Amsterdam, 29 January 2026
EMADOC-1700519818-2501892
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Fintepla

fenfluramine

Procedure no.: EMA/PAM/0000303483

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 30 September 2025, the MAH submitted a completed paediatric study for Fintepla, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy for Seizures in Patients with Rare Seizure Disorders Such as Epileptic Encephalopathies Including Dravet Syndrome and Lennox-Gastaut Syndrome ZX008-1900/EP0215 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The investigational medicinal product was ZX008 (Fenfluramine Hydrochloride, small molecule, Oral Solution, 2.5 mg/mL). The formulation used in this study is the same as the approved one in the EU for the age subsets represented in the study and thus suitable for the purpose.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

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

2.3.2. Clinical study

ZX008-1900/EP0215

Description

ZX008-1900/EP0215 was an international, multicentre (71 enrolling centers), open-label, long-term safety study of ZX008 in participants with epileptic encephalopathy, including Dravet syndrome (DS) or Lennox–Gastaut syndrome (LGS). The main purpose of the study was to continue to provide treatment to patients with DS or LGS who may still have derived clinically meaningful benefit from ZX008 after completing ZX008-1503/EP0212 (an open-label, long-term, safety extension study in participants with DS), ZX008-1601/EP0214 Part 2 (the 1-year open-label, flexible-dose extension for a study in participants with LGS), or ZX008-1602/EP0207 (an open-label, Phase 1 study to assess the safety of ZX008 in combination with cannabidiol in children and young adults with DS or LGS) until the product was approved or a managed access program was established, as allowed per country-specific requirements in addition to legal and regulatory guidelines in the participant's country of residence, or until the

investigational product development for the participant's indication was stopped by the sponsor, whichever came first.

Methods

Study participants

The study enrolled participants with rare seizure disorders such as epileptic encephalopathy, including DS or LGS. Patients eligible for participation were those with DS who were already enrolled in ZX008-1503/EP0212 or those with LGS who had successfully completed ZX008-1601/EP0214 Part 2 and were candidates for continued treatment with ZX008 for an extended period of time, or those with DS, LGS, or another epileptic encephalopathy who had completed participation in another Zogenix-sponsored study, such as ZX008-1602/EP0207.

Treatments

Participants continued to receive ZX008 at the dose prescribed at last visit in ZX008-1503/EP0212, ZX008-1601/EP0214 Part 2, or ZX008-1602/EP0207 but had the volume adjusted according to participant's weight. The starting dose for participants entering this study from another Zogenix-sponsored clinical study of ZX008 (not to exceed 0.8mg/kg/day or 30mg/day) was determined through consultation between the investigator and CRO Medical Monitor. The maximum starting dose was 0.8mg/kg/day divided into 2 daily doses separated by a minimum of 8 hours and a maximum of 12 hours, up to a maximum of 30mg/day (participants taking concomitant stiripentol received up to 0.5mg/kg/day, up to a maximum of 20mg/day).

Changes in dosage of concomitant AEDs could be implemented as clinically necessary, and concomitant AEDs could be withdrawn completely, but all participants had to remain on a minimum of 1 concomitant AED plus ZX008 unless it was deemed clinically appropriate by the investigator (after discussion with the CRO Medical Monitor) to dose as monotherapy. New concomitant AEDs or antiepileptic treatments could be introduced at the investigator's discretion, as would be typically indicated in clinical practice.

ECHOs and other safety assessments detailed in the schedule of assessments were to be conducted every 6 months (every 3 months in France) unless more frequent follow-up was clinically indicated or required by the sponsor or the Independent Data and Safety Monitoring Committee.

Caregivers were asked to use a diary to record the number and type of seizures to support investigator determination of treatment benefit; however, diary data collection was not mandatory, nor was it collected in the database.

Objective(s)

The primary objective was to assess long-term safety and tolerability of ZX008. Secondary objectives were to assess the effect of ZX008 on overall seizure burden and illness severity (assessed by Clinical Global Impression – Improvement Scale (CGI-I)) over time.

Outcomes/endpoints

Primary: AEs, Laboratory safety (hematology, chemistry), Vital signs (blood pressure, heart rate, temperature, and respiratory rate), Physical examination, Neurological examination, ECGs, Doppler ECHOs, Body weight/height, Chest x-ray (participants in France and Netherlands only), and EEGs (in Italy only).

Secondary: Percent improvement in seizure burden as assessed by the investigator or designee (Investigator assessment of overall seizure burden assessment (<25%, ≥25%, ≥50%, ≥75%, or 100% [ie, seizure-free] improvement)), CGI-I (globally and for specific domains) as assessed by investigator or designee, and CGI-I (globally and for specific domains) as assessed by parent/caregiver.

Sample size

No formal sample size calculation was performed due to the exploratory nature of the study design. Approximately 650 participants from the feeder studies were available for potential enrolment.

Randomisation and blinding (masking)

Single-arm, open-label study.

Statistical Methods

Descriptive statistics. The safety population (SAF) includes all participants who received at least 1 dose of ZX008. The modified Intent-To-Treat population includes all participants who received at least 1 dose of ZX008 and had at least 1 valid efficacy assessment after Visit 1 in ZX008-1900/EP0215.

Results

Participant flow

A total of 412 participants were enrolled in the study360 participants (87.4%) completed the study (defined as completion of 36 months of treatment [24 months in Denmark] or transition to commercial drug) and 52(12.6%) discontinued. The majority of participants who discontinued from the study had LGS (44 of 52 non-completers). The most common primary reason for discontinuation from the study was lack of efficacy (24 participants overall (5.8%), 4 (1.5%) with DS, 20 (13.6%) with LGS). Three participants (0.7%) discontinued due to adverse events. Three participants (0.7%) died.

Recruitment

The study included 412 of 650 potential participants.

Baseline data

Table 1:Demographics and Baseline characteristics (SAF)

Variable	Statistic	DS N=265	LGS N=147	All participants N=412
Feeder study				
Study 1503	n (%)	262 (98.9)	0	262 (63.6)
Study 1601 Part 2	n (%)	0	143 (97.3)	143 (34.7)
Study 1602	n (%)	3 (1.1)	4 (2.7)	7 (1.7)
Age (years)	n	265	147	412
	Mean	13.4	15.3	14.1
	SD	6.1	7.7	6.8
	Median	13.0	15.0	13.0
	Min	3	3	3
	Max	33	37	37
Age				
2- <6 yrs	n (%)	15 (5.7)	12 (8.2)	27 (6.6)
6- <12 yrs	n (%)	101 (38.1)	40 (27.2)	141 (34.2)
12- <18 yrs	n (%)	77 (29.1)	40 (27.2)	117 (28.4)
2- <18 yrs	n (%)	193 (72.8)	92 (62.6)	285 (69.2)
≥18 yrs	n (%)	72 (27.2)	55 (37.4)	127 (30.8)
Sex				
M	n (%)	144 (54.3)	77 (52.4)	221 (53.6)
F	n (%)	121 (45.7)	70 (47.6)	191 (46.4)
Race				
American Indian or Alaska Native	n (%)	1 (0.4)	3 (2.0)	4 (1.0)
Asian	n (%)	13 (4.9)	6 (4.1)	19 (4.6)
Black or African American	n (%)	1 (0.4)	10 (6.8)	11 (2.7)

Native Hawaiian or Other Pacific Islander	n (%)	0	1 (0.7)	1 (0.2)
White	n (%)	209 (78.9)	118 (80.3)	327 (79.4)
Other or Mixed	n (%)	3 (1.1)	1 (0.7)	4 (1.0)
Not Reported	n (%)	28 (10.6)	7 (4.8)	35 (8.5)
Unknown	n (%)	10 (3.8)	1 (0.7)	11 (2.7)
Weight (kg)	n	263	144	407
	Mean	40.37	42.74	41.21
	SD	18.22	19.10	18.55
	Median	36.80	39.75	37.50
	Min	13.6	12.8	12.8
	Max	101.6	90.8	101.6
BMI (kg/m^2)	n	261	142	403
	Mean	18.25	18.77	18.44
	SD	4.41	4.66	4.50
	Median	17.33	17.61	17.39
	Min	11.5	10.3	10.3
	Max	38.7	38.5	38.7

Number analysed

Table 2: Disposition of analysis populations (enrolled population)

	Mean daily dose (mg/kg/day)			
Analysis Population	**>0 to <0.4 N=66 n (%)**	**0.4 to <0.6 N=151 n (%)**	**≥0.6 N=195 n (%)**	**All participants N=412 n (%)**
Enrolled				412 (100)
SAF	66 (100)	151 (100)	195 (100)	412 (100)
mITT	65 (98.5)	150 (99.3)	195 (100)	410 (99.5)

mITT=modified Intent-To-Treat population; SAF=safety population

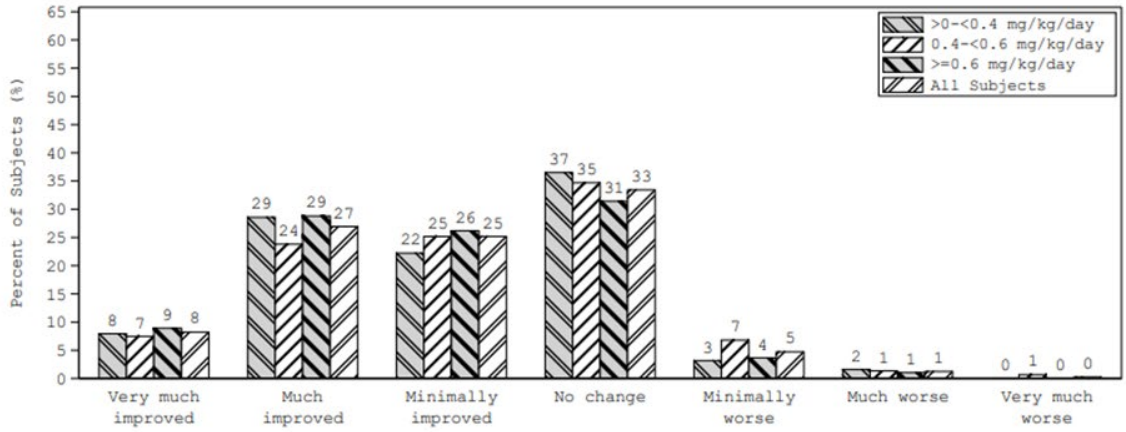
Efficacy results

The majority of participants had an improvement in seizure burden of <25% since a previous assessment over the course of the study. For the improvement categories of ≥25%, ≥50%, ≥75%, and 100%, the percentage of participants achieving improvement in seizure burden tended to decline over time. Overall, 22.7% of participants had an improvement in seizure burden of ≥25% to 100% at Month 36

compared with the previous assessment. At LOTV, the majority of participants had an improvement of <25%, which could indicate little improvement, stable condition, or worsening of seizure burden since the previous visit.

Figure 1: Distribution of CGI-I Global Rating by Investigator - All Seizure Disorders
Analysis Population: mITT Population

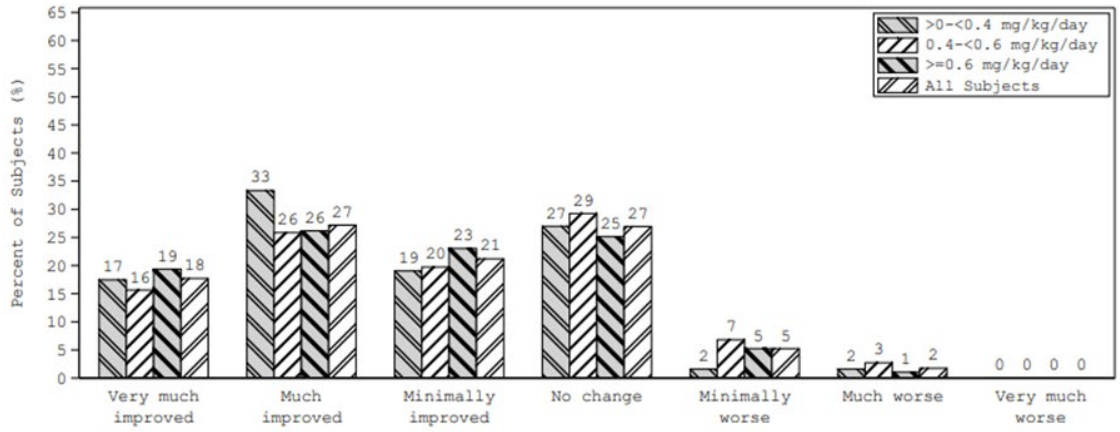
Visit: Last On-Treatment Visit



CGI-I=Clinical Global Impression - Improvement, CGI-S=Clinical Global Impression - Severity, mITT=modified Intent-To-Treat, OLE=open label extension.
Note: CGI-I is assessed at 6-monthly visits beginning at Month 6 (with the exception of France, where CGI-I is assessed by Investigator from Month 3 and every 3 months thereafter) through the end of study and permits a global evaluation of the subject's improvement over time. CGI-I is summarized only at Month 6 and every 6 months thereafter, up to Month 36. The CGI-S results serve as a reference for assessing improvement over the course of the OLE. All subjects were treated with ZX008 prior to baseline for this trial so severity ratings at baseline may reflect previous clinical improvement.

Figure 2: Distribution of CGI-I Global Rating by Parent/Caregiver - All Seizure Disorders
Analysis Population: mITT Population

Visit: Last On-Treatment Visit



CGI-I=Clinical Global Impression - Improvement, CGI-S=Clinical Global Impression - Severity, mITT=modified Intent-To-Treat, OLE=open label extension.
Note: CGI-I is assessed at 6-monthly visits beginning at Month 6 through the end of study and permits a global evaluation of the subject's improvement over time. CGI-I is summarized at Month 6 and every 6 months thereafter, up to Month 36. The CGI-S results serve as a reference for assessing improvement over the course of the OLE. All subjects were treated with ZX008 prior to baseline for this trial so severity ratings at baseline may reflect previous clinical improvement.

Safety results

The most commonly reported serious TEAEs were seizure (17 participants (4.1%)) and status epilepticus (9 participants (2.2%)). There were 9 events that led to permanent discontinuation of study treatment in 7 participants (1.7%). There were 3 TEAEs during the study that led to death (cardiac arrest, non-compaction cardiomyopathy, and status epilepticus). All 3 TEAEs were judged by the investigator as not related to the study medication.

The first case was a participant with LGS in the >0 to <0.4mg/kg/day dose group who died from cardiac arrest 61 days after the last study treatment dose.

The second case was a participant with DS in the 0.4 to <0.6mg/kg/day dose group who developed non-compaction cardiomyopathy 364 days after Visit 1. Study treatment was withdrawn and treatment for the condition was provided. Death occurred 28 days after the last dose of IMP. The cause of participant's cardiomyopathy was considered as probably related to the underlying genetic condition (phosphatidylinositol glycan anchor [PIGA] biosynthesis Class A) mutation, ketogenic diet, and phenytoin.

The third case was a participant with LGS in the ≥0.6mg/kg/day dose group who died from status epilepticus 979 days after Visit 1 while on study treatment.

Decreased appetite was reported by 25 participants (6.1%).

There was no significant effect of ZX008 on ECG parameters (QTcF).

No clinically relevant valvular heart disease (VHD) was observed. There were no cases of pulmonary arterial hypertension or mitral valvulopathy. Three participants exhibited mild aortic valve regurgitation (mild aortic regurgitation without reported symptoms or anatomical abnormalities), which is considered pathological and defined as aortic valvulopathy. Two of these participants experienced mild aortic

regurgitation already at Baseline and throughout the study, and the third participant had a single instance of mild aortic regurgitation at the Month 18 visit. None of the three participants exhibited symptoms of valvular heart disease.

Three participants had 4 TEAEs of echocardiogram abnormal (trace mitral or tricuspid valve regurgitation), 2 of which were considered treatment-related (both were trace tricuspid valve regurgitation)

Table 3: Incidence of TEAEs - overview by mean daily dose - all seizure disorders (SAF)

	Mean daily dose (mg/kg/day)			All participants
	>0 to <0.4 N=66 n (%) [#]	0.4 to <0.6 N=151 n (%) [#]	≥0.6 N=195 n (%) [#]	N=412 n (%) [#]
Any TEAEs	51 (77.3) [237]	107 (70.9) [684]	153 (78.5) [697]	311 (75.5) [1618]
Serious TEAEs	12 (18.2) [18]	24 (15.9) [48]	31 (15.9) [66]	67 (16.3) [132]
Permanent discontinuation from study due to TEAEs	0	3 (2.0) [8]	1 (0.5) [1]	4 (1.0) [9]
Permanent discontinuation of study treatment due to TEAEs	0	5 (3.3) [7]	2 (1.0) [2]	7 (1.7) [9]
Treatment-related TEAEs	7 (10.6) [14]	21 (13.9) [47]	23 (11.8) [32]	51 (12.4) [93]
Treatment-related serious TEAEs	1 (1.5) [1]	3 (2.0) [7]	1 (0.5) [1]	5 (1.2) [9]
Severe TEAEs	5 (7.6) [8]	11 (7.3) [24]	17 (8.7) [26]	33 (8.0) [58]
Deaths (TEAEs leading to death)	1 (1.5) [1]	1 (0.7) [1]	1 (0.5) [1]	3 (0.7) [3]

SAF=safety population; TEAE=treatment-emergent adverse event
Note: n=number of participants reporting at least 1 TEAE in that category.
Note: [#] is the number of individual occurrences of the TEAE in that category.

2.3.3. Discussion on clinical aspects

This open label study included patients with rare Seizure disorders Dravet Syndrome and Lennox-Gastaut Syndrome and fenfluramine was used as an adjunctive therapy for these patients. This is in accordance with the approved indication, meaning the included patients represent the population for which efficacy and safety data were initially obtained and is thus denned suitable to serve as a long term extension to generate data that can be meaningfully compared with the already existing short term data.

The primary objective was to assess long-term safety and tolerability of ZX008.

Regarding the secondary objectives, which were to assess the effect of ZX008 on overall seizure burden and illness severity (assessed by Clinical Global Impression – Improvement Scale (CGI-I)) over time, it should be noted that this is a preselected population as the patients are recruited from three open label studies ZX008-1503/EP0212, ZX008-1601/EP0214 Part 2, or ZX008-1602/EP0207 and the main purpose of the study was to continue to provide treatment to patients with DS or LGS who may still have derived clinically meaningful benefit from ZX008 as assessed by the investigator.

Participants continued to receive ZX008 at the dose prescribed at last visit in the previous study. The maximum starting dose was 0.8mg/kg/day divided into 2 daily doses separated by a minimum of 8 hours and a maximum of 12 hours, up to a maximum of 30mg/day (participants taking concomitant stiripentol received up to 0.5mg/kg/day, up to a maximum of 20mg/day). Thus the doses used do represent the posology in the current SmPC and can be considered representative for safety assessment.

360 participants (87.4%) completed the study (defined as completion of 36 months of treatment [24 months in Denmark] or transition to commercial drug) and 52 (12.6%) discontinued. The majority of participants who discontinued from the study had LGS (44 of 52 non-completers) and the most common primary reason for discontinuation from the study was lack of efficacy (24 participants overall (5.8%), 4 (1.5%) with DS, 20 (13.6%) with LGS). Three participants (0.7%) discontinued due to adverse events. Three participants (0.7%) died.

Efficacy was assessed via the secondary endpoint: Percent improvement in seizure burden as assessed by the investigator or designee (Investigator assessment of overall seizure burden assessment (<25%, ≥25%, ≥50%, ≥75%, or 100% [ie, seizure-free] improvement)), CGI-I (globally and for specific domains) as assessed by investigator or designee, and CGI-I (globally and for specific domains) as assessed by parent/caregiver.

The majority of participants had an improvement in seizure burden of <25% since a previous assessment over the course of the study. For the improvement categories of ≥25%, ≥50%, ≥75%, and 100%, the percentage of participants achieving improvement in seizure burden tended to decline over time. Overall, 22.7% of participants had an improvement in seizure burden of ≥25% to 100% at Month 36 compared with the previous assessment. At last on-treatment visit, the majority of participants had an improvement of <25%, which could indicate little improvement, stable condition, or worsening of seizure burden since the previous visit. These results indicate no relevant further improvement in efficacy after the first year of treatment, especially taking into account the dropouts due to lack of efficacy.

The data show continued long-term treatment with fenfluramine maintained the perceived clinical benefit in the opinion of both the investigator and parent/caregiver for both paediatric and adult patients, as measured using CGI-I global ratings. There were no meaningful differences in CGI-I global ratings at LOTV between age subgroups, either for the ratings by investigator or by parent/caregiver.

Safety was assessed by the primary endpoint: AEs, Laboratory safety (haematology, chemistry), Vital signs (blood pressure, heart rate, temperature, and respiratory rate), Physical examination, Neurological examination, ECGs, Doppler ECHOs, Body weight/height, Chest x-ray (participants in France and Netherlands only), and EEGs (in Italy only).

The most commonly reported serious TEAEs were seizure (17 participants (4.1%)) and status epilepticus (9 participants (2.2%)) as to be expected in this population. There were 9 events that led to permanent discontinuation of study treatment in 7 participants (1.7%). There were 3 TEAEs during the study that led to death (cardiac arrest, non-compaction cardiomyopathy, and status epilepticus) for which detailed narratives were provided. All 3 TEAEs were judged by the investigator as not related to the study medication and deemed very likely related to the underlying disease by the assessor.

There were no dose-related differences in the overall incidence of TEAEs, treatment-related TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to discontinuation from the study, fatal

TEAEs, or other serious AEs. The percentage of participants reporting TEAEs was generally consistent across age groups and regardless of the specific developmental and epileptic encephalopathy.

As to be expected from the substance decreased appetite was seen (reported by 25 participants (6.1%)).

No clinically relevant valvular heart disease (VHD) was observed and there were no cases of pulmonary arterial hypertension or mitral valvulopathy. Three participants exhibited mild aortic valve regurgitation (mild aortic regurgitation without reported symptoms or anatomical abnormalities), which is considered pathological and defined as aortic valvulopathy. Two of these participants, including one paediatric, experienced mild aortic regurgitation already at Baseline and throughout the study, and the third participant had a single instance of mild aortic regurgitation at the Month 18 visit. None of the three participants exhibited symptoms of valvular heart disease.

However, three participants had 4 TEAEs of echocardiogram abnormal (trace mitral or tricuspid valve regurgitation), 2 of which were considered treatment-related (both were trace tricuspid valve regurgitation).

The TEAEs observed in EP0215 were generally consistent with the known safety profile for fenfluramine in paediatric study participants as described in the SmPC Section 4.8. Thus no change is required.

3. CHMP overall conclusion and recommendation

TEAEs observed in the study ZX008-1900/EP0215 were consistent with the known safety profile of fenfluramine and those reported in the previous Phase 3 studies and their OLE, and no new safety signals were observed. In addition, the effect of fenfluramine on the clinical condition of paediatric and adult participants with DS and LGS seemed to be sustained during the study.

No changes to the SmPC are required.

☒ **Fulfilled:**

No regulatory action required.