24 women without history of cardiac disease who had been treated with the combination of fenfluramine and phentermine (Connolly, Crary et al. 1997). On the basis of prepublication notification of this finding, FDA issued a Public Health Advisory in which it requested that other cases be reported. Graham et al. described 28 additional U.S. cases, all in women, with a similar history of VHD in association with the use of a combination of fenfluramine and phentermine (Graham and Green 1997). FDA announced the voluntary withdrawal of fenfluramine and dexfenfluramine from the market on September 15, 1997. As of September 30, 1997, FDA had received 144 individual spontaneous reports involving fenfluramine or dexfenfluramine, with or without phentermine, in association with valvulopathy (Centers for Disease and Prevention 1997). A subsequent meta-analysis of potential cases (n=3,769) indicated that fenfluramine-associated valvular regurgitation was less common than initially reported, but still present in one of eight patients treated for more than 90 days (Sachdev, Miller et al. 2002). Other studies provided additional information, but

[8] EPIDIOLEX U.S. label dated December 12, 2018. Accessed on May 19, 2020, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365s002lbl.pdf
[9] DIACOMIT U.S. label dated August 20, 2018. Accessed on May 19, 2020, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206709s000,207223s000lbl.pdf
[10] See footnote 2

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the prevalence of VHD among obese patients not exposed to fenfluramine is not well-established because such individuals did not routinely have echocardiography prior to exposure, the relative risks of fenfluramine, alone or in combination with phentermine, as well as the effects of dose and duration of exposure, and the risk factors for fenfluramine-associated VHD are not well defined (Jick, Vasilakis et al. 1998, Khan, Herzog et al. 1998, Weissman, Tighe et al. 1998, Li, Serdula et al. 1999, Shively, Roldan et al. 1999). When given alone, phentermine has not been implicated in the pathogenesis of VHD. The suspected mechanism for fenfluramine-induced cardiac valvulopathy is off-target activation of 5-HT_{2B} receptors located in cardiac valves by norfenfluramine (Rothman and Baumann 2009), whereas the mechanisms responsible for PAH remain unresolved (Rothman and Baumann 2002, Rothman, Cadet et al. 2011). Fenfluramine-associated VHD was characterized by thickening of valve leaflets and increased regurgitation of blood, most often detected by echocardiography. The echocardiographic abnormalities in fenfluramine patients were often not accompanied by clinically significant symptoms of VHD (Rothman and Baumann 2009). Diagnosis of PAH is more difficult than that of VHD, as right heart catheterization (RHC) is generally required for definitive PAH diagnosis. However, echocardiography has been used to screen for PAH by estimating pulmonary artery systolic pressure (PASP) as well as evaluation of right heart hemodynamics. A major issue with the use of echocardiography to estimate PASP is lack of correlation with true PASP, when measured by RHC (underestimation more frequent than overestimation) (Milan, Magnino et al. 2010).

Summary of Historical (Observational) Evidence for an Association of Fenfluramine with PAH and VHD at Lower Dosage Strengths When Used for the Treatment of Refractory Seizures

Early reports began to emerge in the 1980s of the potential utility of fenfluramine in epilepsy when investigators reported its use in intractable self-induced neurological disorders (Polster 2019). No cardiac adverse events or valvulopathy were reported in any of the studies, but it is unclear whether the studies specifically assessed for valvulopathy with serial echocardiography.[11] Based on the results of a study in 11 children with refractory epilepsy and self-induced seizures (Boel and Casaer 1996), a Royal Decree in Belgium permitted compassionate use of fenfluramine in an open trial using fenfluramine as an add-on treatment for patients with DS. The mean dosage of fenfluramine was 0.34 (range: 0.12–0.90) mg/kg/day and the mean follow-up duration after the introduction of fenfluramine was 11 years and 4 months (range: 1–22 years). Two out of 12 patients treated with fenfluramine exhibited a mild thickening of one or two cardiac valves without clinical significance (Ceulemans, Boel et al. 2012). In the 5-year follow-up report on ten patients from this original cohort, six patients showed slight thickening of one or more cardiac valves: in four of the patients, the valve thickening was inconsistent and the most recent echocardiographic examination was normal, and the two other patients continued to show slight valve thickening, which remained stable as of the last echocardiographic examination. The study investigators did not identify clinical symptoms or clinically meaningful echocardiographic findings of VHD or PAH in any patient. (Ceulemans, Schoonjans et al. 2016). This program also included a prospective open-label study conducted with a protocol in which the study investigators enrolled a total of nine DS patients who, after a 3-month baseline period, added fenfluramine at a dose of 0.25–1.0 mg/kg/day (maximum of 20 mg/day) to their current antiepileptic drug regimen for up to five years. The patients underwent echocardiographic examinations every three months during the first year of treatment, every six months during the second year of

[11] See footnote 2

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treatment, and annually thereafter. The investigators did not observe echocardiographic evidence of cardiac valvulopathy or PAH with repeated echocardiography (Schoonjans, Paelinck et al. 2017).

Summary of Evidence from the Clinical Trial Drug Development Program for an Association of Fenfluramine with PAH and VHD at Lower Dosage Strengths When Used for the Treatment of Refractory Seizures

The New Drug Application (NDA) submission for FINTEPLA included two pivotal trials, an open-label, uncontrolled, long-term safety study, and an open-label pharmacokinetics study in patients with DS. It also included three studies conducted in healthy volunteers that assessed drug-drug interactions, effect on electrocardiogram, and food effects. The proposed label (as of June 22, 2020) includes a **boxed warning for VHD and PAH** and warnings and precautions for decreased appetite and decreased weight; somnolence, sedation, and lethargy; suicidal behavior and ideation; increase in blood pressure; glaucoma; serotonin syndrome; and FINTEPLA withdrawal.[12] FINTEPLA will be available only through a restricted program called the FINTEPLA Risk Evaluation and Mitigation Strategies (REMS) Program.[13]

The FINTEPLA clinical development included a cardiac monitoring program with baseline monitoring with an echocardiogram during screening, echocardiogram every six weeks for the first three months in the trial, every three months thereafter while subjects were in the open-label extension phase, and, if treatment was discontinued, a final echocardiogram three to six months after the final dose.[14] As part of the NDA, the applicant submitted an Integrated Summary of Cardiovascular Safety (and an update with a cutoff date of October 14, 2019), the purpose of which was to characterize the cardiovascular safety in the FINTEPLA development program. The primary focus of this summary was the echocardiogram in assessment of mitral and aortic valves (particularly for regurgitation); other analyses included measurements of PASP and assessment of tricuspid and pulmonic valves.[15] A total of 138 (40.5%) individuals were treated with fenfluramine for ≥24 months and the median duration of exposure was 639 days (range: 21–1199). No VHD, PAH, or any changes in valve structure consistent with VHD or PAH have been observed at any time in the 341 individuals with DS treated with fenfluramine.[16]

The goal of the FINTEPLA REMS with ETASU (elements to assure safe use) will be to mitigate the risk of VHD and PAH associated with FINTEPLA by ensuring that (1) prescribers are educated on the risk of VHD and PAH associated with FINTEPLA, the need to counsel patients on how to recognize and respond to signs and symptoms of VHD and PAH, the need to enroll patients in the FINTEPLA REMS Program, and the need to submit documentation that baseline and periodic monitoring of patients is being done to identify VHD and PAH; (2) prescribers adhere to enroll patients in the FINTEPLA REMS and the requirement to submit documentation of baseline and periodic monitoring; (3) patients are educated on how to recognize and respond to signs and symptoms of VHD and PAH and the need to have baseline and periodic cardiovascular monitoring; and (4) enrollment of all patients in a registry to

[12] See footnote 7
[13] Ibid.
[14] FINTEPLA (fenfluramine hydrochloride). Risk Evaluation and Mitigation Strategy (REMS). Supporting document. Zogenix, Inc.
[15] See footnote 2
[16] Ibid.

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further support long-term safety and safe use of FINTEPLA.[17]

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	X
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

Although the risk of VHD and PAH in the subpopulation of individuals with DS or other refractory epileptic disorders exposed lifelong to, theoretically, lower doses of fenfluramine is unknown, there is a well-known association between VHD and PAH and fenfluramine use at 60 to 120 mg/day in obese patients. Thus, the FDAAA purpose of this post-marketing requirement (PMR) is to assess a known serious risk in the subpopulation of individuals with DS (or other refractory epileptic disorders) exposed to FINTEPLA at the approved doses.

1.4. Statement of Purpose

The Division of Neurology 2 (DN2), with concurrence from the Office of Surveillance and Epidemiology (OSE), requires a postmarketing observational prospective study to characterize the risk of developing symptomatic or asymptomatic VHD and/or PAH in (non-obese) patients with refractory seizures treated with FINTEPLA. 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 dose-exposure [specified amount of medication taken at one time to which individuals are actually exposed (pharmacokinetic parameters per dose)], duration of use, and cumulative exposure to FINTEPLA on the development of symptomatic or asymptomatic VHD and PAH. The study should have access to the serial echocardiograms to be conducted as part of the REMS and follow patients for five years, or until the last echocardiogram following interruption of FINTEPLA treatment. The rarity of the disease for which FINTEPLA treatment is indicated, the rarity of the outcomes being investigated, the fact that all FINTEPLA users will be closely monitored to detect symptomatic and asymptomatic VHD and PAH, and the absence of FINTEPLA indications for any other populations make it unfeasible to design a sufficiently powered study with an appropriate comparator group. The regulatory goal is signal evaluation.

The purpose of this memo is to evaluate ARIA sufficiency to assess a known serious risk in the subpopulation of individuals with DS (or other refractory epileptic disorders) exposed to FINTEPLA at the approved doses.[18,19]

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[17] ROC Presentation Executive Summary. REMS Oversight Committee Meeting Minutes, January 14, 2020
[18] U.S. Food and Drug Administration. Sentinel. Surveillance Tools. Routine Querying Tools. Accessed on May 14, 2020, at https://www.sentinelinitiative.org/sentinel/surveillance-tools/routine-querying-tools
[19] U.S. Food and Drug Administration. Guidance for Industry. Postmarketing Studies and Clinical Trials — Implementation of Section 505(O)(3) of the Federal Food, Drug, and Cosmetic Act dated April 2011. Accessed on May 26, 2020, at https://www.fda.gov/media/133746/download

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1.5. Effect Size of Interest or Estimated Sample Size Desired

The study design is not inferential, and, therefore, there are no a priori levels of risk to consider. However, the study should include a sufficient number of patients with epilepsy being treated with FINTEPLA to assess the incidence of symptomatic or asymptomatic VHD and/or PAH, to identify risk factors for VHD and PAH, and to evaluate the impact of duration, dose-exposure, and cumulative exposure to FINTEPLA on the development of VHD and PAH.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

FINTEPLA's proposed indication is the treatment of seizures associated with DS in patients two years of age and older. There is an ongoing trial of fenfluramine in children and adults with Lennox-Gastaut syndrome, and the FINTEPLA REMS Program does not restrict the use of fenfluramine to individuals with DS. Therefore, the study population will be comprised of all individuals with refractory seizures, including those with DS, being treated with FINTEPLA.

2.2 Is ARIA sufficient to assess the intended population?

Sentinel's ARIA capabilities include access to individual-level data from 17 data partners,[20] but because (1) DS and other refractory epileptic syndromes, including Lennox-Gastaut syndrome, for which FINTEPLA may be prescribed, are rare disorders, and (2) only prescribers, pharmacies, and patients enrolled in the FINTEPLA REMS program can prescribe, dispense, and receive FINTEPLA, capturing a sufficient sample of FINTEPLA users in Sentinel may be difficult to achieve. In addition, patients who change health insurance while being treated with FINTEPLA may be lost to follow-up because they may enroll in an insurance not included in Sentinel, or because, although they switch to another Sentinel data partner, data linkages between Sentinel data partners are often not possible. Also, there may be issues in regard to sufficient market uptake, given the REMS to address FINTEPLA's risks of VHD and PAH, and the availability of other FDA-approved and unapproved treatments.

3 EXPOSURES

3.1 Treatment Exposure(s)

The exposure of interest is incident use of FINTEPLA. FINTEPLA will be available only through the FINTEPLA REMS Program.[21]

3.2 Comparator Exposure(s)

The proposed postmarketing observational prospective study does not require a comparison group.

3.3 Is ARIA sufficient to identify the exposure of interest?

[20] Sentinel. Accessed on May 18, 2020, at https://www.sentinelinitiative.org/collaborators
[21] See footnote 17

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ARIA is sufficient to capture patients with pharmacy benefits who receive at least one dispensing of FINTEPLA. The dose, duration of use, and cumulative dose can be obtained using prescription fills.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcomes of interest are symptomatic or asymptomatic VHD and/or PAH. The regulatory requirements include an echocardiogram at baseline and at least every six months during FINTEPLA treatment, and then once three to six months after stopping FINTEPLA.

Minimal degrees of regurgitation (i.e., trace or mild mitral regurgitation [MR] or trace aortic regurgitation [AR]) are relatively common in the general population and are not generally considered abnormal. Therefore, these lesser degrees of regurgitation were excluded from the 1997 FDA case definition of fenfluramine or dexfenfluramine-associated valvulopathy. The FDA case definition requires documented mild or greater aortic regurgitation or moderate or greater mitral regurgitation (Centers for Disease and Prevention 1997, Graham and Green 1997). Although not included in the FDA case definition, rates of significant (greater than mild) tricuspid regurgitation may approach those for significant mitral regurgitation. Alternatively, there may be cases where a cardiac valve is abnormally thickened and/or has restricted motion of the valve leaflets, but without at least mild AR or moderate MR. The VHD case definition in this post-marketing safety study should be able to identify any cardiac abnormalities that may represent evidence of VHD prior to onset of valvular regurgitation. Both the VHD and the PAH case definitions should be consistent with the corresponding ones used in the FINTEPLA REMS Program.

A literature review of algorithms or codes to identify VHD in claims databases identified a manuscript reporting, in a stratified random sample of Medicare beneficiaries hospitalized with atrial fibrillation, a positive predictive value (PPV) of 93% for selected International Classification of Diseases Ninth Revision (ICD-9) codes (any diagnosis position) to identify VHD or valve replacement (current or past event). However, this was an enriched population (individuals hospitalized with atrial fibrillation) and, as suggested by the authors, review of additional data (e.g., echocardiographic reports) would be helpful to confirm the presence of current VHD versus history of VHD. Use of only the first diagnosis position could improve specificity, but would decrease sensitivity and select healthier patients (Birman-Deych, Waterman et al. 2005). Alternatively, in a claims setting, an algorithm using a combination of a procedure code (e.g., echocardiogram) followed, a few days later, by a VHD-related diagnosis code by a specialist may indicate a current VHD event, but this would require a validation study in the selected database, for which medical record review may be required.

The algorithms used for identifying patients with PAH in the published literature varied considerably across studies and few are validated (Gillmeyer, Lee et al. 2019, Mathai, Hemnes et al. 2019). The most restrictive algorithms required use of PAH-related diagnosis codes together with PAH-specific medications and procedure codes (RHC or echocardiography). These algorithms would likely maximize PPV and, therefore, the probability that subjects truly have PAH, but may miss patients who are either untreated or do not undergo RHC or echocardiography during the study period (Mathai, Hemnes et al. 2019). Because of the FINTEPLA REMS program, all patients treated with FINTEPLA will undergo regular echocardiograms. However, we would still miss patients not treated with PAH-specific

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medications. The least restrictive algorithms required use of only one component: PAH-related diagnosis codes or PAH-specific medications. These algorithms maximize sensitivity, but perform poorly and require additional requirements to improve PPV (e.g., requiring at least two claims) (Gillmeyer, Lee et al. 2019, Mathai, Hemnes et al. 2019).

4.2 Is ARIA sufficient to assess the outcome of interest?

No, outcome identification and confirmation is a major limiting factor because it will require active surveillance with access to baseline and periodic echocardiograms (and to reports from other diagnostic procedures when performed) to detect and confirm both symptomatic and asymptomatic VHD and PAH cases. ARIA will not be able to successfully identify asymptomatic outcomes. Also, claims data usually lack information on disease severity and on subclinical cardiac manifestations that were identified in the historical data.

5 COVARIATES

5.1 Covariates of Interest

The following covariates have been deemed as relevant for confounding control for the PMR study:

- VHD: age, sex, race, body mass index (BMI), congenital heart diseases, infective endocarditis, rheumatic heart disease, end-stage renal disease, myxomatous degeneration, malignant carcinoid syndrome, drugs (including ergot derivatives), etc.
- PAH: age, sex, race, BMI, heritable PAH, idiopathic pulmonary hypertension, VHD, chronic hemolytic anemia, scleroderma, dermatomyositis, systemic lupus, some infectious diseases (HIV, schistosomiasis), liver disease (portopulmonary hypertension), congenital heart diseases, COPD, pulmonary embolism, pneumonia, drugs (including cocaine, methamphetamines), etc.

5.2 Is ARIA sufficient to assess the covariates of interest?

Most covariates of interest could be retrieved in the Sentinel distributed database by using sophisticated code-based approaches. However, potential concerns are:

- History of some conditions may be difficult to retrieve due to duration of follow-up.
- Insufficient completeness of some covariates (e.g., race).
- BMI is not usually available in claims data. Given that the role of dose-exposure in predicting risk is unclear, BMI constitutes a precisely measured covariate that is critical to the study.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The study design would be a descriptive study.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

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Yes. ARIA is sufficient with respect to design/analytic tools available to assess the question of interest.[22]

7 NEXT STEPS

As a result of the Signal Assessment Meeting (SAM) deliberations and as documented in this ARIA memo, ARIA was deemed insufficient to investigate the risk of VHD and PAH among individuals with refractory seizures treated with FINTEPLA. The major areas where ARIA was not sufficient were those related to the assessment of the intended population and the outcomes of interest. Also, despite most covariates of interest could be retrieved in the Sentinel distributed database by using sophisticated code-based approaches, there were also potential concerns related to the collection of some relevant covariates (e.g. BMI). In comparison to ARIA, the use of data from the REMS Registry and additional data beyond what is collected there provide a more appropriate setting to conduct safety surveillance while potentially maximizing sample size and facilitating long-term follow-up.

The next step is for DN2 to communicate to the sponsor the expectations for the PMR. The proposed PMR language, as of May 20, 2020, reads as follows:

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

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WEI HUA on behalf of SUKHMINDER K SANDHU
06/29/2020 02:35:36 PM

JUDITH W ZANDER
06/29/2020 02:57:20 PM

MICHAEL D NGUYEN
06/29/2020 05:05:30 PM

ROBERT BALL
06/29/2020 05:44:04 PM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	June 24, 2020
Reviewer:	Silvia Perez-Vilar, PharmD, PhD Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
Deputy Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	FINTEPLA (Fenfluramine hydrochloride, ZX008)
Application Type/Number:	NDA 212102
Applicant/sponsor:	Zogenix, Inc.
OSE RCM #:	2020-952

Reference ID: 4630826

1. BACKGROUND INFORMATION

1.1. Medical Product

Fenfluramine hydrochloride[1] (FINTEPLA, Zogenix, Inc.) is an amphetamine analogue that increases the extracellular levels of serotonin (5-HT) in nervous tissue.[2] FINTEPLA, an oral solution containing 2.2 mg/mL fenfluramine equivalent to 2.5 mg/mL of the hydrochloride salt, is a new formulation of a previously approved product, which was initially voluntarily withdrawn from the U.S. market in 1997 due to an association with valvular heart disease (VHD), then subsequently removed by the U.S. Food and Drug Administration in 2015 (Food and Drug Administration 2015). Fenfluramine is not currently marketed in any country.[3] It is a racemic compound of two stereoisomers, (+)-fenfluramine (dexfenfluramine) and (-)-fenfluramine (levofenfluramine), which are N-de-ethylated in the liver to form the main metabolites, (+)- and (-)-norfenfluramine (Rothman and Baumann 2009).[4] Norfenfluramine is then deaminated and oxidized to form inactive metabolites. The half-life is 20 hours following oral administration in healthy subjects.[5]

The new proposed indication is treatment of seizures associated with Dravet syndrome (DS) in patients two years of age and older. DS, previously known as severe myoclonic epilepsy of infancy, is a severe developmental and epileptic encephalopathy characterized by the onset of prolonged febrile and afebrile seizures in infancy, and evolving to drug-resistant epilepsy with accompanying cognitive, behavioral, and motor impairment. It occurs in 1 in 15,700 births in the United States (Wu, Sullivan et al. 2015). Most cases are known to be caused by pathogenic variants in the sodium channel gene SCN1A (Steel, Symonds et al. 2017). Mortality during childhood and adolescence in patients with DS is about 15% (5–20%), primarily due to status epilepticus in the early years and sudden unexpected death in epilepsy patients in adolescence and adulthood (Akiyama, Kobayashi et al. 2010, Cooper, McIntosh et al. 2016). Older children and adults with DS tend to have improved seizure control, but moderate to severe intellectual disability and motor system abnormalities (Connolly 2016). Although FINTEPLA's mechanism of action is unclear and likely depends on multiple factors, it is theorized that it reduces seizures by increasing extrasynaptic serotonin levels through modulation of serotonin receptors (primarily 5-HT_{1A} receptors); however, there is some evidence that the fenfluramine molecule (and possibly its metabolites) reduce seizures by binding at specific receptors. The proposed dosing regimen is initiation of dosing at 0.2 mg/kg/day and increase to 0.4 mg/kg/day on day 7 and 0.7 mg/kg/day (maximum) on day 14 in patients who are not on concomitant stiripentol (STP). For patients taking concomitant STP, the starting dose is 0.2 mg/kg/day with an increase to 0.4 mg/kg/day. The maximum daily dose for patients not on STP is 26 mg and 17 mg for those on concomitant STP.[6]

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[1] N-ethyl-α-methyl-3-(trifluoromethyl)phenethylamine hydrochloride.
[2] FINTEPLA (fenfluramine hydrochloride). Draft clinical review dated May 4, 2020. Division of Neurology 2. U.S. Food and Drug Administration.
[3] Ibid.
[4] ZX008 (fenfluramine HCl) oral solution. 2.5 Clinical Overview. Zogenix, Inc.
[5] Proposed FINTEPLA labeling dated June 22, 2020.
[6] See footnote 2.

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The New Drug Application (NDA) submission included two pivotal trials, an open-label, uncontrolled, long-term safety study, and an open-label pharmacokinetics study in patients with DS. It also included three studies conducted in healthy volunteers that assessed drug-drug interactions, effect on electrocardiogram, and food effects.[7] FINTEPLA's most serious risks are already-known cardiovascular adverse reactions associated with fenfluramine: valvular heart disease and pulmonary arterial hypertension (PAH)(Abenhaim, Moride et al. 1996, Connolly, Crary et al. 1997, Graham and Green 1997). The suspected mechanism for fenfluramine-induced cardiac valvulopathy is off-target activation of 5-HT_{2B} receptors located in cardiac valves by norfenfluramine (Rothman and Baumann 2009) whereas the mechanisms responsible for PAH remain unresolved (Rothman, Cadet et al. 2011). No VHD, PAH, or any changes in valve structure consistent with VHD or PAH have been observed in any subject at any time during FINTEPLA's clinical development program.[8] The proposed label (as of June 22, 2020) includes a boxed warning for VHD and PAH and warnings and precautions for decreased appetite and decreased weight; somnolence, sedation, and lethargy; suicidal behavior and ideation; increase in blood pressure; glaucoma; serotonin syndrome; and FINTEPLA withdrawal.[9]

FINTEPLA will be available only through a restricted program called the FINTEPLA Risk Evaluation and Mitigation Strategies (REMS) Program.[10] The goal of the proposed FINTEPLA REMS with ETASU (elements to assure safe use) is to mitigate the risk of VHD and PAH associated with FINTEPLA by ensuring that (1) prescribers are educated on the risk of VHD and PAH associated with FINTEPLA, the need to counsel patients on how to recognize and respond to signs and symptoms of VHD and PAH, the need to enroll patients in the FINTEPLA REMS Program, and the need to submit documentation that baseline and periodic monitoring of patients is being done to identify VHD and PAH; (2) prescribers adhere to enroll patients in the FINTEPLA REMS and the requirement to submit documentation of baseline and periodic monitoring; (3) patients are educated on how to recognize and respond to signs and symptoms of VHD and PAH and the need to have baseline and periodic cardiovascular monitoring; and (4) enrollment of all patients in a registry to further support long-term safety and safe use of FINTEPLA.[11]

1.2. Describe the Safety Concern

The Division of Neurology 2 (DN2) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based signal detection studies of fenfluramine during pregnancy. Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects in clinically recognized pregnancies is 2–4% (Centers for Disease and Prevention 2008, Food and Drug Administration 2014).

There are no adequate data on the developmental risks associated with the use of FINTEPLA in pregnant women. There were no pregnancies reported during FINTEPLA's development

[7] FINTEPLA (fenfluramine hydrochloride). Draft clinical review dated May 4, 2020. Division of Neurology 2. U.S. Food and Drug Administration.
[8] ROC Presentation Executive Summary. REMS Oversight Committee Meeting Minutes, January 14, 2020.
[9] Proposed FINTEPLA labeling dated June 22, 2020.
[10] Ibid.
[11] See footnote 8.

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program.[12] Reproductive and developmental toxicology studies were not included in the original NDA submission or in the resubmission following refuse-to-file. FDA had previously agreed to the sponsor's proposal to submit these (and carcinogenicity) studies post-approval (IND 125797, PreIND Written Responses, May 16, 2015). However, the sponsor submitted a standard battery of reproductive and developmental toxicology studies to the NDA on March 24, 2020. Because of the late submission, there was insufficient time to conduct a thorough review of the studies. Therefore, it is recommended that they be included as PMRs in the action letter.[13]

In the current proposed labeling, as of June 22, 2020, the Risk Summary in Section 8.1 Pregnancy states:

*"**Pregnancy Exposure Registry***

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), such as FINTEPLA, during pregnancy. Encourage women who are taking FINTEPLA during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling the toll-free number 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org/.

Risk Summary

There are no adequate human or animal data on the developmental risks associated with the use of FINTEPLA in pregnant women.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risks of major birth defects and miscarriage for the indicated populations are unknown. "

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

[12] See footnote 7.

[13] Memorandum NDA 212-102 (fenfluramine) dated June 22, 2020. Division of Pharmacology/Toxicology. U.S. Food and Drug Administration.

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☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: *Single-arm pregnancy safety study, which enrolls exposed pregnancies into a protocol-driven observational cohort study for descriptive analyses and collects follow-up data, including detailed case narratives as needed. These studies do not require inferential analyses and do not have the sample size requirements of a traditional pregnancy registry. A single-arm pregnancy safety study is appropriate because this drug is indicated for a rare disease, and, thus, the study is not required to be sufficiently powered for a comparative analysis.*

Note: There is an existing pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs, such as FINTEPLA, during pregnancy, the North American Antiepileptic Drug (NAAED) Pregnancy Registry (http://www.aedpregnancyregistry.org/), in which the sponsor is expected to enroll.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☒ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes: ARIA lacks access to detailed narratives. Given that the study for broad-based surveillance being considered is descriptive, without sample size requirements, and without a comparison group, having detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and to conduct causality assessments.

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of

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interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

2.5. Please include the proposed PMR language in the approval letter.

The following language has been proposed by the Division of Neurology 2 (DN2) as of May 15, 2020, for the PMR related to pregnancy outcomes:

"Establish 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 (e.g., telephone contact number and/or website in prescribing information), measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring, and plans for comprehensive data analysis and yearly reporting."

3. REFERENCES

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Effectiveness. Docket No. FDA-2015-N-3389. Federal Register. **80, 188:** 58490-58491.

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06/24/2020 04:35:17 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 16, 2020
To:	Stephanie Parncutt, MHA Senior Regulatory Project Manager **Division of Neurology II (DN II)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Dhara Shah, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	FINTEPLA (fenfluramine)
Dosage Form and Route:	oral solution, CIV
Application Type/Number:	NDA 212102
Applicant:	Zogenix, Inc.

1 INTRODUCTION

On February 5, 2019, Zogenix, Inc. submitted for the Agency's review a New Drug Application (NDA) for FINTEPLA (fenfluramine), oral solution, CIV. The purpose of the submission was to seek approval to market FINTEPLA to treat seizures associated with Dravet syndrome in people 2 year of age or older. On April 5, 2019, the sponsor received a Refusal to File (RTF) notification regarding the failure to submit nonclinical studies and the need to conduct and extensive data quality assessment to ensure the accuracy of trial results. On September 25, 2019, the sponsor resubmitted the application for the Agency to review.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology II (DN II) on October 1, 2019 and November 7, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU), for FINTEPLA (fenfluramine), oral solution, CIV.

2 MATERIAL REVIEWED

- Draft FINTEPLA (fenfluramine) MG and IFU received on September 25, 2019, and received by DMPP and OPDP on June 2, 2020.
- Draft FINTEPLA (fenfluramine) Prescribing Information (PI) received on Septermber 25, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 2, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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06/16/2020 10:03:06 AM

LASHAWN M GRIFFITHS
06/16/2020 10:46:19 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 12, 2020

To: Natalie Getzoff, M.D.
Division of Neurology II (DN II)

Stephanie Parncutt, Regulatory Project Manager

Tracy Peters, Associate Director for Labeling, DN I

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for FINTEPLA™ (fenfluramine) oral solution, CIV

NDA: 212102

In response to the DN II consult request dated November 7, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for FINTEPLA™ (fenfluramine) oral solution, CIV.

PI, Medication Guide, IFU: OPDP's comments on the proposed labeling (PI) are based on the draft PI downloaded from DN II SharePoint on June 11, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 15, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

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DHARA SHAH
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M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: June 11, 2020

To: Nick Kozauer, MD, Director
Division of Neurology II

Through: Dominic Chiapperino, PhD, Director
Chad Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff

From: Edward Hawkins, PhD, Pharmacologist
Shalini Bansil, MD, Medical Officer
Controlled Substance Staff

Subject: Fintepla (fenfluramine hydrochloride), NDA 212102
Dosages, formulations, routes: oral solution, max dose of 0.35 mg/kg BID (total daily dose of 30 mg)
IND Number: 125797
Indication(s): treatment of seizures associated with Dravet syndrome in patients 2 years of age and older
Sponsor: Zogenix
PDUFA Goal Date: June 25, 2020

Materials Reviewed:

- NDA 212102 for Fintepla, submitted September 25, 2019, and subsequent amendments

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I. SUMMARY

1. Background

This memorandum responds to a consult request from the Division of Neurology II (DN2) to evaluate abuse-related preclinical and clinical data submitted by Zogenix (Sponsor) under NDA 212102 and IND 125797 for Fintepla (fenfluramine hydrochloride).

Fenfluramine has a long regulatory history regarding its abuse potential. In brief, Fenfluramine was placed into Schedule IV of the Controlled Substances Act (CSA) on June 15, 1973, after approval by the Food and Drug Administration (FDA) as Pondimin. On March 18, 1991, the Sponsor submitted a petition to the Drug Enforcement Administration (DEA) requesting that fenfluramine be removed from all schedules of the CSA based on the lack of a demonstrable abuse potential. The Department of Health and Human Services (HHS) drafted a medical and scientific analysis recommending removal of fenfluramine from the CSA. This recommendation was not acted upon because on July 8, 1997, the Food and Drug Administration (FDA) released a public health advisory on fenfluramine that lead to the drug being voluntarily withdrawn from the market. As a result, the petition to decontrol fenfluramine was also withdrawn. On May 2, 2003, DEA withdrew the proposed rule to decontrol fenfluramine citing health and safety concerns that prompted the drug to be removed from the market (68 FR 26247). A second petition to decontrol fenfluramine was sent from Zogenix (Sponsor) to DEA on October 18,

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2018. As of February 3, 2020, HHS has not received a request from DEA to conduct a medical and scientific analysis on fenfluramine. The Sponsor submitted NDA 212102 on September 25, 2019.

Fenfluramine is a phenethylamine and is structurally similar to the amphetamine class of substances. However, fenfluramine is a serotonin (5-HT) releasing agent that also produces moderate agonist activity at other receptors. Data provided by the Sponsor indicates that fenfluramine produces agonist activity at 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors as well as acting as a positive allosteric modulator (PAM) at the sigma-1 receptor. Substances with this structure and serotonergic functional activity have been shown to produce psychoactive effects akin to hallucinogens or entactogens.

The Sponsor provided references to published data to support their conclusion that fenfluramine should be removed from control in the CSA. As fenfluramine is currently in Schedule IV of the CSA, it can be marketed without a decontrol action if approval is granted by FDA. Therefore, the published data submitted by the Sponsor are not required for approval. The published data provided by the Sponsor consists of nonclinical abuse potential studies and several clinical studies that measured various subjective effects of fenfluramine.

In the NDA submission, the Sponsor proposes to decontrol fenfluramine in the CSA. Fenfluramine will remain in Schedule IV if approved, until a medical and scientific evaluation CSS is conducting to consider whether fenfluramine should remain in schedule IV or can be recommended for decontrol is finalized. Therefore, Fintepla will remain in schedule IV at the time of its potential approval and can be marketed immediately upon approval with labeling noting schedule IV status. Any re-scheduling or decontrol action would be reflected and implemented post-approval, upon DEA publication in the Federal Register to formally revise the control status of fenfluramine and subsequent revision of Fintepla product labeling to reflect the new control status of fenfluramine.

2. Conclusions

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 212102 for Fintepla and concludes that fenfluramine does not have meaningful abuse potential, based on the following data:

- In receptor binding and functional studies, fenfluramine functions as a serotonin releasing agent and has weak to moderate agonist activity at several serotonin receptors (5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C})
- In animal general behavior tests, fenfluramine did not produce significant changes in locomotor activity, motor function, or other behaviors associated with abuse potential.
- In published drug discrimination studies submitted by the Sponsor, fenfluramine generalized to the discriminative stimulus effects of serotonin releasing agents and hallucinogens (MDMA, PMA, quipazine, lisuride, and LSD).
- In published self-administration studies submitted by the Sponsor, fenfluramine did not produce positive reinforcing effects that were significantly greater than placebo. This is consistent with effects produced by serotonergic modulators such as hallucinogens and entactogens.
- The Sponsor did not conduct or submit studies to assess the physical dependence of fenfluramine.

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- Published studies submitted by the Sponsor that assessed the psychoactive effects of fenfluramine reported that single oral doses below 80 mg do not produce significant positive subjective effects. In one study with high doses ranging from 120 to 240 mg, fenfluramine produced positive subjective effects and hallucinations. However, the predominant effects at high doses were aversive and included sedation.
- Phase 1 studies in healthy volunteers did not reveal the presence of abuse-related AEs in subjects receiving fenfluramine at therapeutic doses. Euphoric mood occurred at supratherapeutic doses of fenfluramine in one study (ZX008-1603) but not in another (ZX008-1505). There were no abuse-related AEs reported in a clinical study enrolling recreational drug users or in the Phase 3 studies, however, patients in the Phase 3 studies were severely neurologically impaired.
- Physical dependence was not assessed in humans in Phase 1 studies because they were single dose studies or studies in which short-term treatment was administered (e.g., 6 days). Physical dependence could not be assessed in the Phase 3 studies because medication could not be discontinued abruptly in patients with seizures and these studies included a taper phase. The label recommends that fenfluramine be withdrawn gradually.

3. Recommendations

Based on the CSS determination that fenfluramine does not have demonstrable abuse potential but will remain controlled in schedule IV at the time of possible NDA approval, we conclude that Section 9 (Drug Abuse and Dependence) will be required in product labeling and must reflect in section 9.1 that fenfluramine is a schedule IV substance under the CSA. Therefore, CSS recommends the following content for section 9 of Fintepla labeling until such time that DEA may finalize a scheduling action in the Federal Register to alter the control status of fenfluramine, such as an action to decontrol it.

9 Drug Abuse and Dependence

9.1 Controlled Substance

FINTEPLA contains fenfluramine, a schedule IV controlled substance.

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II. DISCUSSION

1. Chemistry

The chemical properties of a substance impact the assessment of abuse potential because they determine possible synthetic pathways and methods of administration. An understanding of the chemical properties of a substance may help determine if an individual with a basic knowledge of chemistry can synthesize the substance based upon the availability of the starting materials and complexity of the synthetic path. Furthermore, an understanding of the physicochemical properties of a substance can help predict if a person can produce a solution for injection upon extraction of the active pharmaceutical ingredient, or if the drug can be vaporized or smoked and inhaled. An evaluation of the chemical properties of fenfluramine and its known active metabolites is given below.

1.1 Substance Information

Fenfluramine is the active pharmaceutical ingredient in a solution formulated with (b) (4) API which is equivalent to 2.5 mg/mL fenfluramine hydrochloride (HCl). Fintepla is designed to be orally administered at a starting dose of 0.1 mg/kg BID and increased to a maximum maintenance dose of 0.35 mg/kg BID. Fenfluramine, also known by the developmental code ZX008 is the nonproprietary name of N-ethyl-α-methyl-3-(trifluoromethyl)phenethylamine hydrochloride. Fenfluramine HCl has a molecular weight of 267.72 g/mol, a chemical formula of $C_{12}H_{16}F_3N$ • HCl, and CAS # of 404-52-0 (HCl salt). Fenfluramine is a white to off-white powder that is soluble in water at a pH (b) (4) and has a melting point of 172°C (**TABLE 1**). (b) (4)

Table 1: General Chemical Properties of Fenfluramine

Nomenclature	
International Non-proprietary Name (INN)	fenfluramine hydrochloride
Chemical Abstract Number (CAS)	404-52-0 (HCl salt)
Chemical Name (IUPAC)	N-ethyl-α-methyl-3-(trifluoromethyl)phenethylamine hydrochloride
Substance codes	ZX008
Structure	
Molecular Formula	$C_{12}H_{16}F_3N$ • HCl
Molecular mass	267.72 g mol-1

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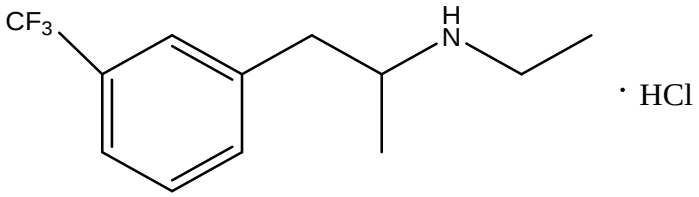
Structure	
General Properties	
Appearance	White to almost white powder
pKa	(b) (4)
Solubility (b) (4)	(b) (4)
Melting point	172°C
Chirality/Stereochemistry	(b) (4)

(b) (4)

Excipients in the tablet

Fintepla contains a series of excipients to aid in the oral formulation and taste of the drug product. The excipients and their functions are listed in **Table 2**. The excipients in Fintepla do not have a known abuse liability.

Table 2: Composition of Excipients Used to Manufacture Fenfluramine

Component	Function	Quantity (mg/mL)[a]
Fenfluramine HCl	Active	2.5
Methylparaben (b) (4)	(b) (4)	
Ethylparaben (b) (4)		
Sucralose		
Hydroxyethylcellulose		
Cherry flavoring (b) (4)		
Potassium citrate (b) (4)		
Citric acid (b) (4)		
Water (b) (4)		
		(b) (4)

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1.2 In Vitro Manipulation and Extraction Studies for Products with Abuse-Deterrent Features

The Sponsor is not seeking abuse-deterrent labeling and did not conduct in vitro manipulation and extraction studies on the to-be-marketed formulation.

2. Nonclinical Pharmacology

Receptor binding and activity assays can give an indication as to whether or not a substance affects a receptor pathway that is known to be associated with abuse potential. For substances that are CNS active, the Sponsor is required to determine if their active pharmaceutical ingredient and any major metabolites will bind to and have activity at these receptors. The data collected by the Sponsor indicate that fenfluramine is primarily a serotonin (5-HT) releasing agent (Baumann et al., 2014), with no dopamine releasing activity and mild norepinephrine releasing activity. The major circulating active metabolite of fenfluramine, norfenfluramine, has similar activity to the parent compound.

2.1 Receptor Binding and Functional Assays

Binding Studies

The Sponsor conducted a series of binding studies (Study numbers 10026029, AM335, AM354, XS-0691, and ZOG-1211515) to determine the mechanism of action of fenfluramine and its major circulating active metabolite norfenfluramine. The data from study reports XS-0691, and ZOG-1211515, indicate that fenfluramine and norfenfluramine do not bind significantly to receptors, ion channels, and transporters that are known to be associated with abuse potential (i.e., $GABA_A$ receptor, cannabinoid receptor (CB1), and sodium channels). The opioid receptors were not included, however, there is no indication from in vivo studies that fenfluramine or norfenfluramine have activity at mu, delta, or kappa opioid receptors.

According to the Sponsor, fenfluramine or norfenfluramine binds to six receptor types (defined as greater that 30% inhibition in a competitive binding assay); the beta-adrenergic receptor, the beta 2-adrenergic receptor, the $5\text{-}HT_{1A}$ receptor, the sigma-1 receptor, the muscarinic M1 receptor, and the sodium ion channel. The binding affinity for fenfluramine and norfenfluramine are presented in **Table 3** and **Table 4** respectively.

However, published literature indicate that the major mechanism of action of fenfluramine for seizure reduction is as an agonist at serotonin receptor subtypes $5\text{-}HT_{1D}$, $5\text{-}HT_{2C}$, and sigma-1 receptors (Sourbron et al., 2016).

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Table 3: Fenfluramine Specific Receptor Binding Targets

Receptor/ Molecular Target	**K_i[1] (μM)**
Adrenergic β_1	17.5
Adrenergic β_2	12.6
Muscarinic M1	11.3
Na channel	4.84
Serotonin 5-HT_{1A}	0.33
Sigma non-selective	0.27

Table 4: Norfenfluramine Specific Receptor Binding Targets

Receptor/ Molecular Target	**K_i (μM)**
Adrenergic β_1	12.0
Adrenergic β_2	8.8
Muscarinic M1	3.74
Na channel	4.74
Serotonin 5-HT_{1A}	0.67
Sigma non-selective	2.9

Activity Studies

beta-1 Adrenergic, beta-2 Adrenergic, 5-HT_{1A}, and Muscarinic M1 receptors

The functional activity of fenfluramine and norfenfluramine was tested at the receptors listed in Table 3 (Study # 100026029). No agonist activity was found for the test compounds when tested against beta-1 adrenergic, beta-2 adrenergic, 5-HT_{1A}, and muscarinic M1 receptors. Antagonist activity was found for fenfluramine at the beta-2 adrenergic and muscarinic M1 receptors at concentrations of 49 μM and 83 μM respectively. Norfenfluramine produced beta-2 adrenergic antagonistic effects at 67 μM and at the muscarinic M1 receptor at 95 μM.

Sigma-1 receptor

Three studies were conducted to elucidate the activity of fenfluramine and norfenfluramine at the non-specific sigma receptor, sigma-1. The first study used guinea pig vas deferens tissue to test the agonist and antagonist activity of the compounds. The second study was an in vitro study in which Chinese hamster ovary (CHO) cells expressing sigma-1 receptors were grown in 24-well plates, exposed to the compounds for 1 hour at concentrations of 1 μM or 10 μM. The results of these two studies indicate that fenfluramine may act as a positive allosteric modulator (PAM) of the sigma-1 receptor, as alone the drug produced no agonist or antagonist activity. However, in the presence of sigma-1 receptor agonists (+)-

[1] K_i – The inhibitory constant is a measure of the binding affinity of a substance to its substrate or receptor

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SKF-10,047 or PRE084, fenfluramine increased the activity at the receptor in comparison to drug alone. The result was confirmed in the third study (Study # AM335), which was a Binding Immunoglobulin Protein (BiP) assay. In this assay CHO cells expressing BiP and sigma-1 receptors were treated with PRE-084 (0.1, 1, 10 μM) and/or fenfluramine (0.1, 1, 10 μM). After a 30-minute incubation a co-immunoprecipitation for BiP was performed and measured using an ELISA assay. PRE-084 caused a significant and dose dependent increase in the BiP/sigma-1 receptor dissociation of sigma-1. Fenfluramine alone had no effect and co-administration of fenfluramine with PRE-084 increased the dissociation above that of an equivalent dose of PRE-084 alone. This study confirmed that fenfluramine functions as a PAM of the sigma-1 receptor at doses between 1 and 10 μM.

Sodium Channel

Study ZOG121515-1 was conducted to assess the activity of fenfluramine and norfenfluramine at eight voltage gated sodium channels: hNav1.1, hNav1.2, hNav1.3, hNav1.4, hNav1.5, hNav1.6, hNav1.7, and hNav1.8. Activity was only determined at the hNav1.5 channel at which fenfluramine produced an IC_{50}[2] of 21.9 μM.

Published Literature

5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}

Published literature indicates that fenfluramine may bind to and have activity at several 5-HT receptors that may be responsible for other effects attributed to the drug. For example, fenfluramine produced weak binding at the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors, however, norfenfluramine (metabolite) demonstrated moderate binding affinity at these receptors (**Table 5**) (Fitzgerald et al., 2000).

Table 5: In Vitro Binding of Isomers of Fenfluramine and Norfenfluramine at the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors *

Receptor Subtype	K_i (nM)			
	d-Fenfluramine	*l*-Fenfluramine	*d*-Norfenfluramine	*l*-Norfenfluramine
5-HT_{2A}	2470 ± 240	1430 ± 330	187 ± 10	267 ± 16
5-HT_{2B}	3920 ± 830	680 ± 16	27 ± 7	65 ± 23
5-HT_{2C}	2080 ± 480	1620 ± 340	56 ± 19	99 ± 12

* Data obtained from (Fitzgerald et al., 2000)

The 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors are G-protein coupled receptors (GPCRs) that function through a second messenger mechanism that releases inositol trisphosphate (IP_3) and intracellular calcium. The activity of these receptors can be measured through a phosphoinositide (PI) hydrolysis assay (Fitzgerald et al., 2000). The data in Table 6 present the half-maximal excitatory response (EC_{50}) in nM of *d*-fenfluramine and *l*-norfenfluramine at the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors. Interestingly, *d*-fenfluramine is a potent agonist of the 5-HT_{2B} receptor despite its weak binding affinity,

[2] IC_{50} - Half maximal inhibitory concentration of a substance.

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has moderate agonist activity at the 5-HT_{2C} receptor, and little to no activity at the 5-HT_{2A} receptor. The major active circulating metabolite, *l*-norfenfluramine, demonstrated moderate activity at 5-HT_{2B} and weak to no activity at 5-HT_{2C} and 5-HT_{2A} respectively.

Table 6: In Vitro Activity of *d*-Fenfluramine and *l*-Norfenfluramine at the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors *

Receptor Subtype	EC_{50} (nM)	
	d-Fenfluramine	*l*-Norfenfluramine
5-HT_{2A}	3100 ± 330	26,600 ± 4,290
5-HT_{2B}	24 ± 3.7	292 ± 50
5-HT_{2C}	190 ± 16	727 ± 45

* Data obtained from (Fitzgerald et al., 2000)

Conclusion

Section 1 of this review (Chemistry) indicates that (b) (4) (b) (4) (b) (4) Binding and activity studies indicate that fenfluramine causes release and prevents reuptake of serotonin as well as having antagonist activity at the beta-2 adrenergic receptor, the muscarinic M1 receptor, the hNav1.5 ion channel, and PAM activity at the non-specific sigma-1 receptor. Published data indicate that *d*-fenfluramine is a potent agonist of the 5-HT_{2B} receptor despite its weak binding affinity, has moderate agonist activity at the 5-HT_{2C} receptor, and weak activity at the 5-HT_{2A} receptor whereas *l*-norfenfluramine, demonstrated moderate activity at 5-HT_{2B} and weak activity at 5-HT_{2C} and 5-HT_{2A} respectively.

2.2 Safety Pharmacology/Metabolites

Absorption

The absorption of fenfluramine was assessed in multiple species after single and repeated administration. The review of the data in this section will focus on the studies that are most relevant to the assessment of the abuse potential of fenfluramine and include studies that were conducted in mice, rats, and dogs. The data include data from published literature and study reports provided by the Sponsor.

Study XT158035 was conducted to assess the permeability of fenfluramine and norfenfluramine across Caco-2 cells which express P-glycoprotein (P-gp) transporters. These transporters are known to actively transport foreign substances out of cells and the CNS. The data indicate that both fenfluramine and norfenfluramine are highly permeable and that this permeability was not affected by the P-gp antagonist valspodar (10 μM). These results suggest fenfluramine and norfenfluramine will pass easily into the CNS.

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The pharmacokinetics of single oral doses of fenfluramine were determined by the Sponsor and published literature. These studies were conducted in mice and rats and the data are presented in **Table 7** where they are also compared to parameters measured in healthy human adults (Caccia et al., 1981; Caccia et al., 1982; Spinelli et al., 1988). The data indicate that a single oral dose of fenfluramine in mice produces a Cmax of 0.26 µg/mL and an AUC of 1.4 µg/mL*hr, results similar to that of a 60 mg BID dose in healthy human adults. The same dose (20 mg/kg PO) in rats produced a Cmax of 0.36 µg/mL and an AUC of 5.15 µg/mL*hr, values higher than those seen in the mouse at the same dose. The Tmax of fenfluramine in rats ranged from 0.5 – 2 hours and the half-life was 2.5 hours.

The Sponsor also provided pharmacokinetic data on norfenfluramine, the major circulating active metabolite of fenfluramine. The data indicate that mice do not produce norfenfluramine to an appreciable extent compared to rats and humans. Therefore, rats are a more appropriate species in which to measure the behavioral effects of fenfluramine. In summary, the data indicate that a single oral dose of racemic fenfluramine is rapidly absorbed in rats with a Tmax of approximately 30 minutes and a half-life of 2.5 hours.

Table 7: PK Parameters of a Single Oral Doses of (±)-Fenfluramine or (±)-Norfenfluramine in Male Mice, Male Rats, and Healthy Adult Humans

		(±)-Fenfluramine		**(±)-Norfenfluramine**		
Species	**Dose (mg/kg)**	***d*-Fenfluramine**	***l*-Fenfluramine**	***d*-Norfenfluramine**	***l*-Norfenfluramine**	**Reference**
Cmax (µg/mL)						
Mice	20	0.27 ± 0.04	0.26 ± 0.05	0.03 ± 0.00	0.05 ± 0.00	Caccia et al., 1982
Rat	6.25	NA	0.12 ± 0.07	NA	0.32 ± 0.05	Spinelli et al., 1988
Rat	20	0.36		0.44		Study # 8001991
Healthy Human (Adult)*	0.8	0.059		0.016		Study # 1505
	60 mg BID	0.234		0.1		Study # 1603
Tmax (hours)						
Mice	20	0.25	0.25	4.0	4.0	Caccia et al., 1982
Rat	6.25	NA	0.6 ± 0.3	NA	4.0 ± 0.4	Spinelli et al., 1988
Rat	20	0.5 - 2		NA		Study # 8001991
Healthy Human (Adult)*	0.8	3		12		Study # 1505
	60 mg BID	4		8		Study # 1603
$T_{1/2}$ (hours)						
Mice	20	4.3	3.7	7.7	7.7	Caccia et al., 1982
Rat	6.25	NA	1.1 ± 0.2	NA	11.9 ± 3.2	Spinelli et al., 1988
Rat	20	2.51		NA		Study # 8001991
Healthy Human (Adult)*	0.8	20		23		Study # 1505
	60 mg BID	20		23		Study # 1603

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AUC (μg/mL*hr)						
Mice	20	1.39	1.1	0.5	0.8	Caccia et al., 1982
Rat	6.25	NA	0.2 ± 0.07	NA	6.51 ± 1.41	Spinelli et al., 1988
Rat	20	5.15		7.76		Study # 8001991
Healthy Human (Adult)*	0.8	1.47		0.027		Study # 1505
	60 mg BID	2.49		1.14		Study # 1603

Distribution

Study XS-0688 was conducted to determine the protein binding of fenfluramine and norfenfluramine in male rat, dog, and human plasma by equilibrium dialysis and analysis by LC-MS/MS. Plasma was collected under fasted conditions and incubated with fenfluramine at concentrations of 10 or 100 ng/mL. The results indicate a protein bound percentage of 50.4% and 46.2% for rat, 62.2% and 52.1% for dog, and 44.8% and 50.1% for human, respectively. The mean in vitro plasma protein binding of norfenfluramine at final concentrations of 10 and 100 ng/mL were 43.8% and 55.5% for rat, 50.7% and 51.0% for dog, and 49.7% and 48.0% for human, respectively. In summary, fenfluramine and norfenfluramine produced approximately 50% protein specific binding in human and rat plasma.

The Sponsor also refers to several studies in the published literature which measured the distribution of fenfluramine or its individual isomers in the rat.

1. (Spinelli et al., 1988) – Male rats were administered a single IV dose of 1.25 to 12.5 mg/kg. Two hours post-dose the rat's brain was removed and the concentration of *l*-fenfluramine and *l*-norfenfluramine were determined and compared to the compound's plasma concentration. Concentrations in the brain were 15-20-fold higher in the brain then in the plasma.
2. (Caccia et al., 1982) – Male rats were administered a single oral dose of 5 mg/kg fenfluramine or 2.5 mg/kg *d*-fenfluramine. Concentrations of the compounds were measured and determined to be 40-fold higher in the brain compared to the plasma.
3. (Clausing et al., 1998) – Three separate groups of male rats were dosed with *d*-fenfluramine.
    a. Group 1 – 5 mg/kg SC; three times every 2 hours
    b. Group 2 – single dose of 2 mg/kg SC
    c. Group 3 – single dose of 1 mg/kg IP

    Measurements were made of plasma and brain (frontal cortex, hypothalamus, caudate/putamen, and substantia nigra). Concentrations of fenfluramine and norfenfluramine from brain and each brain region were 50- to 60-fold greater than those in the plasma from each group. Fenfluramine is found in the highest concentrations in the brain regions of the cortex, hippocampus, and striatum.

Metabolism

The metabolism of fenfluramine was determined using in vitro and in vivo studies. The studies concluded that there are species differences between the metabolism of fenfluramine, however, the

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human metabolites are present in the rat metabolic profile (i.e., norfenfluramine). Norfenfluramine and its N-oxygenation product (C2) were the only metabolites detected in liver S9 fractions in both rats and human samples (Study # XT154063). Norfenfluramine was also determined to be at higher concentration in the rat than in human plasma after similar exposure levels of fenfluramine.

Excretion

According to the Sponsor, published literature indicates that fenfluramine and its active metabolites are excreted renally (> 80%) with a small amount in the feces (Marchant et al., 1992). Excretion of unchanged l-fenfluramine was approximately 3-4% of the parent after oral or IV administration in rats and norfenfluramine was approximately 20% (Spinelli et al., 1988).

2.3 Findings from Safety Pharmacology and Toxicology Studies

Safety Studies

The Sponsor conducted and provided studies from the literature to address the safety of fenfluramine in the CNS, respiratory system, cardiovascular system, and gastrointestinal system.

Central Nervous System (CNS) effects

Study # 9000406 was a toxicokinetic study that contained a functional observational battery (FOB) typically used to elucidate the CNS mediated behavioral effects of a drug. Rats were administered doses of 0, 3.5, 9, or 20 mg/kg/day of fenfluramine orally for 10 weeks. Animals were assessed in the FOB on day 58 and day 91 of the study. There was a significant decrease in rectal temperature, rearing, and motor activity after repeated administration of fenfluramine.

Respiratory effects

According to Pondimon (NDA 16-618) in data obtained by the Sponsor, dogs administered fenfluramine 1 – 10 mg/kg IV or 5 – 10 mg/kg orally had slightly decreased respiratory levels followed by an increase.

Cardiovascular effects

There are severe cardiovascular effects that are attributed to fenfluramine that resulted in it being voluntarily removed from the market. These issues were addressed by a consult to the Division of Cardiovascular and Renal Products. There were no indications of cardiovascular effects in the clinical studies conducted as part of NDA 212102.

2.4 Animal Behavioral Studies

Several types of in vivo behavioral studies are used to ascertain the reinforcing effects and pharmacodynamic effects of a drug. These studies help to determine whether or not a substance has abuse potential and to what pharmacological class of drugs the substance is most similar.

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General CNS effects

The Sponsor referenced published data indicating that rats administered 3 or 10 mg/kg IP fenfluramine did not produce any locomotor effects different from control (Baumann et al., 2000). This result is supported by the FOB conducted as part of Study # 9000406 which also did not find a locomotor effect of fenfluramine. These data indicate that although fenfluramine is a phenethylamine, similar in structure to the stimulant, amphetamine, it did not produce locomotor activity at the doses tested.

Reinforcing effects

The Sponsor provided a review of the literature to assess the reinforcing effects of fenfluramine in conditioned place preference, self-administration, and intracranial self-stimulation studies.

Conditioned Place Preference

Conditioned place preference (CPP) is a paradigm used to measure the rewarding effects of a drug. This procedure uses a neutral stimulus, such as an environmental cue, and pairs it with an unconditioned stimulus, or the drug. Mice or rats are habituated to the test apparatus which is typically composed of two parts of equal space that have different environmental cues (e.g., floors, walls, and lighting) so that the animal can discriminate between the two. The animal then undergoes a preference testing phase in which the experimenter determines which of the two compartments the animal prefers by timing how long they spend in a particular compartment. The conditioning phase is when the drug is given to the animal and they are locked into only one compartment of the apparatus. This is done several times in order to associate the motivational effects of the drug with the unconditioned stimulus. The conditioning phase is typically done in either a biased or unbiased method. For the biased method, drug is given and the animal is placed in the compartment they prefer the least as established by the preference phase. In the unbiased method, the researcher chooses which compartment will be associated with the drug cue. In the testing phase, the animals are allowed free access to both of the compartments. A rewarding drug stimulus is associated with the animal going to the conditioned compartment in which they received drug (Cunningham et al., 2006).

The Sponsor provided published literature indicating that five different CPP assays were conducted using fenfluramine as the unconditioned stimulus. Although the studies were conducted in different rat species, with different doses, and in different formats, the results were consistent in indicating that fenfluramine does not produce a rewarding drug stimulus. Rats demonstrated place aversion at doses between 2.5 and 10 mg/kg IP (Davies and Parker, 1993; Meehan and Schechter, 1994; Marona-Lewicka et al., 1996; Turenne et al., 1996; Rea et al., 1998), whereas phentermine produced significant preference to the phentermine associated chamber (Rea et al., 1998).

Self-administration

A self-administration assay is an experimental paradigm in which animals identify if a substance has positive reinforcing effects. Positive reinforcement occurs when the presentation of a desired stimulus results in an increase in behavior that is associated with the administration of the desired stimulus (Gauvin et al., 2017). For example, for abuse assessment purposes, animals are first trained to press a

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lever (behavior) resulting in the administration (typically IV) of a training drug (desired stimulus) known to be a drug of abuse (e.g., cocaine). Once properly trained, the animals undergo an extinction test to confirm that the training drug is the stimulus responsible for the reinforcing effects and not some other cue in the assay. Animals then receive a test drug, and rates of lever pressing and injections are measured. If the rates of administered drug are significantly different from placebo and the animals are not motor impaired by the drug, as measured by rates of lever pressing, the drug is said to be self-administered (Gauvin et al., 2017).

The Sponsor provided published self-administration studies in which fenfluramine was tested in rats, dogs, and nonhuman primates (baboons and rhesus monkeys). In the rat studies, the animals were trained to self-administer amphetamine or *d*-amphetamine and then tested with doses of fenfluramine between 0.0625 and 1.0 mg/kg/infusion IV. The studies concluded that the number of responses for fenfluramine did not differ from saline in rats (Gotestam and Andersson, 1975; Gotestam, 1977; Papasava et al., 1986). Rats tested with *d*-fenfluramine (0.05, 0.1, 0.25, and 1.0 mg/kg) or *l*-fenfluramine (0.1, 0.5, 1.0, and 2.0 mg/kg) also produced saline-like responding (Dahl and Götestam, 1989).

Beagle dogs were used to assess the relative reinforcing efficacy of cocaine, amphetamine, mazindol, and fenfluramine using a progressive ratio schedule of reinforcement. The dogs were initially trained to an FR30 with three of the dogs receiving cocaine (0.4 mg/kg/injection) and three receiving *d*-amphetamine (0.07 mg/kg/injection). After training, the dogs were moved to the testing phase in which successive increases in the FR were introduced in order to determine the breakpoint of each test drug. Fenfluramine was tested at 0.0625, 0.25, 1.0, and 4.0 mg/kg/infusion and none of the doses maintained self-administration above the minimum number of bar presses (30) (Risner and Silcox, 1981).

Griffiths conducted two studies aimed at determining the reinforcing effects of stimulants in baboons. In these studies, baboons were maintained on cocaine (0.4 mg/kg IV) to an FR 160. In the first study, eight different phenethylamines were tested and fenfluramine was the only drug that did not maintain self-administration at any of the tested doses (0.1, 0.5, and 1 mg/kg/infusion) (Griffiths et al., 1976). In the second study, cocaine was replaced by drug and if animals maintained six or more infusions per day for 2 days the ratio requirement was systematically increased (progressive ratio design) until the “break point.” Fenfluramine (0.02 – 5.0 mg/kg/infusion) did not maintain self-administration at any dose tested (Griffiths et al., 1978) and did not produce a reinforcing effect in baboons at the doses tested.

Several self-administration studies were also conducted to determine the reinforcing effects of fenfluramine in rhesus monkeys. The following studies trained rhesus monkeys to respond to cocaine (IV) under various reinforcement schedules ranging from FR10 to FR100. Fenfluramine failed to maintain drug appropriate responding in all of the studies at doses ranging from 0.003 to 1 mg/kg/infusion IV (Woods and Tessel, 1974; Aigner and Balster, 1979; Locke et al., 1996). However, positive controls used in the studies such as methohexital, d-amphetamine, morphine, oxymorphone, codeine, and pentazocine all produced reinforcing effects.

Intracranial Self-Stimulation (ICSS)

Intracranial self-stimulation (ICSS) is a behavioral paradigm in which operant responding is maintained or manipulated by pulses of electrical brain stimulation (Carlezon and Chartoff, 2007). Different

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regions of the brain can be targeted to study a desired effect. In the case of abuse-related drug effects, placement of the electrode is targeted to the medial forebrain bundle at the level of the lateral hypothalamus (Negus and Miller, 2014). Stimulation of this area can be manipulated through frequency or amplitude to engender a variety of response rates. The abuse potential of a substance is inferred through a comparison of response rates in the naïve state versus drug treatment. For example, drug-induced increases in low rates of responding maintained by low frequencies/amplitudes of stimulation may infer an abuse-related effect (Negus and Miller, 2014).

Two studies were conducted to assess the reinforcing effects of fenfluramine using the ICSS model. In the first study, electrodes were implanted into the medial forebrain bundle in adult male rats. Four to six days post-surgery, animals were trained to self-stimulate with increasing stimulus intensity until a threshold of 3000 or more responses were elicited during each of the last six training sessions. This was determined to be the baseline lever pressing value for the naïve animal. Treatments consisted of fenfluramine 20 mg/kg IP or amphetamine 2 mg/kg IP. Fenfluramine depressed lever activity suggesting fenfluramine does not produce a drug-induced reinforcing effect. A second treatment of fenfluramine after retraining produced a similar drop below baseline responding. Administration of amphetamine significantly increased lever responding (Olds and Yuwiler, 1992).

The second study was conducted to compare 11 monoamine releasers that vary in their selectivity for altering serotonergic and dopaminergic signaling. An electrode was inserted into the medial forebrain bundle of male rats and a baseline level of responding was determined for a specific frequency. Similar to the previous study, fenfluramine (0.1 – 10 mg/kg) produced dose-dependent decreases in responding suggesting that fenfluramine is devoid of reinforcing effects. Amphetamine and methamphetamine increased responding indicating that these drugs produce reinforcing effects and validating the study (Bauer et al., 2013).

Conclusion of Nonclinical Reinforcing Effects Studies

The reinforcing effects of fenfluramine and its isomers were assessed in a series of different nonclinical models including CPP, self-administration, and ICSS. The drug was also assessed in different animal species including rats, dogs, and nonhuman primates. All 17 studies that directly assessed the reinforcing effects of fenfluramine determined that the drug responded similarly to placebo and does not produce reinforcing effects. These data are consistent with 5-HT agonists that are phenethylamines and lack stimulant activity (Sanders-Bush et al., 1988; Nichols, 2004). As described in sections 1 and 2, fenfluramine is a phenethylamine that produces serotonergic agonist activity. Therefore, fenfluramine may be expected to produce placebo-like responding in these reinforcing assays. A serotonergic mechanism of action, specifically agonists of 5-HT_{2A}, is consistent with hallucinogenic or entactogenic activity (Nichols, 2004).

One caveat to these studies is that the pharmacokinetics of fenfluramine and its active metabolites were not determined, therefore, it is not possible to correlate how the doses used in these studies compare to human oral doses.

<u>Discriminative Stimulus Effects – Drug Discrimination</u>

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Drug discrimination is an experimental method in which animals identify whether a test drug produces physical or behavioral effects (an interoceptive response) similar to those produced by another drug with known pharmacological properties. If the known drug is one with abuse potential, drug discrimination can be used to predict if a test drug will have abuse potential in humans (Balster and Bigelow, 2003). For abuse assessment purposes, an animal is first trained to press one bar when it receives a known drug of abuse (the training drug) and another bar when it receives placebo. A challenge session with the test drug determines which of the two bars the animal presses more often, as an indicator of whether the test drug is more like the known drug of abuse or more like placebo. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing ≥80% on the bar associated with the training drug (Sannerud and Ator, 1995; Doat et al., 2003). A test drug that generalizes to a known drug of abuse will likely be abused by humans (Balster and Bigelow, 2003).

The Sponsor collected drug discrimination studies in which fenfluramine was tested against a range of different drug classes and drugs with different mechanisms of action. Drug classes in which fenfluramine was tested for its discriminative stimulus effects that are associated with abuse include stimulants, hallucinogens, and opioids.

Drug Discrimination studies with Stimulants:

As a phenethylamine, fenfluramine has a similar structure to stimulants such as amphetamine and methamphetamine. As a result, many drug discrimination studies were conducted to assess the discriminative stimulus effects of fenfluramine against stimulants using rats and nonhuman primates.

Twelve studies were conducted in rats trained to distinguish various stimulants from placebo. Fenfluramine did not produce full generalization (> 80% drug appropriate responding) in studies in which rats were trained to discriminate *d*-amphetamine (at doses ranging from 0.8 – 4 mg/kg IP) from placebo (Schechter and Rosecrans, 1973; Schechter, 1981; Schechter and Finkelstein, 1985; Locke et al., 1996). These data were supported by a study in rhesus monkeys that were trained to discriminate *d*-amphetamine or phenobarbital from saline using a signaled shock avoidance procedure. The animals were tested against families of compounds with similar mechanisms of action. Fenfluramine did not generalize to *d*-amphetamine and was not tested against the phenobarbital trained animals (Johanson, 1984; de la Garza and Johanson, 1987). Fenfluramine produced partial generalization (62%) to the *d*-amphetamine cue in one of the studies (Schechter and Finkelstein, 1985).

In another study, rats were trained to discriminate cocaine (10.0 mg/kg) from saline using a two-lever operant procedure. Dose-effect curves were determined for the substitution of cocaine for: diethylproprion, methylphenidate, phenmetrazine, phentermine, and fenfluramine. Fenfluramine was the only drug that did not fully generalize to the discriminative stimulus effects of cocaine. Fenfluramine at a dose of 2.5 mg/kg partially generalized (~40%) to the discriminative stimulus of cocaine (Wood and Emmett-Oglesby, 1988).

Drug discrimination studies were also conducted to directly assess the discriminative stimulus effects of fenfluramine by training rats to discriminate fenfluramine (at doses between 1 and 3 mg/kg), or its active metabolite, norfenfluramine (1.4 mg/kg), from saline. In these studies, the animals were then tested against a panel of other substances to better elucidate the discriminative stimulus effects of fenfluramine. Fenfluramine fully generalized to norfenfluramine (100%), lisuride (89% at 0.04 mg/kg),

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quipazine (87% at 4.0 mg/kg), MK-212 (97% at 0.5 mg/kg), and *p*-chloroamphetamine (PCA) (97% at 2.0 mg/kg) (Goudie, 1977; White and Appel, 1981; Boja and Schechter, 1988). Norfenfluramine fully generalized to the serotonergic agonists *meta*-chlorophenylpiperazine (mCPP) (94.4 % at 1 mg/kg), 2,5-dimethoxy-4-iodoamphetamine (DOI) (88.9% at 1.0 mg/kg), 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) (94.4% at 3.0 mg/kg), and lysergic acid diethylamide (LSD) (83.3% at 0.06 mg/kg) (Boja and Schechter, 1988).

In another study, three groups of rats were trained to discriminate either fenfluramine (1.0 mg/kg IP), phentermine (1.0 mg/kg IP), and a 1:1 mixture of fenfluramine:phentermine (1 mg/kg of each IP) from saline under an FR10 schedule of reinforcement. The doses of fenfluramine and phentermine were increased to 2 mg/kg IP in order for the rats to acquire stimulus control. Cocaine (0.03 – 10.0 mg/kg IP), amphetamine (0.1 – 3.0 mg/kg IP), and nicotine (0.1 – 0.8 mg/kg IP), did not generalize or only partially generalized to the fenfluramine, phentermine, or fenfluramine/phentermine cue (Shoaib et al., 1997).

In separate studies, fenfluramine did not generalize to the discriminative stimulus effects of S(-)-methcathinone (0.5 mg/kg IP) (Young and Glennon, 1998), methamphetamine (1.0 mg/kg) (Munzar et al., 1999), or *dl*-cathinone (2.0 mg/kg) (Goudie et al., 1986).

The discriminative stimulus effects of fenfluramine were also assayed in pigeons trained to discriminate amphetamine (2 mg/kg IM) (Johanson, 1984; Evans and Johanson, 1987; Evans et al., 1990) or methamphetamine (1.0 – 1.7 mg/kg IM) from saline (Sasaki et al., 1995). In pigeons trained to discriminate amphetamine from saline, fenfluramine (1.0 – 17.0 mg/kg) partially substituted for the amphetamine cue (Johanson, 1984; Evans and Johanson, 1987). However, in the methamphetamine trained pigeons, fenfluramine (3.0 – 10 mg/kg) produced full substitution in three of four birds at doses that had minimal effect on response rates.

In general, these studies indicate that fenfluramine does not produce a discriminative stimulus cue that is similar to classically defined stimulants.

Drug Discrimination studies with Serotonergic Modulators

There are a group of substances that, like fenfluramine and norfenfluramine, have a phenethylamine structure and do not produce stimulant-like effects. These substances can be psychoactive and produce entactogenic or hallucinogenic effects such as increasing emotional awareness or seeing or hearing things that are not present. Many of these substances produce these effects through modulation of the serotonergic system (Nichols, 2004). As a result, many drug discrimination studies were conducted to determine if and how fenfluramine or norfenfluramine modulate serotonergic signaling and if the stimulus effects were similar to that of known entactogens or hallucinogens.

The first indication that fenfluramine produced stimulus effects through modulation of the serotonergic system in a drug discrimination assay was conducted by Barrett in 1982. In this study, rats were trained to discriminate L-5-hydroxytryptophan (L-5-HTP) (30 mg/kg SC) in a two-lever drug discrimination assay using a variable interval (VI) 20 schedule of reinforcement. L-5-HTP is a precursor to 5-HT and increases 5-HT levels and signaling in the brain. Fenfluramine fully generalized to the L-5-HTP cue at 2.5 mg/kg (86%) and 3.0 mg/kg (100%) but did not generalize to amphetamine (Barrett et al., 1982).

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The studies that follow were conducted on different serotonin signaling agents to determine the specific stimulus effects that fenfluramine and norfenfluramine produce. In the first group of studies presented here, rats were trained to discriminate fenfluramine from saline in a two- or three- lever paradigm and then tested against a panel of other drugs. Serotonin antagonists attenuated the fenfluramine cue and norfenfluramine (100% at 3 mg/kg), *p*-fluoro-amphetamine (100% at 4 mg/kg), and *p*-chlordiazepoxide (CIV) (~92% at 0.5 mg/kg) fully generalized to the fenfluramine cue (McElroy and Feldman, 1984). Fenfluramine also fully generalized to 1-(m-trifluoro-methylphenyl)piperazine (TFMPP) (91% at 1.6 mg/kg and 92% at 0.8 mg/kg) (Cunningham and Appel, 1986; McKenney and Glennon, 1986). The Schechter lab conducted a series of drug discrimination studies with fenfluramine. These studies determined that:

1. There was no difference in the rate of learning of the fenfluramine cue between obese and lean Zucker rats (Schechter, 1986b)
2. Fenfluramine generalized to tetrahydro-beta-carboline (THBC) trained rats and THBC generalized to fenfluramine trained rats (Schechter, 1986c; Schechter, 1987)
3. *l*-Fenfluramine produced 85% responding on the fenfluramine appropriate lever at 2.5 mg/kg and (±)-norfenfluramine (2.0 mg/kg) produced a faster onset with 84% responding on the drug appropriate lever (Schechter, 1990b)
4. Fawn hooded rats were used in a drug discrimination study to assess fenfluramine because of their increased sensitivity to serotonergic signaling. In these rats, 3,4-Methylenedioxy methamphetamine (MDMA) fully substituted (92.9%) for fenfluramine. TFMPP (72%), m-CPP (77.8%), quipazine (75%), and fluoxetine (78.6%) all partially generalized to fenfluramine (Schechter, 1997b).
5. Rats were trained to discriminate between *d*-amphetamine (0.4 mg/kg IP) and norfenfluramine (0.7 mg/kg IP). Dopaminergic and serotonergic drugs were tested in order to determine if rats could distinguish between the effects produced by these pathways. MDMA, at the highest dose tested of 2.0 mg/kg IP produced 83.3% responding on the norfenfluramine lever. LSD at the highest dose of 0.12 mg/kg produced 83.3% responding on the norfenfluramine lever (Schechter, 1997a).
6. Schecter and colleagues investigated how toxic doses of fenfluramine would affect the discriminative stimulus effects of fenfluramine. Male rats were trained to discriminate fenfluramine (2.0 mg/kg IP) from vehicle using a food reinforced, two-lever operant task, with an FR10 level of reinforcement. Once training criteria were achieved, the animals were tested with 0.5, 1.0, or 1.5 mg/kg IP fenfluramine to establish a baseline. Doses of 1.5 mg/kg and 2.0 mg/kg produced 100% responding on the drug appropriate lever, while 1.0 mg/kg produced 54.6%, and 0.5 mg/kg produced 36.4% responding. The animals were then given saline or a toxic dose of fenfluramine (6.25 mg/kg IP) for four days and allowed to equilibrate for 14 days. Animals dosed with toxic doses of fenfluramine significantly increased their level of fenfluramine-appropriate responding compared to the saline control group. According to the authors, this suggests that a supersensitivity to serotonergic signaling may occur after damage to serotonergic neurons (Schechter, 1990a).

The drug discrimination studies presented here support that the discriminative stimulus effects of fenfluramine are through serotonergic signaling pathways. To better differentiate these pathways, specific studies were conducted to isolate possible serotonergic signaling pathways with comparisons to

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serotonergic agonists with known psychoactive effects. The purpose of the following studies was to investigate the role of 5-HT receptors in the discriminative stimulus effects of fenfluramine.

The 5-$HT_{2C/1B}$ receptor agonist mCPP and the 5-HT_{2C} receptor agonist MK-212 fully generalized to the discriminative stimulus cue of fenfluramine suggesting a possible mechanism of action for fenfluramine (McCreary et al., 2003). These data were supported in further studies for mCPP for low doses of fenfluramine (1 and 2 mg/kg IP). However, as doses increased, responding on the drug-appropriate lever decreased as response rates were attenuated (13% of control) (Callahan and Cunningham, 1994; Bourson et al., 1996; Gommans et al., 1998). In a similar study male rats were trained to discriminate MK-212 (0.5 mg/kg) from saline in a two-lever discrimination task to a FR20 schedule of reinforcement. Fenfluramine (100% at 2.0 mg/kg) and mCPP (~98% at 1 mg/kg) fully substituted for the stimulus effects of MK 212 at doses that severely affected response rates (Cunningham et al., 1986). These studies indicate that fenfluramine may function as an agonist at the 5-HT_{1B} or the 5-HT_{2C} receptors. In a study by Gardner and colleagues, fenfluramine and yohimbine did not substitute for the stimulus effects of the 5-HT receptor (5-HT_{1A} and 5-HT_{1B}) agonist RU-24969 (Gardner, 1989). The 5-HT_{1A} and 5-HT_{1B} receptors are not typically associated with abuse potential. The 5-HT2C receptor modulates hallucinogenic activity that is induced by other serotonin receptors (Canal et al., 2010).

The following study sought to determine whether quipazine (serotonin agonist) and ketanserin (serotonin antagonist) discrimination is sensitive to changes in serotonin neurotransmission which is mediated through the 5-HT_{2A} receptor. Rats were trained to discriminate quipazine (0.35 mg/kg) from ketanserin (1.0 mg/kg) on a VI-30 schedule of reinforcement. In this study, fenfluramine (1.0 mg/kg) and norfenfluramine (3.0 mg/kg) fully substituted for the stimulus effects of quipazine (Smith et al., 2002). These results indicate the fenfluramine and norfenfluramine may act as agonists at the 5-HT_{2A} or 5-HT_3 receptors and activation of 5-HT_{2A} is correlated to the psychoactive effects produced by hallucinogens (Nichols, 2004).

The possible activation of fenfluramine at the 5-HT_{2A} receptor leads to the hypothesis that it produces psychoactive effects similar to hallucinogens. In rats, fenfluramine (1 mg/kg) did not substitute for the stimulus effects of LSD (9%), partially substituted for the discriminative stimulus effects of mescaline (53%) (Callahan and Appel, 1988), and chose 3,4-methylenedioxymethamphetamine (MDMA) (CI) (~80% at 2 mg/kg) over LSD in a 3-choice drug discrimination procedure (Goodwin et al., 2003). Three other studies produced results demonstrating that MDMA produces a similar discriminative stimulus effect as fenfluramine. MDMA fully generalized to the discriminative stimulus effects of fenfluramine at doses of 2 to 4 mg/kg IP (Schechter, 1986a; Baker et al., 1997; Goodwin and Baker, 2000). In the Goodwin study, fenfluramine (2.0 mg/kg IP) produced 75% drug-appropriate responding on the MDMA lever with eight of ten animals demonstrating complete, greater than >80%, MDMA lever responding. Rates of responding decreased by half at 2 mg/kg fenfluramine and decreased to almost zero at 4 mg/kg fenfluramine (Goodwin and Baker, 2000). MDMA's primary mechanism of action is as a monoaminergic releasing agent of serotonin, norepinephrine, and dopamine into the synaptic cleft (Nichols, 2004). Fenfluramine also fully generalized to LSD (83.3% at 0.06 mg/kg) (Boja and Schechter, 1988) and *d*-Fenfluramine fully generalized to the serotonin release agent 5-methoxy-6-methyl-2-aminoindan (MMAI) (Marona-Lewicka and Nichols, 1994).

Fenfluramine partially generalized (58.3%) to ibogaine, a serotonin reuptake inhibitor that also has some opioid effects (Schechter and Gordon, 1993). Fenfluramine also partially generalized (66% at 1.00

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mg/kg IP) to the discriminative stimulus cue of para-methoxy-N-methylamphetamine (PMMA) which is similar to para-methoxyamphetamine (PMA) (CI) and is proposed to be a serotonin selective releasing agent (Glennon et al., 1997). However, fenfluramine partially generalized (68%), and in another study, fully generalized to the monoamine releasing agent 4-methyl methcathinone (mephedrone or 4-MMC) (Varner et al., 2013; Berquist et al., 2017). These studies indicate that fenfluramine produces effects similar to other serotonin releasing agents.

Fenfluramine did not generalize to the discriminative stimulus cue produced by dizocilpine (MK-801) (Zajaczkowski et al., 1996), CGP 37849 (Zajaczkowski et al., 1996), 5,6,7,8-Tetrahydro-1,3-dioxolo[4,5-g]isoquinoline (TDIQ) (Young and Glennon, 2002), 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) (CI) (Li et al., 2009), 3,4-methylenedioxypyrovalerone (MDPV) (CI) (Berquist and Baker, 2017).

Two studies were conducted using pigeons as the test species. In the first study, pigeons were trained to discriminate (+)-amphetamine (1.7 or 3.0 mg/kg), fenfluramine (5.6 or 10 mg/kg), and saline in a three-choice drug discrimination assay. The results of the study indicate that pigeons can discern between the stimulus effects of (+)-amphetamine and fenfluramine. The serotonin agonists, quipazine and MK 212, produced fenfluramine-appropriate responding in two pigeons and amphetamine appropriate responding in one pigeon (Evans et al., 1990). In the second study, different groups of pigeons were trained to discriminate quipazine (1.0 mg/kg) from saline or *l*-5-hydroxytryptophan (*l*-5-HT) (18 mg/kg) from saline in a two-choice discrimination procedure to an FR40. Fenfluramine at doses of 10 and 18 mg/kg evoked > 90% responding on the drug-appropriate lever in both training groups suggesting that fenfluramine produces effects that are mediated through serotonergic pathways (Walker et al., 1991).

Drug Discrimination Studies with Other Drug Classes

Several studies were conducted to assess the discriminative stimulus effects of a substance in which fenfluramine was used as part of a panel to ascertain the stimulus effects of that substance. In general, these studies used similar paradigms in which rats were trained to discriminate the effects of the substance to saline in a drug discrimination procedure. Fenfluramine did not generalize to any of the drugs discussed in this section. Specifically, fenfluramine did not generalize to the discriminative stimulus effects of the beta blocker propranolol (Young and Glennon, 2009), the kappa opioid receptor (KOR) agonist spiradoline (Holtzman and Steinfels, 1994), the phenethylamine cathine (Schechter, 1991), the β2 agonist clenbuterol (McElroy and O'Donnell, 1988), and phenethylamine (Reid and Goudie, 1986).

Conclusion of Nonclinical Drug Discrimination Studies

Fenfluramine was first thought of as a stimulant based on its phenethylamine structure. However, fenfluramine did not generalize to stimulants in published studies that tested the discriminative stimulus effects of fenfluramine against a range of stimulant drugs. When rats were trained to discriminate fenfluramine from vehicle or other drugs, it became evident that fenfluramine produced discriminative stimulus effects similar to those of serotonin releasing agents and serotonin agonists such as quipazine and MK-212. Substances that act as agonists at specific serotonin receptors, such as 5-HT_{2A} can produce psychoactive effects such as hallucinations or entactogenic effects. Fenfluramine fully

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generalized to drugs that do not have abuse potential such as lisuride, quipazine, and TFMPP, and generalized to some drugs that do have abuse potential such as MDMA and LSD.

2.5 Tolerance and Physical Dependence Studies in Animals

The Sponsor did not conduct or provide any data assessing the tolerance or physical dependence of fenfluramine in animals.

3. Clinical Pharmacology

Determining the clinical pharmacology of a drug is an important aspect in understanding the mechanism of action of a drug of abuse. Understanding the PK parameters can give an indication as to how a drug will be abused and therefore how it should be tested in a human abuse potential study.

3. 1 Absorption, Distribution, Metabolism, Elimination (ADME)

The Sponsor provided published data and data from their clinical studies indicating that fenfluramine is well-absorbed. According to the Sponsor, the absorption of a dose of 15 mg BID (the maximum therapeutic dose) is not affected by food as indicated by Cmax, Tmax, and AUC (Study #1505 part 2). The literature indicates that the oral bioavailability of fenfluramine is 68% to 74% (Bever and Perry, 1997). Fenfluramine distributes throughout the body with high concentrations in the brain, kidney, liver, and urine (Pinder et al., 1975). The mean protein binding of fenfluramine and norfenfluramine were approximately 50%. Fenfluramine is metabolized by N-dealkylation to norfenfluramine both of which are excreted in the urine (Beckett and Brookes, 1967; Bruce and Maynard, 1968; Marchant et al., 1992). The majority of radiolabeled drug and metabolites are excreted in the urine with a small amount in the feces.

The Sponsor conducted several studies to assess the efficacy, safety, and tolerability of fenfluramine in diseased subjects or in healthy subjects. Healthy subjects typically produce a more stable and comparative analysis of pharmacokinetic parameters to use as a comparison between dosing for animal and human studies. To that end, one part of clinical Study # ZX008-1505 was conducted to determine the food effect on the PK of fenfluramine in healthy subjects. In this study 90 healthy subjects were given a single oral dose of 0.8 mg/kg fenfluramine and the PK parameters of fenfluramine and norfenfluramine were determined in 19 of those subjects (**TABLE 8**). The Sponsor proposes that the maximum dose of fenfluramine will be (b) (4). The data indicate that at the highest proposed therapeutic dose, fenfluramine is readily absorbed orally and has an extremely long half-life of 19.8 hours. Its major active metabolite, norfenfluramine, reaches its Tmax at 12 hours and produces half the total exposure of fenfluramine with a longer half-life of 23.4 hours.

Table 8: Pharmacokinetic Parameters of Fenfluramine and Norfenfluramine After a Single Oral Dose of Fenfluramine (0.8 mg/kg) in Healthy Subjects (Study # ZX008-1505)

	Fenfluramine	**Norfenfluramine**

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Cmax (ng/mL)	61.9 (14.1)	15.8 (31.1)
Tmax (h)	3	12
$AUC_{0\text{-}inf}$ (ng·hr/mL)	1660 (28.9)	836 (9.5)
$t_{1/2}$ (h)	19.84 (16.1)	23.4 (9.9)

Study # ZX008-1603 examined the PK at steady state. Healthy subjects were orally administered 15 mg BID (total of 30 mg/day) or 60 mg BID (total of 120 mg/day) of fenfluramine for seven days at which time PK parameters were assessed (**TABLE 9**).

Table 9: Pharmacokinetic Parameters of Fenfluramine and Norfenfluramine After a Single Oral Dose of Fenfluramine at Steady State in Healthy Subjects (Study # ZX008-1603)

Dose	**15 mg/kg BID**		**60 mg/kg BID**	
	Fenfluramine	**Norfenfluramine**	**Fenfluramine**	**Norfenfluramine**
Cmax (ng/mL)	44.84 (26.0)	24.06 (33.8)	233.7 (31.7)	101.9 (38.9)
Tmax (h)	5.5	8	4	8
$AUC_{0\text{-}12}$ (ng·hr/mL)	478.2 (26.8)	269.1 (33.5)	2493 (33.1)	1141 (39.1)

4. Clinical Studies

4.1 Human Abuse Potential Studies

The Sponsor did not conduct a human abuse potential study to assess the subjective effects of fenfluramine. The Sponsor did provide summaries of published studies in which the subjective effects of fenfluramine was assessed in humans. Note, several studies in the published literature involve the use of fenfluramine but did not directly assess its abuse potential. As a result, these studies are not included in this assessment.

1. (Gotestam and Gunne, 1972) – In this study the subjective effects of fenfluramine and AN 448 were evaluated in amphetamine-dependent subjects. The study was a placebo- and positive-controlled, double-blind, four-way cross-over study to assess single doses of fenfluramine (80 mg PO), AN 448 (2 mg PO), (±)-amphetamine (50 mg PO), and placebo. Twenty-two imprisoned male volunteers who were amphetamine-dependent completed the study. Self-rating scales for “happiness” and “tiredness” were assessed on a one to nine scale (no effect to extreme effect) at 1, 3, and 6 hours post-administration. These scores were put into an equation to produce a relative “CS effect.” The “CS effect” determined that amphetamine produced significantly higher scores than placebo at 3 and 6 hours, whereas fenfluramine and AN 448 produced placebo level responding. The subjects also determined that fenfluramine did not produce effects similar to amphetamine and were not significantly different from placebo. This study concluded that the subjective effects of fenfluramine (80 mg) did not differ from placebo.

2. (Levin, 1973) – This is an anecdotal report that stated that over the course of 2 years he treated patients in South Africa who claimed to abuse fenfluramine at doses of approximately 80 mg.

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These patients claimed to experience euphoria, derealization, and perceptual changes as well as tolerance. Most subjects claimed that they only used fenfluramine as a replacement for other drugs of abuse and the majority preferred other drugs. The article notes that there were two subjects who had severe adverse events that discouraged further use of the drug.

3. (Holmstrand and Jonsson, 1975) – This study was a double-blind cross-over trial of AN 448 (1 mg) and fenfluramine (40 mg) given BID for 3 weeks to 9 healthy subjects. Self-rating scales for appetite, mood, ability to concentrate, and quality of sleep were administered daily. A decrease in the ability to concentrate was seen after administration of fenfluramine for the first week, as was a decrease in mood. These measurements were back to normal by the end of the second week of administration.

4. (Griffith et al., 1975) – This study compared the subjective effects of amphetamine and fenfluramine in eight incarcerated volunteers who had various drug use experience including narcotics, cocaine, LSD, amphetamine, and hallucinogens. The doses of (±)-amphetamine 20 and 40 mg PO were determined from prior studies and (±)-fenfluramine doses (60, 120, and 240 mg) were consistent with doses that were previously marketed (60 and 120 mg PO) to supratherapeutic (2-fold). A subject given 270 mg of fenfluramine reported paranoid thoughts leading to the use of the highest dose of 240 mg. Subjective effects were determined through a series of questionnaires: Single Dose Opiate Questionnaire (subjects and observers), Addiction Research Center Inventory (ARCI) Morphine-Benzedrine group scale (MBG), Lysergic Acid Diethylamide (LSD) group scale, a measure of dysphoric and somatic symptoms, and an Amphetamine Scale. The Amphetamine, MBG, and Subject's Liking Scale Scores all indicated that (±)-amphetamine produced significant drug liking with no dysphoric effects. (±)-Fenfluramine produced substantial variability between doses, and in response to the same dose on the Subject's Liking Scale Scores. Three subjects indicated that the 60 mg dose of (±)-fenfluramine was psychoactive, this number increased at the 120 mg dose, however dysphoric effects increased dramatically through to the 240 mg dose. According to the authors, the dysphoric effect became the prevailing and predominant effect at the higher doses. The MBG scales were not different from placebo, however, an analysis of peak scores indicated that there were significant increases in fenfluramine's affects. Fenfluramine at 240 mg produced sedation in five of the eight subjects, these subjects did not have hallucinogenic phenomena. Three of the subjects did have varying degrees of hallucinations two of which were characterized as unpleasant. This study determined that fenfluramine at doses of 120 mg and 240 mg was able to produce euphoric and hallucinogenic effects, however, the predominant effect at these doses was aversive (dysphoric) and produced sedation.

5. (Bigelow et al., 1980) – This study was designed to evaluate the reinforcing effects of stimulants. Fifty-nine overweight subjects were randomly assigned to receive either *d*-amphetamine (5 mg), fenfluramine (20 mg), or placebo in a double-blind procedure. Subjects were given medication during a 4-week period and advised on how to take the medication. The recommended dose was 1 pill/day, however, subjects could take more (0 to 6 pills) based on individual effects. Self-administration of the *d*-amphetamine group was well maintained but did not differ from placebo. However, significantly fewer doses of fenfluramine were self-administered than *d*-amphetamine or placebo. The fenfluramine group also discontinued their treatment more quickly than the placebo or the *d*-amphetamine groups because of gastrointestinal distress.

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6. (Johanson and Uhlenhuth, 1982) – The authors designed a nine-session study divided into two parts. In part 1, which consisted of four sessions, subjects were given two drugs and mood questionnaires were filled out pre-dose and 1, 3, and 6 hours post-dose. In part 2, subjects chose which of the drugs they would like to self-administer. In part 1 subjects chose amphetamine (5 mg) over placebo. In part 2, fourteen subjects were used in a three-choice experiment comparing amphetamine (5 mg), fenfluramine (20 mg), and placebo. In this experiment, none of the results were statistically significant, however, subjects chose amphetamine over placebo 3-fold more often and amphetamine over fenfluramine at a similar rate. The Profile of Mood States (POMS) and ARCI measurements were similar for fenfluramine and placebo, and significantly less than the scores for amphetamine.

7. (Brauer et al., 1996) – This study evaluated the subjective effects of phentermine and fenfluramine alone and in combination. Seven male and five female normal healthy subjects tested d-amphetamine (10 and 20 mg), phentermine (30 mg), fenfluramine (40 and 80 mg), combinations of phentermine and fenfluramine and placebo in an eight-session double-blind study. Several dependent measures were utilized in the study including a POMS, ARCI (A, BG, LSD, MBG, and PCAG), including several Visual Analog Scales (VAS). Amphetamine and phentermine produced scores on VAS of "Drug Liking" and "Want More" that were significantly greater than placebo. However, fenfluramine produced scores on VAS of "Feel Drug," "Anxious," and "Down," and on the POMS increasing measures of positive mood, elation, confusion, and anxiety that were significantly different from placebo. Subjects who took fenfluramine did not have scores different from placebo on VAS measures of "Want More", "Feel High", or "Like Drug."

8. (Foltin et al., 1996) – This study was designed to assess the subjective effects of fenfluramine (20 or 40 mg PO BID) compared to placebo in healthy adults (5M:4F). Eighteen VAS scales were administered as part of the assessment; however, they are not detailed in the published article. Fenfluramine produced significant differences in scales of "Alert," "Tired," "Friendly," "Irritable," and "Talkative," and it is assumed it had no significant effect on the remaining13 scales not listed in the paper. As such, although an assessment of VAS measures associated with abuse potential may have been conducted, they are not discussed in the paper.

9. (Chait et al., 1986) – The discriminative stimulus and subjective effects of *d*-amphetamine, phenmetrazine, and fenfluramine were studied in 14 subjects trained to discriminate *d*-amphetamine (10 mg) from placebo. Subjective effects were assessed using POMS, ARCI (A, BG, LSD, MBG, and PCAG), and several Visual Analog Scales (VAS). Doses of 20 and 40 mg fenfluramine did not generalize to *d*-amphetamine (10 mg) in healthy human subjects. Amphetamine and phentermine produced subjective scores significantly different from placebo. According to the authors, fenfluramine produced essentially no measurable subjective effects with the only significant effect of VAS "High" ($P < 0.02$) being higher than placebo.

Conclusion of Clinical Studies on the Subjective Effects of Fenfluramine

A review of the published literature on the subjective effects of fenfluramine in humans indicates that single oral doses below 80 mg do not produce significant positive subjective effects and high doses

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ranging from 120 to 240 mg can produce positive subjective effects. However, the predominant effects at high doses were aversive and include sedation. There are anecdotal reports of abuse from doctors, however, they mention that subjects prefer other drugs. This statement is consistent with the measures indicating that subjects are tired, do not appreciate the psychoactive effects of fenfluramine, and do not "Want More" of the drug when asked.

4.2 Adverse Event Profile Through all Phases of Development

The Sponsor conducted clinical trials to assess the safety and efficacy of fenfluramine hydrochloride. The following is a description and analysis of abuse-related adverse events (AEs) found during different phases of clinical development. All AEs, including abuse-related AEs were coded to a Medical Dictionary for Regulatory Activities (MedDRA) and the MedDRA system organ class (SOC) and preferred term (PT).

Phase1 studies:
A Two Part, Randomized, Open-label, Single-dose, 3-way Crossover Study to Evaluate the Drug-drug Interaction Between ZX008 (Fenfluramine Hydrochloride) Oral Solution and Stiripentol Regimen (Stiripentol/Clobazam/Valproate) (Part 1) and Single-dose, 2-way Crossover Food Effect of ZX008 (Part 2) in Healthy Volunteers ZX008-1505

The primary objective of the study was:

- To assess the pharmacokinetic (PK) profile of ZX008 administered as a single oral dose with and without stiripentol regimen (stiripentol/clobazam[CLB; a benzodiazepine]/ valproate [VPA]), and in the fed and fasted state

Part 1
Subjects were randomized on Day 1 of Period 1 to receive each of the following oral doses over 3 study periods, separated by at least a 17-day washout period:

- Regimen A: 0.8 mg/kg ZX008
- Regimen B: 3500 mg stiripentol capsules, plus 20 mg CLB tablet and 25 mg/kg VPA
- Regimen C: 0.8 mg/kg ZX008 plus 3500 mg stiripentol, 20 mg CLB tablet and 25 mg/kg VPA

Part 2
Part 2 of this study was conducted using an open-label, randomized, single-dose, 2-period crossover design to evaluate the effect of food on the PK of ZX008. Subjects were admitted to the clinical unit on the evening before dosing and randomized on Day 1 of Period 1 to receive each of the following oral doses over 2 study periods, separated by at least a 9-day washout period:

- Regimen D: 0.8 mg/kg ZX008 following an overnight fast
- Regimen E: 0.8 mg/kg ZX008 following a high-fat breakfast.

The abuse-related AEs in study ZX008-1505 are displayed in **Tables 10 and 11**

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Table 10: Abuse-related AEs ZX008-1505 (n%) Part 1

Preferred Term	ZX008 N=20	Stiripentol N=21	ZX008+Stiripentol (N=25)
Somnolence	1 (5)	12 (57.1)	19 (76)
Disturbance in attention	1 (5)	0	0
Feeling Drunk	0	0	2 (8)
Anxiety	2 (10)	0	2 (8)
Euphoric mood	0	1 (4.8)	2 (8)
Depressed mood	0	0	2 (8)
Agitation	1 (5)	0	0
Hyperhidrosis	0	1(4.8)	0

Table 11: Abuse-related AEs ZX008-1505 (n%) Part 2

Preferred Term	ZX008 Fasted (N=14)	ZX008 Fed (N=13)
Somnolence	1(7.1)	1 (7.7)

In this study, supratherapeutic doses (0.8 mg/kg) of ZX008, when administered alone do not produce abuse-related AEs. Euphoria, 'feeling drunk' occur in combination with other anti-seizure drugs. This is not unexpected because clobazam is a benzodiazepine, a drug with abuse potential.

An Open-label, 1-way Treatment Sequence, Drug-drug Interaction Study to Evaluate the Pharmacokinetics of ZX008 (Fenfluramine Hydrochloride) Oral Solution Administered as a Single Dose with and Without Cannabidiol BID for 18 Days in Recreational Drug Users ZX008-1604

The primary objective was to assess the pharmacokinetic (PK) profiles of fenfluramine and norfenfluramine following a single dose of ZX008 0.4 mg/kg oral solution administered with a meal, with and without co-administration of cannabidiol (CBD), in otherwise healthy, adult recreational drug users.

This Phase 1 study was a single-center, 1-sequence treatment, single-dose, drug-drug interaction (DDI) study of ZX008 (fenfluramine HCl) and CBD in otherwise healthy, adult recreational drug users.
Inclusion criteria:

Healthy male or female subjects who were non-dependent, recreational drug users who had used cannabinoids (e.g., smoked marijuana or hashish or used oral THC) at least 10 times in the year prior to screening. **Recreational drug users with recent experience using cannabis products were chosen for enrollment because they were anticipated to be less affected by the THC component of the treatment than cannabis-naïve, healthy volunteers**.

Exclusion criteria:

Subjects were not considered eligible to participate in this study if any one of the following exclusion criteria were satisfied:

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1. Substance or alcohol dependence within the past 2 years (excluding nicotine and caffeine).
2. Positive urine drug screen.

A dose of ZX008 0.4 mg/kg (the maximum single therapeutic dose is 0.35mg/kg) was selected for this DDI study. For the purpose of this study, the available CBD product contained 5% THC (the ratio of CBD to THC was 20 to 1).

Subjects were admitted to the CRU and on Day 1, received a single dose of ZX008 (0.4 mg/kg) oral solution with a meal; PK sample collection and safety assessments were conducted in the CRU up to at least 48 hours postdose (Day 3). Subjects were discharged from the CRU after the 48-hour PK sample collection. Subjects returned to the CRU on Day 13 (7 days after the last visit) for the second inpatient visit. On Day 14, subjects began a titrated dosing regimen of CBD up to 500 mg BID. On Day 22, subjects also received a single dose of ZX008 0.4 mg/kg concomitantly with the CBD morning dose in order to characterize the PK profiles of fenfluramine and norfenfluramine following co-administration of ZX008 with the interaction drug CBD. Subjects continued to receive CBD alone until Day 31. The abuse-related AEs in study ZX008-1604 are displayed in **Table 12.**

Table 12: Abuse-related AEs ZX008-1604 n (%)

Preferred Term	ZX008 0.4 mg/kg (N=32)	CBD 100 mg (N=17)	CBD 200 mg (N=24)	CBD 300 mg (N=17)	CBD 400 mg (N=15)	CBD 450 mg (N=5)	CBD 500 mg (N=7)	ZX008 0.4 mg/kg + CBD 400 mg (N=14)
Feeling abnormal	0	0	0	0	0	0	1(14.3)	0
Feeling of relaxation	0	0	0	1 (5.9)	0	0	0	0
Disturbance in attention	0	0	1 (4.2)	0	0	0	0	0
Lethargy	0	0	0	0	0	0	1 (14.3)	0
Somnolence	0	6 (35.3)	4 (16.7)	3 (17.6)	12 (80)	1 (20)	3 (42.9)	0
Agitation	0	0	0	0	1 (6.7)	0	0	0
Anxiety	0	0	0	0	1 (6.7)	0	0	0
Disorientation	0	0	0	0	1 (6.7)	0	0	0
Dissociation	0	0	0	0	0	0	1 (14.3)	0
Euphoric mood	0	1 (5.9)	6 (25)	4 (23.5)	6 (40)	5 (100)	7 (100)	1 (7.1)
Hypervigilance	1 (3.1)	0	0	0	0	0	0	0
Irritability	0	0	0	0	1 (6.7)	0	0	0
Paranoia	0	0	0	0	1 (6.7)	0	0	0
Restlessness	0	0	0	1 (5.9)	0	0	2 (28.6)	0
Hyperhidrosis	0	0	0	0	0	1 (20)	0	0

Reference ID: 4620035

In this study of recreational drug users, euphoria was reported in subjects administered CBD but not in subjects receiving fenfluramine

A Multicenter Trial to First Assess the Pharmacokinetic and Safety Profile of a Single Dose of ZX008 (Fenfluramine Hydrochloride) Oral Solution When Added to Standard of Care Treatment in Children and Young Adults with Dravet Syndrome; Study ZX008-1504 Cohort 1.
Study 1504 was a 2-part study conducted in separate cohorts. Cohort 1 was an open-label single-dose PK study to assess the PK and safety of low doses of ZX008 when administered with a standard treatment regimen and to provide data in order to identify the dose of ZX008 to be tested in the second part (Cohort 2).
Objectives

- To assess the PK profile of fenfluramine hydrochloride oral solution (ZX008) administered as a single oral dose with clobazam (CLB) + valproate (VPA) or with CLB + VPA + stiripentol (STP) in subjects aged 2 to 18 years with Dravet syndrome

Subjects in Cohort 1 received a single dose of 0.2 or 0.4 mg/kg of ZX008 added to their usual doses of CLB + VPA or CLB + VPA + STP. After completion, eligible subjects who intended to enroll in the separate open-label extension study entered the Transition Period at a fixed dose of ZX008 0.2 mg/kg/day for up to 24 weeks.

No abuse-related AEs were reported but these would be difficult to ascertain in a population with neurological impairments on multiple medications in a study with no placebo group.

A Randomized, Double-Blind, Double-Dummy, Placebo and Positive-Controlled, 3-Arm, 4-Treatment, Parallel Study to Evaluate the Effect of Multiple Doses of ZX008 on the QTc Interval in Healthy Adult Subjects ZX008-1603

The primary objective of this study was to evaluate the effects of multiple oral administrations of a therapeutic and supratherapeutic dose of ZX008 on the QT interval.

This was a randomized, double-blind, placebo- and positive-controlled, multiple-dose, 3-arm (therapeutic dose, supratherapeutic dose, and control), 4-treatment, parallel study in healthy adult subjects. Within the control arm, a randomized crossover was employed (with the subjects in this arm receiving both controls: the positive control [moxifloxacin] and the placebo control). One hundred and eighty (180) healthy, adult male and female subjects were enrolled.

Subjects were randomized to 1 of 3 treatment arms: therapeutic treatment arm (60 subjects Treatment A; 15 mg ZX008), supratherapeutic treatment arm (60 subjects Treatment B; 60 mg ZX008), or control treatment arm (60 subjects). Subjects enrolled in the control treatment arm were further randomized to receive 1 of 2 treatments (30 subjects for each treatment).

Subjects enrolled in the therapeutic treatment arm (Cohort 1, Treatment A) and supratherapeutic treatment arm (Cohort 2, Treatment B) received multiple oral doses of ZX008 twice daily (BID) on

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Days 1 to 6 with a single ZX008 dose administered on the morning of Day 7. Moxifloxacin matching placebo was coadministered with ZX008 on the morning of Day 1 and administered alone on Day 8.

Subjects enrolled in the control treatment arm (Cohort 3) were further randomized to receive 1 of 2 treatments (Treatment C or D). Moxifloxacin prolongs QT interval duration and was used as a positive control and 30 subjects each received Treatment C (Moxifloxacin/Placebo) and Treatment D (Placebo/Moxifloxacin). **Table 13** displays the abuse-related AEs in study ZX008-1603

Table 13: Abuse-related AEs ZX008-1603

	Treatment A 15 (mg ZX008) (N = 60)			*Treatment B (60 mg ZX008) (N = 60)*			*Treatment C (Moxifloxacin/Placebo) (N = 30)*			*Treatment D (Placebo/Moxifloxacin) (N = 30)*		
PT	*E*	*n*	*(%)*	*E*	*n*	*(%)*	*E*	*n*	*(%)*	*E*	*n*	*(%)*
Affect lability	0	0	0	1	1	1.67	0	0	0	0	0	0
Amnesia	1	1	1.67	0	0	0	0	0	0	1	1	3.33
Anxiety	2	2	3.33	2	2	3.33	1	1	3.33	0	0	0
Depressed mood	0	0	0	3	3	5	0	0	0	0	0	0
Disturbance in attention	0	0	0	2	2	3.33	0	0	0	0	0	0
Euphoric mood	0	0	0	4	4	6.67	0	0	0	0	0	0
Feeling abnormal	0	0	0	1	1	1.67	0	0	0	0	0	0
Feeling drunk	1	1	1.67	1	1	1.67	0	0	0	0	0	0
Hallucination, auditory	0	0	0	1	1	1.67	0	0	0	0	0	0
Hallucination, visual	0	0	0	1	1	1.67	0	0	0	0	0	0
Hyperhidrosis	1	1	1.67	0	0	0	0	0	0	0	0	0
Paranoia	0	0	0	1	1	1.67	0	0	0	0	0	0
Restlessness	0	0	0	1	1	1.67	0	0	0	0	0	0
Somnolence	7	7	11.67	9	9	15	1	1	3.33	0	0	0

E=Events

As displayed in **Table 13,** somnolence and euphoric mood occurred to a greater extent in fenfluramine treated subjects than in controls. Somnolence is a non-specific AE which does not necessarily imply abuse potential. Euphoric mood occurred at supratherapeutic doses of fenfluramine.

<u>Conclusions on Phase 1 studies</u>: Phase 1 studies in healthy volunteers did not reveal the presence of abuse-related AEs in subjects on fenfluramine at therapeutic doses. Euphoric mood occurred at supratherapeutic doses of fenfluramine in one study (ZX008-1603) but not in another (ZX008-1505). Abuse-related AEs did not occur in healthy recreational drug users. Thus, the AE profile of Phase 1 studies does not indicate that fenfluramine has abuse potential.

<u>Phase 3 studies</u>

Reference ID: 4620035

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome ZX008 Study 1

The primary objective of Study 1 was:

To demonstrate that ZX008 0.8 mg/kg/day is superior to placebo as adjunctive therapy in the treatment of Dravet syndrome in children and young adults. Subjects who qualified for the study were randomized (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; maximum dose: 30 mg/day) or placebo. Following titration, subjects continued treatment at their randomly-assigned dose during a 12-week Maintenance period. At the end of the Maintenance period (or early discontinuation), all subjects underwent a 2-week blinded taper or transition. A total of 119 subjects were randomized. **Table 14** displays the abuse-related AEs in ZX008 Study 1.

Table 14 Abuse-related AEs ZX008 Study 1

	ZX008 0.2 mg/kg/day (N = 39)			*ZX008 0.8 mg/kg/day (N = 40)*			*Placebo (N = 40)*		
PT	*E*	*Number of subjects*	*Proportion (%)*	*E*	*Number of subjects*	*Proportion (%)*	*E*	*Number of subjects*	*Proportion (%)*
Abnormal behaviour	0	0	0	4	3	7.5	0	0	0
Aggression	1	1	2.56	2	1	2.5	0	0	0
Agitation	0	0	0	3	1	2.5	0	0	0
Apathy	0	0	0	1	1	2.5	0	0	0
Disturbance in attention	1	1	2.56	2	1	2.5	0	0	0
Hypersomnia	1	1	2.56	0	0	0	0	0	0
Irritability	0	0	0	1	1	2.5	0	0	0
Lethargy	6	4	10.26	9	7	17.5	2	2	5
Mood swings	1	1	2.56	1	1	2.5	0	0	0
Psychomotor hyperactivity	0	0	0	0	0	0	1	1	2.5
Restlessness	0	0	0	1	1	2.5	0	0	0
Somnolence	6	6	15.38	4	4	10	4	3	7.5

E =events

In this study, the occurrence of AEs that could indicate abuse potential were greater in fenfluramine treated patients than in the placebo group. However, no events of euphoria, hallucinations, or 'feeling drunk', which are stronger indicators of abuse potential, occurred. The elicitation of AEs may be limited by the presence of baseline neurological impairment

A Multicenter, Randomized, Double-blind, Placebo-controlled Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of ZX008 (Fenfluramine Hydrochloride) Oral Solution, as Adjunctive

Reference ID: 4620035

Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome; Study ZX008-1504 Cohort 2.

Study 1504 Cohort 2 was a multicenter, randomized, double-blind, placebo-controlled parallel group evaluation of the efficacy, safety, and tolerability of ZX008 (fenfluramine hydrochloride) oral solution when added to standard-of-care treatment that included stiripentol (STP) in the treatment of seizures in children and young adults with Dravet syndrome. Subjects who qualified for the study were randomized (1:1) in a double-blind manner to receive ZX008 (at a dose of 0.5 mg/kg/day; maximum dose of 20 mg/day) or placebo. At the end of the maintenance period (or early discontinuation), eligible subjects had an option to enter the long-term extension study (Study 1503). Subjects who chose to enter the extension study entered a transition period for 14 days. Subjects who did not want to enter the extension study entered a taper period for 14 days.

Upon completion of the Baseline period, subjects who qualified for Cohort 2 were randomized (1:1) in a double-blind manner to one of the following treatment arms:

- ZX008 0.5 mg/kg/day (maximum dose 20 mg/day), administered in equally divided doses BID in addition to their stable dose of STP plus CLB and/or VPA
- placebo, administered in equally divided doses BID in addition to their stable dose of STP plus CLB and/or VPA

Table 15: Abuse-related AEs Study ZX008-1504 Cohort 2.

PT	*ZX008 N=43 Events*	*ZX008 N=43 Number of subjects*	*ZX008 N=43 Proportion (%)*	*Placebo N=44 Events*	*Placebo N=44 Number of subjects*	*Placebo N=44 Proportion (%)*
Abnormal behaviour	4	4	9.3	1	1	2.27
Aggression	2	2	4.65	0	0	0
Agitation	1	1	2.33	1	1	2.27
Cognitive disorder	1	1	2.33	0	0	0
Depressed level of consciousness	1	1	2.33	0	0	0
Disturbance in attention	1	1	2.33	0	0	0
Hallucination	1	1	2.33	0	0	0
Irritability	4	4	9.3	2	2	4.55
Lethargy	6	6	13.95	2	2	4.55
Mood swings	1	1	2.33	0	0	0
Restlessness	1	1	2.33	0	0	0
Sedation	1	1	2.33	0	0	0
Somnolence	4	3	6.98	3	3	6.82

In this study, the occurrence of AEs that could indicate abuse potential were greater in fenfluramine treated patients than in the placebo group. However, no events of euphoria, or ‘feeling drunk’, which are stronger indicators of abuse potential, occurred. There was one episode of hallucination. The elicitation of AEs may be limited by the presence of baseline neurological impairment

Reference ID: 4620035

An Open-Label, Proof of Concept Study of Fenfluramine for the Treatment of Patients with Dravet Syndrome (Investigator Initiated Study) ZXIIS2015-004.
This is an ongoing, prospective, open-label, single-center study of fenfluramine used as adjunctive therapy in children and adults with refractory Dravet syndrome. The most common AEs reported were anorexia, somnolence, fatigue, mood changes/behavioral problems, aggressive behavior, sleep difficulties, balance problems, and seizures. Fourteen (14) patients have been enrolled in this prospective cohort. However, abuse-related AEs are difficult to assess in this open-label, non-placebo controlled study of patients with baseline neurological disorder on concomitant antiseizure medications.

An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome (ZX008-1503)

Study 1503 is an international, multicenter, open-label, long-term safety study of ZX008 in pediatric and young adult subjects with Dravet syndrome. Placebo was not administered in this open-label study. No subjects have yet completed this ongoing study. This study consists of an open-label treatment period and a taper/transition period for those who discontinue treatment. **Table 16** displays the abuse-related AEs. Again, this study is of limited value in assessing abuse-related AEs since patients may have had baseline neurological impairment and there was no placebo group.

Table 16: Abuse-related AEs ZX008-1503 n (%)

Preferred Term	N=232
Altered state of consciousness	1 (0.43)
Hypersomnia	1 (0.43)
Lethargy	5 (2.2)
Loss of consciousness	1 (0.43)
Psychomotor hyperactivity	2 (0.86)
Somnolence	10 (4.3)
Abnormal behavior	7 (3.0)
Affect lability	1 (0.43)
Aggression	8 (3.4)
Agitation	4 (1.7)
Apathy	1 (0.43)
Depressed mood	1 (0.43)
Irritability	4 (1.7)
Mental status changes	1 (0.43)

The Day 120 Safety Update includes safety information on 330 subjects enrolled through the data cutoff date of 14 October 2019. Additional information is included in this Day 120 Safety Update from additional clinical studies, including the cohort of adult subjects enrolled in Study 1503 and an EU Expanded Access program in Dravet syndrome that were not available at the time of the ZX008 NDA submission. No additional abuse-related AEs of concern were reported in this update.

Reference ID: 4620035

Conclusions on Phase 3 studies: In these studies, the occurrence of AEs that could indicate abuse potential were greater in fenfluramine treated patients than in the placebo group. However, events of euphoria, or 'feeling drunk', which are stronger indicators of abuse potential did not occur. Hallucination was reported in 1 subject across all studies. The elicitation of AEs is limited by the presence of baseline neurological impairment. Studies with no placebo group are of limited value in assessing abuse-related AEs in this population of patients with neurological impairment.

4.3 Safety Profile

Assessment of abuse-related AEs during Phase 3 studies may be limited because subjects had neurological impairments and were on other antiseizure medications. Phase 1 studies in healthy volunteers did not reveal the presence of abuse-related AEs in subjects on fenfluramine at therapeutic doses. Euphoric mood occurred at supratherapeutic doses of fenfluramine in one study (ZX008-1603) but not in another (ZX008-1505). Abuse-related AEs did not occur in healthy recreational drug users. Thus, the AE profile of Phase 1 studies does not indicate that fenfluramine has abuse potential.

4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials

According to the Sponsor, drug accountability logs did not indicate diversion or misuse in any Zogenix sponsored clinical trial. Treatment compliance data in Phase 3 studies showed that compliance rates were less than 110% in all studies, indicating that subjects or caregivers were not utilizing more drug than prescribed.

4.5 Tolerance and Physical Dependence Studies in Humans

Physical dependence was not assessed in humans in Phase 1 studies because they were single dose studies or studies in which treatment was administered for only 6 days. Physical dependence could not be assessed in the Phase 3 studies because medication could not be discontinued abruptly in patients with seizures and these studies included a taper phase. The label recommends that fenfluramine be withdrawn gradually.

5. Regulatory Issues and Assessment

The following dates outline the regulatory history regarding the control of fenfluramine in the CSA.

- On June 14, 1973, Fenfluramine was approved by FDA as Pondimin.
- On June 15, 1973, placement of fenfluramine and its isomers in Schedule IV of the CSA became effective.

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- On March 18, 1991, a petition from Interneuron Pharmaceuticals, Inc., was filed with the Drug Enforcement Administration (DEA) requesting the decontrol of fenfluramine from Schedule IV of the Controlled Substances Act (CSA) based on the lack of demonstratable abuse potential.

- On December 2, 1991, the Administrator of DEA requested that the Assistant Secretary for Health and Human Services conduct a scientific and medical evaluation (Eight Factor Analysis) pursuant to 21 U.S.C. 811(c), on fenfluramine based on the petition.

- On September 29, 1995, a joint Session of the Drug Abuse and the Endocrinologic and Metabolic Advisory Committees convened and recommended that fenfluramine and its isomers be decontrolled.

- In June of 1996, DEA received the medical and scientific evaluation from HHS along with a recommendation to decontrol fenfluramine. DEA had several concerns with the evaluation provided by HHS.

- On August 23, 1996, DEA requested information on trafficking of fenfluramine from law enforcement.

- On November 5, 1996, DEA detailed their issues and asked for clarification with the medical and scientific analysis conducted by HHS on fenfluramine.

- On January 5, 1997, HHS responded to the DEA letter by stating that after an extensive review of the medical and scientific literature, HHS concluded that the decontrol of fenfluramine is warranted. If DEA would like HHS to review more data than a formal request would be appropriate through the mechanisms stipulated in the CSA.

- On May 6, 1997, a proposed rulemaking entitled “Schedules of Controlled Substances: Proposed Removal of Fenfluramine From the Controlled Substances Act" was published in the Federal Register (62 FR 24620).

- On July 8, 1997, FDA issued a public health advisory regarding the use of fenfluramine and this resulted in a voluntary withdrawal of the marketed fenfluramine products Pondimin and Redux by the pharmaceutical manufacturers.

- On March 8, 1999, FDA issued a final rule listing the drug products that were withdrawn or removed from the market because they contained fenfluramine (64 FR 10944) (21 CFR 216.24).

- In a letter dated February 27, 2003, Indevus Pharmaceuticals, Inc., formerly known as Interneuron Pharmaceuticals, Inc., informed the agency that they are withdrawing the petition to decontrol fenfluramine because it is no longer marketed.

- On May 2, 2003, DEA withdrew the proposed rule to decontrol fenfluramine citing the health and safety concerns that prompted the drug to be removed from the market (68 FR 26247)

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- On October 18, 2018, a petition was sent to the Acting Administrator of DEA by Zogenix, Inc., to once again decontrol fenfluramine and remove it from the CSA.
    - As of February 3, 2020, HHS has not received a request from DOJ/DEA to conduct a medical and scientific analysis on fenfluramine.
- On September 25, 2019, Zogenix, Inc., submitted NDA 212102 for the adjunctive treatment for seizures associated with Dravet syndrome with a PDUFA date of March 25, 2020. The Sponsor requested that the drug be decontrolled.

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Reference ID: 4620035

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/s/

EDWARD G HAWKINS
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CHAD REISSIG
06/12/2020 01:42:40 PM

DOMINIC CHIAPPERINO
06/12/2020 02:03:18 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memorandum

Date:	June 9, 2020
Reviewer:	Karen Long, PharmD, Safety Evaluator Division of Pharmacovigilance I (DPV I)
Team Leader:	Allen Brinker, MD, MS DPV I
Product Name:	Fenfluramine
Subject:	Overdose
Application Type/Number:	NDA 212102
Applicant:	Zogenix Inc
OSE RCM #:	2020-1186

Reference ID: 4620096

1 INTRODUCTION

This pharmacovigilance memo summarizes case reports from the medical literature reporting overdose with fenfluramine. This descriptive analysis is intended to assist the Office of New Drugs, Division of Neurology 2 safety review of NDA 212102 submitted by Zogenix Inc.

Fenfluramine was initially approved by FDA in 1973 for the management of obesity. The recommended dosing was 20 mg three times daily, with a maximum recommended dose of 40 mg three times daily (120 mg daily). Its proposed mechanism involved increasing satiety by elevating serum levels of serotonin in the central nervous system (CNS) through inhibiting the reuptake of serotonin in the CNS and, when metabolized to norfenfluramine, increasing the release of serotonin at the receptor sites. On September 15, 1997, FDA announced the withdrawal of fenfluramine and its isomer, dexfenfluramine, from the U.S. market because of safety concerns with the development of cardiac valvular disease and pulmonary hypertension. On November 25, 2019, Zogenix announced FDA accepted for filing the NDA for FINTEPLA® (ZX008, fenfluramine oral solution) for the treatment of seizures associated with Dravet syndrome. The proposed dosing is 0.1 mg/kg twice daily which can be titrated to a maximum recommended maintenance dose of 0.35 mg/kg twice daily (maximal daily dose of 26 mg/day).[1,2,3,4,5]

2 METHODS AND MATERIALS

DPV searched the medical literature for case reports of overdose reported with fenfluramine with the strategy described in **Table 1.**

Table 1. Literature Search Strategy	
Date of search	May 28, 2020
Database	1. PubMed 2. Embase
Search terms	1. ((fenfluramine) OR (fenfluramine[MeSH Terms])) AND ((overdose) OR (overdose[MeSH Terms]) OR (toxicity) OR (drug toxicity[MeSH Terms])) 2. ('fenfluramine'/exp OR fenfluramine) AND ('drug overdose'/exp OR 'drug overdose' OR 'intoxication'/exp OR intoxication OR 'drug intoxication'/exp OR 'drug intoxication' OR 'toxicity'/exp OR toxicity)
Years included in search	All years through May 28, 2020

Reference ID: 4621016

3 RESULTS

DPV identified 55 cases of overdose reported with fenfluramine in the medical literature, summarized in Table 2. One article described a case series of 38 patients (34 non-fatal and 4 fatal) from a poison control center with aggregated data for the 34 non-fatal cases (Von Mühlendahl 1979). Appendix A provides a line listing of the 55 literature cases.

Table 2. Descriptive Characteristics of Overdose Literature Cases With Fenfluramine Published Through May 28, 2020 (N=55)

	All Cases (n=55)	Non-Fatal (n=45)	Fatal (n=10)
Publication year			
1999	1	1	0
1979	38	34	4
1975	2	0	2
1974	2	2	0
1972	2	1	1
1969	9	6	3
1967	1	1	0
Age (years)	(n=21)	(n=11)	(n=10)
Median	5	13	4.4
Mean	10.3	11.5	8.8
Range	1.75-34	2.4-28	1.75-34
Sex			
Female	13	7	6
Male	5	4	1
Unknown	37	34	3
Reported outcomes			
Death	10	0	10
Recovered	45	45	0
Reported ingested dose (mg)*	(n=16)	(n=9)	(n=7)
Median	650	440	1000
Mean	822.5	651	1042.9
Range	200-2000	200-1600	400-2000
Reported ingested dose (mg/kg)*	(n=16)	(n=9)	(n=7)
Median	28.9	15.4	33.3
Mean	29.5	22.5	38.5
Range	6.5-70	6.5-70	17.5-70
Time to presentation (hours)†	(n=16)	(n=9)	(n=7)
Median	1	1.5	1
Mean	1.5	1.7	1.2
Range	0.5-3.5	0.5-3.5	1-2
Time to death (hours)†	(n=10)	(n=0)	(n=10)
Median	8.5	-	8.5
Mean	62.3	-	62.3
Range	2-240	-	2-240
Recovery/hospitalization time (days)	(n=20)	(n=10)	(n=10)
Median	1.5	2.5	1
Mean	4.9	6.8	3.1
Range	1-26	1-26	1-10

Reference ID: 4620096

Table 2. Descriptive Characteristics of Overdose Literature Cases With Fenfluramine Published Through May 28, 2020 (N=55)

	All Cases (n=55)	Non-Fatal (n=45)	Fatal (n=10)
Reported adverse events‡	(n=55)	(n=45)	(n=10)
Mydriasis	50	45	5
Tachycardia	44	40	4
Flushing/redness	28	26	2
Tremor/twitching/muscle spasm	28	24	4
Agitation/restlessness/anxiety	22	19	3
Increased muscle tone/rigor/opisthotonus	21	20	1
Respiratory distress or failure	19	9	10
Seizure	19	10	9
Diaphoresis	17	14	3
Nystagmus	17	14	3
Coma	16	9	7
Fever/hyperthermia	15	12	3
Cardiac arrest	9	0	9
Increased blood pressure	9	8	1
Somnolence/drowsiness	9	8	1
Confusion/delirium or dysarthria	5	3	2
Gastrointestinal symptoms	4	3	1
Cardiac arrhythmia	2	0	2
Dizziness or difficulty walking	2	1	1
Decreased blood pressure	1	0	1
Hypothermia	1	0	1
Therapeutic interventions§	(n=21)	(n=11)	(n=10)
Gastric lavage	14	9	5
Cardiopulmonary resuscitation	8	0	8
Diazepam or other seizure treatment	8	4	4
Intubation/mechanical ventilation	8	1	7
Intravenous fluids	5	3	2
Induced emesis	4	3	1
Calcium (intravenous)	3	0	3
Ammonium chloride/forced acid diuresis	3	3	0
Epinephrine or isoproterenol	2	0	2
Defibrillation	2	0	2
Neuromuscular paralysis	2	1	1
Other seizure treatment	2	1	1
Antiarrhythmic	1	0	1
Atropine, bicarbonate, and mannitol	1	0	1
Chlorpromazine and procaine	1	0	1
Hemodialysis	1	0	1
Labetalol	1	1	0

* If an interval was given for ingested dose, the highest number was used in the aggregate calculation. If a weight was not reported, the average weight using the CDC growth chart for pediatrics[6] or 70 kg/57 kg for a reference man/woman[7] was utilized. Note: 2 fatal cases reported an unknown fenfluramine ingestion amount of up to 4000 mg taken among 3 children, which was not included in the aggregate calculation (Gold 1969).

† If an interval was given for time to presentation or death, the lowest number was used in the aggregate calculation.

‡ A case may report more than one adverse event.

§ A case may report more than one therapeutic intervention. Other seizure treatments include paraldehyde and thiopental.

Reference ID: 4621016

4 REVIEWER'S COMMENTS

DPV identified 55 cases from the medical literature reporting overdose with fenfluramine, including 10 fatal cases. The most commonly reported adverse events in all cases included mydriasis, tachycardia, flushing, tremors/twitching/muscle spasms, agitation/restlessness/ anxiety, increased muscle tone/rigor/opisthotonos, respiratory distress or failure, and seizure. The most commonly reported adverse events in the 10 fatal cases included seizure, coma, and cardiorespiratory arrest resulting in death.

Most cases of fenfluramine overdose occurred in pediatric patients <17 years of age. Of the 21 cases reporting an age, most cases (17 of 21) occurred in patients <17 years of age, with 12 of these cases occurring in patients ≤6 years of age. Of the 10 fatal cases, 8 cases occurred in pediatric patients <17 years of age (median 4.4 years).

Non-fatal cases of fenfluramine overdose reported lower ingested doses in milligram per kilogram (mg/kg) of body weight than fatal cases, and generally reported more mild adverse events. Of the 16 cases reporting an ingestion amount in mg/kg, the non-fatal cases reported a median dose of 15.4 mg/kg and fatal cases reported a median dose of 33.3 mg/kg. Cases with ingested doses <17 mg/kg (n=6) were non-fatal and generally presented with more mild adverse events including mydriasis, tachycardia, flushing/redness, tremor/twitching/muscle spasm, nystagmus, fever/hyperthermia, or gastrointestinal symptoms. Cases with ingested doses >17 mg/kg (n=10) included 7 fatal cases and 3 non-fatal cases; these cases generally reported more severe adverse events, including seizure, respiratory distress or failure, cardiac arrest or arrhythmias, or coma.

Cases presented with symptoms from fenfluramine overdose from 0.5-3.5 hours (median 1 hour), and some patients quickly deteriorated despite receiving prompt therapeutic interventions. Of the 16 cases reporting a time to presentation, 9 cases presented to the hospital with adverse events within 1 hour of ingestion. The median time to death after ingestion was 8.5 hours (range 2-240 hours), and 5 fatal cases reported death within 3.5 hours of ingestion. The 21 cases reporting hospitalization and treatment for fenfluramine overdose required prompt therapeutic interventions to mitigate the adverse events if possible.

Reference ID: 4621016

5 REFERENCES

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Reference ID: 4620016

6 APPENDICES

6.1 APPENDIX A. LINE LISTING OF LITERATURE CASES OF OVERDOSE WITH FENFLURAMINE (N=55)

Citation (Sorted by Descending Year of Publication)	Age/ Sex	Exposure	Reported Adverse Events	Treatment
Koury R, Stone CK, Stapczynski JS, Blake J. Sympathetic overactivity from fenfluramine-phentermine overdose. Eur J Emerg Med. 1999;6(2):149-152.	24 M	Unknown amount of fenfluramine/ phentermine	presented at unknown time after ingestion with sympathetic overactivity; flushing, tachycardia, increased blood pressure, mydriasis, fever, diaphoresis, hyperventilation, increased muscle tone, combativeness, agitation, delirium, suicide attempt (2nd degree burns)	intubation, mechanical ventilation, sedation, neuromuscular paralysis, labetalol, skin grafts, supportive care; hospitalized for 26 days
Von Mühlendahl KE, Krienke EG. Fenfluramine poisoning. Clin Toxicol. 1979;14(1):97-106. (Case series of n=53; 38 from poison center + 15 previously published literature cases; description of 38 cases (34 non-fatal and 4 fatal cases) are summarized here)	unknown for non-fatal cases ages 1.9-3.7 for fatal patients	fenfluramine unknown doses for non-fatal cases fenfluramine 28.7-46.7 mg/kg reported for fatal cases	aggregate data presented for n=38 cases from poison control center, including 4 deaths unknown presentation for non-fatal cases; presentation at 1-1.5 hours for fatal cases; death reported 43 hours to 7 days after ingestion symptoms for all 38 cases included mydriasis (n=35); nystagmus (n=9); increased muscular tone, rigor, opisthotonos (n=16); hyperreflexia, tremor, clonus (n=17); CNS excitation (n=12); somnolence (n=4); coma (n=13); seizure (n=12); tachycardia (n=31); increased blood pressure (n=5); tachypnea (n=5); hyperthermia (n=9); diaphoresis (n=10); flushing/redness (n=18) symptoms reported in 4 fatal cases included cardiac and respiratory arrest (n=4), coma (n=4), seizure (n=4), hyperthermia (n=1), hypothermia (n=1)	not reported for aggregate non-fatal cases treatment reported in fatal cases included cardiopulmonary resuscitation, mechanical ventilation, and hemodialysis
Von Mühlendahl KE, Krienke EG. Fenfluramine poisoning. Clin Toxicol. 1979;14(1):97-106. (Case series of n=53; 38 from poison center + 15 previously published literature cases; fatal case 1)	3.1 unknown sex	fenfluramine 28.7 mg/kg (estimated 400 mg)	death reported 144 hours; presented at 1 hour with coma, seizure, cardiorespiratory arrest	cardiopulmonary resuscitation

Reference ID: 4620790

Citation (Sorted by Descending Year of Publication)	Age/ Sex	Exposure	Reported Adverse Events	Treatment
Von Mühlendahl KE, Krienke EG. Fenfluramine poisoning. Clin Toxicol. 1979;14(1):97-106. (Case series of n=53; 38 from poison center + 15 previously published literature cases; fatal case 2)	3.7 unknown sex	fenfluramine 46.7 mg/kg (estimated 700 mg)	death reported after 43 hours; presented at 1.5 hours with coma, seizure, cardiorespiratory arrest	cardiopulmonary resuscitation
Von Mühlendahl KE, Krienke EG. Fenfluramine poisoning. Clin Toxicol. 1979;14(1):97-106. (Case series of n=53; 38 from poison center + 15 previously published literature cases; fatal case 3)	3.1 unknown sex	fenfluramine unknown dose	death reported after 240 hours; presented at unknown time with coma, seizure, cardiorespiratory arrest	cardiopulmonary resuscitation, hemodialysis
Von Mühlendahl KE, Krienke EG. Fenfluramine poisoning. Clin Toxicol. 1979;14(1):97-106. (Case series of n=53; 38 from poison center + 15 previously published literature cases; fatal case 4)	1.9 F	fenfluramine 33.3 mg/kg (estimated 400 mg)	death reported after 7 days after; presented at 1 hour with cardiorespiratory arrest, hypothermia, seizure, coma	mechanical ventilation, cardiopulmonary resuscitation
Simpson H, McKinlay I. Letter: Poisoning with slow-release fenfluramine. Br Med J. 1975;4(5994):462-463.	5 F	Ponderax Pacaps (fenfluramine slow release) 1200 mg (70 mg/kg)	death 3 hours after ingestion; presented 1 hour after ingestion with flushing, drowsiness, dysarthria, tremors, nystagmus, tachycardia, seizure, cardiorespiratory arrest	gastric lavage, diazepam (for seizure), intubation, cardiorespiratory resuscitation, sodium bicarbonate, calcium, mannitol, atropine, epinephrine, defibrillation
Veltri JC, Temple AR. Fenfluramine poisoning. J Pediatr. 1975;87(1):119-121.	17 F	fenfluramine 1600 mg (estimated 29 mg/kg)	death 3 hours after ingestion; presented “shortly” after ingestion with agitation, tachycardia, diaphoresis, mydriasis, seizure, cardiac arrhythmia, cardiorespiratory arrest	ipecac, gastric lavage, intravenous fluids, intubation, mechanical ventilation, cardiorespiratory resuscitation
Darmady JM. Diazepam for fenfluramine intoxication. Arch Dis Child. 1974;49(4):328-330. (Case 1)	3.5 F	fenfluramine 1120 mg (70 mg/kg)	presented 1.5 hours after ingestion with difficulty walking, restlessness, flushing, mydriasis, tachycardia, increased blood pressure, semi-voluntary movements, opisthotonos, diaphoresis, stiff limbs, semiconscious, nystagmus, agitation, muscle spasms, irregular and rapid respirations	ipecac, diazepam (for agitation and muscle spasms), intravenous fluids; hospitalized for 3 days

Reference ID: 4620790

Citation (Sorted by Descending Year of Publication)	Age/ Sex	Exposure	Reported Adverse Events	Treatment
Darmady JM. Diazepam for fenfluramine intoxication. Arch Dis Child. 1974;49(4):328-330. (Case 2)	2.9 M	fenfluramine 400 mg (30 mg/kg)	presented 2 hours after ingestion with flushing, restlessness, muscle twitching, irregular and rapid respirations, tachycardia, increased blood pressure, mydriasis, nystagmus	gastric lavage, oxygen, intravenous fluids, diazepam (for muscle twitching); hospitalized for a “couple of day”
Haines AP, Shoenberg PJ. Hyperpyrexia and overdose. Br Med J. 1972;1(5800):632-633.	34 F	fenfluramine 1000 mg (estimated 17.5 mg/kg)	death after 13.5 hours; presented at unknown time after ingestion with unconsciousness, hyperventilation, respiratory distress, tachycardia, diaphoresis, rigid and irregular body movements, nystagmus, fever, hyperpyrexia, hypotension	diazepam (for irregular movements), calcium, chlorpromazine, succinylcholine, intubation, mechanical ventilation, procaine (for hyperpyrexia), intravenous fluids
Wolfsdorf J, Kanarek KS. Fenfluramine overdosage in childhood. Case report. S Afr Med J. 1972;46(21):651.	2.4 F	Ponderax (fenfluramine) 160-200 mg (estimated 15.4 mg/kg)	presented 1 after ingestion with fever, flushing, dry mucous membranes, mydriasis, seizure, opisthotonos, tachycardia	gastric lavage, paraldehyde and diazepam (for seizure), intravenous fluids, supportive care; hospitalized for 1 day
Riley I, Corson J, Haider I, Oswald I. Fenfluramine overdosage. Lancet. 1969;2(7631):1162-1163. (Case 1)	16 F	fenfluramine 800 mg (13.5 mg/kg)	presented 3.5 hours after ingestion with agitation, anxiety, uncooperative, flushing, diaphoresis, tachycardia, mydriasis, nystagmus, tremor, hyperventilation, abnormal EEG	gastric lavage, forced acid diuresis, supportive care; hospitalized for 19 days
Riley I, Corson J, Haider I, Oswald I. Fenfluramine overdosage. Lancet. 1969;2(7631):1162-1163. (Case 2)	16 F	fenfluramine 600 mg (10.6 mg/kg)	presented 2.5 hours after ingestion with burning in epigastrium, feeling hot, flushing, blurred vision, mydriasis, tachycardia, fever, nystagmus, tremor, generalized hyperreflexia and ankle clonus, abnormal EEG	gastric lavage, supportive care; hospitalized for 11 days
Riley I, Corson J, Haider I, Oswald I. Fenfluramine overdosage. Lancet. 1969;2(7631):1162-1163. (Case 3)	16 F	fenfluramine 400 mg (6.5 mg/kg)	presented 2.5 hours after ingestion with burning in epigastrium, feeling hot, flushing, tachycardia, mydriasis, nystagmus, abnormal EEG	gastric lavage, supportive care; hospitalized for 3 days
Richards AJ. Fenfluramine overdosage. Lancet. 1969;2(7634):1367.	28 M	Ponderax (fenfluramine) 1600 mg (16.5 mg/kg)	presented at unknown time after ingestion with disturbed consciousness, shivering, tremor, incontinence, mydriasis	gastric lavage, induced vomiting, ammonium chloride, supportive care; hospitalized for 1 day

Reference ID: 4620096

Citation (Sorted by Descending Year of Publication)	Age/ Sex	Exposure	Reported Adverse Events	Treatment
Gold RG, Gordon HE, Da Costa RW, Porteous IB, Kimber KJ. Fenfluramine overdosage. Lancet. 1969;2(7633):1306. (Case 1)	6 F	Ponderax (fenfluramine) unknown amount, 200 tablets taken between 3 children	death within 2-4 hours of ingestion; presented ~1-3 hours after ingestion with abdominal pain, dizziness, shaking/shivering, eyes rolling, talking strangely, coma, seizure, twitching, respiratory distress, mydriasis, cardiorespiratory arrest	gastric lavage, intubation, mechanical ventilation, cardiorespiratory resuscitation
Gold RG, Gordon HE, Da Costa RW, Porteous IB, Kimber KJ. Fenfluramine overdosage. Lancet. 1969;2(7633):1306. (Case 2)	1.75 F	Ponderax (fenfluramine) unknown amount, 200 tablets taken between 3 children	death within 3-5 hours of ingestion; presented ~1-3 hours after ingestion with flushing, mydriasis, seizure, cardiorespiratory arrest	gastric lavage, paraldehyde and thiopental (for seizure), intubation, cardiopulmonary resuscitation, epinephrine, isoprenaline, calcium
Gold RG, Gordon HE, Da Costa RW, Porteous IB, Kimber KJ. Fenfluramine overdosage. Lancet. 1969;2(7633):1306. (Case 3)	3 M	Ponderax (fenfluramine) unknown amount, 200 tablets taken between 3 children	presented ~1-3 hours after ingestion with strange behavior, twitching, flushing, mydriasis, tachycardia	gastric lavage, supportive care; hospitalized for 1 day
Fleisher MR, Campbell DB. Fenfluramine overdosage. Lancet. 1969;2(7633):1306-1307.	13 M	fenfluramine 2000 mg (estimated 44.4 mg/kg)	death 3.5 hours after ingestion; presented 2-2.5 hours after ingestion with diaphoresis, malaise, restlessness, anxiety, tremor, fever, increased blood pressure, mydriasis, muscle twitches, seizure, unconsciousness, tachycardia, ventricular fibrillation, cardiorespiratory arrest	gastric lavage, intubation, mechanical ventilation, diazepam (for seizure), lidocaine, defibrillation
Campbell DB, Moore BW. Fenfluramine overdosage. Lancet. 1969;2(7633):1307.	2.5 F	fenfluramine 440 mg (estimated 33.8 mg/kg)	presented 1 hour after ingestion with disturbed consciousness, diaphoresis, agitation, confusion, mydriasis, tachycardia, seizure	induced emesis, gastric lavage, diazepam (for seizure), ammonium chloride, supportive care; recovery within 24 hours
White AG, Beckett AH, Brookes LG. Fenfluramine overdosage. Br Med J. 1967;1(5542):740.	13 F	Ponderax (fenfluramine) 300 mg (estimated 6.5 mg/kg)	presented 0.5-1 hour after ingestion with drowsiness, uncooperative, vomiting, shivering, mydriasis	gastric lavage, supportive care

Reference ID: 4620096

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/s/

KAREN M LONG
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06/09/2020 12:30:20 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 19, 2020
Requesting Office or Division:	Division of Neurology 2 (DN2)
Application Type and Number:	NDA 212102
Product Name and Strength:	Fintepla (fenfluramine) Oral Solution, 2.2 mg/mL
Applicant/Sponsor Name:	Zogenix, Inc.
OSE RCM #:	2019-394-2
DMEPA Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

On May 15, 2020, the Applicant submitted revised labels and labeling in response to recommendations that we made during a previous label and labeling review[a] for Fintepla (fenfluramine) Oral Solution. The Division of Neurology 2 (DN2) requested that we review the revised labels and labeling (See Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Weitzman B. Label and Labeling Review for Fintepla (NDA 212102). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 22. RCM No.: 2019-394-1.

Reference ID: 4640902

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/s/

BEVERLY WEITZMAN
05/19/2020 11:49:58 AM

BRIANA B RIDER
05/19/2020 02:38:57 PM

Clinical Inspection Summary

Date	30 April 2020
From	Cheryl Grandinetti, PharmD Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Stephanie Parncutt, RPM Natalie Getzoff, MD, Clinical Reviewer Philip Sheridan, MD, Clinical Team Leader Nick Kozauer, MD, Acting Division Director, Division of Neurology Products II (DNII)
NDA #	212102
Applicant	Zogenix International Limited, Inc.
Drug	Fenfluramine (Fintepla)
NME	No
Proposed Indication	For the treatment of seizures associated with Dravet syndrome in patients 2 years and older
Consultation Request	1 November 2019
Summary Goal Date	15 May 2020
Action Goal Date	1 June 2020
PDUFA Date	25 June 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical investigators, Drs. Nabbout, Nikanorova, Talwar, and Wirrell, were inspected in support of this NDA (NDA 212102). The inspection covered two clinical studies, ZX008-VS01 and ZX008-1504-C2.

Significant data reliability concerns were identified during FDA inspections of Drs. Nabbout, Nikanorova, Talwar, and Wirrell. Specifically, the sponsor contracted with (b) (4) (b) (4) to manage the electronic diary (eDiary) data used to support the primary efficacy endpoint. Both protocols and investigational plans pre-specified and described the use of eDiaries by caregivers to contemporaneously complete questionnaires and to document the subject's daily seizure frequency. However, there was a retrospective collection of the eDiary data during the conduct of both trials that was not pre-specified in the protocols. In particular, the subjects' seizure frequency (observed by the caregivers) was collected by clinical investigators (e.g., by interviewing the caregivers and reviewing the caregivers' personal paper seizure diaries) and entered into the eDiary database (i.e., (b) (4) online portal) by (b) (4) using (b) (4) data clarification request (DCR) process as much as 1 year after the subjects'

seizure events occurred. Caregivers should have entered this data directly and contemporaneously in the eDiaries at the time of seizure occurrence.

Of note, clinical investigators and delegated site personnel retrospectively collected the eDiary data in variety of ways, for example, by conducting in-person and phone interviews with the caregiver and collecting and reviewing the caregiver's personal diaries and notes. The various source records for the retrospective Diary data included the following:

- Caregiver's Personal Diaries: paper diaries completed by the caregivers
- Caregiver's Seizure Calendar: paper calendars completed by the caregivers
- Seizure Diary Entry Template: paper forms completed by clinical investigators or delegated site personnel during interviews with the caregiver or after review of caregiver's personal diaries or seizure calendars
- End of Day Review Diary Capture Forms: paper forms completed by clinical investigators or delegated site personnel during interviews with the caregiver or after review of caregiver's personal diaries or seizure calendars
- Legally Authorized Representative's (LAR's) seizure notes and other caregiver notes: – paper notes completed by the caregiver or LAR
- Medical Records and Physician Notes: electronic and or paper medical records completed by the physician during interviews with the subject and caregiver

In a response to an Information Request, dated 13 January 2020, Zogenix provided an extensive listing of all retrospective seizure data for Protocols ZX008-VS01 and ZX008-1504-C2. The sponsor's response shows that clinical investigators retrospectively collected seizure frequency eDiary data for 114 of the 119 randomized subjects in Study ZX008-VS01 and 78 of the 87 randomized subjects in Study ZX008-1504-C2. As determined by FDA's Office of Biostatistics, this retrospective collection encompassed approximately 8.6% of the total seizure frequency eDiary data in Study ZX008-VS01 and 9.2% of the total seizure frequency data in Study ZX008-1504-C2.

The root cause of the retrospective collection of the eDiary data included the following:

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

In addition, the following inspectional observations, described in more details in this Clinical Inspection Summary (CIS), further affect the reliability of the eDiary data collected

retrospectively:

1. Complete and adequate source records (as described above) that were necessary to verify the retrospectively collected eDiary data were not consistently maintained and retained at the sites

2. For source records that were available, numerous discrepancies were noted when verifying the source records (e.g., the caregiver's personal diaries, seizure calendars, Seizure Diary Entry Template, and caregiver's seizure notes) for the retrospectively collected seizure diary data against the sponsor's data listings submitted to FDA

3. Lack of consistent methods (e.g., caregiver interviews, use of the caregivers' personal seizure diaries and calendars, and other medical records) and sponsor and vendor processes and procedures for communicating, reporting, verifying, and documenting retrospectively collected eDiary data for (b) (4) entry into the online portal, which contributed to the incomplete and inadequate source records available at the site

(b) (4) inspectional findings were communicated to OSI and are further described in this CIS. The (b) (4) inspectional findings included (but were not limited to) the following:

- Retrospective collection by clinical investigators of the caregivers' eDiary data including numerous discrepancies between the source records and the sponsor's data listings
- Inadequate centralized and ineffective on-site monitoring and sponsor oversight of monitoring performed by the CRO
- Inadequate processes and procedures for identifying, classifying, and reporting of protocol deviations
- Inadequate and inaccurate drug accountability records

Because of the potential for recall bias and the inspectional observations listed above, the retrospectively collected seizure data impact the accuracy and reliability of the efficacy results of the two studies. A post hoc sensitivity analysis compared to the primary analysis has been conducted by both (b) (4) and FDA's Office of Biostatistics on the primary efficacy endpoint with regard to the retrospectively collected eDiary data.

Notwithstanding the retrospectively collected eDiary data, including the inspectional findings such as lack of original study source documents and numerous data discrepancies between the source records and the sponsor's data listings, the eDiary seizure frequencies and other eDiary data entered contemporaneously into the SitePads and LogPads by caregivers as pre-specified in the protocol appear acceptable in support of the respective indication.

II. BACKGROUND

This application was submitted in support of the use of Fintepla (fenfluramine HCl) oral solution for the adjunctive treatment of seizures in children and young adults with Dravet syndrome. The key studies supporting the application were the following:

- ZX008-VS01, "A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome"

- ZX008-1504-C2, "A Multicenter, Randomized, Double-blind, Placebo-controlled Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of ZX008 (Fenfluramine Hydrochloride) Oral Solution, as Adjunctive Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome; Study ZX008-1504 Cohort 2"

Protocols ZX008-VS01

ZX008-VS01 is the prospective, merged analysis of two identical double-blind, placebo-controlled studies, ZX008-1501 and ZX008-1502. Study 1501 and Study 1502 were conducted in parallel. Study 1501 was conducted at approximately 30 sites in North America; Study 1502 was conducted at approximately 30 sites in Europe and Australia. ZX008-VS01 (i.e., Study ZX008-1501 and ZX008-1502) was a multicenter, randomized, double-blind, parallel group, placebo-controlled trial to assess the efficacy, safety, and pharmacokinetics of two fixed doses of fenfluramine hydrochloride oral solution when used as adjunctive therapy in pediatric and young adult subjects with Dravet syndrome.

- *Subjects:*
  - 173 subjects were screened
  - 119 subjects were randomized (40 subjects in the placebo; 39 subjects in the fenfluramine 0.2 mg group; and 40 subjects in the fenfluramine 0.8 mg group)
  - 110 subjects completed the study
  - Of note, Study ZX008-VS01 is comprised of the first 119 subjects who were consecutively randomized into Studies 1501 or 1502; the following 120 subjects randomized into Studies 1501 or 1502 (b) (4)

- *Sites:* 38 sites enrolled at least 1 subject

- *Study Initiation and Completion Dates:* 15 Jan 2016 to 14 August 2017

- *Database Lock:* 18 September 2017

The primary efficacy objective of ZX008-VS01 was to demonstrate that fenfluramine 0.8 mg/kg/day is superior to placebo as adjunctive therapy in the treatment of Dravet syndrome in children and young adults based on change in the frequency of convulsive seizures between baseline and the combined Titration and Maintenance Periods.

During the 6- week Baseline Period (Day -42 to Day-1), initial eligibility was established at the screening visit. The screening visit was followed by an observation period where subjects were assessed for baseline seizure activity based on recordings of daily seizure activity entered into an eDiary by the subject's caregiver.

After completion of the Baseline Period (on Study Day -1), eligible subjects were stratified by age group (< 6 years, ≥6 years) and randomized in a 1:1:1 ratio to one of the following three treatment groups:

- Fenfluramine 0.2 mg/kg/day
- Fenfluramine 0.8 mg/kg/day
- Matching Placebo

The study drug was blinded to ensure that the volume of study medication taken could not be associated with the dose group. Randomization and blinding were performed via an Interactive Voice Response (IVR)/Interactive Web Response (IWR) system to different concentrations of the fenfluramine oral solution (1.25 mg/mL, 2.5 mg/mL, and/or 5 mg/mL). The IVR/IWR system instructed site personnel to the volume of oral solution to be administered based on that subject's weight.

The maximum daily dose of Fenfluramine was 30 mg. Each subject was administered study medication as equal doses twice daily in the morning and in the evening with food. All subjects received fenfluramine or matching placebo for up to approximately 16 weeks (Titration Period=2 weeks; Maintenance Period=12 weeks; Taper/ Transition Period=2 weeks).

Protocol ZX008-1504-C2

ZX008-1504-C2 was a randomized, double-blind, placebo-controlled study of the efficacy, safety, and tolerability of fenfluramine hydrochloride oral solution 0.5 mg/kg/day as add-on therapy in children and young adults with Dravet syndrome who were still experiencing uncontrolled seizures on stabilized standard of care treatment which included stiripentol plus clobazam and/or valproic acid.

The primary efficacy objective of this multicenter study was to demonstrate that fenfluramine was superior to placebo for the treatment of Dravet syndrome in children and young adults stabilized on a stiripentol regimen based on the change in convulsive seizure frequency from Baseline to the combined Titration and Maintenance periods.

- *Subjects:* 87 subjects in Study 1504 Cohort 2 were randomized to study treatment and received study drug (Placebo: 44 subjects; Fenfluramine 0.5 mg/kg/day: 43 subjects) and 77 subjects (88.5%) completed the study

- *Sites:* 28 sites in Canada, France, Germany, the Netherlands, Spain, the United Kingdom, and the United States

- *Study Initiation and Completion Dates:* 27 January 2017 to 05 June 2018

- *First Database Lock:* 2 July 2018; *Final Database Lock:* 20 August 2018

Initial eligibility for subjects was established during a Screening Visit followed by a 6-week observation period, during which subjects were assessed for baseline seizure activity based on recordings of daily seizure activity entered into a diary. Upon completion of the Baseline Period, eligible subjects were stratified by age group (< 6 years, ≥ 6 years) and randomized (1:1) via an IVR/IWR in a double-blind manner to one of the following treatment arms:

- Fenfluramine 0.5 mg/kg/day (maximum dose 20 mg/day), administered in equally divided doses BID in addition to their stable dose of Stiripentol plus clobazam and/or valproic acid
- Placebo, administered in equally divided doses BID in addition to their stable dose of Stiripentol plus clobazam and/or valproic acid

All subjects were titrated, in a blinded fashion, to their randomized dose over a 3-week Titration Period. Following titration, subjects continued treatment at their randomly assigned dose of fenfluramine 0.5 mg/kg/day or placebo for 12 weeks. The total treatment time for the full Titration and Maintenance Period was a maximum of 15 weeks. At the end of the Maintenance Period (or early discontinuation), all subjects entered either a taper or transition period based on whether they exited the study or were enrolled in the separate long-term open-label extension trial, respectively.

<u>For Both Protocols, ZX008-VS01 and ZX008-1504-C2</u>

The primary safety objectives for both protocols were similar and were to compare the safety and tolerability of fenfluramine to placebo with regard to adverse events, laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate, temperature, and respiratory rate), ECGs, ECHOs, and body weight, and assessment of cognitive function.

Because products containing fenfluramine and the D-enantiomer were withdrawn from the market globally in the late 1990's after reports of serious adverse events associated with heart valve disease and pulmonary hypertension, all subjects were to receive the following cardiovascular safety assessments:

- ECHOs were performed during screening to determine eligibility, and then at Visit 8 (study Day 43) and Visit 12 (study Day 99).
- ECGs were performed during screening and at Visit 3 (study Day -1), Visit 8 (study Day 43), and Visit 12 (study Day 99).

Follow-up cardiovascular safety assessments, including ECGs and ECHOs, were performed 3 to 6 months following the last dose of study medication for early termination, or for those subjects who completed the study but did not enter the open-label extension study. Subjects from France, Germany, and the Netherlands were required to have a cardiovascular safety follow-up visit approximately 24 months after the last dose of active study medication.

The *primary efficacy endpoint* was the change in the mean convulsive seizure frequency per 28 days during the Titration and Maintenance Periods (Day 1 to Day 85) compared with the Baseline Period (Day -42 to Day -1). Each day, parents/caregivers of subjects in the study recorded the number/type of seizures, dosing, and use of rescue medication during Baseline and the Titration and Maintenance Periods in an eDiary.

Both protocols and investigational plans pre-specified and described the use of eDiaries by caregivers to contemporaneously complete questionnaires and to document the subject's daily seizure frequency. The sponsor contracted with (b) (4) to provide caregivers with eDiaries (i.e., SitePads and LogPads) and to manage the eDiary data. The caregiver used the SitePad at the clinical trial site to answer eDiary questionnaires and the LogPad at home to complete the daily diaries. The eDiary data were subsequently transmitted electronically from the devices (i.e., SitePad and LogPad) to (b) (4) database on a periodic basis. For the purposes of the inspections, (b) (4) database was considered the location of the eDiary source data that was contemporaneously entered in the SitePads and LogPads by the caregivers.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, protocol deviations, and prior inspectional history.

III. RESULTS (by site):

1. Rima Nabbout, MD
   ZX008-1504-C2
   Site #1001
   HÔPITAL NECKER Chu Paris - Hôpital Neckerenfants Malades
   Cic Bât. Imagine Rdc-149 Rue De Sèvres
   Paris, 75015 France
   Inspection Dates: 3 - 7 February 2020

At this site for Protocol ZX008-1504-C2, 13 subjects were screened, 11 were randomized, 7 completed the study, and 4 subjects withdrew early. One subject subsequently entered the open-label study and the others withdrew due to adverse events, lack of efficacy, and a family decision to withdraw.

An audit of the study records for all 13 screened subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments, ethics committee submissions, approvals, and correspondence, subject eligibility criteria, informed consent, source data and records, electronic case report forms, primary efficacy endpoint data, including retrospective seizure diary source records, adverse event reporting, protocol deviations, and monitor logs and follow-up letters.

An adverse event of right eye trauma that occurred on 10 May 2018 for Subject # (b) (6) (placebo) was noted in the source records, but the clinical investigator did not report this adverse event to the sponsor. Other that this one instance, there was no evidence of underreporting of adverse events.

Reviewer's comment: This unreported adverse event was an isolated finding.

The source data for the primary efficacy endpoint were reviewed and verified against the data listings provided by the sponsor for all 11 randomized subjects. Of note, review of the primary efficacy endpoint source records included the following:

- A CD containing certified copies of the eDiary source data maintained in (b) (4) (b) (4) online portal
- Paper source records for the retrospectively collected eDiary data that included the Caregiver's Personal Diaries, Caregiver's Seizure Calendar, Seizure Diary Entry Template, End of Day Review Diary Capture Forms, and LAR's seizure notes and other caregiver and physician notes at the site.

The sponsor reported in a response to an Information Request, dated 13 Jan 2020, that a portion of the Study Medication, Seizure, and End of Day eDiary data had been collected retrospectively for the 11 randomized subjects. It was observed during this inspection that many of the source records necessary to verify all retrospective entries were missing, or, when available, were incomplete and often contained discrepant and conflicting information.

Examples of eDiary data discrepancies noted during the inspection included (but were not limited to) the following found in Table 1 below.

Table 1: Examples of eDiary Data Discrepancies for Site #1001 (ZX008-1504-C2)

Subject Number (Treatment Assignment)	Type of Source Record Reviewed	Date of Seizure Diary Data	Original Diary Data Collection Method/Enter	Data in Source Record	Sponsor Data Listings Reported to FDA

			ed in (b) (4) Online Portal By:		
(b) (6) (placebo)	Caregiver's Personal Seizure Diary	6 July 2017	Retrospectively collected eDiary data by the investigator but not entered in the (b) (4) online portal	Single Isolated Seizure Time of Seizure: Evening Seizure Type: Type 1 Seizure Duration: 2 to 10 minutes	Missing
(b) (6) (placebo)	Caregiver's Personal Seizure Diary	7 July 2017	Retrospectively collected eDiary by the investigator but not entered in the (b) (4) online portal	Single Isolated Seizure Time of Seizure: Afternoon Seizure Type: Type 1 Seizure Duration: 2 to 10 minutes	Missing
(b) (6) (placebo)	Caregiver's Personal Seizure Diary	17 July 2017	Retrospectively collected eDiary by the investigator but not entered in the (b) (4) online portal	Single Isolated Seizure Time of Seizure: Afternoon Seizure Type: Type 1 Seizure Duration: 2 to 10 minutes	Missing

Reviewer's comment: Retrospective collection of the eDiary data by clinical investigators as much as 1 year after the subject's seizure event occurred can introduce recall bias and may impact the accuracy and reliability of this eDiary data used to support the primary efficacy endpoint. See Section I for overall recommendation regarding retrospectively collected eDiary data.

Of note, there was one questionable eDiary entry entered directly (and contemporaneously) by the caregiver in the LogPads that was missing from the sponsor's data listings. This entry documented a single seizure of more than 10 minutes that occurred in the early morning on 17

Feb 2017 in Subject (b) (6). Otherwise there were no other discrepancies noted in the eDiary data entered contemporaneously by the caregivers.

2. Marina Nikanorova, MD
   ZX008-VS01
   Site #0701
   Doctor Sells Vej 23
   Dianalund, Sjalland 4293
   Denmark
   Inspection Dates: 20 – 24 January 2020

At this site for Protocol ZX008-VS01, the sponsor noted that 9 subjects were screened, 7 were randomized, 6 completed the study, and 1 subject withdrew early and subsequently entered the open-label extension study.

An audit of the study records for all 9 screened subjects was conducted. Records reviewed included, but were not limited to, the study protocol and amendments, ethics committee submissions, approvals, and correspondence, subject eligibility criteria, informed consent, source data and records, electronic case report forms, primary efficacy endpoint data, including retrospective seizure diary source records, adverse event reporting, protocol deviations, and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. However, there was evidence of unreported protocol deviations. A dosing error, not initially reported to FDA, occurred in subject (b) (6) (placebo). Specifically, for this subject, site personnel entered an incorrect weight (1 kg, for a calculated dose of 0.1 mL BID) in the IVR/IWR system and subsequently corrected the weight to 17 kg. However, despite the weight correction in the IVR/IWR system, the site personnel did not discover that the originally calculated dose of 0.1 mL BID remained. The subject received an incorrect volume of study drug (placebo) for 3 days of the dose titration period.

Reviewer's comment: Of note, the Division of Neurology Products II sent an information request to the sponsor on 2 March 2020 requesting a listing of all unreported protocol deviations and dosing errors for Study ZX008-VS01. This dosing error that initially had not been reported to FDA was subsequently reported in the sponsor's response to the IR, dated 13 March 2020. Subject # (b) (6) was randomized to placebo, and the error occurred for only 3 days during the dose titration period. Therefore, the dosing error is not likely to have had an effect on the overall efficacy or safety results of the study.

The sponsor reported to FDA in an information request response, dated 13 Jan 2020, that a portion of the Study Medication, Seizure, and End of Day eDiary data had been collected retrospectively for 5 of the 7 randomized subjects (Subject #s (b) (6), (b) (6)).

The eDiary source data for the primary efficacy endpoint were reviewed and verified against the data listings provided by the sponsor for all 7 randomized subjects. Of note, review of the primary efficacy endpoint source records included the following:

- Over-the-shoulder access to eDiary data in (b) (4) online portal
- Paper source records for the retrospectively collected eDiary data that included the Caregiver's Personal Diaries, Caregiver's Seizure Calendar, Seizure Diary Entry Template, End of Day Review Diary Capture Forms, and LAR's seizure notes and other caregiver and physician notes at the site.

It was observed during this inspection that the source records necessary to verify these retrospective entries were often missing, or, when available, were incomplete and contained discrepant and conflicting information. Examples of eDiary data discrepancies noted during the inspection included (but were not limited to) the following found in Table 2 below.

Table 2: Examples of eDiary Data Discrepancies for eDiary Data Collected Retrospectively by Clinical investigators and Entered in (b) (4) for Site #0701 (ZX008-VS01)

Subject Number (Treatment Assignment)	Type of Source Record Reviewed	Date of Missing Seizure Diary Data	Data in Source Record	Sponsor Data Listings Reported to FDA
(b) (6) (placebo)	LAR's Seizure Notes	26 Aug 2016	7 Tonic seizures (3 diurnal and 4 nocturnal) • Seizure time and duration not documented	1 Tonic seizure • Seizure duration <2 min
(b) (6) (placebo)	LAR's Seizure Notes	27 Aug 2016	2 Focal seizures, 2 Tonic Diurnal + 3 Tonic Nocturnal • Longer than 2 min • Received Diazepam 7.5 mg rescue medication • Seizure time and duration not documented	3+ Cluster Tonic seizure • Seizure Time: Evening • Seizure duration 2-10 min 1 focal seizure • Seizure duration <2 min
(b) (6) (placebo)	LAR's Seizure Notes	28 Aug 2016	1 Focal, 2 Tonic Nocturnal • Seizure time and duration not documented	1 Tonic Evening • Seizure Time: Evening • Seizure duration <2 min 1 Focal seizure

				• Seizure duration <2 min
(b) (6) (placebo)	LAR's Seizure Notes	29 Aug 2016	3 Focal, 4 Tonic • 3 of them longer than 2 min • Received Diazepam 7.5 mg rescue medication • Seizure time not documented	3 Tonic • Seizure duration < 2 min for 2 tonic seizures and 2-10 min for 1 tonic seizure 1 Focal seizure • Seizure duration <2 min
(b) (6) (placebo)	LAR's Seizure Notes	30 Aug 2016	4 Tonic seizures • Seizure time and duration not documented	1 Tonic seizure • Seizure duration <2 min
(b) (6) (placebo)	LAR's Seizure Notes	31 Aug 2016	4 Focal, 4 Tonic seizures • Seizure time and duration not documented	1 tonic seizure • Seizure duration <2 min 1 focal seizure • Seizure duration <2 min
(b) (6) (placebo)	LAR's Seizure Notes	29 Sep 2016	3 Focal, 3 Tonic • The last one longer than 2 mi • Received Diazepam 7.5 mg rescue medication • Seizure time and duration not documented	2 Tonic seizures • First seizure duration 2-10 min • Second seizure duration <2 min
(b) (6) (placebo)	Seizure Diary Entry Template	26 Sep 2016	1 Generalized Tonic Clonic seizure • Start time of Seizure not documented • Seizure duration: < 2 min	2 Generalized Tonic Clonic Seizures • First seizure: duration of Seizure: < 2 min • Second seizure: start time: afternoon; Seizure

				duration: 2-10 min
(b) (6) (placebo)	Seizure Diary Entry Template	27 Oct 2016	Start time of seizure not documented	Start Time of seizure: Afternoon
(b) (6) (placebo)	Seizure Diary Entry Template	29 Oct 2016	1 Generalized Tonic Clonic seizure • Start time of seizure not documented; Seizure duration: < 2 min	2 Generalized Tonic Clonic Seizures Second seizure • Start time of seizure: evening; Seizure duration: 2-10 min
(b) (6) (placebo)	Caregiver's Seizure Calendar	12 Sep 2016	• 19 seizures listed on Caregiver's Seizure Calendar • 1 seizure listed in (b) (4) online portal	• 3 Generalized Tonic Clonic Convulsions listed in the sponsor's data listings

Reviewer's comment: The numerous retrospective data discrepancies were discussed with Dr. Nikanorova during the inspection closeout meeting. After further exploring the root cause of the data discrepancies with the sponsor, Dr. Nikanorova explained that the site would record multiple seizure events experienced on a single date or on multiple dates for a particular subject on one form (e.g., either a single paper source record and/or single DCR form). (b) (4) personnel responsible for entering the retrospectively collected information in the database often interpreted the multiple seizure events documented on the source records and DCR forms incorrectly as one seizure event.

In addition, the paper source records for the retrospective diary data were incomplete and did not contain the necessary information to fully describe the seizure episode. For example, many of the paper source records that were available did not reveal the seizure type, whether it was a single or cluster, the time the seizure began, the seizure duration, and whether the subject received rescue medication (or the dose of rescue medication received). Thus, it was not possible to verify the accuracy of this information in the cases (in Table 2) noted above where this information was included in the sponsor's data listing but not included in the source records. Also, as noted above, not all retrospective seizure data that the investigator obtained from the caregivers (that was documented in the paper source records) were entered in (b) (4) (b) (4) database.

The root cause for these observed discrepancies demonstrates a larger systemic issue of a lack of clear sponsor and vendor processes and procedures for communicating, collecting, reporting, verifying, and documenting retrospectively collected eDiary data for (b) (4) entry into

the online portal.

See Section I for overall recommendation regarding retrospectively collected eDiary data.

3. Dinesh Talwar, MD
   ZX008-VS01
   Site #0107
   Center for Neurosciences –Tucson
   2450 E River Rd
   Tucson, AZ 85718-6522
   Inspection Dates: 16 – 19 December 2019

At this site for Protocol ZX008-VS01, 4 subjects were screened, all of whom were randomized and completed the study. An audit of the study records for all 4 randomized subjects was conducted. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject eligibility criteria, informed consent, source data and records, electronic case report forms, primary efficacy endpoint data, including retrospective seizure diary source records, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. However, there were 23 protocol deviations documented by the clinical investigator in the source records that had not been reported to FDA, the most significant of which was the following:

- For subject (b) (6) (randomized to 0.2 mg/kg/day treatment arm), site personnel entered the subject's weight into the IVR/IWR system in pounds (116.8 lbs.), even though the system required the weight to be entered in kilograms. Subject (b) (6) should have received a dose of 12 mg/day at Visit 8 through Visit 12. Instead, this subject received the maximum dose of 30 mg/day (over two times the correct dose).

Reviewer's comments: As mentioned above, the Division of Neurology Products II sent an information request to the sponsor on 2 March 2020 requesting a listing of all unreported dosing errors for both pivotal studies. In the sponsor's response, dated 13 March 2020, the sponsor submitted additional major protocol deviation that had not been previously reported to FDA for Studies ZX008-VS01. The dosing error for Subject (b) (6) was not included in the sponsor's initial data listings nor was it included in their 13 March 2020 response to the IR. This additional dosing error should be noted in the review of this NDA. See Section III.5.C of this CIS for further details describing a larger systemic issue of the sponsor misclassifying many protocol deviations as minor, instead of major.

The sponsor reported to FDA in a response to an information request, dated 13 Jan 2020, that a portion of the End of Day eDiary data (i.e., used to confirm seizure -free days) had been collected retrospectively for all 4 subjects.

The eDiary source data for the primary efficacy endpoint were reviewed and verified against the data listings provided by the sponsor for all 4 subjects enrolled. Of note, review of the eDiary primary efficacy endpoint source records included the following:

- Flat reports (in excel and pdf formats) containing the eDiary data entries generated directly from (b) (4) online portal; certified copies of the eDiary data containing audit trail information were not reviewed
- Paper source records for the retrospectively collected eDiary data ranged from a highly detailed log of seizure type, duration, rescue medication use, and seizure medication, a moderate detailed log of seizure type and frequency to End of Day Review Diary Data Capture Form used by site personnel to interview the caregiver to determine basic YES, seizures occurred, OR NO, seizures did not occur.

The eDiary data collected retrospectively for Subjects # (b) (6), and (b) (6) could not be verified because the source documents (e.g., End of Day Review Diary Data Capture Form or other source records identified above) that were necessary to verify the retrospective eDiary data were not available.

The following eDiary data discrepancy in Table 3 was noted when comparing the End of Day Review Diary Data Capture Form source record against the sponsor's data listings:

Table 3: eDiary Data Discrepancy for Subject (b) (6):

Subject Number (Treatment Assignment)	Type of Source Record Reviewed	Date of Missing Seizure Diary Data	Original Diary Data Collection Method/Entered in (b) (4) Online Portal By:	Data in Source Record	Sponsor Data Listings Reported to FDA
(b) (6) (placebo)	End of Day Review Diary Data Capture	12 Oct 2016	Retrospective collection by investigator for entry by (b) (4)	No seizures occurred	Cluster Seizure • 2 hemiclonic, left body seizure • Start time of seizure: morning • Seizure duration: 0:05

Reviewer's comments: See Section I for overall recommendation regarding retrospectively collected data.

4. Elaine Wirrell, MD
   ZX008-VS01 and ZX008-1504-C2
   Site #0109
   MAYO CLINIC
   200 1st St SW
   Rochester, MN 55905

Inspection Dates: 16 - 19 December 2019

At this site for Protocol ZX008-VS01, 5 subjects were screened and 3 subjects were randomized, all of whom completed the study. For Protocol ZX008-1504-C2, 4 subjects were screened, all of whom were randomized and completed the study.

An audit of the study records for all 3 randomized subjects for Protocol ZX008-VS01 and all 4 randomized subjects for Protocol ZX008-1504-C2 was conducted. Records reviewed included, but were not limited to, the study protocol and amendments, IRB submissions and approvals, subject eligibility criteria, informed consent, source data and records, electronic case report forms, eDiary primary efficacy endpoint data, drug accountability, adverse event reporting, protocol deviations, and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events.

The sponsor reported to FDA in a response to an information request, dated 13 Jan 2020, that a portion of the eDiary data was collected retrospectively for all 3 randomized subjects for Protocol ZX008-VS01 and for 3 of the 4 randomized subjects in Protocol ZX008-1504-C2.

The ORA Investigator reported that the eDiary source data for the primary efficacy endpoint were reviewed and verified against the data listings provided by the sponsor for all randomized subjects for both protocols. The eDiary data collected retrospectively could not be verified because the source documents that were necessary to verify the retrospective eDiary data were not available.

Reviewer's comments: See Section I for overall recommendation regarding retrospectively collected data.

5. (b) (4)

(b) (4)

(b) (4)

Reviewer's comment: The Division of Neurology Products II previously sent an information request to the sponsor on 4 March 2019, requesting information on actual doses administered. In the sponsor's response to the IR, dated 26 March 2019, the sponsor provided the calculated dosages the subjects should have received based on the randomize dose group. The sponsor was unable to provide the actual doses the subjects received based on drug dispensing and accountability records. This, in addition to (b) (4) *inspection findings, likely points to the larger systemic issue of unreliable and inaccurate study drug accountability records.*

(b) (4)

(b) (4)

Reviewer's comment: The retrospective collection of eDiary data was also an observation noted during FDA inspections of the clinical investigators, including the missing and incomplete source records and discrepant information when comparing the source records against the sponsor's data listings. See Section I for overall recommendation regarding retrospectively collected eDiary data.

(b) (4)

(b) (4)

Reviewer's comment: The (b) (4) finding above, including unreported protocol deviations observed during FDA and (b) (4) inspections of the clinical investigators, points to a larger systemic issue with the processes and procedures for reviewing, classifying and reporting of protocol deviations. Thus, Division of Neurology Products II sent an IR, dated 2 March 2020 to the sponsor requesting a listing of all unreported dosing errors for both pivotal studies. In the sponsor's response, dated 13 March 2020, the sponsor submitted additional major protocol deviation that had not been previously reported. Study ZX008-VS01 included 42 protocol deviations that were previously unreported (of which 30 protocol deviations were originally classified as minor but were then reclassified as major). Study ZX008-1504-C2 included 10 unreported protocol deviations that were previously unreported (in which 7 were originally classified as minor but were then reclassified as major). There were an additional 10 unreported protocol deviations related to subjects being randomized before the sites received the final central reader's ECHO report in ZX008-VS01 (n = 8) and ZX008-1504-C2 (n = 2).

Furthermore, per the sponsor data listings and in the sponsor's 13 March 2020 response to an IR, dosing errors occurred in 8 subjects for ZX008-VS01 and in 5 subjects for ZX008-1504-C2. Dosing errors for 4 subjects enrolled in ZX008-VS01 were not initially reported to FDA in the sponsor's data listings (i.e., Subject #s (b) (6), and (b) (6)-(b) (6)). In addition, a dosing error was found during inspection of Site #0107 for Subject # (b) (6) that was not included in the sponsor's data listing, nor was it included in the sponsor's 13 March 2020 response to the IR (for more information, see FDA inspection summary for Site #0107).

- Critical deviation for inadequate centralized and/or ineffective on-site monitoring: (b) (4) noted that the on-site monitoring process was ineffective as it had failed to identify, escalate, and remedy systemic errors and data discrepancies that occurred during the trial conduct. This included, but was not limited to, data discrepancies related to retrospectively collected eDiary data, incomplete and missing source records necessary to verify the retrospective eDiary data, underreporting of adverse events, IMP-related dosing errors, and inaccurate and unreliable drug accountability issues found at the sites. Moreover, the sponsor noted that centralized monitoring procedures were not used as part of the overall monitoring program.

Reviewer's comment: (b) (4) Similar GCP noncompliance issues (e.g., missing eDiary data, missing source documents, retrospective collection of eDiary data, underreporting of protocol deviations and adverse events and

data discrepancies) were also observed during FDA site inspections of the clinical investigators. Many of these issues could be attributed to ineffective onsite monitoring and a lack of centralized monitoring.

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
Clinical Pharmacologist
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm. NDA 212102
DNII /Project Manager/ Stephanie Parncutt
DNII/Medical Officer/ Natalie Getzoff
DNII/Clinical Team Leader/ Philip Sheridan
DNII/Division Director/ Nick Kozauer
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Cheryl Grandinetti
OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database Project Manager/Dana Walters

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/s/

CHERYL A GRANDINETTI
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PHILLIP D KRONSTEIN
04/29/2020 01:09:10 PM

KASSA AYALEW
04/29/2020 01:49:54 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 22, 2020
Requesting Office or Division:	Division of Neurology 2 (DN2)
Application Type and Number:	NDA 212102
Product Name and Strength:	Fintepla (fenfluramine) Oral Solution, 2.2 mg/mL
Applicant/Sponsor Name:	Zogenix, Inc.
OSE RCM #:	2019-394-1
DMEPA Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

On April 9, 2020, the Applicant submitted revised labels and labeling and responses to recommendations that we made during a previous label and labeling review[a] for Fintepla (fenfluramine) Oral Solution. The Division of Neurology 2 (DN2) requested that we review the revised labels and labeling and the Applicant's responses to our comments to determine if they acceptable from a medication error perspective.

2 CONCLUSION

The Applicant's responses to our comments (See Appendix A) regarding the images of the supplies presented in the Instructions for Use (IFU) labeling (e.g., syringes and dispensing bottle) adequately addresses our previous concerns from a medication error perspective. However, the revised container labels and carton and IFU labeling (See Appendix B) are unacceptable from a medication error perspective for the following reason:

- The statement "[redacted] (b) (4)" in the IFU labeling (Step 2) does not cite to any images or text informing patients how to properly dispose of unused FINTEPLA.
- The active ingredient (i.e., fenfluramine) as part of the established name lacks prominence on the container label and carton labeling. Per our Guidance for Industry:

[a] Weitzman B. Label and Labeling Review for Fintepla (NDA 212102). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 18. RCM No.: 2019-394.

Reference ID: 4600275

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors[b], the proprietary name, established name, strength, route of administration, and warnings (if any) or cautionary statements (if any) should be the most prominent information on the principal display panel (PDP).

- The product strength is located to the left of the dosage form. This is not the customary location (i.e. Proprietary name (active ingredient) dosage form, strength) and may hinder a provider's ability to quickly and easily identify the product strength on the label.

3. RECOMMENDATIONS FOR ZOGENIX, INC.

We recommend the following be implemented prior to approval of this NDA 212102:

A. Instructions for Use (IFU) labeling:
   1. The statement "[redacted] (b) (4) " appears within Step 2 of the IFU. However, disposing instructions are not provided in the IFU. We are concerned that this may lead to confusion concerning how to properly dispose of unused FINTEPLA. Revise the IFU to address this concern.

B. Carton labeling and Container Labels (30 mL and 360 mL):
   1. The active ingredient (i.e., fenfluramine) as part of the established name lacks prominence on the container label and carton labeling. For example, the medication guide and net quantity statements on the principal display panel (PDP) of the carton labeling appear more prominent than the active ingredient statement. Per our Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*[c], the proprietary name, established name, strength, route of administration, and warnings (if any) or cautionary statements (if any) should be the most prominent information on the PDP. Increase the prominence of the active ingredient (i.e., fenfluramine), taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
   2. We note that the statement of strength is located to the left of the dosage form. This is not the customary location (i.e. Proprietary name (active ingredient) dosage form, strength) and may hinder a provider's ability to quickly and easily identify this information on the labels and labeling. Relocate the statement of product strength to follow the dosage form in accordance with our Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (lines 336-342)[c] as follows:

      Fintepla
      (fenfluramine)
      Oral Solution
      2.2 mg/mL

[b] Available from:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf
[c] Available from:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 18, 2020
Requesting Office or Division:	Division of Neurology 2 (DN2)
Product Name and Strength:	Fintepla (fenfluramine) Oral Solution, 2.2 mg/mL
Application Type and Number:	NDA 212102
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Zogenix, Inc.
FDA Received Date:	September 25, 2019
OSE RCM #:	2019-394
DMEPA Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

Reference ID: 4648009

1 REASON FOR REVIEW

As part of the approval process for Fintepla (fenfluramine) Oral Solution, the Division of Neurology 2 (DN2) requested that we review the proposed prescribing information (PI), medication guide (MG), instructions for use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

On August 20, 2018, Zogenix, Inc. (Zogenix) submitted a use-related risk analysis (URRA) and comparative analyses under IND 125797 to support that a Human Factors (HF) validation study was not needed to support the safe and effective use of their proposed Fintepla (fenfluramine) oral solution. In OSE #2018-1835[a], dated November 20, 2018, we determined that a HF validation study is not required to be submitted for Agency review in support of fenfluramine oral solution.

Zogenix submitted NDA 212102 for Fintepla (fenfluramine) Oral Solution on February 5, 2019. However, a refuse to file (RTF) notification was sent to the Applicant on April 5, 2019.

Zogenix resubmitted NDA 212102 on September 25, 2019 (subject of this review).

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other - Information Request	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

[a] Stewart, J. Human Factors Use-Related Risk Analysis Review for Fenfluramine (IND 125797). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 20. RCM No.: 2018-1835.

Reference ID: 4648009

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), medication guide, container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Neurology Products (DNP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The dosing information in Table 1 (i.e., 0.10 mg/kg and 0.20 mg/kg) is expressed with the use of trailing zeros.	The use of trailing zeros should be avoided to prevent the risk of medication dosing errors per ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations.	Remove all instance of trailing zeros to avoid misinterpretation.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The packaging configuration/units in which dosage form is ordinarily available for prescribing by practitioners is omitted from the 'How Supplied' section (16.1). Additionally, we note that the National Drug Code (NDC) numbers are not included in Section 16.1.	Per 21 CFR 201.57(c)(17), the 'How Supplied/Storage and Handling' section of the PI must include the packaging configuration/ units in which the dosage form is ordinarily available for prescribing and appropriate information to facilitate identification of the dosage form (such as, the NDC number).	Revise Section 16.1 to indicate how the product will be supplied and include the associated NDC numbers. For example: Fintepla is supplied as: Carton containing one 360 mL bottle (NDC# 43376-322-36) Carton containing one 30 mL bottle (NDC # 43376-322-30)
Full Prescribing Information – Section 17 Patient Counseling			
1.	We note the statement "Advise patients who are prescribed FINTEPLA to use the oral dosing syringes provided" under 'Administration Information' in section 17 of PI.	This statement may mislead readers to believe that the oral dosing syringes are co-packaged with the product and the statement can be revised for clarity.	We recommend revising the statement to read: "Advise patients who are prescribed FINTEPLA to use the oral dosing syringes provided by the pharmacy."

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Table 3. Identified Issues and Recommendations for Zogenix, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			(b) (4)
Instructions for Use (IFU)			
1.	In your December 16, 2019 response to the Agency's December 9, 2019 Information Request, you state:	It is unclear whether the images used in the Instructions for Use (e.g., 3 mL and 6 mL oral syringes, dispensing bottle, location	Please explain, how you can ensure that the images of the supplies in the IFU (e.g., 3 mL and 6 mL oral syringes, dispending bottle, location

Reference ID: 4648009

Table 3. Identified Issues and Recommendations for Zogenix, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	• the 30 mL and 360 mL commercial bottles will not be dispensed to patients; • the specialty pharmacy will dispense the medication into a separate bottle; and • the syringes, bottle adapter, and dispensing bottles are sourced by the specialty pharmacy and not provided by Zogenix.	and format of 'discard after' date on the dispensing bottle) are representative of the supplies that will be provided by the specialty pharmacy.	and format of 'discard after' date on the dispensing bottle) are representative of what the specialty pharmacy will provide.

5 CONCLUSION

Our evaluation of the proposed Fintepla (fenfluramine) oral solution prescribing information (PI), medication guide (MG), instruction for use (IFU), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Zogenix, Inc. so that recommendations are implemented prior to approval of this NDA.

Reference ID: 4648009

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Fintepla that Zogenix, Inc. submitted on September 25, 2019.

Table 4. Relevant Product Information for Fintepla	
Initial Approval Date	N/A
Active Ingredient	Fenfluramine hydrochloride
Indication	FINTEPLA® is indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older.
Route of Administration	Oral
Dosage Form	Solution
Strength	2.2 mg/mL equivalent to 2.5 mg/mL of the hydrochloride salt
Dose and Frequency	Starting dose is 0.1 mg/kg twice daily which can be increase to 0.2 mg/kg twice daily on day 7 and 0.35 mg/kg twice daily on day 14. The maximum daily maintenance dose of FINTEPLA is 0.35 mg/kg twice daily, not to exceed a total daily dose of 26 mg. Dosage adjustments in patients receiving Stiripentol plus Clobazam, with or without Valproate: The maximum daily maintenance dose is 0.2 mg/kg twice daily, not to exceed a total daily dose of 17 mg.
How Supplied	30 mL and 360 mL Cherry flavored clear colorless liquid in white HDPE plastic bottle with CRC.
Storage	Store FINTEPLA at room temperature between 68°F to 77°F (20°C to 25°C); excursions are permitted between 59°F to 86°F (15°C to 30°C). Do not refrigerate or freeze.
Container Closure	HDPE bottles with CRC.

Reference ID: 4640009

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 12, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, fenfluramine, IND 125797 and NDA 212102 . Our search identified one previous review[b] and we considered our previous recommendations to see if they are applicable for this current review.

Table 5. Summary of Previous DMEPA Reviews for Fintepla

OSE RCM #	Review Date	Summary of Recommendations
2018-1835	November 23, 2018	HUMAN FACTORS USE-RELATED RISK ANALYSIS REVIEW: The comparative analyses did not identify any new or unique risks when compared to Epidiolex (cannabidiol) oral solution (NDA 210365) and Quillivant XR (methylphenidate HCl) for extended release oral suspension (NDA 202100). Therefore, based on the review of the URRA and comparative analyses, it was determined that a human factors validation study was not required to be submitted for Agency review in support of the Sponsor's fenfluramine oral solution.

URRA Review Available in DARRTS via:
https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804c6b5a&_afrRedirect=1727130964261105

[b] Stewart, J. Label and Labeling Review for fenfluramine oral solution (IND 125797). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 23. RCM No.: 2018-1835.

Reference ID: 4648009

APPENDIX E. INFORMATION REQUEST

E.1 Information Request (ISSUED DECEMBER 9, 2019)

During our review of the labels and labeling we identified that the following items should be addressed:

- Clarify the lowest expected starting dose in mL for your proposed product.
- Clarify how the specialty pharmacy will obtain the bottle adapter, and 3 mL and 6 mL oral dosing syringes to supply with your proposed product.
- In the proposed Instructions for Use (IFU), the 3 mL syringe has dose markings in 0.1 mL increments and the 6 mL syringe has dose markings in 0.5 mL increments. However, it is unclear whether doses need to be rounded to the nearest 0.1 mL for doses 3 mL or less and rounded to the nearest 0.5 mL for doses 3.5 mL to 6 mL. Explain how you intend for your proposed product to be dosed using the 3 mL and 6 mL oral syringes described in the IFU.
- You submitted proposed container labels and carton labeling for a 30 mL and 360 mL bottle configuration. However, from your submission, it is unclear whether these packaging configurations are intended to be used by the specialty pharmacy as stock bottles or whether they are intended to be dispensed to patients. Please clarify.
- To assist with our review, we request you provide the Agency with five (5) intend-to-market samples of your proposed product, including the 30 mL bottle with carton, 360 mL bottle with carton, bottle adapter, 3 mL oral syringe and 6 mL oral syringe.

E.2 Response

The Sponsor responded to DMEPA's Information Request on December 16, 2019. In their response, Zogenix, Inc. addressed all the items identified in the IR letter.

Response available in EDR via: \\cdsesub1\evsprod\nda212102\0025\m1\us\111-info-amend\resp-info-req-20191209.pdf

Reference ID: 4648009

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Fintepla labels and labeling submitted by Zogenix, Inc.

- Container label(s) received on September 25, 2019
- Carton labeling received on September 25, 2019
- Instructions for Use (Image not shown) received on September 25, 2019

  Refer to link in ERD for Instructions for Use:

  \\cdsesub1\evsprod\nda212102\0011\m1\us\114-label\1141-draft-label\fintepla-medguide-word.docx
- Medication Guide (Image not shown) received on September 25, 2019

  Refer to link in EDR for Medication Guide:

  \\cdsesub1\evsprod\nda212102\0011\m1\us\114-label\1141-draft-label\fintepla-medguide-word.docx
- Prescribing Information (Image not shown) received on September 25, 2019

  Refer to link in EDR for Prescribing Information:

  \\cdsesub1\evsprod\nda212102\0011\m1\us\114-label\1141-draft-label\proposed.docx

F.2 Label and Labeling Images

Container label(s)

(b) (4)

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[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Reference ID: 4648019

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/s/

BEVERLY WEITZMAN
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BRIANA B RIDER
01/19/2020 07:35:25 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: 18 December 2019

From: Shetarra Walker MD, MSCR, FAAP

Through: Martin Rose MD, JD
Norman Stockbridge MD, PhD

To: Nick Kozauer MD, Acting Division Director, DNII

Subject: Consult Request: Review cardiovascular safety data from NDA 212102

This memo responds to your clinical consult to us received on 01 October 2019 requesting we review the cardiovascular safety analyses and Zogenix's proposed risk management plan to address the cardiovascular risk of fenfluramine. To address this consult request, we reviewed the integrated cardiovascular summary of safety and other pertinent information for and data from cardiovascular assessments. In addition, we reviewed the Zogenix's proposed plan for risk mitigation to address the cardiovascular risk of fenfluramine.

Conclusion

To date, there is no evidence of cardiac valvulopathy or pulmonary arterial hypertension (PAH) in pediatric patients treated with fenfluramine. It is unclear if the risk for fenfluramine-induced cardiac valvulopathy or PAH are primarily due to dose-exposure or duration of therapy. Because of limited extended long-term safety data and lack of comparative dose-exposure information, we cannot conclude that lower total daily fenfluramine doses administered to Dravet syndrome (DS) patients, compared to higher doses prescribed to obese adult patients, confers a reduced risk for cardiac valvulopathy or PAH. Given the mechanism of action, fenfluramine has the potential to increase heart rate and blood pressure.[1] Vital sign data in this submission did not show consistent increases in heart rate or blood pressure associated with fenfluramine treatment.

[1] "Fenfluramine." *DrugBank*, https://www.drugbank.ca/drugs/DB00574.

Reference ID: 4640085

Given the known association of cardiac valvulopathy and PAH with fenfluramine, we support a Risk Evaluation and Mitigation Strategy (REMS) for this product to mitigate cardiac valvulopathy and PAH. In addition, we encourage DNII to add information to labeling to inform prescribers of the potential risk for elevated heart rate and blood pressure. Further comments on components of the REMS are outside the scope of this consult. We will work with DNII to develop those elements.

Background and Regulatory History

Zogenix is developing ZX008 (fenfluramine hydrochloride), an amphetamine analogue, for treatment of DS, a severe and refractory form of epilepsy that commonly presents during the first year of life. DS is associated with increased risk of sudden death in childhood and deterioration of intellectual development by around two years of age. To date, FDA has approved two drug therapies for DS, Diacomit® (stiripentol) and Epidiolex® (cannabidiol). FDA previously approved fenfluramine for obesity treatment, but it was withdrawn from the market because of reported cases of cardiac valvular heart disease (VHD), primarily left-sided, and PAH. Division of Neurology Products, now DNII, thrice consulted the Division of Cardiovascular and Renal Products regarding cardiovascular (CV) safety monitoring and assessments.

Reviewer Comments: *Although fenfluramine-associated VHD preferentially affects left-sided heart valves, right-sided heart valve involvement has been reported in published literature.*[2] *Fenfluramine-induced VHD and PAH may result in irreversible structural and/or physiologic changes. Moreover, some patients with fenfluramine-induced PAH may develop progressive disease similar to idiopathic and heritable forms of PAH.*[3]

Since September 2018, Zogenix has provided multiple submissions as part of their rolling submission for NDA 212102. On 05 February 2019, Zogenix submitted clinical data to NDA 212102. However, the Agency issued a refuse-to-file (RTF) letter on 05 April 2019 because of insufficient nonclinical data and submission of erroneous datasets with data quality concerns for the one of the pivotal clinical studies. On 25 September 2019, Zogenix resubmitted clinical and nonclinical data to address RTF issues.

Synopses of Clinical Studies, Cardiovascular Safety Monitoring, and Statistical Analysis Plan

In this submission, Zogenix provided data from two randomized double-blind Phase 2 clinical studies, Study 1 and Study 1504 Cohort 2 in addition to an interim analysis (IA) from an open-label extension study, Study 1503. Study 1504 Cohort 1, (b) (4) and Study 1503 are ongoing. Study 1 compared 2 doses of ZX008, 0.8 mg/kg/day and 0.2 mg/kg/day, to placebo in subjects receiving standard of care (SoC) anti-epileptic drugs (AEDs) excluding stiripentol (STP). Study 1504 Cohort 2 compared ZX008 0.5 mg/kg/day to placebo in subjects receiving SoC AEDs where administration of STP (in combination with clobazam and/or valproate) was mandatory. Both studies enrolled subjects stable on SoC AEDs but still experiencing high seizure burden.

The primary efficacy measure in both randomized studies was change from baseline in the frequency of convulsive seizures (per 28 days) during the combined 14-week (Study 1) or 15-week (Study 1504 Cohort 2)

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[2] *Connolly, H. M., et al. (1997). "Valvular Heart Disease Associated with Fenfluramine–Phentermine." New England Journal of Medicine 337(9) 581-588.*

[3] *Montani, D, et al. (2013). "Drug-induced pulmonary arterial hypertension a recent outbreak." European Respiratory Review 22 (129) 244-250.*

Reference ID: 4642085

treatment period. Key secondary objectives in both studies included a comparison of subjects who experienced at least a 50% reduction in monthly convulsive seizure frequency (also known as the ≥ 50% Responder Rate) and the median longest seizure-free interval between convulsive seizures. Table 1 shows all studies, completed and ongoing, in the ZX008 DS development program.

Table 1. ZX008 Clinical Studies for the Dravet Syndrome Development Program

Study Number	Phase	Study Status	Description	Dose mg/kg/day	Planned (Actual) Number of Subjects	Duration of Exposure
Study 1	3	Complete	Efficacy and Safety	Placebo, 0.2, 0.8	120 (119)	16 weeks
Study 1504 Cohort 2	3	Complete	Efficacy and Safety	Placebo, 0.5	80 (87)	17 weeks
Study1503	3	Ongoing	Open-label extension (for subjects from Study 1, (b) (4) and Study 1504)	0.2, 0.4, 0.5, 0.6, 0.8	340 (ongoing)	Up to 3 years
Additional Clinical Studies						
(b) (4)						
Study 1504 Cohort 1	1	Complete	PK/Safety	0.2, 0.4	20 (18)	2 to 24 weeks
Study 1603	1	Complete	TQT Safety	Placebo, 15, 60 mg twice daily (BID)	180 (180)	1 to 8 days

Source Adapted from Sponsor Table 5, CV ISS, p31 of 158

Zogenix analyzed echocardiogram (ECHO) and electrocardiogram (ECG) data in three populations described below:

- *ISS-DB (ISS Double-blind) Population*, N=206: includes subjects from completed double-blind Study 1 and Study 1504 Cohort 2 who received at least 1 dose of study medication. Data were pooled from placebo groups, while the ZX008 dose groups were considered separately.
- *LTS-DB (Long-term Safety Double-blind) Population*, N=158: includes ISS-DB subjects from Study 1 and Study 1504 Cohort 2 who entered Study 1503 by the cut-off date of 13 March 2018 and received at least 1 dose of study medication.
- *LTS (Long-term Safety) Population*, N=232: includes subjects who entered Study 1503 from Study 1, Study 1504 Cohort 1 or Cohort 2, (b) (4) by the cut-off date of 13 March 2018, and

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received at least 1 dose of study medication.

A separate statistical analysis plan (SAP) was provided for analyses of ECG and ECHO safety endpoints. All CV safety data were reported as summary statistics with no adjustments for multiplicity made. ECGs and ECHOs were blindly reviewed centrally by two board-certified cardiologists with plan for adjudication by another board-certified cardiologist in case of discrepancy between the two central readers. The adjudication cardiologist reviewer selected whichever echo result from the two central readers with which he/she agreed as the "official" ECHO reading. In select cases, the international pediatric cardiac advisory board (IPCAB) acted as the final adjudicator.

The focus of ECG review was QTcF although other ECG variables were assessed. Missing data were not imputed, and missing data points did not exclude the rest of the subject's data from analyses. The focus of ECHO evaluations was change from baseline in the regurgitation "score" for mitral and aortic valves at each time-point and development of clinically meaningful changes in valve regurgitation or PAH. Below are the primary ECHO assessments defined in the study protocol:

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

Reviewer Comments:

- *The FDA criteria for VHD was described in a Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report published in 1997 on cardiac valvopathy associated with exposure to fenfluramine or dexfenfluramine. The publication includes a summary of cardiac findings from 113 spontaneous reports meeting the VHD case definition. Median duration of drug use was 9 months with most cases (77%) symptomatic and 24% requiring cardiac valve-replacement surgery from which three patients died post-surgery. FDA assessed prevalence of valve lesions in asymptomatic patients by survey and found a prevalence of VHD meeting the case definition ranging from 30-38% (number of patients surveyed not provided). At the time of publication, the data suggested that prevalence of valvopathy may be higher among patients exposed to drug for at least 6 months.*
- *Given that various external factors e.g., patient agitation can transiently increase PASP, it is reasonable to obtain a repeat ECHO to confirm presence of PAH.*

Secondary ECHO Analyses included:

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

Zogenix also conducted secondary ECG analyses that included assessments of heart rate (HR) and other ECG intervals as described in the study protocol. Table 2 below shows the schedule of ECG and ECHO assessments for each clinical study.

Table 2. 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

Reference ID: 4642087

CV events were considered adverse events of special interest (AESIs). CV assessments included ECGs and ECHOs with doppler performed in all studies, but timing of cardiac assessments varied across protocols as shown in Table 2. Subjects who completed Study 1 and Study 1504 but did not enter the open label extension (OLE) - Study 1503, or discontinued a study were to return for post-treatment cardiac follow-up at 3 months, 3-6 months, or 12 months post-treatment depending on duration of fenfluramine treatments or presence of cardiac signs or symptoms at any time while on study drug. In Study 1503 (OLE), post-treatment cardiac follow-up was to be performed at months 3 and 6 or at early termination. Prior to study initiation, Zogenix developed standard protocols for age-appropriate evaluation of cardiac valves and non-invasive estimation of PAH in addition to pre-specified thresholds for abnormalities of valve function and estimated PASP. ECHOs were performed only at facilities with pediatric expertise. In the case of worsening severity of ECHO findings for subjects remaining in the study, predefined increasing oversight by the independent data safety monitoring committee (IDSMC) and IPCAB was specified.

Initially, all observations of aortic or mitral regurgitation regardless of severity or associated symptoms were recorded as AESIs. Because of the number of trivial or trace aortic or mitral regurgitation observations, Zogenix amended study protocols to exclude trivial or trace regurgitation as an AESI. This protocol modification primarily affected Study 1504.

Dose Exposure Across Clinical Studies

Table 3 below shows the number of subjects receiving ZX008 stratified by duration of treatment and mean daily dose in Study 1503 (OLE).

Table 3. Number of Subjects Receiving ZX008 According to Mean Daily Dose and Duration of Treatment (Study 1503)

Duration (Months)	Number of Subjects Receiving ZX008 Mean Daily Dose				
	>0 to 0.2 mg/kg/d (N)	>0.2 to <0.4 mg/kg/d (N)	0.4 to 0.6 mg/kg/d (N)	>0.6 to 0.8 mg/kg/d (N)	Total N (%)
<=1	0	0	0	0	0
>1 to ≤ 2	0	1	0	0	1 (0%)
>2 to ≤ 3	3	4	4	1	12 (5%)
>3 to ≤ 4	3	10	2	0	15 (6%)
>4 to ≤ 5	2	7	7	2	18 (9%)
>5 to ≤ 6	3	8	4	3	18 (8%)
>6 to ≤ 7	6	9	6	1	22 (10%)
>7 to ≤ 8	3	5	7	9	24 (10%)
>8 to ≤ 9	0	2	6	4	12 (5%)
>9 to ≤ 10	3	4	5	2	14 (6%)

Reference ID: 4642087

Duration (Months)	Number of Subjects Receiving ZX008 Mean Daily Dose				
	>0 to 0.2 mg/kg/d (N)	>0.2 to <0.4 mg/kg/d (N)	0.4 to 0.6 mg/kg/d (N)	>0.6 to 0.8 mg/kg/d (N)	Total N (%)
>10 to ≤ 11	0	4	6	5	15 (6%)
>11 to ≤ 12	3	5	9	3	20 (9%)
>12 to ≤ 18	2	6	20	25	53 (23%)
>18 to ≤ 24	1	1	0	6	8 (3%)
Total (Any Duration) n (%)	29 (13%)	66 (28%)	76 (33%)	61(26%)	232 (100%)

Source Adapted from Sponsor Table 6, CV ISS, p32 of 158

In Study 1503 (OLE), 24/232 (10.3%) and 31/232 subjects (13.4%) were exposed to "high dose," >0.6 to 0.8mg/kg/day for at least 6 months and at least one year, respectively. In addition, 39/232 (16.8%) and 20/232 (6.3%) subjects were exposed to 0.4 to 0.6 mg/kg/day for at least 6 months and at least one year, respectively. Most subjects in the 0.4 to 0.6 mg/kg/day dose cohort were taking concomitant STP at the maximum allowed dose per protocol. Table 4 shows duration of ZX008 exposure across all clinical studies included in this submission.

Table 4. Duration of ZX008 Exposure Across *Active* Subjects in Safety Population*

	Study 1504 C1 Transition Period ZX008 0.2 mg (N=15)	Study 1 and Study 1502 C2 Active ZX008 DB Any Dose *(placebo patients not included)* (N=122)	Study 1503 ZX008 Dose (N=174)	ALL *Active* ZX008 Treated Subjects *(core study + OLE)* (N=204)
Summary Statistics				
N	15	122	174	204
Mean (days)	142.1	109.8	311.9	342.3
SD	56.90	23.51	134.22	178.30
Median	169.0	113.5	320.5	348.0
Min, Max	0, 174	21, 145	57, 634	21, 703
Duration of Exposure				
<1 month	1 (6.7%)	2 (1.6%)	0	2 (1.0%)
1 to <3 months	2 (13.3%)	11 (9.0%)	8 (4.6%)	16 (7.8%)
3 to <6 months	12 (80.0%)	109 (89.3%)	26 (14.9%)	29 (14.2%)
6 to <12 months	0	0	75 (43.1%)	57 (27.9%)

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12 to <18 months	0	0	57 (32.8%)	70 (34.3%)
18 to <24 months	0	0	8 (4.6%)	30 (14.7%)
>=24 months	0	0	0	0

*Source Adapted from Sponsor Table 5, ISS, p35 of 636; C1 = Cohort 1, C2 = Cohort. *Data is from the ISS-ALL Population that contains subjects from Study 1, Study 1504 Cohort 1 (PK study), Study 1504 Cohort 2, most of whom entered the OLE study 1503, but does not include subjects who entered Study 1503* (b) (4) *(n=58).*

As shown in Table 4, 204 subjects received at least one dose of ZX008 either in Studies 1504 (Cohorts 1 and 2) or Study 1 with most active subjects exposed to any dose of ZX008 for 3 to <6 months. In Study 1503 (OLE), most subjects, 132/174 (75.9%), were exposed to any dose of ZX008 from 6 to <18 months with 8/174 (4.6%) exposed to ZX008 from 18 to <24 months.

For all ZX008-treated subjects (n=224), 62/224 (27.7%) and 162/224 subjects (72.3%) were <6 years or ≥6 years of age, respectively. Both age cohorts had comparable proportions of subjects per stratum of exposure duration with most subjects, 40.3% (<6 years of age) and 33.3% (≥6 years of age), exposed to ZX008 for 12 to <18 months.

Summary of Cardiovascular Safety Data

Zogenix presented CV safety data in a separate CV integrated summary of safety (ISS), from 206 subjects in double-blind, placebo-controlled studies [Study 1 (N=119) and Study 1504 Cohort 2 (N=87)] with 122 of the 206 subjects treated with ZX008. Continuation data from Study 1503 (OLE) are included in the CV ISS for 232 subjects (N=110 from Study 1, N=48 from Study 1504 Cohort 2, N=16 from Study 1504 Cohort 1, (b) (4) In addition, Zogenix provided a summary of CV safety data from Study 1504 Cohort 1 (N=18) (b) (4)

ECG Safety Data

A Thorough QT (TQT) trial, Study 1603, was conducted in healthy subjects and reported separately. Study 1603 was a randomized, double-blind, double-dummy, placebo- and positive-controlled, multiple-dose, parallel study. Subjects were randomized into one of three treatment arms – therapeutic dose (15 mg BID), supratherapeutic dose (60 mg BID), and control. The positive control was moxifloxacin. One hundred eighty (180) healthy adult male and female subjects were enrolled. Subjects were dosed over an 8-day period. The primary ECG endpoint was change from baseline in QTcF of ZX008 and placebo at each time point.

Mean QT intervals remained within normal limits across treatments, with mean decreases noted at most time points. The maximum mean QT interval and interval increase from baseline of 417.87 ms (+9.25 ms) occurred on Day 1 at Hour 4 following Moxifloxacin/Placebo. Changes from baseline for QTcF following therapeutic and supratherapeutic doses of ZX008 were decreased at post-dose time points and similar between treatments. For active treatment, the maximum difference in in mean QTcF from baseline was -9.3 ms on Day 1 Hour 1 for 60 mg ZX008. The maximum mean QTcF interval following active treatment on Day 7 Hour 15 with ZX008 15 mg of about 396 ms (baseline decrease of -2.6 ms). Study 1603 showed there is no significant effect of ZX008 on QTc prolongation at either therapeutic or supratherapeutic doses. All other mean ECG parameters

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were within normal limits. There were no deaths or SAEs in the study. The most common TEAEs were headache and diarrhea with more subjects reporting TEAEs at the 60 mg dose (67%) compared to the 15 mg dose (42%).

Among pediatric subjects exposed to ZX008 in this submission (N=232), there were no effects of ZX008 on cardiac repolarization or other ECG parameters. Across the ISS-DB, LTS-DB, and LTS populations, all QTcF values were within normal range for all subjects treated with ZX008 and in placebo group. No subject met the high QTcF criteria and no subject had a QTcF >450 ms or change from baseline >60 ms. Across all study populations, few subjects (1.3-3.4%) had a change from baseline QTcF >30 to 60 ms.

As shown in Table 5 below, the proportions of subjects with ECGs classified as abnormal fluctuated among study visits, but there was no obvious pattern of a dose-dependent relationship. In the LTS Population, there were three subjects with post-treatment ECGs categorized as “abnormal ECG potentially clinically significant” and all read out as first-degree AV block. One subject was enrolled (b) (4) and the other subjects were in the OLE, 0.2 mg/kg dose group. The proportion of subjects with ECG parameters considered outliers was comparable across treatment groups and dose cohorts.

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Table 5. ECG Classification of Subjects by Cohort/Study and Study Day -LTS Population *(Adapted from Sponsor Table 44 in CV ISS p136 of 158)*

ECG Classification LTS Population	Placebo - ZX 008 OLE (N=64) n (%)	ZX008 0.2 mg - ZX 008 OLE (N=54) n (%)	ZX008 0.5 mg - ZX 008 OLE (N=21) n (%)	ZX008 0.8 mg - ZX 008 OLE (N=35) n (%)	(b) (4) - ZX 008 OLE (N=58) n (%)	All Subjects (N=232) n (%)
Baseline-OLE						
Normal	59 (95.2%)	47 (90.4%)	18 (90.0%)	32 (94.1%)	53 (93.0%)	209 (92.9%)
Abnormal, Clinically Insignificant	3 (4.8%)	5 (9.6%)	2 (10.0%)	2 (5.9%)	4 (7.0%)	16 (7.1%)
Abnormal, Potentially Clinically Significant	0	0	0	0	0	0
Study Day 30						
Normal	59 (93.7%)	49 (94.2%)	17 (85.0%)	31 (88.6%)	48 (85.7%)	204 (90.3%)
Abnormal, Clinically Insignificant	4 (6.3%)	3 (5.8%)	3 (15.0%)	4 (11.4%)	8 (14.3%)	22 (9.7%)
Abnormal, Potentially Clinically Significant	0	0	0	0	0	0
Study Day 60						
Normal	51 (87.9%)	48 (94.1%)	16 (94.1%)	29 (85.3%)	46 (86.8%)	190 (89.2%)
Abnormal, Clinically Insignificant	7 (12.1%)	3 (5.9%)	1 (5.9%)	5 (14.7%)	6 (11.3%)	22 (10.3%)
Abnormal, Potentially Clinically Significant	0	0	0	0	1 (1.9%)	1 (0.5%)
Study Day 90						
Normal	52 (96.3%)	46 (86.8%)	11 (84.6%)	32 (91.4%)	43 (95.6%)	184 (92.0%)
Abnormal, Clinically Insignificant	2 (3.7%)	7 (13.2%)	2 (15.4%)	3 (8.6%)	2 (4.4%)	16 (8.0%)
Abnormal, Potentially Clinically Significant	0	0	0	0	0	0
Study Day 180						
Normal	37 (92.5%)	45 (90.0%)	3 (100.0%)	29 (87.9%)	15 (100.0%)	129 (91.5%)
Abnormal, Clinically Insignificant	3 (7.5%)	4 (8.0%)	0	4 (12.1%)	0	11 (7.8%)
Abnormal, Potentially Clinically Significant	0	1 (2.0%)	0	0	0	1 (0.7%)
Study Day 270						
Normal	25 (96.2%)	35 (87.5%)	0	24 (92.3%)	0	84 (91.3%)
Abnormal, Clinically Insignificant	1 (3.8%)	4 (10.0%)	0	2 (7.7%)	0	7 (7.6%)
Abnormal, Potentially Clinically Significant	0	1 (2.5%)	0	0	0	1 (1.1%)
Study Day 365						
Normal	14 (100.0%)	13 (92.9%)	0	12 (85.7%)	0	39 (92.9%)
Abnormal, Clinically Insignificant	0	1 (7.1%)	0	2 (14.3%)	0	3 (7.1%)
Abnormal, Potentially Clinically Significant	0	0	0	0	0	0
Study Day 455						
Normal	3 (100.0%)	6 (100.0%)	0	5 (100.0%)	0	14 (100.0%)
Abnormal, Clinically Insignificant	0	0	0	0	0	0
Abnormal, Potentially Clinically Significant	0	0	0	0	0	0

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Reviewer Comments: *As described later in the review, a small proportion of patients were reported to have abnormalities in heart rate as TEAEs. However, no rhythm abnormalities were captured in the ECG data. Lack of clinically significant ECG findings in the pediatric study are supported by findings from the TQT study in which healthy subjects were dosed with significantly higher doses of ZX008.*

ECHO Safety Data

Overall Summary of Valvular ECHO Findings Across All Pediatric Studies

At time of the interim-cut-off for Study 1503 (OLE), 1648 ECHOs had been performed in 280 unique subjects with mean number of ECHOs (SD) of 5.9 (2.6) per subject with a range of study duration from 63 to 823 days. No subject developed VHD of any cardiac valve at any timepoint in any study. Of those subjects with trace or greater mitral regurgitation (MR), all but one subject had trace MR and no subjects had moderate or greater MR. Aortic regurgitation (AR) was observed rarely but no more severe than trace. Trace tricuspid regurgitation (TR) and pulmonary regurgitation (PR) were observed frequently among study subjects across studies, but no subjects developed moderate or severe TR or PR.

Reviewer Comments: *In the absence of structural valve abnormalities, I would consider the following as clinically non-significant or physiologic: trace to mild MR, trace AR, trace to mild TR and PR. Therefore, I have no clinical concern about the observations of numerous subjects with trace valvar regurgitation as described in detail later in this review.*

Zogenix provides a case narrative for Subject (b) (6), a 10-year-old male, randomized to ZX008 0.2 mg/kg/day in Study 1 then treated in Study 1503 (OLE) for 466 days. The ECHO performed at Month 15, after the Study 1503 IA cut-off date, reported mild AR by one central reader but trace AR by the second central reader. The IPCAB Chair read the ECHO as trace to mild AR therefore a repeat ECHO was performed less than 3 weeks later with core lab read out citing presence of an AR jet with "peculiar features." Therefore, the subject was recommended for a transesophageal ECHO (TEE) and computed tomography (CT) angiogram to rule out aortic valve pathology and possible dilated aortic root. The subject remained on ZX008 treatment during this adjudication period. The CT angiogram was read out as normal aortic valve with mild aortic dilatation. The TEE was read out as normal aortic valve pathology with either absent or "very trace" or fleeting AR and trace MR. The adjudication resulted in a conclusion that this subject has no clinically significant valvar regurgitation with absent mitral and aortic regurgitation. Regardless, the family opted to discontinue from the study because of lack of efficacy and desire to initiate a new medication.

Reviewer Comment: *ECHOs performed under sedation such as a TEE in a pediatric patient can discourage AR due to decreased systemic vascular resistance from anesthetic or sedative agents. However, absence of structural valve abnormalities in Subject* (b) (6) *is reassuring for no evidence of VHD.*

Zogenix searched free-text comments on ECHO reports to determine if any structural changes to valves were observed. The Sponsor searched and reviewed 6252 observations and compared comments against a set of terms associated with valvular and non-valvular structural abnormalities of interest based on published cardiology guidelines. Only one report (Subject (b) (6)) included a comment describing possible annulus thickening of the tricuspid valve observed by one central ECHO reader but not the other on Study Day 90 in Study 1503 (OLE). Both ECHO reviewers noted that images of the tricuspid valve were suboptimal for

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measurements. Two subsequent ECHOs for this subject did not contain notations about possible tricuspid valve annulus thickening. The subjects exited the trial 1-month later due to lack of efficacy with ECHOs conducted at time of study discontinuation and 3-month follow-up showing no mitral, aortic, or tricuspid regurgitation and trace PR. Zogenix did not find any other free-text comments consistent with observed valvular or non-valvular cardiac structural abnormalities.

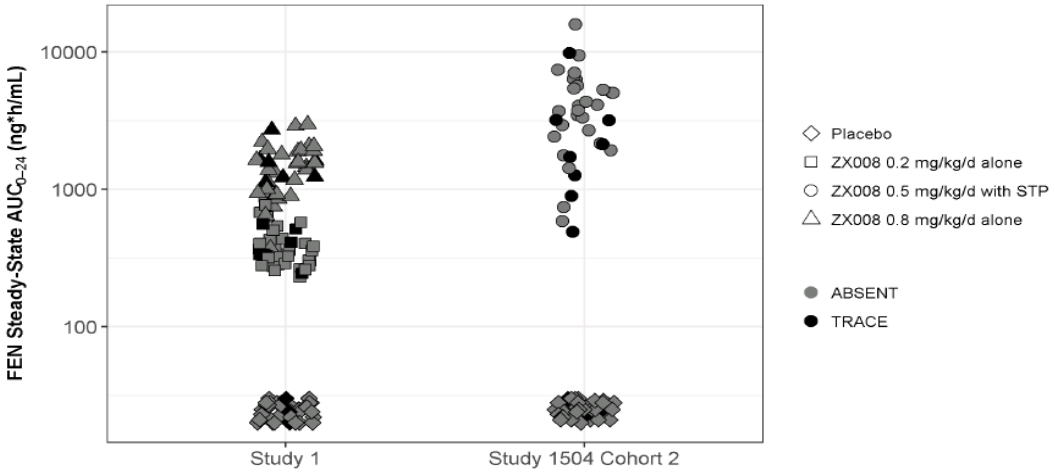
Reviewer Comment: *Zogenix's approach to identifying structural valve abnormalities from ECHO report free text is acceptable.*

Summary of Valvular ECHO Results by Population

I reviewed summary data provided in the CV ISS for ISS-DB, LTS-DB, and LTS populations for all valvar regurgitation. There are differences in the prevalence of trace or greater MR with increased prevalence rates sometimes observed with increasing ZX008 dose and study time points. However, these differences were not consistent across study populations. Moreover, differences in prevalence of MR among dose cohorts and time points were driven by trace MR, which is not pathologic in the absence of structural valve abnormalities. In the absence of no valvular structural abnormalities, I agree with Zogenix's rationale that observations of trace MR are random rather than associated with dose or treatment duration.

Zogenix provided summary statistics for all three study populations in the CV ISS. Because the LTS population included the most pediatric subjects, I will describe summary data for only this population in this section. Trace MR was observed at any time point in 53/232 subjects (22.8%). The incidence of trace MR was similar across timepoints, ranging from 19.3% to 29.5%. The lowest incidence of 19.5% was observed in subjects exposed to study drug the longest, at least 361 days. The prevalence of trace MR was comparable between subjects receiving a mean daily dose of either more or less than 0.48 mg/kg/day, 26/114 (22.8%) versus 27/118 (22.9%), respectively. Figure 1 and Figure 2 below show the full range of fenfluramine exposures and associated ECHO findings of MR.

Figure 1. Scatterplot of Steady-State fenfluramine AUC_{0-24} concentration Versus Absence or Presence of Mitral Regurgitation by Study and Dose



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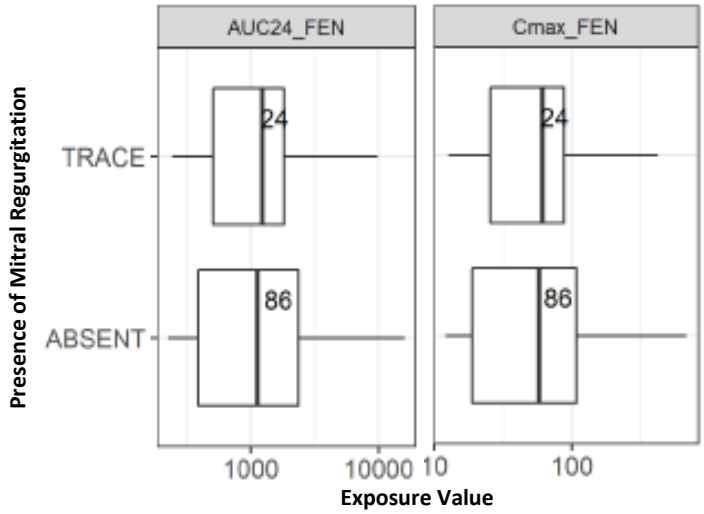
Source Figure 8, CV ISS, p61 of 158

Figure 2. Horizontal Box-and-Whisker Plots Showing Distributions of PK Exposure, Stratified by Presence of Absence of Trace Mitral Regurgitation



*Source Adapted from Figure 9, CV ISS, p62 of 158; AUC units = ng*h/mL, C_{max} units = ng/mL*

Both figures support Zogenix's conclusion there is no obvious association between fenfluramine exposure and absence or presence of MR.

Trace AR was observed in 1/232 subjects (0.4%). There were no reports of AR in the LTS population after Study Day 30. About 95% of subjects in the LTS population had absent or trace TR at any timepoint. Six out of 232 subjects (2.6%) had mild TR at any timepoint. About 99% of subjects had absent or trivial PR at any timepoint. There were only three reports of mild PR in 2/218 subjects (0.9%) at Study Day 30 and 1/218 subjects (0.5%) at Study Day 90. No subject had moderate or severe PR in any study.

Reviewer Comments: *Zogenix concludes that duration of treatment did not increase point prevalence for MR in any treatment arm or study subject. I agree that, to date, there is no evidence of an association between duration of study treatment and development of VHD in pediatric patients studied. However, based on available data on development of VHD in adults treated with fenfluramine, it is unclear if the risk for VHD is related more so to duration of therapy versus drug exposure. In this submission, Zogenix did not provide comparative drug-exposure data between adults and children. Therefore, it is unclear how exposures in pediatric patients would compare to those administered to obese adult patients. Moreover, long-term safety data for pediatric patients in this submission are somewhat limited in interpretation because it is unclear if an extended period of exposure, likely for this chronic condition, would increase risk for fenfluramine-induced VHD or PAH..*

Summary of PAH ECHO Findings

PASP was estimated only from subjects with measurable TR velocity jets. In the ISS-DB population, 106/206 subjects (51.5%) were evaluated, 46/84 (54.8%) exposed to placebo and 60/122 (49.2%) exposed to ZX008. In

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the LTS-DB population, 125/158 (79.1%) subjects were evaluable for PAH. In the LTS population, 125/232 subjects (53.9%) had a baseline PASP available, 176/232 (75.9%) had an estimated PASP at the last visit prior to the IA cut-off date, and 109/232 (47.0%) were analyzed for mean change in estimated PASP from baseline.

Zogenix did not observe any cases of PAH across studies in any subject. In the LTS population, estimated mean (SD) end of study PASP was 19.2 (6.3) with mean change from baseline 0.2 (7.2) mmHg. However, in the LTS-DB population, 2/125 evaluable subjects (1.6%) had an estimated PASP of > 35 mmHg, each at one reading. One subject, Subject (b) (6), had an estimated PASP of ~40 mmHg on Study Day 365. Repeat echo performed 2 weeks later showed an estimated PASP ~19 mmHg. Follow up ECHOs obtained on Study Day 455 were read out as "normal pressure" but no PASP estimate provided and on Study Day 545 estimated PASP was ~24 mmHg. The other subject, Subject (b) (6), had an estimated PASP of ~36 mmHg on Study Day 180. Follow up ECHOs were performed on Study Day 270, which "was not available," Study Day 365 with estimated PASP of ~ 26 mmHg, and Day 455 with estimated PASP ~29 mmHg. Because all follow up ECHOs during the OLE for these subjects had normal PASP estimates, core lab and IPCAB cardiologists determined that neither subject had PAH.

Of those subjects who had PASP estimates, there was no obvious dose-dependent increase from baseline in estimated PASP compared to placebo. Zogenix assessed for relative increases in estimated PASP from baseline of at least 5 mmHg, 10 mmHg, or 15 mmHg. Most patients had a change in estimated PASP from baseline of less than 10 mmHg. In the ISS-DB population. Table 6 below shows relative increase in estimated PASP stratified by study treatment and timepoint in the ISS-DB population.

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Table 6. Number of Subjects with Increase in PASP from Baseline ≥5, 10, and 15 mmHg – ISS-DB Population*

Parameter/Time Point	Placebo (N=84) n/m (%)	ZX008 0.2 mg (N=39) n/m (%)	ZX008 0.5 mg (N=43) n/m (%)	ZX008 0.8 mg (N=40) n/m (%)	Any DB ZX008 (N=122) n/m (%)
Subjects with Change in PASP >= 5					
Visit 8	5 / 30 (16.7%)	2 / 9 (22.2%)	4 / 18 (22.2%)	3 / 14 (21.4%)	9 / 41 (22.0%)
Visit 12/EOS	6 / 27 (22.2%)	1 / 12 (8.3%)	2 / 19 (10.5%)	3 / 13 (23.1%)	6 / 44 (13.6%)
Any Post-Baseline	10 / 35 (28.6%)	3 / 14 (21.4%)	6 / 23 (26.1%)	5 / 15 (33.3%)	14 / 52 (26.9%)
Subjects with Change in PASP >= 10					
Visit 8	0 / 30	0 / 9	0 / 18	1 / 14 (7.1%)	1 / 41 (2.4%)
Visit 12/EOS	3 / 27 (11.1%)	0 / 12	0 / 19	1 / 13 (7.7%)	1 / 44 (2.3%)
Any Post-Baseline	3 / 35 (8.6%)	0 / 14	0 / 23	2 / 15 (13.3%)	2 / 52 (3.8%)
Subjects with Change in PASP >= 15					
Visit 8	0 / 30	0 / 9	0 / 18	0 / 14	0 / 41
Visit 12/EOS	0 / 27	0 / 12	0 / 19	0 / 13	0 / 44
Any Post-Baseline	0 / 35	0 / 14	0 / 23	0 / 15	0 / 52

*Source Adapted from Table 23, CV ISS, p81 of 158 * Subjects counted in 1 PASP-bin are also counted in the lower threshold bin.*

In the LTS-DB population, 2/74 subjects (2.7%) originally treated with placebo before entering the OLE had estimated PASP changes from baseline >15 mmHg. One subject, Subject (b) (6), had an estimated PASP in Study 1503 ~13 mmHg that increased to ~29 mmHg at Study Day 270 and subsequent increases of 3 and ~10 mmHg above baseline at Study Days 90 and 180, respectively but no PASP estimates beyond Study Day 270 before study termination at Month 15. The other subject, Subject (b) (6), had an estimated PASP ~27 mmHg at baseline, at Visit 1 (Study 1503) ~14 mmHg then ~15 mmHg, ~16 mmHg, and ~36 mmHg on Study Days 30, 90, and 180, respectively. The increase between Study Days 90 and 180 represented an increase of about ~22 mmHg from baseline. In the LTS population, a third subject had an estimated PASP change > 15 mmHg. Subject (b) (6) had an estimated PASP ~16 mmHg at Visit 1 in the OLE. No estimated PASP was available at Study Day 30, but estimated PASP was ~32 mmHg on Study Day 90, an increase of ~16 mmHg, but on Study Day 180, the estimated PASP was ~14 mmHg. No subjects in the ISS-DB population had an increase in PASP of 15 mmHg or greater.

***Reviewer Comments**:*

- *I agree with Zogenix there is no evidence of PAH in pediatric subjects with available PASP estimates. Zogenix indicates that PASP could not be estimated in roughly half of subjects because of absent TR or*

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a TR jet velocity that was inadequate or immeasurable. This is not surprising. Typically, in the absence of PAH or tricuspid valve abnormalities, children would not be expected to have more than trace to mild TR on ECHO. The interpretation of PASP data are somewhat limited by missing data and limitations of ECHO in pediatric patients who may be uncooperative because of age or cognitive impairment. Despite these limitations, there were no reports of cardiac signs and symptoms concerning for new onset PAH or right ventricular systolic dysfunction, which is reassuring.

- *Similar to VHD, it is unclear if treatment duration or drug exposure is a more important risk for development of PAH in patients taking fenfluramine. Moreover, it is unclear if certain patients who develop PAH after fenfluramine exposure may have other predisposing factors that increase their risk for PAH development.*

Summary of Cardiovascular Adverse Events for Studies 1504 Cohort 2, Study 1, and Study 1503 (OLE)

Study 1504 Cohort 2

Eight-four subjects (96.6%) reported at least one treatment-emergent adverse event (TEAE) with serious TEAEs reported in 15.9% versus 14.0% in placebo and ZX008 treatment groups, respectively. "Blood pressure diastolic increased" and "blood pressure increased" were reported as TEAEs only in placebo group, both in 3/44 subjects (6.8%). "echocardiogram abnormal" was reported only in patients on ZX008 0.5 mg/kg/day, 4/43 (9.3%). "Heart rate increased" was reported in one subject (2.3%) each in placebo and ZX008 0.5 mg/kg/day groups. All abnormal ECHOs reported as TEAEs had trace regurgitation except in one patient with mild MR who had pre-existing mild MR and was erroneously enrolled in the trial. No subjects died and none of the reported serious TEAEs were cardiac-related. No cardiac TEAE led to study drug discontinuation.

TEAEs reported due to abnormal vital signs included the cardiac AEs described above plus one subject with bradycardia (2.3%) in the ZX008 0.5 mg/kg/day treatment group and one subject (2.3%) with sinus tachycardia in the placebo group. No trends in blood pressure were observed over time between treatment groups as shown in Table 7 below.

Table 7. Change from Baseline in Systolic and Diastolic Blood Pressure by Age and Study Visit (Safety Population)

	Placebo (N=44)	**ZX008 0.5 mg/kg/day (N=43)**	**Total (N=87)**
Age 2 to 4 years, n	**11**	**11**	**22**
Systolic Pressure (mmHg), mean (SD)			
Visit 5	7.3 (8.23)	–6.1 (15.83)	0.3 (14.24)
Visit 6	2.5 (15.11)	0.2 (9.16)	1.4 (12.38)
Visit 8	–3.0 (19.08)	1.0 (11.07)	–0.9 (15.07)
Visit 10	7.9 (12.52)	–6.3 (12.09)	0.0 (13.95)
Visit 12/EOS	3.7 (18.65)	–8.8 (11.89)	–2.2 (16.69)
Diastolic Pressure (mmHg), mean (SD)			
Visit 5	1.6 (13.27)	–1.2 (13.57)	0.1 (13.17)

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Visit 6	–5.8 (11.18)	1.9 (14.29)	–2.1 (13.04)
Visit 8	–9.9 (9.74)	0.3 (10.83)	–4.5 (11.32)
Visit 10	0.1 (15.64)	–1.2 (11.67)	–0.6 (13.16)
Visit 12/EOS	–0.5 (12.26)	–2.0 (16.47)	–1.2 (14.06)

	Placebo (N=44)	**ZX008 0.5 mg/kg/day (N=43)**	**Total (N=87)**
Age 5 to 12 years, n	**19**	**22**	**41**
Systolic Pressure (mmHg), mean (SD)			
Visit 5	–0.6 (6.82)	–4.4 (15.97)	–2.6 (12.60)
Visit 6	–0.5 (16.49)	–3.9 (15.23)	–2.3 (15.74)
Visit 8	–3.2 (9.83)	–3.0 (15.07)	–3.1 (12.39)
Visit 10	–2.2 (12.25)	–4.8 (13.09)	–3.4 (12.54)
Visit 12/EOS	–5.6 (12.21)	–5.3 (12.55)	–5.4 (12.24)
Diastolic Pressure (mmHg), mean (SD)			
Visit 5	–1.2 (9.32)	–3.1 (11.42)	–2.2 (10.41)
Visit 6	–0.7 (12.48)	–3.8 (6.97)	–2.3 (10.02)
Visit 8	0.5 (8.45)	–1.1 (7.93)	–0.3 (8.13)
Visit 10	–2.3 (12.39)	–0.5 (8.85)	–1.4 (10.75)
Visit 12/EOS	–2.4 (10.36)	–3.0 (10.35)	–2.7 (10.23)
Age 13 to 19 years, n	**14**	**10**	**24**
Systolic Pressure (mmHg), mean (SD)			
Visit 5	–2.9 (12.74)	–6.5 (13.31)	–4.4 (12.82)
Visit 6	–2.4 (11.08)	–9.5 (11.17)	–5.4 (11.44)
Visit 8	–2.7 (9.24)	–8.9 (13.62)	–5.3 (11.42)
Visit 10	2.5 (14.22)	–9.8 (13.21)	–2.3 (14.85)
Visit 12/EOS	4.6 (15.61)	–2.0 (13.00)	1.8 (14.66)
Diastolic Pressure (mmHg), mean (SD)			
Visit 5	–4.1 (10.85)	–4.7 (14.09)	–4.4 (12.01)
Visit 6	–4.9 (10.98)	0.9 (14.84)	–2.5 (12.76)
Visit 8	–3.4 (11.07)	–5.7 (11.25)	–4.4 (10.96)
Visit 10	–3.8 (12.22)	–4.7 (12.51)	–4.1 (12.06)
Visit 12/EOS	0.1 (15.84)	–4.4 (13.94)	–1.8 (14.93)

Source Adapted from Table 45 in CSR for Study 1504-C2, p146 of 742

Study 1503

At least one TEAE was reported in 208/232 subjects (89.7%) with abnormal ECHO among the most common

Reference ID: 4640087

TEAEs (reported in ≥ 10% of subjects) in 33/232 subjects (14.2%). All TEAEs reported as abnormal ECHO were limited to trace or physiologic regurgitation. At least one serious TEAE was reported in 35/232 subjects (15.1%) and one subject died due to sudden unexpected death in epilepsy. Five subjects (2.2%) discontinued study treatment because of a TEAE. Of all cardiac TEAEs reported, only one was considered severe – one subject (0.4%) with bradycardia. One serious cardiac TEAE occurred in a subject (0.4%) with second-degree atrioventricular block, described below.

Subject (b) (6) is an 8-year-old female with a complicated past medical history. She was initiated in the OLE on ZX008 0.2 mg/kg/day with uptitration to 0.8 mg/kg/day by Study Day 90. On Study Day 3, she presented with an increase in seizures and persistent left sided weakness for which an MRI was obtained. After the MRI procedure, performed on Study Day 8, she was noted to "skip beats" in the post-anesthesia care unit and during overnight ECG monitoring. She was diagnosed with "mild second-degree atrioventricular block" but remained hemodynamically stable and was discharged from the hospital on Study Day 9 without cardiac intervention. She underwent 24-hour Holter monitoring that showed second degree atrioventricular block while the patient was asleep. No dose adjustment was made to study drug and the event was considered resolved by Study Day 66.

Reviewer Comment: *Based on the information provided for this case report, I do not know if this subject had a Mobitz Type I versus II second-degree atrioventricular block. Mobitz Type I second-degree atrioventricular block can occur in healthy subjects, especially young people with high vagal tone, without underlying cardiac pathology. Regardless, I could not find any published literature associating fenfluramine with development of atrioventricular block. Because the second-degree atrioventricular block was only reported in one subject and this ECG abnormality spontaneously resolved without adjustment to study drug, it is unlikely that the observation of second-degree atrioventricular block was related to study treatment.*

Because of known fenfluramine toxicities, Zogenix prespecified a list of 23 AESIs including signs and symptoms related to possible VHD or PAH such as persistent cough, pulmonary rales, tachycardia, and hypertension. Overall, 62/232 subjects (26.7%) reported at least one AESI with 1/232 subjects (0.4%) reporting at least one serious AESI. Reported cardiac AESIs included "mitral valve incompetence" (1/232, 0.4%), tachycardia (2/232, 0.9%), "blood pressure diastolic increased" (5/232, 2.2%), "blood pressure increased" (6/232, 2.6%), "blood pressure systolic increased" (1/232, 0.4%), cardiac murmur (1/232, 0.4%), "echocardiogram abnormal" -limited to trace/physiologic regurgitation (33/232, 14.2%), and "HR increased" (3/232, 1.3%). Zogenix clarified that "mitral valve incompetence" was miscoded and the actual AESI was trace regurgitation. The cardiac murmur was described as a vibratory murmur, not clinically significant.

Overall, 5/232 subjects (2.2%) discontinued study treatment because of TEAEs. One subject (0.4%) who discontinued study treatment had TEAEs of "echocardiogram abnormal" and "generalized tonic-clonic seizure." The "abnormal" echocardiogram only showed trace MR. `

Abnormal vital signs resulting in TEAE reports occurred in 86/232 subjects (37%). Cardiac vital sign TEAEs included "blood pressure diastolic increased" (5/232, 2.2%), "blood pressure increased" (6/232, 2.6%), "blood pressure systolic decreased" (1/232, 0.4%), "blood pressure systolic increased" (1/232, 0.4%), and "HR increased" (4/232, 1.7%). There was no obvious pattern of HR or BP changes associated with fenfluramine use

Reference ID: 4642085

in the OLE study as shown in Table 8 below.

Table 8. Change from Baseline in Systolic and Diastolic Blood Pressure, Heart Rate

	Mean (SD) Change in Systolic Pressure from Baseline (mmHg)	Mean (SD) Change in Diastolic Pressure from Baseline (mmHg)	Mean (SD) Change in Mean Heart Rate from Baseline (beats/min)
Month 1 (n=228)	-2.5 (14.62)	-2.3 (11.93)	1.4 (15.89)
Month 2 (n=225)	-1.4 (14.17)	-0.4 (13.08)	-0.7 (16.14)
Month 3 (n=222)	-1.2 (15.17)	-1.1 (11.56)	0.4 (16.25)
Month 6 (n=164)	-1.9 (15.40)	-2.5 (13.53)	-1.5 (17.29)
Month 9 (n=113)	-1.7 (16.92)	-2.0 (13.51)	-2.8 (16.00)
Month 12 (n=56)	-4.1 (13.83)	-4.7 (16.67)	-2.3 (18.38)
Month 15 (n=25)	-1.4 (18.46)	-6.8 (16.35)	-3.4 (18.36)
Month 18 (n=7)	5.7 (12.65)	-6.1 (6.52)	7.1 (19.98)
Month 21 (n=1)	-5.0	7.0	11.0

Source Adapted from Table 43 Study 1503 CSR, p 131 of 1027

Study 1

Overall, 101/119 subjects (84.9%) reported at least one TEAE and 13/119 subjects (10.9%) reported at least one serious TEAE. Five subjects (4.2%) discontinued study treatment due to a TEAE. Of the most common TEAEs reported (occurring in ≥ 10% subjects in at least one ZX008 treatment group), "echocardiogram abnormal" was reported in 12.5%, 17.9%, and 22.5% in placebo, ZX008 0.2 mg/kg/day, and ZX008 0.8 mg/kg/day groups, respectively. Other reported cardiac TEAEs are shown in Table 9 below.

Table 9. Cardiac Treatment Emergent Adverse Events Occurring in ≥ 5% of Subjects in Any Treatment Group by Preferred Term (Safety Population)

MedDRA Preferred Term	Placebo (N=40) n (%)	ZX008 0.2 mg/kg/day (N=39) n (%)	ZX008 0.8 mg/kg/day (N=40) n (%)	Total (N=119) n (%)
Blood pressure diastolic increased	1 (2.5)	3 (7.7)	3 (7.5)	7 (5.9)
Blood pressure increased	0	3 (7.7)	2 (5.0)	5 (4.2)
Blood pressure systolic increased	0	2 (5.1)	0	2 (1.7)
Echocardiogram abnormal	5 (12.5)	7 (17.9)	9 (22.5)	21 (17.6)
Heart rate increased	1 (2.5)	3 (7.7)	1 (2.5)	5 (4.2)

Source Adapted from Tables 31 and 36 in Study 1 CSR, p128 of 675.

No subject died during the study and no cardiac TEAE was reported as severe or serious. Reported cardiac AESIs were the same as those TEAEs shown in Table 9 above. No subject discontinued study treatment

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because of a cardiac TEAE.

In addition to TEAEs listed in Table 9 above, additional TEAEs due to abnormal vital signs were reported and included “heart rate decreased” [ZX008 0.2 mg/kg/day, 1/39 subjects (2.6%)], tachycardia [placebo, 1/40 subjects (2.5%)], hypertension [ZX008 0.2 mg/kg/day, 1/39 subjects (2.6%)], and diastolic hypertension [ZX008 0.8 mg/kg/day, 1/40 subjects (2.5%)].

Reviewer Comments: *Changes in HR, SBP, or DBP do not appear to be associated with ZX008 dose in any of the populations analyzed. Given that DS is associated with cognitive impairment, it is possible that increases in vital sign measures may have been attributable to the mental state of the subject at time of vital sign assessment. For example, Zogenix remarked that a 5-year-old subject had a heart rate recorded as 166 bpm, which was 100 bpm above her baseline. However, the subject was described as “fidgety” with HR count difficult to obtain by auscultation.*

Because fenfluramine is a centrally acting amphetamine, there is potential risk for elevations in heart rate and increased systemic blood pressure. Although the vital signs data did not clearly demonstrate a dose-dependent increased risk for abnormalities in HR, SBP, or DBP, we believe prescribers should monitor for abnormal increases in these parameters in DS patients prescribed fenfluramine.

Reference ID: 4642085

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/s/

SHETARRA E WALKER
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NORMAN L STOCKBRIDGE
01/06/2020 02:45:27 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memo

Date:	January 6, 2020
Reviewer:	Karen Long, PharmD, Safety Evaluator Division of Pharmacovigilance I (DPV I)
Team Leader:	Allen Brinker, MD, MS DPV I
Product Name:	Fenfluramine
Subject:	Overview of adverse events in patients ≤16 years (pediatric age)
Application Type/Number:	NDA 212102
Applicant/Sponsor:	Zogenix Inc
OSE RCM #:	2019-2391

Reference ID: 4640286

1 INTRODUCTION

This pharmacovigilance memo summarizes the pediatric postmarketing adverse experience of fenfluramine in the FDA Adverse Event Reporting System (FAERS) database. This descriptive analysis is intended to assist the Office of New Drugs, Division of Neurology II safety review of NDA 212102 submitted by Zogenix Inc. For the purposes of this analysis pediatric age was define as age ≤16 years.

Fenfluramine was initially approved by FDA in 1973 for the management of obesity. The recommended dosing was 20 mg three times daily, with a maximum recommended dose of 40 mg three times daily (120 mg daily). Its proposed mechanism involved increasing satiety by elevating serum levels of serotonin in the central nervous system (CNS) through inhibiting the reuptake of serotonin in the CNS and, when metabolized to norfenfluramine, increasing the release of serotonin at the receptor sites. On September 15, 1997, FDA announced the withdrawal of fenfluramine and its isomer, dexfenfluramine, from the U.S. market because of safety concerns with the development of cardiac valvular disease and pulmonary hypertension. On November 25, 2019, Zogenix announced FDA accepted for filing the NDA for FINTEPLA® (ZX008, fenfluramine oral solution) for the treatment of seizures associated with Dravet syndrome.[1,2,3,4,5]

2 METHODS AND MATERIALS

DPV searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	November 12, 2019
Time period of search	All reports through November 11, 2019
Search type	FBIS Quick Query
Product terms	Active ingredient: FENFLURAMINE;FENFLURAMINE HYDROCHLORIDE
MedDRA search terms (Version 22.1)	All PT terms
Other criteria	All reports were screened for pediatric ages (≤16 years) Narrative text searches were performed for the following texts: ped, child, infant, boy, girl
* See Appendix A for a description of the FAERS database.	

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3 RESULTS

Our FAERS search retrieved 102 reports. A total of 21 reports were not included in the analysis for the following reasons:

- Duplicate reports (n=19)
- Incorrectly coded age (n=2)

The remaining 81 cases are described in the following sections below:

- Pediatric cases reporting therapeutic use of fenfluramine (n=17)
  - Obesity (n=10)
  - Autism (n=4)
- Pediatric cases reporting overdose or misuse of fenfluramine (n=7)
- Pediatric cases reporting in utero or transmammary exposure of fenfluramine (n=57)

Appendix B contains a line listing of the 81 cases described in this memo.

3.1 PEDIATRIC CASES REPORTING THERAPEUTIC USE OF FENFLURAMINE (N=17)

DPV identified 17 pediatric cases reporting the use of fenfluramine for a therapeutic effect, summarized in Table 2; cases are stratified by reason for use.

Most cases (11 of 17) reported concomitant use of another weight loss drug (i.e., phentermine, dexfenfluramine, or sibutramine). The onset of the reported adverse events ranged from 1 day to 5 years (median 88, mean 255 days) in the 16 cases reporting this information. Most cases (11 of 17) reported discontinuation of fenfluramine; of those 11 cases, 5 cases reported a positive dechallenge. Two cases were reported by an attorney. Pertinent cases are highlighted below.

Table 2. Descriptive Characteristics of Pediatric FAERS Cases Reporting Therapeutic Use of Fenfluramine, Received by FDA through November 11, 2019 (N=17)

	All cases (n=17)	Weight loss/obesity (n=10)	Autism (n=4)
Age (years)			
Median	15	15.5	8
Mean	13.3	15.2	8.3
Range	4-16	12-16	4-13
Sex			
Female	13	9	2
Male	3	1	1
Unknown	1	0	1
Country			
United States	15	9	4
Foreign	2	1	0
Report type			
Direct	2	0	2
Expedited	3	2	0
Non-Expedited	12	8	2

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Table 2. Descriptive Characteristics of Pediatric FAERS Cases Reporting Therapeutic Use of Fenfluramine, Received by FDA through November 11, 2019 (N=17)			
	All cases (n=17)	**Weight loss/obesity (n=10)**	**Autism (n=4)**
FDA initial received year			
1984	3	0	3
1989	1	0	1
1991	1	0	0
1998	9	7	0
1999	1	1	0
2000	1	1	0
2010	1	1	0
Dose (mg)/day	(n=10)	(n=6)	(n=3)
Median	25	30	30
Mean	33	36.6	30
Range	20-60	20-60	20-40
Weight (kg)	(n=10)	(n=6)	(n=3)
Median	80	87	14.5
Mean	75	101.5	21.4
Range	12.3-156.8	59-156.8	12.3-37.3
Height (cm)	(n=7)	(n=5)	(n=1)
Median	170.2	175.3	93
Mean	160.2	173.2	93
Range	93-182.9	160-182.9	93
BMI (kg/m^2)	(n=7)	(n=5)	(n=1)
Median	29	29	14.2
Mean	30.4	33.9	14.2
Range	14.2-46.9	23-46.9	14.2
Reported reason for use	Weight loss/obesity 10 Autism 4 Not reported 3	Weight loss/obesity 10	Autism 4
Reported adverse events*	Shortness of breath 6 Psychiatric/behavioral 5 Chest pain/pressure 4 Cognitive 3 Fatigue/malaise 3 Seizure 3 Syncope 3 Blood pressure changes 2 Gastrointestinal 2 Headache 2 Skin/hair 2 Valvular heart disease 2 Dizziness 1 Hematuria 1 Hypoglycemia 1 Infection 1 Cardiac 1 Pulmonary HTN 1 Stroke/vasculitis 1	Shortness of breath 5 Psychiatric/behavioral 4 Chest pain/pressure 3 Cognitive 1 Fatigue/malaise 1 Syncope 2 Gastrointestinal 2 Headache 2 Skin/hair 2 Valvular heart disease 2 Dizziness 1 Hypoglycemia 1 Infection 1 Cardiac 1 Pulmonary HTN 1 Stroke/vasculitis 1	Seizure 2 Blood pressure changes 1 Cognitive 1 Fatigue/malaise 1 Hematuria 1 Syncope 1

Reference ID: 4640286

Table 2. Descriptive Characteristics of Pediatric FAERS Cases Reporting Therapeutic Use of Fenfluramine, Received by FDA through November 11, 2019 (N=17)						
	All cases (n=17)		**Weight loss/obesity (n=10)**		**Autism (n=4)**	
Pertinent concomitant medications†	(n=12)		(n=10)		(n=1)	
	Phentermine	10	Phentermine	9	Haloperidol	1
	Dexfenfluramine	1	Dexfenfluramine	1	Benzotropine	1
	Sibutramine	1	Sibutramine	1		
	Fluvoxamine	1	Fluvoxamine	1		
	Haloperidol	1	Brompheniramine	1		
	Benzotropine	1				
	Brompheniramine	1				
Serious outcomes‡	(n=16)		(n=10)		(n=3)	
Death	2		2		0	
Hospitalization	4		2		1	
Disability	1		1		0	
Other serious	13		8		2	

* A case may report more than one adverse event. Cardiac includes cardiac murmur and heart failure. HTN=hypertension.
† A case may report more than one pertinent concomitant medication.
‡ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A case may have more than one serious outcome.
BMI=body mass index

One case reported valvular heart disease, pulmonary hypertension, and death, described below.

FAERS #3032936v3, MCN: 8-98105-031B, USA, 1998
An attorney reported a 12-year-old female experienced heart valve damage (valvular heart disease), pulmonary hypertension, anxiety, fatigue, memory loss, shortness of breath, heart murmurs, infections, congestive heart failure, and/or swelling after taking fenfluramine, dexfenfluramine, and phentermine for several years for obesity (doses not reported). Medial history included Prader-Willi syndrome, obesity, congestive heart failure at age 3, mild right ventricular dilatation and possible atrial septal defect, renal insufficiency (not a candidate for dialysis), episode of chest pain, and no known medication allergies. Other concomitant medications, weight, and height were not reported. The report stated the use of "diet drugs" caused and/or contributed to her death; medical records indicated the cause of death was renal failure and Prader-Willi syndrome.

One case reported stroke, possible vasculitis, and valvular heart disease, described below.

FAERS #3501687v3, MCN: HQ7706322JUN2000, USA, 2000
An attorney reported a 16-year-old female developed stroke, possible vasculitis, and valvular heart disease after receiving fenfluramine and phentermine for obesity for approximately 6-12 months (doses not reported) and brompheniramine for nasopharyngitis for 1 day. Medical history included transient ischemic attack, migraines, depression, obsessive compulsive disorder, hypothyroidism, obesity, drug hypersensitivities to penicillin and Ceclor, seafood allergy, congenital bilateral hip

Reference ID: 4640286

dysplasia, appendectomy, tonsillectomy, adenoidectomy, polycystic ovaries, ankle sprains, anorexia, and bulimia nervosa. Concomitant medications included fluvoxamine, ethinyl estradiol/norethindrone oral contraceptive, and levothyroxine. The patient was hospitalized for a stroke of the temporoparietal and right cerebellar area, with a cerebral angiogram consistent with vasculitis. A transesophageal echocardiogram revealed mild mitral valve regurgitation. The patient received aspirin and steroids, and had prolonged rehabilitation therapies for several years after the event. At the time of the report the events were recovering with sequelae.

One case reported death from suicide, described below.

FAERS #3175658v1, #3156778v4; MCN: 8-98338-003L, 8-98287-033A; USA, 1998
A literature article[6] and additional attorney report described a 15-year-old boy committed suicide after receiving approximately 14 months of therapy with fenfluramine 20 mg TID and phentermine 30 mg daily for weight loss. Medical history was negative for personal or family psychiatric problems, and included skull fracture at 5 months, nasal/sinus allergies, irregular heart rate, sleep apnea, appendectomy, gynecomastia. Weight was 136.36 kg, height 175.26 cm, and body mass index 44.4 kg/m^2. Concomitant medications were not reported. The patient was described as a happy, outgoing, energetic, and involved young man. On the day of his death, he was called to the principal's office at school and questioned about advances toward a female friend. After school he wrote six suicide notes and committed suicide with a gunshot to the head. Post mortem analysis documented the presence of fenfluramine and phentermine in his blood. His plasma serotonin level was 44 ng/ml (normal range 90-210 ng/ml); the article stated the use of fenfluramine may affect brain serotonin neurons, and the attorney report stated his suicide "resulted from depression caused by a severe decrease of serotonin."

3.2 PEDIATRIC CASES REPORTING OVERDOSE OR MISUSE OF FENFLURAMINE (N=7)

DPV identified 7 pediatric cases reporting overdose (6) or misuse (1) of fenfluramine, summarized in Table 3.

Most cases (5 of 7) reported intentional overdose of fenfluramine, with one of these cases resulting in death from ventricular fibrillation. One case reported accidental overdose in a 19-month-old male. One case reported misuse of fenfluramine by a 6-year-old male who inadvertently took one dose of his mother's fenfluramine instead of his clonidine. All cases of fenfluramine overdose reported therapeutic interventions for the overdose. Three cases were reported by an attorney.

Reference ID: 4640286

Table 3. Descriptive Characteristics of Pediatric FAERS Cases Reporting Overdose or Misuse of Fenfluramine, Received by FDA through November 11, 2019 (N=7)			
Age in years	Median	12	
	Mean	9.6	
	Range	19 months-14 years	
Sex	Female	2	
	Male	5	
Country	United States	6	
	Foreign	1	
Report type	Direct	2	
	Expedited	1	
	Non-Expedited	4	
FDA initial received year	1974 (2), 1975 (1), 1981 (1), 1983 (1), 1994 (1), 2003 (1)		
Total mg dose (n=6)		Overdose (n=5)	Misuse (n=1)
	Median	800	20
	Mean	948	20
	Range	740-1600	20
Reported adverse events*	Hyperactivity/excitation	3	
	Mydriasis	3	
	CNS depression	2	
	Anxiety/agitation	1	
	Muscle hypertonus	1	
	Nystagmus	1	
	Tachycardia	1	
	Ventricular fibrillation	1	
	Visual hallucinations	1	
	Vomiting	1	
Pertinent concomitant medications (n=2)†	Barbiturates	1	
	Methyprylon	1	
Therapeutic interventions (n=6)‡	Gastric lavage	4	
	Forced diuresis	3	
	Activated charcoal	1	
	Ipecac-induced emesis	1	
	Milk of magnesia	1	
	Resuscitation	1	
	Urine acidification	1	
Serious outcomes (n=5)§	Death	1	
	Hospitalization	1	
	Other serious	3	

* A case may report more than one adverse event. CNS=central nervous system
† Methyprylon is a sedative used to treat insomnia.
‡ A case may report more than one therapeutic intervention.
§ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. One case (FAERS #4287709v1) was incorrectly coded with the outcome of death.

Reference ID: 4640286

3.3 PEDIATRIC CASES REPORTING IN UTERO OR TRANSMAMMARY EXPOSURE OF FENFLURAMINE (N=57)

DPV identified 57 pediatric cases reporting in utero (56) or transmammary (1) exposure of fenfluramine. More than half of cases (31 of 57) reported cardiac-related congenital anomalies or adverse events, with or without other organ system congenital anomalies or adverse events. The remainder of cases reported non-cardiac-related congenital anomalies or adverse events (20), or unspecified congenital anomalies (6). Approximately one-third of cases (21 of 57) were reported by an attorney. Most cases (55 of 57) reported concomitant use of phentermine, and 5 of these cases also reported concomitant use of dexfenfluramine.

One case reported transmammary exposure of fenfluramine, described below.

> **FAERS #3023632v1, MCN: 8-97296-001S, USA, 1998**
> An 18-month-old male developed a heart murmur and mitral and tricuspid regurgitation after transmammary exposure to fenfluramine. At one month of age, the patient had a normal echocardiogram, which was performed because his sibling had congenital heart disease. The patient's mother received fenfluramine 20 mg daily and phentermine 30 mg daily for approximately 4 months while breastfeeding (patient age during exposure ~5-9 months). At age 18 months, the patient developed a heart murmur and had an echo showing mitral and tricuspid regurgitation. The mother did not have valvular abnormalities. The physician reporter stated "all other possible causes were excluded."

The preferred terms (PTs) reported in at least three pediatric FAERS cases reporting in utero or transmammary exposure of fenfluramine are listed in Table 4. The complete list of PTs reported for all pediatric FAERS cases reporting in utero or transmammary exposure of fenfluramine are listed in Appendix C.

Table 4. Preferred Terms in Pediatric FAERS Cases Reporting In Utero or Transmammary Exposure of Fenfluramine with N≥3, Sorted by Descending Number of Reports

	Preferred Term (PT)	Number of Reports
1	Maternal drugs affecting foetus	42
2	Congenital anomaly	10
3	Premature baby	10
4	Cardiac murmur	9
5	Heart disease congenital	9
6	Atrial septal defect	8
7	Ventricular septal defect acquired	7
8	Cardiomegaly	6
9	Developmental delay	6
10	Apgar score low	5
11	Multiple congenital abnormalities	5
12	Tricuspid valve incompetence	5
13	Caesarean section	4
14	Cardiac disorder	4
15	Mitral valve incompetence	4
16	Neonatal disorder	4

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Table 4. Preferred Terms in Pediatric FAERS Cases Reporting In Utero or Transmammary Exposure of Fenfluramine with N≥3, Sorted by Descending Number of Reports		
	Preferred Term (PT)	**Number of Reports**
17	Oxygen saturation decreased	4
18	Patent ductus arteriosus	4
19	Pulmonary artery atresia	4
20	Cardiac failure congestive	3
21	Cardiac valve disease	3
22	Coarctation of the aorta	3
23	Congenital cardiovascular anomaly	3
24	Congenital pulmonary artery anomaly	3
25	Dysmorphism	3
26	Fallot's tetralogy	3
27	Pregnancy	3
28	Pulmonary malformation	3
29	Pulmonary valve stenosis congenital	3
30	Sensory disturbance	3
31	Ventricular septal defect	3

4 REVIEWER'S COMMENTS

DPV identified 81 pediatric FAERS cases reporting the therapeutic use of fenfluramine (17), overdose or misuse of fenfluramine (7), or in utero or transmammary exposure of fenfluramine (57). Approximately one-third of cases (26 of 81) were reported by an attorney, with the majority of these cases (21 of 26) describing in utero exposure of fenfluramine; this may reflect a stimulus of reporting after fenfluramine was withdrawn from the U.S. market. Based on the reports reviewed in this analysis, no new safety signals were identified.

Most of the adverse events reported with the therapeutic use of fenfluramine represented the experience of obese teenagers (median age 15 years). The adverse events as reported were consistent with the known adverse events of fenfluramine in adults, including two cases reporting valvular heart disease, one of which also reported pulmonary hypertension.[2] Many cases reported unlabeled adverse events, but these cases did not provide sufficient information for causality assessment or reported other contributory factors. The cases reporting use for obesity or weight loss reported the unlabeled events of suicidal behavior, stroke and possible vasculitis, infection, hypoglycemia, gastritis, and alopecia). The cases reporting use for autism reported the unlabeled events of seizure and hematuria.

All of the adverse events reported in the pediatric cases reporting overdose or misuse of fenfluramine were consistent with the known adverse events of fenfluramine at supratherapeutic dosing, including cardiac arrest resulting in death.[2] Most of the pediatric cases reporting in utero exposure of fenfluramine also reported concomitant use of phentermine; therefore, the contributory effects of phentermine cannot be ruled out. The single case of transmammary exposure also reported the use of both fenfluramine and phentermine; it is unknown if fenfluramine and phentermine are excreted in human milk, however, other amphetamines are present in human milk.[2,7]

Reference ID: 4640286

5 REFERENCES

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Reference ID: 4640286

6 APPENDICES

6.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Reference ID: 4640286

6.2 APPENDIX B. LINE LISTING OF PEDIATRIC FAERS CASES REPORTING FENFLURAMINE (N=81)

Pediatric Cases Reporting Therapeutic Use of Fenfluramine (N=17)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*	Reason for Use	Daily Dose (mg)	Concomitant Medications	Reported Adverse Events
1	1/5/1984	4430395	1		Direct	4	F	USA	HO	autism	20	none	seizures
2	1/5/1984	4430394	1		Direct	7	F	USA	OT	autism	30	none	seizures
3	7/7/1989	4662610	1	0788004205	Non-Expedited	9	U	USA		autism	U	NR	microscopic hematuria
4	4/24/1998 4/24/1998	3032936 3031631	3 3	8-98105-031B 8-98105-032B	Non-Expedited	12	F	USA	DE,OT	obesity	U	dexfenfluramine, phentermine	valvular heart disease, pulmonary hypertension, anxiety, fatigue, memory loss, shortness of breath, heart murmurs, infections, congestive heart failure, swelling
5	2/5/1991	4773599	1	891023001F	Expedited	13	F	FRA	HO,OT	NR	20	NR	withdrawal "infraclinical status-epilepticus" with symptoms of confusion, strange behavior, disorientation in time and space
6	7/19/1984	4430824	1	0284	Non-Expedited	13	M	USA	OT	autism	40	haloperidol, benztropine	syncope, fluctuating blood pressure, malaise, CNS depression
7	7/31/1998	3215606	1	8-97323-010K	Non-Expedited	14	F	USA	OT	NR	U	phentermine	shortness of breath, exhaustion, hypertension
8	7/31/1998	3206711	1	8-97301-004N	Non-Expedited	14	M	USA	OT	NR	U	NR	chest pain
9	11/12/2010	7666746	1	HK-ABBOTT-10P-075-0684699-00	Expedited	15	F	HKG	HO	obesity	U	sibutramine, caffeine, herbals	psychosis (delusive thoughts and aggressive behavior)
10	7/31/1998	3248064	1	8-98030-014K	Non-Expedited	15	F	USA	OT	obesity	20	phentermine	severe gastritis, vomiting, blood with bowel movement, rash, chest pain, shortness of breath
11	7/31/1998	3233273	1	8-97323-036J	Non-Expedited	15	F	USA	OT	obesity	20	phentermine	fainting, low blood sugar, trouble breathing, headache, dizziness, abdominal pain
12	12/10/1998 10/19/1998 9/2/1999	3175658 3156778 3342568	1 4 1	8-98338-003L 8-98287-033A MPI-1999-01772(0)	Expedited	15	M	USA	DE DE DE,OT	obesity	60	phentermine	suicide gun shot wound to head
13	8/2/1999	3320458	1	8-99006-083A	Non-Expedited	16	F	USA	OT	obesity	U	phentermine	emotionally stressed out and began doing strange things
14	7/31/1998	3231327	1	8-97329-007J	Non-Expedited	16	F	USA	OT	obesity	20	phentermine	fainting, headaches, shortness of breath, chest pain
15	7/31/1998	3202215	1	8-98096-002K	Non-Expedited	16	F	USA	OT	obesity	60	phentermine	chest heaviness, shortness of breath
16	7/31/1998	3275718	1	8-98008-046B	Non-Expedited	16	F	USA	OT	obesity	40	phentermine	hair loss
17	7/14/2000	3501687	3	HQ7706322JUN2000	Non-Expedited	16	F	USA	DS,HO	obesity	U	phentermine, fluvoxamine, brompheniramine, levothyroxine, loestrin	stroke of temporoparietal and right cerebellar area and possible vasculitis, mitral valve regurgitation, drug interaction phentermine fenfluramine fluvoxamine

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: DE=Death, HO=Hospitalization, DS= Disability, OT=Other Medically Significant, F=female, M=male, U=unknown, NR=not reported

Reference ID: 4640086

Pediatric Cases Reporting Overdose or Misuse of Fenfluramine (n=7)												
	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*	Dose (mg)	Concomitant Medications	Reported Adverse Events
1	7/1/1974	4287609	1		Non-Expedited	1.58	M	USA		740	barbiturates, aspirin	overdose, drowsy
2	7/1/1974	4287709	1		Non-Expedited	6	M	USA		800	none	overdose, acutely ill, semi-conscious, generalized muscle hypertonus, mydriasis
3	5/3/1994	5111773	1	894116001F	Expedited	12	F	ESP	HO	600	NR	overdose, excitation, visual hallucinations, nystagmus, vomiting
4	12/1/1981	4348938	1		Non-Expedited	14	F	USA	OT	1600	NR	tachycardia, anxiety, agitation, mydriasis
5	1/1/1975	4291355	1		Non-Expedited	14	M	USA	OT	1000	NR	mydriasis
6	10/21/1983	4454092	1		Direct	14	M	USA	DE	U	methyprylon	ventricular fibrillation, death
7	8/14/2003	3988580	1		Direct	6	M	USA	OT	20	clonidine	hyperactivity

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: DE=Death, HO=Hospitalization, DS= Disability, OT=Other Medically Significant, F=female, M=male, U=unknown, NR=not reported

Reference ID: 4640280

Pediatric Cases Reporting In Utero or Transmammary Exposure of Fenfluramine (n=57)										
	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*	Exposure
1	3/5/1999	6663322	1		Direct	-1.43	M	USA	CA	in utero
2	3/9/2000	3443262	2	8-99232-014A	Expedited	-0.62	M	USA	CA,DS,HO	in utero
3	11/13/1998 8/17/1998 10/1/1997 11/21/1997	3166428 3140216 3142259 3003552	2 1 2 3	8-97272-005S 8-97272-006S 897272005S 8-97317-021L	Expedited	-0.38	M	USA	CA,DE,HO CA CA,DE,HO CA,DE	in utero
4	1/21/2000	3426133	2	HQ0569818JAN2000	Expedited	-0.11	U	USA	HO	in utero
5	5/24/1999 6/9/1999	3275377 3285454	1 1	MPI-98492 (1) 105-99	Expedited	0	F	USA	CA,DS,HO,RI	in utero
6	11/6/1997 12/3/1997 9/30/1997	3000466 3003087 3065097	1 2 1	8-97265-016N 8847-AR 897265016N	Expedited	0	F	USA	CA	in utero
7	4/28/2000	3463821	1		Direct	0	F	USA	CA,HO,LT	in utero
8	5/26/1998	3116936	1	8-98134-003J	Expedited	0	F	USA	CA	in utero
9	4/16/1999	3253418	1	8-99102-092A	Expedited	0	M	CAN	CA	in utero
10	5/23/2000	3476946	1	HQ6114519MAY2000	Expedited	0	M	USA	CA,DE	in utero
11	5/26/1998	3037965	4	8-98114-011A	Expedited	0	M	USA	CA,HO,RI	in utero
12	2/24/1998	3021073	1	8-97268-010N	Expedited	0	M	USA	CA	in utero
13	7/16/1998	3124623	3	8-97325-011L	Expedited	0	M	USA	CA,HO	in utero
14	10/19/1998	3153699	3	8-98280-048A	Expedited	0	M	USA	CA,DE	in utero
15	3/30/1998 6/18/1998 9/29/1997	3027204 3125981 3060122	2 1 1	MPI-98609 8-97262-014S 897262014S	Expedited	0	M	USA	CA,HO CA,HO CA,OT	in utero
16	1/14/1998	3008215	3	8-98002-009H	Expedited	0	M	USA	CA	in utero
17	2/9/2012	8402084	1		Direct	0	M	USA	CA,DS	in utero
18	10/22/1998	3156985	2	8-98289-057A	Expedited	0	M	USA	CA	in utero
19	3/19/1999	3232385	2	8-98316-094A	Non- Expedited	0	M	USA	CA	in utero
20	9/7/2000	3533715	1		Direct	0	M	USA	CA,HO,LT,RI	in utero
21	7/12/1999	3305166	2	8-99189-012L	Expedited	0	M	USA	DE,HO,OT	in utero
22	11/17/1997	3001006	1	8-97317-004N	Expedited	0	U	USA	DE,OT	in utero
23	1/21/2000	3426125	1	HQ0569918JAN2000	Expedited	0	U	USA	CA	in utero
24	7/23/1998	3133491	2	8-98197-007A	Expedited	0	U	USA	CA,LT,RI,OT	in utero
25	2/3/1998	3014251	1	8906-AR	Expedited	0.00274	F	NULL	CA,OT	in utero
26	3/27/1998	3024124	1	8-97176-006S	Expedited	0.00274	F	USA	CA,DE,HO	in utero
27	11/21/1997 8/29/1997 8/28/1997	3003647 3044981 3049989	1 1 1	MPI-97516 897226011N 897226001L	Expedited	0.00274	F	USA	CA CA,OT CA	in utero
28	5/25/2001	6962668	1	HQ0891615MAY2001	Expedited	0.00274	F	USA	CA,OT	in utero
29	5/11/1999	3266539	1	MPI-1999-00971 (0)	Expedited	0.00274	M	USA	OT	in utero

Reference ID: 4640086

Pediatric Cases Reporting In Utero or Transmammary Exposure of Fenfluramine (n=57)										
	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*	Exposure
30	6/9/1998	3119793	2	8-98141-002J	Non- Expedited	0.00274	M	USA	CA,HO,OT	in utero
31	1/5/1998	3031832	3	8-97358-011L	Expedited	0.00274	M	USA	OT	in utero
32	11/21/1997	3001449	1	8-97318-005F	Expedited	0.00274	U	USA	CA	in utero
33	1/5/1998	6663307	1		Direct	0.00548	M	USA	CA,DE	in utero
34	3/17/1998	3029228	1	MPI-98561	Expedited	0.05769	U	USA	HO,LT	in utero
35	9/23/1997	3061029	1	MPI97252	Expedited	0.08333	F	USA	CA,DE	in utero
36	7/15/1997	5587987	1		Direct	0.08333	M	USA	CA	in utero
37	10/31/1997	3066420	1	897293007N	Expedited	0.08333	U	USA	HO,LT	in utero
38	12/19/1997	3116793	1	1828977-1997-00007	Expedited	0.16427	M	USA	HO,LT,RI	in utero
39	10/22/1997	3070859	1		Direct	0.16667	F	USA		in utero
40	11/4/1998	3160374	1	30295-AR	Expedited	0.16667	M	USA	CA,HO,LT,OT,RI	in utero
41	10/28/1997	3190126	4	8-97289-007T	Expedited	0.16667	M	USA	CA,HO,LT,RI	in utero
42	2/12/1998 10/17/1997	3014377 3063465	1 1	MPI-98318 897282004N	Expedited	0.17	F	USA	CA	in utero
43	11/18/1997 1/12/1998	3016113 3009146	2 2	MPI-97465 8-97280-002N	Expedited	0.19	M	USA	CA OT	in utero
44	2/12/1998	3011800	1	MPI-98320	Expedited	0.5	U	USA	CA,DE,HO	in utero
45	1/14/1998	3009057	1	8-98002-012J	Expedited	0.58333	F	USA	OT	in utero
46	3/7/2001	3618280	2	HQ7795228FEB2001	Expedited	0.91667	M	USA	CA	in utero
47	3/12/1998 10/31/1997 2/10/1998 10/12/1997	3023632 3066403 3016045 3061371	1 1 2 1	8-97296-001S 897296001S MPI-98093	Expedited Expedited Expedited Direct	1.5	M	USA	DS OT OT DS	transmammary
48	7/19/1999	3310640	1	8-99188-194A	Expedited	2	F	DEU	CA	in utero
49	3/25/1998	3123834	1		Direct	infant	F	USA	CA	in utero
50	5/11/1999	3266535	1	MPI-1999-00972 (0)	Expedited	infant	F	USA	OT	in utero
51	2/11/1999	3206777	1	107881USA	Expedited	infant	F	USA	CA	in utero
52	10/23/2000	3557836	1	200021268US	Expedited	infant	F	USA	CA	in utero
53	12/18/1997 11/7/1997	3004070 3000106	3 1	8-97336-010J MPI-97444	Expedited	infant	M	USA	CA,HO,RI CA	in utero
54	6/16/1998	3041888	1	MPI-98359	Expedited	infant	M	USA	CA	in utero
55	6/5/1998	3115788	1	9684-AR	Expedited	infant	M	USA	CA	in utero
56	9/16/1998	3147084	1	8-98251-100A	Expedited	infant	M	USA	CA,DE	in utero
57	12/1/1997	3034054	1	8-97325-011L	Expedited	infant	U	USA	CA,HO	in utero

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, CA= Congenital Anomaly, OT=Other Medically Significant, RI=Required Intervention, F=female, M=male, U=unknown

Reference ID: 4640086

6.3 APPENDIX C. PREFERRED TERMS IN PEDIATRIC FAERS CASES REPORTING IN UTERO OR TRANSMAMMARY EXPOSURE OF FENFLURAMINE

Preferred Terms in Pediatric FAERS Cases Reporting In Utero or Transmammary Exposure of Fenfluramine, Sorted by Descending Number of Reports		
	Preferred Term (PT)	**Number of Reports**
1	Maternal drugs affecting foetus	42
2	Congenital anomaly	10
3	Premature baby	10
4	Cardiac murmur	9
5	Heart disease congenital	9
6	Atrial septal defect	8
7	Ventricular septal defect acquired	7
8	Cardiomegaly	6
9	Developmental delay	6
10	Apgar score low	5
11	Multiple congenital abnormalities	5
12	Tricuspid valve incompetence	5
13	Caesarean section	4
14	Cardiac disorder	4
15	Mitral valve incompetence	4
16	Neonatal disorder	4
17	Oxygen saturation decreased	4
18	Patent ductus arteriosus	4
19	Pulmonary artery atresia	4
20	Cardiac failure congestive	3
21	Cardiac valve disease	3
22	Coarctation of the aorta	3
23	Congenital cardiovascular anomaly	3
24	Congenital pulmonary artery anomaly	3
25	Dysmorphism	3
26	Fallot's tetralogy	3
27	Pregnancy	3
28	Pulmonary malformation	3
29	Pulmonary valve stenosis congenital	3
30	Sensory disturbance	3
31	Ventricular septal defect	3
32	Anomaly of external ear congenital	2
33	Aortic valve disease	2
34	Aortic valve stenosis	2
35	Apnoea	2
36	Benign congenital hypotonia	2
37	Cerebral palsy	2
38	Cleft palate	2
39	Congenital aortic anomaly	2

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Preferred Terms in Pediatric FAERS Cases Reporting In Utero or Transmammary Exposure of Fenfluramine, Sorted by Descending Number of Reports		
	Preferred Term (PT)	**Number of Reports**
40	Congenital brain damage	2
41	Congenital mitral valve incompetence	2
42	Congenital musculoskeletal anomaly	2
43	Cyanosis	2
44	Cytogenetic abnormality	2
45	Dysphagia	2
46	Ear malformation	2
47	Echocardiogram abnormal	2
48	Hypertension	2
49	Hypotonia	2
50	Infantile vomiting	2
51	Jaundice neonatal	2
52	Lung disorder	2
53	Mitral valve disease	2
54	Neonatal respiratory distress syndrome	2
55	Premature rupture of membranes	2
56	Pulmonary hypertension	2
57	Pyrexia	2
58	Selective eating disorder	2
59	Spleen malformation	2
60	Transposition of the great vessels	2
61	Vomiting	2
62	Abnormal labour	1
63	Accidental exposure to product	1
64	Acidosis	1
65	Alcohol interaction	1
66	Amblyopia	1
67	Anal atresia	1
68	Aneurysm	1
69	Apraxia	1
70	Arnold-Chiari malformation	1
71	Arterial graft	1
72	Ascites	1
73	Aspiration	1
74	Asthma	1
75	Autism spectrum disorder	1
76	Bezoar	1
77	Bicuspid aortic valve	1
78	Blood bilirubin increased	1
79	Blood calcium increased	1
80	Blood glucose decreased	1
81	Blood pH decreased	1

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Preferred Terms in Pediatric FAERS Cases Reporting In Utero or Transmammary Exposure of Fenfluramine, Sorted by Descending Number of Reports		
	Preferred Term (PT)	**Number of Reports**
82	Blood pressure fluctuation	1
83	Bradycardia foetal	1
84	Brain hypoxia	1
85	Bronchiolitis	1
86	Calcinosis	1
87	Capillary leak syndrome	1
88	Cartilage development disorder	1
89	Chordee	1
90	Clavicle fracture	1
91	Cleft lip	1
92	Coloboma	1
93	Complication of pregnancy	1
94	Condition aggravated	1
95	Congenital aortic atresia	1
96	Congenital aortic valve stenosis	1
97	Congenital genital malformation	1
98	Congenital hair disorder	1
99	Congenital hypertrichosis	1
100	Congenital nose malformation	1
101	Congenital optic nerve anomaly	1
102	Congenital pulmonary valve disorder	1
103	Congenital tracheomalacia	1
104	Congenital ureteric anomaly	1
105	Cor pulmonale	1
106	Cryptorchism	1
107	Culture positive	1
108	Cyanosis neonatal	1
109	Dacryostenosis acquired	1
110	Decreased appetite	1
111	Dermatitis	1
112	Developmental coordination disorder	1
113	Dextrocardia	1
114	Digeorge's syndrome	1
115	Diplegia	1
116	Eczema	1
117	Enteritis necroticans	1
118	Eye disorder	1
119	Failure to thrive	1
120	Fluid overload	1
121	Foetal disorder	1
122	Foetal distress syndrome	1
123	Foetal exposure during pregnancy	1

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Preferred Terms in Pediatric FAERS Cases Reporting In Utero or Transmammary Exposure of Fenfluramine, Sorted by Descending Number of Reports		
	Preferred Term (PT)	**Number of Reports**
124	Foetal macrosomia	1
125	Gallbladder disorder	1
126	Gastrooesophageal reflux disease	1
127	Haematocrit decreased	1
128	Haemorrhage	1
129	Heart rate decreased	1
130	Hemihypertrophy	1
131	Hydronephrosis	1
132	Hyperbilirubinaemia	1
133	Hyperbilirubinaemia neonatal	1
134	Hyperkinesia neonatal	1
135	Hyperreflexia	1
136	Hypoglycaemia neonatal	1
137	Hypotension	1
138	Hypoventilation	1
139	Hypoxia	1
140	Infant	1
141	Infantile apnoea	1
142	Intestinal perforation	1
143	Kidney malformation	1
144	Lethargy	1
145	Limb reduction defect	1
146	Mastication disorder	1
147	Maternal condition affecting foetus	1
148	Maternal exposure during pregnancy	1
149	Measles	1
150	Melanocytic naevus	1
151	Nasopharyngitis	1
152	Neonatal anoxia	1
153	Nervous system disorder	1
154	Neurofibromatosis	1
155	No adverse event	1
156	Oedema	1
157	Oesophageal atresia	1
158	Oliguria	1
159	Ovarian atrophy	1
160	Pallor	1
161	Peripheral ischaemia	1
162	Photophobia	1
163	Photosensitivity reaction	1
164	Pneumonia	1
165	Pneumothorax	1

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Preferred Terms in Pediatric FAERS Cases Reporting In Utero or Transmammary Exposure of Fenfluramine, Sorted by Descending Number of Reports		
	Preferred Term (PT)	**Number of Reports**
166	Polyuria	1
167	Prader-Willi syndrome	1
168	Pre-eclampsia	1
169	Prophylaxis	1
170	Pulmonary congestion	1
171	Pulmonary hypoplasia	1
172	Pulmonary valve stenosis	1
173	Renal tubular necrosis	1
174	Respiratory acidosis	1
175	Respiratory disorder	1
176	Respiratory disorder neonatal	1
177	Respiratory rate increased	1
178	Retching	1
179	Retinopathy of prematurity	1
180	Rhinorrhoea	1
181	Rubinstein-Taybi syndrome	1
182	Sepsis neonatal	1
183	Sinusitis	1
184	Skin depigmentation	1
185	Sleep apnoea syndrome	1
186	Small for dates baby	1
187	Somnolence neonatal	1
188	Spine malformation	1
189	Strabismus	1
190	Supravalvular aortic stenosis	1
191	Supraventricular tachycardia	1
192	Tachycardia	1
193	Tachypnoea	1
194	Twin pregnancy	1
195	Ultrasound scan abnormal	1
196	Umbilical cord around neck	1
197	Univentricular heart	1
198	Ventriculo-vascular shunt	1
199	Weight decrease neonatal	1
200	Weight decreased	1
201	Wolff-Parkinson-White syndrome	1

Reference ID: 4640286

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KAREN M LONG
01/06/2020 11:59:52 AM

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