18 December 2020
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EMA/OD/0000024920
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Fintepla (fenfluramine hydrochloride)
Treatment of Dravet syndrome
EU/3/13/1219
Sponsor: Zogenix ROI Limited

Note

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

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1. Product and administrative information

Product	
Active substances at the time of orphan designation	Fenfluramine hydrochloride
International Non-Proprietary Name	Fenfluramine hydrochloride
Tradename	Fintepla
Orphan condition	Treatment of Dravet syndrome
Sponsor's details:	Zogenix ROI Limited Trinity House Charleston Road Ranelagh Dublin 6 D06 C8X4 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Brabant Pharma Limited
COMP opinion date	6 November 2013
EC decision date	16 January 2014
EC registration number	EU/3/13/1219
Post-designation procedural history	
Sponsor's name change	Name change from Brabant Pharma Limited to Zogenix International Ltd – EC letter of 16 December 2015
Transfer of sponsorship	Transfer from Zogenix International Ltd to Zogenix GmbH – EC decision of 9 November 2018
Transfer of sponsorship	Transfer from Zogenix GmbH to Zogenix ROI Limited – EC decision of 20 May 2019
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Mark Ainsworth / Johann Lodewijk Hillege
Applicant	Zogenix ROI Limited
Application submission date	5 February 2019
Procedure start date	28 February 2019
Procedure number	EMA/H/C/003933
Invented name	Fintepla
Proposed therapeutic indication	Treatment of seizures associated with Dravet syndrome as an add-on therapy to other antiepileptic medicines for patients 2 years of age and older Further information on Fintepla can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/fintepla
CHMP opinion date	15 October 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Dinah Duarte / Giuseppe Capovilla
Sponsor's report submission date	23 January 2020

COMP discussion and adoption of list of questions	14-16 July 2020
COMP opinion date (adoption via written procedure)	21 October 2020

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2013 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing fenfluramine hydrochloride was considered justified based on preliminary clinical data showing reduction in the number of seizures in patients affected by the condition;
- the condition is chronically debilitating due to psychomotor and cognitive impairment and the occurrence of convulsive seizures, and life-threatening in particular due to sudden unexpected death in epilepsy;
- the condition was estimated to be affecting less than 0.5 in 10,000 persons in the European Union, at the time the application was made;
- in addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing fenfluramine hydrochloride could be of significant benefit to those affected by the condition. This is based on data showing a reduction in seizure frequency and severity as an add-on to other available treatments. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Dravet syndrome (DS) is one of the most severe types of genetic epilepsy. The condition was first described by Charlotte Dravet in 1979.

In 2001, de novo mutation in alpha-1 subunit of voltage-gated calcium channel gene (SCN1A) was identified in seven totally unrelated DS patients. These mutations were located on chromosome 2q24. More than 90% of these mutations were de novo whereas familial mutations such as missense in nature were located only in 5%-10%. There are no identifiable mutations in SCN1A in about 10%-20% of patients with DS.

The other theory that has been investigated in the pathophysiology of DS is loss of function of inhibitory neurons. SCN1A gene (Nav1.1) protein product has been the primary voltage-gated sodium channel of these inhibitory neurons. Impairment of Nav 1.1 located in cell bodies and dendrites results

in uncontrolled firing from gamma-aminobutyric acid-ergic (GABAergic) neurons (Chopra R, Isom LL: Epilepsy Curr. 2014, 14:86-89)

The condition has been previously designated by the COMP

The approved therapeutic indication "*Fintepla is indicated for the treatment of seizures associated with Dravet syndrome as an add-on therapy to other antiepileptic medicines for patients 2 years of age and older"* falls within the scope of the designated orphan condition "Treatment of Dravet syndrome".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed based on the positive benefit/risk assessment by the CHMP.

Chronically debilitating and/or life-threatening nature

Presentation of seizures varies with age. Most of the patients are seizure free up to the age of five months and first seizure appears between the age of five to eight months due to any kind of trigger like fever, vaccination, bathing and sometimes in absence of the trigger. After the age of one year, a child can have focal or generalized tonic-clonic epilepsy or absence seizure. It may result in loss of consciousness or altered level of consciousness.

Developmental delay is noted with the progression of the age. Hypotonia can be detected in the majority of patients around the age of one year. Ataxia is noted when a child starts walking, dysautonomia as variation in sweating or heat and pyramidal signs have a different frequency and variation (Wical B, Leighty D, Tervo M, et al.: Epilepsia. 2009, 50:3-164). Usually, there is no sign of neuro-developmental delay until the start of seizure activity but soon after the first seizure, neuro-developmental delay signs like unsteady gait, language deficit in constructing a sentence, the deficit in fine motor abilities begin and progress shortly thereafter.

The most common behavioural disturbances are in DS are in the form of autism, attention deficit-hyperactivity disorder (ADHD), aggressiveness, irritability, relational difficulties, and opposition. Motor and cognitive impairment also influence behavioural changes. These features along with cognitive deficit significantly affect social life and adaptive behaviour.

Regarding prognosis two studies have reported that the two most common reason for premature mortality in DS patients is sudden unexpected death in epilepsy (SUDEP) and status epilepticus. It is estimated that 10%-20% of individuals with DS die within 10 years of age (Shmuely S et al., Epilepsy Behav. 2016, 64:69-74.

Number of people affected or at risk

The sponsor has provided literature data from their initial orphan designation in 2013 and complemented it with three new publications that have appeared since. These publications are summarised in the table below.

Table 1. Summary of Prevalence Data on Dravet Syndrome Identified Post 2013

Prevalence Source	Region	Years	Prevalence of Dravet syndrome per 10,000 of population
Rosander and Hallbook 2015	Sweden	2007-2011	0.2
Syvertsen 2015	Norway	1999-2014	0.1
Gil-Nagel 2019	Spain	2016-2017	0.1

This condition does not follow a classical inheritance pathway as 90% of the mutations are de novo, therefore establishing birth incidence is difficult. The most recent (2015) population-based estimates of Dravet syndrome incidence lie between 1 in 15,000 and 1 in 33,000 live births and are based on three studies from Sweden, Norway, and the United States (Wu 2015, Rosander 2015, Bayat 2015). Before this, a 1990 study estimated the incidence at 1 in 40,000 live births (Hurst 1990). Earlier studies estimated an incidence of 1 in 30,000 to 1 in 40,000 live births on the basis of extrapolations from the percentage of patients with DS identified in cohorts of paediatric epilepsy cases (Yakoub 1992). There is an additional study by Hurst D, Epilepsia Vol31, issue 4 August 1990 Pages 297-400 where the incidence is suggested to be 1 in 40,000.

Although premature mortality is high the overall life-expectancy of these patients is not well known. A calculation based on incidence and duration of the condition is therefore not feasible for the prevalence estimate. It has however recently been reported by Cooper et al. (2016) that the Dravet-specific mortality rate appears to be 15.84 per 10,000 person years which translated to an almost 15% risk of death after 10 years of follow up post diagnosis of Dravet syndrome. Given the physiological and genetic nature of the condition and that many adult patients are currently underdiagnosed with Dravet syndrome, the mortality risks associated with seizures are likely to continue into adulthood.

The sponsor therefore proposes to use the prevalence reported in the literature which includes values from Sweden, Norway and Spain. They propose a corrected value of 0.2 in 10,000. This is lower that the initial orphan designation from 2013, but includes more recent data and thus could be accepted by the COMP.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Dravet syndrome (DS) is one of the most pharmacoresistant epilepsy syndromes.

Sodium valproate and clobazam are recommended in Dravet syndrome and may therefore be considered as a satisfactory method of treatment.

Since 2007 only two products have been authorised as ODs in Europe for use specifically in Dravet syndrome:

- Stiripentol is indicated as an adjunctive therapy with valproate and clobazam, for treatment of not adequately controlled patients.

- Cannabidiol (Epidyolex) is indicated as adjunctive therapy of seizures associated with Lennox Gastaut syndrome (GS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older

Table 2. Other drugs listed in the following tables are used in DS to treat the different seizure types.

Strategy	Options	Comments
First line	Valproic Acid[b] or Clobazam[b]	If the first choice is not effective, ADD the second line.
Second line	Addition of Stiripentol[bc] or Topiramate[b] or Ketogenic Diet[b]	Stiripentol is used in combination with drugs with Valproic acid and Clobazam. The diet for < 2 years is Traditional Ketogenic Diet, 2-12 years is Traditional or Modified Atkins Diet and >12 years is Modified Atkins Diet.
Third line	Clonazepam[b], Levetiracetam[b], Zonisamide[b], Ethosuximide[a], Phenobarbital[a] OR Vagus Nerve Stimulation (VNS)[a]	Ethosuximide is for atypical absence seizure. VNS is recommended with evaluation at a Comprehensive Evaluation Center.

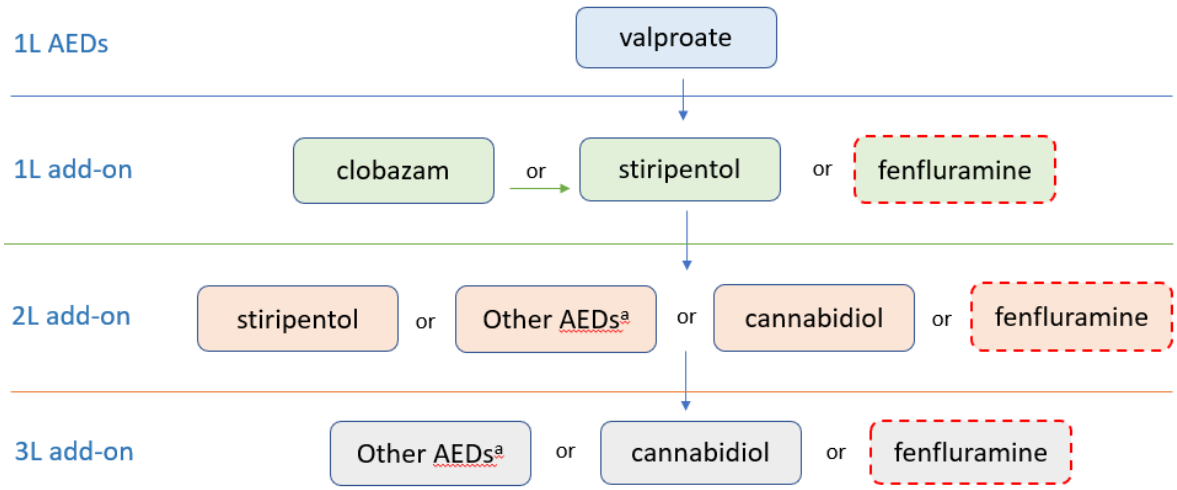
Table 3.

Drugs	Starting Dose	Maintenance Dose	Side Effects	Comments
Valproate MOA- Its action is due to blockage of Na+ and Ca++ channels, thus reducing excitability [30]	10 to 15 mg/kg/day in two or three divided doses.	25 to 60 mg/kg/day.	Vomiting, nausea, hair loss, sedation, weight gain, pancreatitis, and blood dyscrasias and hyperammonemia.	Routine monitoring (at baseline and every 6 months) of serum lipase, liver functions, and serum drug level Contraindicated: In pregnancy due to its teratogenic effect.
Topiramate MOA- Its main mechanism of action is due to interaction with the GABA receptor [30]	0.5 to 2 mg/kg/day.	8 to 12 mg/kg/day.	Weight loss, anorexia, renal stones, and behavioral changes.	It has a good safety profile and less interaction with other drugs. A good option when the patient is on several medications.
Stiripentol MOA- It is an allosteric modulator of GABA-A receptor [30]	50 mg/kg per day.	75-100 mg/kg per day.	Decreases appetite and sedation.	It can interact with cytochrome P450 and increase the concentration of other anti-seizure medication.
Levetiracetam MOA- It binds with synaptic vesicle protein 2A and increases GABA [31]	10 mg/kg in two divided doses.	25 mg/kg/dose twice daily	Irritability, depression, and aggression.	It has a minimal drug interaction potential and is generally well tolerated
Cannabidiol MOA- It binds with CB1 and CB2 receptors and counteracts reactive oxygen species [32]	2.5 mg/kg twice daily by mouth.	20 mg/kg per day.	Decreased appetite, diarrhea, somnolence, malaise, and increased transaminase level.	Liver functions must be checked before the start of treatment and after every 3 months.

Significant benefit

The sponsor is claiming that their product, fenfluramine will offer a clinically relevant advantage when used in combination with antiepileptic medicines in the treatment of Dravet syndrome. The following algorithm is proposed.

Figure 1.



1L: first-line, 2L: second-line, 3L: third-line, AEDs: antiepileptic drugs
[a] AEDs licensed for general epilepsy are used in Dravet syndrome on an experimental or off-label basis

Brabant Pharma Ltd (now Zogenix ROI Ltd) received Protocol Assistance on Significant Benefit in September 2014 (EMA/COMP/367491/2014).

The advice to the sponsor stated:

"*At the time of MAA, in order to maintain its orphan designation, the Applicant will be requested to demonstrate significant benefit of fenfluramine hydrochloride over the currently authorised AEDs used in Dravet syndrome. This could be done by using fenfluramine hydrochloride as add-on to standard of care (SOC), (physician's best choice).*

….. it was stated that the inclusion criteria would allow for fenfluramine add-on of up to three AEDs. This could therefore include the above-mentioned stiripentol combination as a background therapy."

The proposed indication to CHMP is as follows:

Fintepla is indicated for the treatment of seizures associated with Dravet syndrome as an add-on therapy to other antiepileptic medicines for patients 2 years of age and older.

The authorised indications for stiripentol and cannabidiol are:

- Stiripentol is indicated as an adjunctive therapy with valproate and clobazam, for treatment of not adequately controlled patients.
- Cannabidiol (Epidyolex) is indicated as adjunctive therapy of seizures associated with Lennox Gastaut syndrome (GS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older

The proposed therapeutic indication and the clinically relevant advantage, which overlaps with it, are based on clinical data generated by the sponsor.

The primary clinical data used in support of the Marketing Authorisation as well as the maintenance of orphan status is derived from study ZX008-1504. Its primary aim was to compare fenfluramine and placebo, as add-on therapy to a treatment regimen containing stiripentol (STP), whereby these subjects were obtaining only partial seizure reduction with an optimal dose of STP.

Concomitant Anti-Epileptic Medications/Therapies

All subjects were to be receiving at least one concomitant anti-epileptic treatment during the study. Table 15 summarizes the number of concomitant AEDs taken by subjects by treatment group in the SAF population. Most subjects (97.6%) received between 1 and 4 AEDs. In addition to AEDs, 9 subjects were on the ketogenic diet (1 on placebo, 4 on fenfluramine 0.2 mg/kg/day, and 4 subjects on fenfluramine 0.7 mg/kg/day), and 23 subjects had a vagal nerve stimulator implantation (9 subjects on placebo, 8 subjects on fenfluramine 0.2 mg/kg/day, and 6 subjects on fenfluramine 0.7 mg/kg/day). One subject in the fenfluramine 0.2 mg/kg/day treatment group did not receive any concomitant AED medication during the study but did have a vagal nerve stimulator implanted.

Table 4. Number of Concomitant AEDs Taken by Subjects (Safety Population)

	Placebo (N=40)	ZX008 0.2 mg (N=39)	ZX008 0.8 mg (N=40)	Total (N=119)
Number of Concomitant AED Treatments				
1	6 (15.0)	5 (12.8)	8 (20.0)	19 (16.0)
2	15 (37.5)	16 (41.0)	16 (40.0)	47 (39.5)
3	14 (35.0)	9 (23.1)	13 (32.5)	36 (30.3)
4	5 (12.5)	6 (15.4)	3 (7.5)	14 (11.8)
5	0 (0.0)	2 (5.1)	0 (0.0)	2 (1.7)

Counts do not include ketogenic diet or vagal nerve stimulator.
Source: Table 14.1.4.4.2
AED=Anti-Epileptic Drug.

Dose expressed as fenfluramine hydrochloride (i.e. 0.8 mg/kg/day equivalent to 0.7 mg/kg/day fenfluramine. Fenfluramine hydrochloride 0.2 mg/kg/day rounds to 0.2 mg/kg/day when expressed as fenfluramine base)

Table 4 presents a summary of all concomitant AEDs for the SAF population. The most commonly used background AEDs were clobazam (58.8%); topiramate (25.2%); valproate, which includes both formulations of salts and acids (valproate sodium, 23.5%; valproate semisodium, 21.8%; and valproic acid, 14.3%); and levetiracetam (21.8%). Differences of ≥ 10% between any of the treatment groups were noted for the following concomitant AEDs (placebo, fenfluramine 0.2 mg/kg/day, fenfluramine 0.7 mg/kg/day, respectively): levetiracetam (27.5%, 28.2%, 10.0%), zonisamide (20.0%, 10.3%, 7.5%), potassium bromide (20.0%, 2.6%, 7.5%), any bromide (20.0%, 7.7%, 15.0%). Although there was a difference of ≥ 10% between treatment groups for various forms of valproate (placebo, fenfluramine 0.2 mg/kg/day, fenfluramine 0.7 mg/kg/day, respectively): valproate sodium (22.5%, 17.9%, 30.0%), valproic acid (12.5%, 25.6%, 5.0%), the overall concomitant use of valproate from any form was similar between treatment groups (55.0%, 61.5%, and 62.5%, respectively).

Table 5. Concomitant Anti-Epileptic Treatments, (Safety Population)

Drug Class ATC Level 2 Preferred Term	Placebo (N=40)	ZX008 0.2 mg (N=39)	ZX008 0.8 mg (N=40)	Total (N=119)
Subjects with at least one concomitant AED*	40 (100.0)	38 (97.4)	40 (100.0)	118 (99.2)
Analgesics, N02	0 (0.0)	2 (5.1)	1 (2.5)	3 (2.5)
Clonidine	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.8)
Verapamil	0 (0.0)	1 (2.6)	1 (2.5)	2 (1.7)
Antiepileptics, N03	40 (100.0)	38 (97.4)	39 (97.5)	117 (98.3)
Brivaracetam	1 (2.5)	0 (0.0)	0 (0.0)	1 (0.8)
Clobazam	22 (55.0)	24 (61.5)	24 (60.0)	70 (58.8)
Clonazepam	3 (7.5)	5 (12.8)	5 (12.5)	13 (10.9)
Diazepam	1 (2.5)	1 (2.6)	0 (0.0)	2 (1.7)
Ergenyl Chrono	1 (2.5)	0 (0.0)	1 (2.5)	2 (1.7)
Ethosuximide	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.8)
Felbamate	1 (2.5)	1 (2.6)	2 (5.0)	4 (3.4)
Lacosamide	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.8)
Lamotrigine	1 (2.5)	0 (0.0)	0 (0.0)	1 (0.8)
Levetiracetam	11 (27.5)	11 (28.2)	4 (10.0)	26 (21.8)
Lorazepam	3 (7.5)	0 (0.0)	1 (2.5)	4 (3.4)
Mesuximide	0 (0.0)	2 (5.1)	1 (2.5)	3 (2.5)
Perampanel	1 (2.5)	1 (2.6)	0 (0.0)	2 (1.7)
Pregabalin	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.8)
Rufinamide	0 (0.0)	1 (2.6)	2 (5.0)	3 (2.5)
Sultiame	3 (7.5)	3 (7.7)	0 (0.0)	6 (5.0)
Topiramate	9 (22.5)	10 (25.6)	11 (27.5)	30 (25.2)
Valproate semisodium	8 (20.0)	7 (17.9)	11 (27.5)	26 (21.8)
Valproate sodium	9 (22.5)	7 (17.9)	12 (30.0)	28 (23.5)
Valproic acid	5 (12.5)	10 (25.6)	2 (5.0)	17 (14.3)
Zonisamide	8 (20.0)	4 (10.3)	3 (7.5)	15 (12.6)
Muscle Relaxants, M03	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.8)
Tizanidine	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.8)
Other alimentary tract and metabolism products, A16	1 (2.5)	4 (10.3)	1 (2.5)	6 (5.0)
Levocarnitine	1 (2.5)	4 (10.3)	1 (2.5)	6 (5.0)
Psycholeptics, N05	10 (25.0)	4 (10.3)	6 (15.0)	20 (16.8)
Bromides	0 (0.0)	1 (2.6)	3 (7.5)	4 (3.4)
Ethyl Loflazepate	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.8)
Midazolam	1 (2.5)	0 (0.0)	0 (0.0)	1 (0.8)
Nitrazepam	1 (2.5)	0 (0.0)	0 (0.0)	1 (0.8)
Potassium Bromide	8 (20.0)	1 (2.6)	3 (7.5)	12 (10.1)
Sodium Bromide	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.8)
Vitamins, A11	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.8)
Pyridoxine	0 (0.0)	0 (0.0)	1 (2.5)	1 (0.8)
Uncoded				
Ketogenic Diet	1 (2.5)	4 (10.3)	4 (10.0)	9 (7.6)
Vagal Nerve Stimulator Implantation	9 (22.5)	8 (20.5)	6 (15.0)	23 (19.3)

*Does not include ketogenic diet or vagal nerve stimulator.
Source: Tables 14.1.4.4.1 and 14.1.4.4.2
Note: Multiple occurrences of the same antiepileptic treatment are counted once for each subject within a drug class and preferred drug name.
Note: A concomitant antiepileptic treatment (AEDs) is defined as antiepileptic treatment with a start or stop date after the first dose of study treatment. Missing or partial start or stop dates for concomitant AEDs are handled as specified in SAP Section 6.2.5.
Drug dictionary used for coding is WHODDE 201512.

Doses expressed as fenfluramine hydrochloride (0.8 mg/kg/day equivalent to 0.7 mg/kg/day fenfluramine. Fenfluramine hydrochloride 0.2 mg/kg/day rounds to 0.2 mg/kg/day when expressed as fenfluramine base)

A 0.4 mg/kg/day dose of fenfluramine was selected as the dose for Study 1504 Cohort 2 to account for the anticipated drug interaction when fenfluramine is administered in combination with STP.

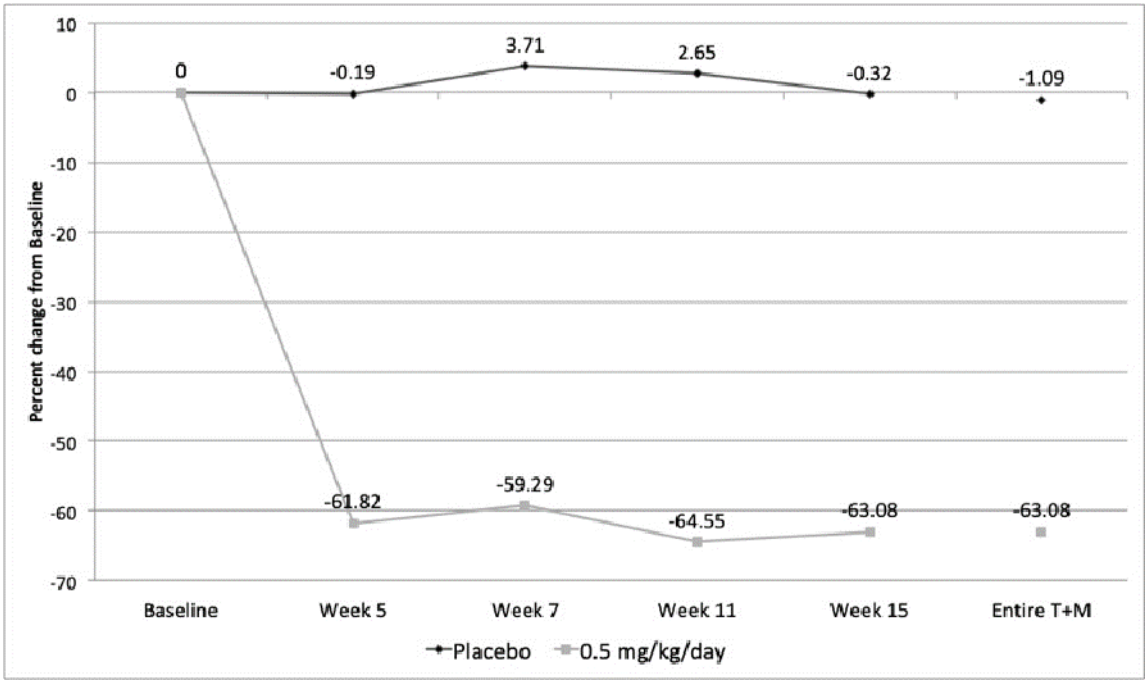
Following the Baseline period, subjects were randomized to one of 2 treatment groups (ZX008 0.4 mg/kg/day or placebo) and entered a 3 weeks titration period followed by a 12-week Maintenance period for a total of 15 weeks treatment. Enrolment included 105 subjects screened of which 87 were randomized approximately equally to ZX008 0.4 mg/kg/day or placebo.

The primary efficacy measure was the change from baseline in the frequency of convulsive seizures (per 28 days) during the 15-week trial period. Convulsive seizures are the core feature of Dravet syndrome and thus appropriate for selection as the primary efficacy endpoint and measuring convulsive seizure frequency during the Baseline Period to convulsive seizure frequency during the T+M Period was considered by FDA and EMA an adequate manner to measure efficacy.

The primary objective of Study 1504 was to determine whether fenfluramine 0.4 mg/kg/day (maximum 17 mg/day) reduced MCSF relative to placebo in patients with Dravet syndrome who were taking STP-inclusive regimens. Seizure types contributing to the primary endpoint were GTC, secondarily GTC, clonic, drop seizures (tonic-atonic), hemiclonic, and focal seizures with a clear and observable motor component. Key secondary objectives included a comparison of the proportion of subjects who achieved a reduction of ≥50% in CSF and the median change in longest seizure-free interval between the fenfluramine 0.4 mg/kg/day group and the placebo group. Secondary endpoints also included the number of subjects with ≥75% reduction from Baseline in CSF, and the Clinical Global Impression of Improvement (CGI-I). The efficacy results are as follows:

- The study met its primary efficacy endpoint. Patients randomized to fenfluramine (0.4 mg/kg/day) achieved an estimated 54.0% (95% CI, 35.6%-67.2%) greater reduction in mean MCSF between their baseline and T + M periods than those that had received placebo ($p < 0.001$).
- At the end of the T+M period, the median (max, min) change from baseline in MCSF was -1.1% (-82.8, 435.1) for the placebo group and -63.1% (-100.0, 115.0) for the fenfluramine 0.4 mg/kg/day group. The median percent reduction in convulsive seizures observed by Week 5 (3 weeks titration and 2 weeks maintenance) was consistent throughout the entire T+M period

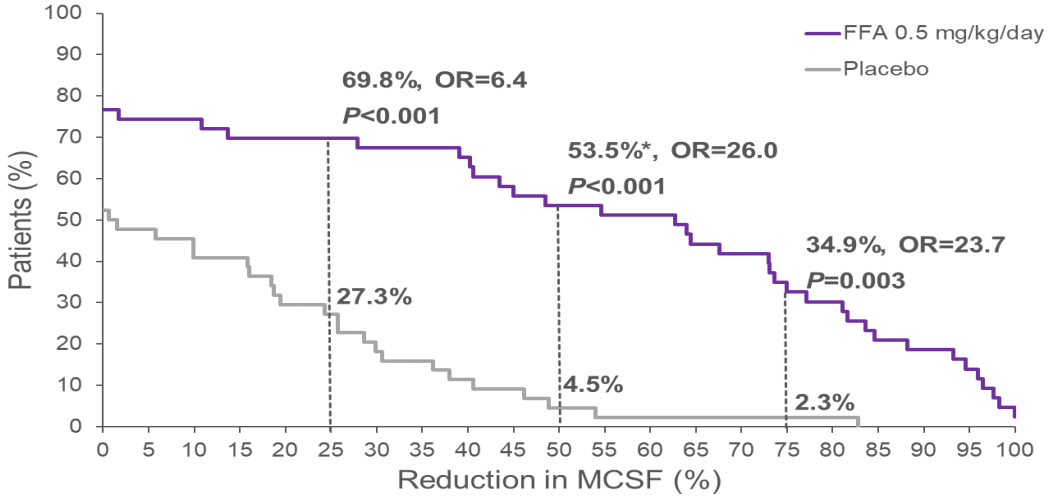
Figure 2. Median % Change from Baseline CSF per adjusted 28 days (mITT)



Dose expressed as fenfluramine hydrochloride (equivalent to 0.4 mg/kg/day fenfluramine)

- The proportion of patients with a clinically meaningful ≥50% reduction in mean MCSF during the T+M period was 54% for fenfluramine 0.4 mg/kg/day compared to 5% for placebo (p<0.001), with an Odds ratio (95% CI) of 26.0 (5.5, 123.2) (see Figure below).
- The proportion of patients with a ≥ 75% reduction in monthly convulsive seizures during the T+M period, a threshold considered profound by study investigators, was 35% for fenfluramine 0.4 mg/kg/day and 2% for placebo (p=0.003), with an Odds ratio of 23.7 (2.9, 191.8) (see Figure below).

Figure 3. Responders with ≥ 50% & ≥75% Reduction in Convulsive Seizure Frequency (mITT Population)



[a] A logistic regression model that included a categorical response variable (achieved XX% percentage point reduction, yes or no) as a function of treatment group (active or placebo), age group (< 6 years, ≥ 6 years), and baseline CSF was used.

Dose expressed as fenfluramine hydrochloride (equivalent to 0.4 mg/kg/day fenfluramine)

- The median longest convulsive seizure-free interval was 22.0 days (range: 3.0 - 105.0) for subjects in the fenfluramine 0.4 mg/kg/day group vs 13.0 days (range: 1.0 - 40.0) in the placebo group (p = 0.004) and near convulsive seizure freedom (i.e., at most 1 seizure during the 14 week T+M period) was achieved in 5 of 43 subjects (12%) treated with fenfluramine 0.4 mg/kg/day and no subjects treated with placebo (p = 0.03).
- The CGI-I as rated by the investigator showed a significant and clinically meaningful improvement (i.e., had a score of [2] "much improved" or [1] "very much improved") in patients treated with fenfluramine, compared to their scores at baseline. Compared to the placebo group nineteen patients (44%) receiving fenfluramine 0.4 mg/kg/day achieved a clinically meaningful improvement during the T+M period, whereas only seven placebo-treated patients (16%) achieved the same response (p = 0.008)

The sponsor has shown additive effects to standard of care + stiripentol which was considered sufficient to support the clinically relevant advantage. The sponsor also offered an indirect comparison to cannabidiol. It was noted that the data submitted for cannabidiol did not include combination use with stiripentol just data in combination with AEDs.

The indirect comparison between cannabidiol and fenfluramine used in the same context showed a clinically superior effect for fenfluramine. As there is no comparison to cannabidiol used in combination with stiripentol and AEDs as is presented with fenfluramine the proposed indirect comparison does not seem to offer a complete picture. This is reflected in the proposed target patient population for fenfluramine in the approved therapeutic indication thus it is understood that the patient population is larger than that targeted with cannabidiol which can per se be considered a clinically relevant advantage.

Major contribution to patient care considerations

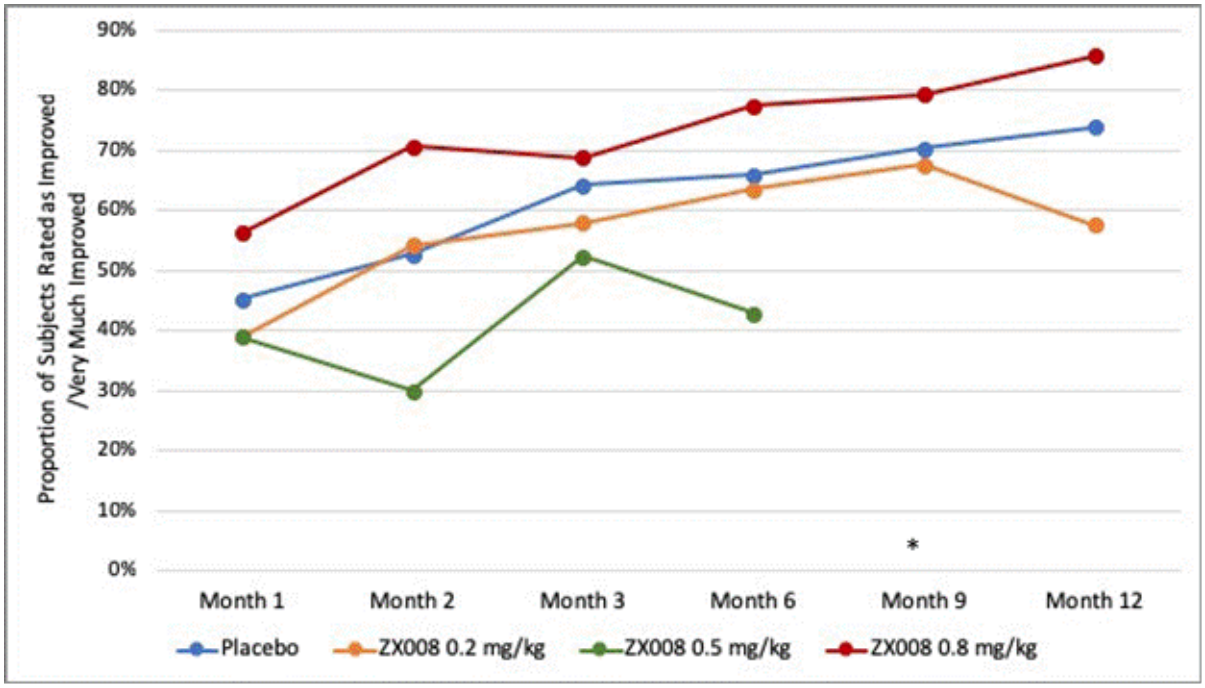
Non-seizure outcomes were measured to evaluate if the effect of fenfluramine on convulsive seizures would translate to improvement on comorbidities associated with Dravet syndrome. These other measures of efficacy, such as CGI-I, BRIEF, QOLCE, PedsQL, showed improvement, underscoring the enhanced efficacy when fenfluramine was added to the subject's standard of care. The CGI-I provides a holistic assessment of the overall clinical status of the subject, and more subjects taking fenfluramine compared to placebo were rated by their parent/caregiver and their study doctor as very much or much improved, ratings that represent clinically meaningful changes. Results from the CGI-I were supported by directional improvements on the QOLCE in which subjects randomized to fenfluramine 0.7 mg/kg/day were improved on several subscales during double-blind period, including physical restrictions, attention/concentration, language, other cognition, social interactions, and social activities, as well as the Overall Quality of Life score.

During the double-blind studies, further evidence for an overall impact on quality of life was supported with the PedsQL and PedsQL Family Impact Module, where directional improvements were seen for subjects randomized to ZX008 on several scales. These results provide further evidence for an effect of fenfluramine on overall quality of life of the patient and the family.

With increasing time in open label extension (OLE), the number of subjects rated with clinically meaningful improvement increased for both parent/caregiver and investigator ratings. The sustained clinically meaningful reductions in convulsive seizures also translated to improvements in quality of life during OLE, where statistically significant improvements from the core study. Baseline were observed

on the General Health and Quality of Life Items, and the overall QOL score of the QOLCE, and directional improvements were observed on the PedsQL, and the PedsQL Family Impact Module.

Figure 4. Parent/Caregiver Ratings of Much Improved/Very Much Improved During OLE – LTE-DB Population



*n=3 at Month 9 for ZX008 0.4 mg/kg/day; 2/3 rated as minimally improved, 1/3 rated as no change

Evaluating trends of rescue medication use during the OLE shows that all subjects, regardless of original randomized dose group during the double-blind period, had numerically fewer days of rescue medication use during OLE compared to their pre-double-blind baseline and Month 1 of the OLE.

Major contribution to patient care is supported by some data which offers evidence as can be seen in the CGI data. The QoL data supports this however the COMP noted that the claim of an improvement in patient/parent well-being was not fully substantiated.

During the assessment of Fintepla, on 7 September and 12 September 2020, the CHMP received from the Dravet syndrome European Federation a correspondence and survey analyses regarding the benefit of fenfluramine from the perspective of DS patients. The correspondences and data highlighted the importance of increased treatment options for the DS patients and supported the Marketing Authorisation of Fintepla.

This data was also presented to the COMP which noted those interventions.

The sponsor has provided sufficient data and argumentation to support significant benefit for the purpose of maintaining the orphan designation for fenfluramine in the treatment of Dravet syndrome.

4. COMP position adopted on 21 October 2020

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of Dravet syndrome (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be 0.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to psychomotor and cognitive impairment and the occurrence of pharmaco-resistant convulsive and non-convulsive seizure starting early in life and continuing in adults and can be life threatening for a major risk of occurrence of sudden unexpected death due to epilepsy, compared both to the general population and other epilepsies in general;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Fintepla may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical data which shows a significant reduction in seizures when Fintepla is used alone or in combination with stiripentol and/or (sodium) valproate and clobazam, which, although not formally authorised for this condition, are recommended and may therefore be considered as a satisfactory method of treatment in Dravet syndrome patients as defined in the granted therapeutic indication. Fintepla also targets a broader patient population than cannabidiol.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Fintepla, fenfluramine hydrochloride for treatment of Dravet syndrome (EU/3/13/1219) is not removed from the Community Register of Orphan Medicinal Products.