24 January 2023
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EMADOC-1700519818-996966
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for type II variation application

Fintepla (fenfluramine hydrochloride)
Treatment of Lennox-Gastaut syndrome
EU/3/17/1836

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	
Designated active substance(s)	Fenfluramine hydrochloride
Other name(s)	--
International Non-Proprietary Name	Fenfluramine hydrochloride
Tradename	Fintepla
Orphan condition	Treatment of Lennox-Gastaut 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	Zogenix International Limited
COMP opinion	19 January 2017
EC decision	27 February 2017
EC registration number	EU/3/17/1836
Post-designation procedural history	
Transfer of sponsorship	Transfer from Zogenix International Limited to Zogenix GmbH – EC decision of 9 Nov 2018 Transfer from Zogenix GmbH to Zogenix ROI Limited – EC decision of 20 May 2019
Type II variation procedural history	
Rapporteur / Co-rapporteur	Thalia Marie Estrup Blicher / Johann Lodewijk Hillege
Applicant	Zogenix ROI Limited
Application submission	17 December 2021
Procedure start	23 January 2022
Procedure number	EMEA/H/C/003933/II/0012
Invented name	Fintepla
Proposed therapeutic indication	Extension of indication to include treatment of seizures associated with Lennox-Gastaut syndrome as an add-on therapy to other anti-epileptic 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 ema.europa.eu/en/medicines/human/EPAR/fintepla
CHMP opinion	15 December 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Joao Rocha
Sponsor's report submission	25/01/2022
COMP discussion	8-10 November 2022 and 6-8 December 2022

COMP opinion (adoption via written procedure)	16 December 2022

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2013 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 observations in treated patients who responded with reduced number of epileptic seizures;
- the condition is chronically debilitating due to epileptic seizures, psychomotor delay and behavioural symptoms such as hyperactivity, aggressiveness and autistic tendencies;
- the condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made;

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

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 will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations in patients resistant to previous treatments, who responded with reduced numbers of seizures after addition of fenfluramine to their therapeutic regimen. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing fenfluramine hydrochloride as an orphan medicinal product for the orphan indication: treatment of Lennox-Gastaut syndrome.

3. Review of criteria for orphan designation at the time of type II variation

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

Lennox-Gastaut syndrome (LGS) is a rare epilepsy disorder characterised by the presence of multiple seizure types, slow (≤2.5 Hz) spike-waves EEG abnormalities with frequent abnormal background activity when awake and a particular EEG pattern of fast rhythms (10–20 Hz) during sleep. The seizure types vary among patients: the most invalidating are sudden drop attacks (myoclonic, atonic or myoclono-atonic) but can also include focal, tonic, tonic-clonic, atonic, atypical absence, and myoclonic

seizures. In the past, LGS was subdivided into cryptogenic and symptomatic types by the presence or absence of an underlying cause. The new classification (Scheffer et al, 2017) has introduced many other aetiological categories and this distinction is no more valid. The aetiology of LGS is extensive and diverse, varying from congenital to acquired causes. Among these, frequent causes include malformations of cortical development, tuberous sclerosis, hereditary metabolic diseases, sequelae of hypoxic–ischemic encephalopathy and of other perinatal injuries, lesions secondary to inflammatory brain diseases such as encephalitis, meningitis and congenital infections as toxoplasmosis and cytomegalovirus. About one-third of LGS cases occur without antecedent history or evidence of brain pathology and these patients tend to have a better prognosis than those with brain lesions. The sponsor acknowledged the release of a revised classification of seizure and epilepsy types in March 2017, which did not alter the classification of epilepsy syndromes (Scheffer et al, 2017).

The International League Against Epilepsy (ILAE) Task Force most recently classified the disorder as an epileptic encephalopathy. In the ILAE developed diagnostic criteria, LGS is characterized by the presence of (1) multiple types of drug-resistant seizures with onset prior to 18 years (one of which must include tonic); (2) cognitive and often behavioural impairments, which may not be present at seizure onset; and (3) diffuse slow spike-and-wave and generalized paroxysmal fast activity on EEG (Specchio et al.,Epilepsia. 2022 Jun;63(6):1398-1442).

Altogether, Lennox-Gastaut Syndrome (LGS) remains a recognised electroclinical epilepsy syndrome.

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

Intention to diagnose, prevent or treat

The medical plausibility been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

LGS is a severe epilepsy syndrome with onset in childhood characterised by drug-resistant seizures and other symptoms such as impaired intellectual functioning or information processing, along with developmental delays (20-60% of patients) and behavioural disturbances being very common and often profound. In LGS seizures tend to persist on a daily or weekly basis in over two-thirds of the patients, with generalised tonic seizures being most resistant to therapy the mortality rate associated with LGS ranges from 3% to 7% within 10 years of the diagnosis, due to poorly controlled seizures and injuries from falls (Crumrine, J Child Neurol. 2002, 70-75, Cherian 2020.). For patients with refractory epilepsy, such as LGS, the lifetime risk of sudden unexpected death in epilepsy (SUDEP)exists. The condition is therefore both chronically debilitating and life-threatening.

Number of people affected or at risk

The sponsor provides an overview of the publications which were used for prevalence estimates at the time of the submission of the original orphan designation in 2016 and highlights two new articles which have appeared since:

- Chin et al. (2021) reported a minimum total prevalence of 0.58 per 10,000 people in the UK in 2017, although it was noted by the authors that this was lower than reported elsewhere and may

be an underestimate. To be noted, UK data is supportive but less relevant since the UK is no longer part of the EU.

- A retrospective study reported by Strzelczyk (2020), utilised healthcare insurance claims data from 2007-2016 to assess the prevalence of LGS in Germany, estimated a point prevalence between 0.65 -3.92 per 10,000. Notably, the database did not include the diagnosis LGS by physicians, but it was post-hoc designation, based on certain criteria. The estimate of 0.65 was based on a narrow definition (≥1 ICD-10 diagnosis of epilepsy / status epilepticus before their 6th birthday and ≥ 1 claim of Rufinamide /felbamate, medications that are specifically used for LGS), and the high estimate was based on a broad definition (without any age restriction for the first seizure). As the median age of diagnosis of LGS is 3 years, this is likely an overestimate.

Table 1. Publications used to establish prevalence in Lennox-Gastaut

Prevalence Source	**Region**	**Years**	**Age Range (years)**	**Point prevalence (per 10,000)**
Sidenvall, 1996	Sweden	1985	0 - 16	2.0
Eriksson and Koivikko, 1997	Finland	1992	0 - 15	0.7
Waaler, 2000	Norway	1994-1996	6 - 12	2.1
Olafsson and Hauser, 1999	Iceland	1993	All ages	0.9
Beilmann, 1999	Estonia	1995-1997	1 month – 19	1.0
Syvertsen, 2015	Norway	1999-2014	All ages	0.3
Strzelczyk 2020	Germany	2016	All ages	0.65 a 3.92 b

a = strict criterion: ≥1 ICD-10 diagnosis of epilepsy / status epilepticus before their 6th birthday and ≥ 1 claim of Rufinamide /felbamate), b = broad criterion, without any age restriction for the first seizure

Lennox-Gastaut syndrome (LGS) accounts for approximately 2-5% of all childhood epilepsies, but it is responsible for roughly 10% of epilepsy cases occurring before the age of five years. The incidence of LGS is estimated at 0.1 to 0.28 per 100,000 population. There are no reports of a founder effect. (Lennox Gastaut Syndrome Chaitanya Amrutkar; Rosario M. Riel-Romero. Lennox Gastaut Syndrome - StatPearls - NCBI Bookshelf (nih.gov))

The sponsor notes that Strzelczyk (2020) reported a mortality rate of 2.88% in Germany, which is comparable with other published data for patients with LGS, which report mortality between 3% and 7% (van Rijckevorsel 2008, Cherian 2020).

Cherian (2020) reported a mortality rate of 3% after a follow-up period of 8.5 years to 7% after a mean follow-up period of 9.7 years. This indicates a survival rate at 9.7 years of 93%. Therefore, the median survival of patients with LGS is in excess of 9.7 years and it is appropriate to use point prevalence to estimate the number of people affected.

In conclusion, based on the totality of the prevalence data described above, the point prevalence of LGS in the EU is still likely to be no higher than 2 people per 10,000 total population, based on the latest published population of the EU (EU27, Norway, Iceland and Lichtenstein)

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

The Sponsor provided an overview of products that can be used in the treatment of LGS.

Table 2. Anti-seizure medications that can be used in the treatment of LGS

Category	**Treatment**
AEDs authorised in the EU specifically for LGS (evidence base: randomised, placebo-controlled trials)	Cannabidiol (Epidyolex) Rufinamide (Inovelon) Lamotrigine Topiramate Felbamate
AEDs authorised specifically in the EU for LGS (evidence base: clinical experience)	*Clonazepam* *Nitrazepam*
Authorised AEDs used off-label for LGS (evidence base: randomised, placebo-controlled trials)	Clobazam
Authorised AEDs used off-label for LGS (evidence base: clinical experience)	Valproate *Levetiracetam* *Zonisamide* *Perampanel* *Lacosamide* *Brivaracetam*

In *italics*, products that were not considered satisfactory by the Sponsor

Five products are currently authorised in the EU specifically for the treatment of LGS, namely cannabidiol, rufinamide, lamotrigine, topiramate, and felbamate.

Table 3. Summary of Approved Treatment Options for Lennox-Gastaut Syndrome

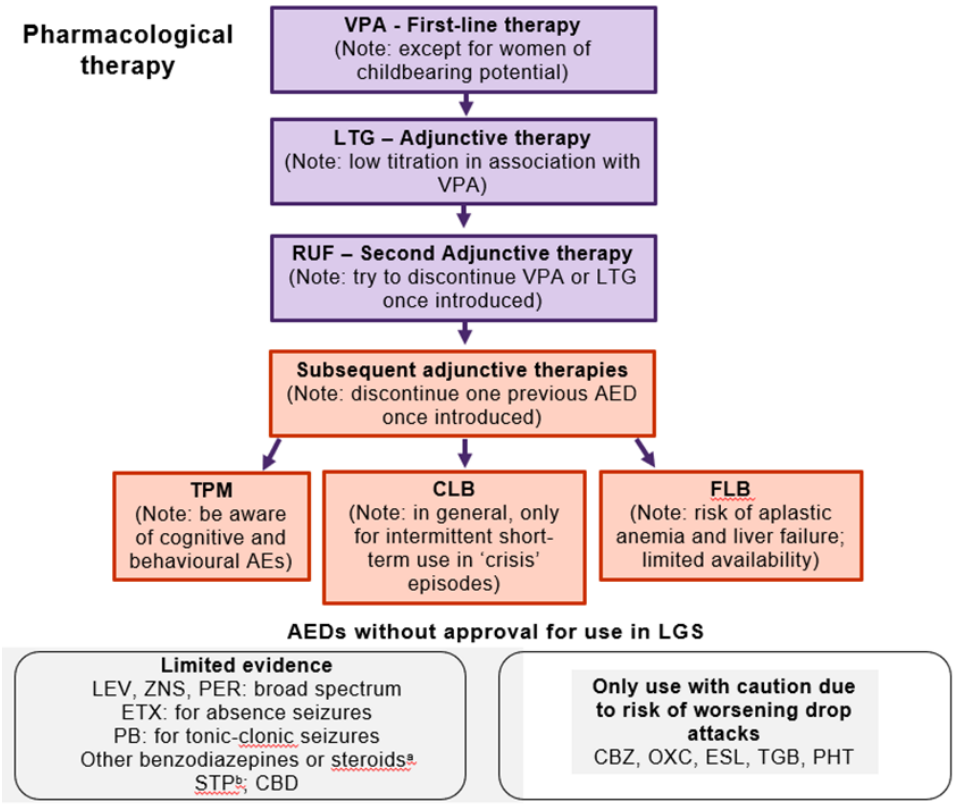
Treatment	Authorisation in the EU	Therapeutic Indications
Rufinamide (RUF)	Approved via the centralised procedure on 16/01/2007	Adjunctive therapy in the treatment of seizures associated with Lennox Gastaut syndrome in patients 1 years of age and older
Lamotrigine (LTG)	First approval August 1997	Seizures associated with Lennox-Gastaut syndrome
Topiramate (TPM)	Nationally approved; Date of first authorisation in UK: 18/07/1995	Adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalisation or primary generalised tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome
Felbamate (FLB)	Nationally approved: Date of first authorisation in France: 16/05/1994	Adjunctive therapy in the treatment of partial and generalised seizures associated with Lennox-Gastaut syndrome in children. For use only in those patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anaemia and/or liver failure is deemed acceptable
Cannabidiol (CBD)	Epidyolex received a marketing authorisation valid throughout the EU on 19 September 2019	Epidyolex is indicated for use as adjunctive therapy of seizures associated with Lennox Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older.

Fenfluramine (Fintepla) indication: *Fintepla is indicated for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older* overlaps with lamotrigine, rufinamide, topiramate, felbamate and cannabidiol. The significant benefit demonstrated over FLB, indicated as a last-line resort for patients who are refractory to all other LGS AEDs due to the risk of serious side effects, shows that Fintepla also offers an effective treatment option, with a unique mechanism of action, for patients that have exhausted all other lines of therapy ..

There are currently no agreed pan-EU treatment guidelines for LGS, instead most guidelines are country-specific (Chin 2021). In 2017, prior to the EU approval of Epidyolex, the lack of guidance on the management of LGS motivated a panel of 5 leading European epileptologists to propose an algorithm for the treatment of newly diagnosed patients with LGS (Cross, 2017) (Figure 1).

Consistent with country-specific guidelines (Chin 2021), the algorithm recommends first line treatment with VPA (valproid acid), with LTG (lamotrigine) added as the first adjunctive therapy for a newly diagnosed de novo LGS patient. If VPA plus LTG does not provide adequate seizure control, RUF (Rufinamide) should be added as adjunctive therapy. When adding a new adjunctive therapy, the algorithm recommends attempting to discontinue one of the two previous ASMs, since there is no evidence for the effectiveness of more than two ASMs in combination, and the use of multiple ASMs unnecessarily raises the risk of side effects and/or drug-drug interactions (DDIs). If the addition of RUF does not achieve adequate seizure control, the choice of the next adjunctive therapy should be discussed with the patient's support team but may typically include TPM (Topiramate), CLB (Clobazam)or FLB (Felbamate). Non-pharmacological treatment approaches (e.g., ketogenic diet, resective surgery, vagus nerve stimulation, callosotomy) may also be considered alongside the use of ASMs (Cross, 2017).

Figure 1. Treatment algorithm for a newly diagnosed patient with LGS; pharmacological interventions only (adapted from Cross 2017)



AE, adverse event; ASM, antiseizure medication; CBD, cannabidiol; CBZ, carbamazepine; CLB, clobazam; ESL, eslicarbazepine acetate; ETX, ethosuximide; FLB, felbamate; LEV, levetiracetam; LGS, Lennox–Gastaut syndrome; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PHT, phenytoin; RUF, rufinamide; STP, stiripentol; TGB, tiagabine; TPM, topiramate; VPA, sodium valproate; ZNS, zonisamide. a Not in combination and only for intermittent, short-term treatment of "crisis" episodes; b In combination with VPA and/or CLB

Over time, this algorithm has evolved from the initial hypothesis and in 2021 two European experts proposed a revised treatment algorithm with the approval of Epidyolex (Cannabidiol, CBD) (used in

conjunction with CLB) added in as a subsequent adjunctive therapy, and CLB not just being used for intermittent short-term use but having an important role as a first-line adjunctive therapy option. FLB is generally recommended as a last-line resort for patients with highly refractory epilepsy due to the risk of serious side effects (Strzelczyk 2021). This latest algorithm is consistent with the latest Orphanet summary on LGS, published in April 2021, and reviewed by 3 European experts from EpiCARE reference centres (Orphanet, 2021) which recommends valproic acid as a first line treatment and confirms that the use of FLB is limited by adverse side effects.

The Sponsor considered the following products as satisfactory, which should be taken into account for the significant benefit assessment:

- authorised treatments with the LGS indication: LTG (lamotrigine), RUF (rufinamide), TPM (topiramate), CBD (cannabidiol), FLB (felbamate)
- not-specifically indicated products such as clobazam (CLB), and valproic acid (VPA)

Clonazepam and nitrazepam were not considered satisfactory by the Sponsor, although they are authorised and indicated for the treatment of LGS in a few EU Member States via national procedures. This is because the level of evidence is limited to empiric experience or small, uncontrolled trials. These products should be avoided for prolonged therapy because of tolerance, somnolence, and risk of withdrawal seizures (van Rijckevorsel 2008).

Some other AEDs, including levetiracetam (LEV), zonisamide (ZNS) and perampanel (PER), not approved for use in LGS, may be useful in treating multiple seizure types due to their broad-spectrum efficacy profile. However, there is a paucity of evidence regarding use of LEV, ZNS and PER in LGS and robust evidence from randomised, controlled trials (RCTs) in LGS is lacking (Cross 2017, Strzelczyk 2021, Montouris 2020). Similarly, lacosamide and brivaracetam are considered potentially valuable in the treatment of LGS but lack systematic trial data to support efficacy (Mastrangelo 2017, Montouris 2020). Carbamazepine, oxcarbazepine, eslicarbazepine, tigabine, phenytoin, vigabatrin, pregabalin and gabapentin are infrequently used, with some of them having negative recommendations for the treatment of LGS (Chin 2021b), and there may be potential for aggravating certain seizure types with these AEDs (Asadi-Pooya, 2018, Cross 2017, Strzelczyk 2021, Montouris 2020).

The COMP considered that felbamate is not a satisfactory method, as its use is restricted to last line treatment, given its high risk (agranulocytosis and fatal liver injury) and Fintepla can be used in a broader population.

Neither is Epydiolex considered a satisfactory method for the entirety of the target population, as this must be used in combination with clobazam according to the wording of the indication, while Fintepla can be used in a broader target population. Not all patients tolerate clobazam.

It is agreed with the Sponsor that VPA, RUF, LTG, TPM and CLB are satisfactory methods, that need to taken into account of the assessment of Significant Benefit.

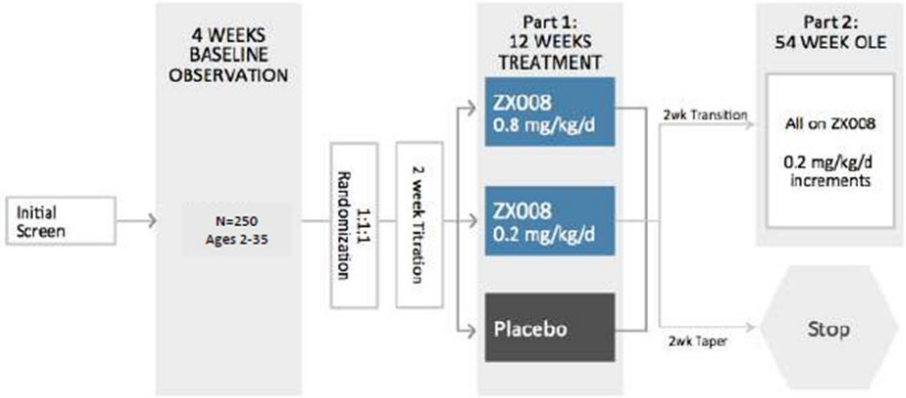
Significant benefit

The sponsor claimed that Fintepla can offer a clinically relevant advantage through an improved reduction in seizure frequency (Drop in seizure Frequency=DSF) in patients who are inadequately controlled on other approved LGS treatments. This is based on data from the pivotal randomised Phase III study ZX008-1601.

The Fintepla LGS clinical development program includes the following Phase 3 studies conducted in children and adults (2 to 35 years) with LGS:

- Study ZX008-1601, which is comprised of 2 parts analysed separately:
  - Study ZX008-1601 Part 1, Phase 3, randomized, double-blind, placebo-controlled, efficacy and safety evaluation in subjects with LGS. This arm was 12 weeks duration and included two dose levels of fenfluramine.
  - Study ZX008-1601 Part 2, a Phase 3, open-label, long-term extension in subjects with LGS from Part 1
- Study ZX008-1900, which is a Phase 3, open-label, long-term extension study in subjects with epileptic encephalopathies, including LGS and Dravet syndrome.

Figure 2. 1601 Study Schema



Subjects with LGS in this development program were highly treatment-refractory, with seizures that were difficult to control. The enrolled subjects had failed a median of 7 anti-epileptic drugs (AEDs) (range: 1 to 20) and were stabilized on standard of care AEDs at the time of enrolment (see Table 15 and 4 below for details). The vast majority used 2-4 ASMs as background therapy during the trial (95.4%). However, most were still experiencing high seizure burden during Baseline, ranging from a median of 53 to 85 drop seizures per 28 days across the treatment groups despite being treated with other ASMs and antiepileptic therapies.

The change from Baseline in the frequency of seizures leading to drops (i.e, drop seizure frequency per 28 days [DSF]) after the 12-week maintenance treatment for fenfluramine hydrochloride 0.8 mg/kg/day compared with placebo was the primary efficacy endpoint for Study 1601 Part 1.

The change from Baseline in the frequency of seizures leading to drops (i.e, drop seizure frequency per 28 days [DSF])

The most common concomitant medications and therapies (≥15% of subjects overall) included the following: VNS (82 subjects [31.2%]). Note that no subjects received concomitant STP.

The patients included in the pivotal trial had failed a median of 7 prior lines of therapy which include four of the five currently authorised in Europe namely: rufinamide, lamotrigine, topiramate, and felbamate. There is data at the time of recruitment to the study indicating that 27% patients had already been treated with cannabidiol and failed the treatment. These discontinuations as well those for other AEDs used are summarised in Table 6. Table 7 presents the concomitant AEDs used during the trial.

Table 4. Number of Concomitant Antiepileptic Drugs Taken per Subject (Safety Population)

	Placebo (N=87) n (%)	ZX008 0.2 mg/kg/day (N=89) n (%)	ZX008 0.8 mg/kg/day (N=87) n (%)	All Subjects (N=263) n (%)
Subjects with ≥1 concomitant AED	86 (98.9)	89 (100)	86 (98.9)	261 (99. 2)
Number of concomitant AEDs				
1	12 (13.8)	11 (12.4)	4 (4.6)	27 (10.3)
2	19 (21.8)	24 (27.0)	24 (27.6)	67 (25.5)
3	34 (39.1)	30 (33.7)	32 (36.8)	96 (36.5)
4	21 (24.1)	23 (25.8)	26 (29.9)	70 (26.6)
5	0	1 (1.1)	0	1 (0.4)

Table 5. Prior Antiepileptic Drugs Taken by ≥25% of All Subjects (Safety Population)

Drug Class ATC Level 2 Preferred Term	Placebo (N=87)	ZX008 0.2 mg/kg/day (N=89)	ZX008 0.8 mg/kg/day (N=87)	All Subjects (N=263)
Subjects with ≥1 prior AED	87 (100%)	88 (98.9%)	86 (98.9)	261 (99.2)
Cannabidiol	26 (29.9)	22 (24.7)	24 (27.6)	72 (27.4)
Clobazam	36 (41.4)	47 (52.8)	41 (47.1)	124 (47.1)
Clonazepam	33 (37.9)	25 (28.1)	28 (32.2)	86 (32.7)
Ethosuximide	21 (24.1)	27 (30.3)	24 (27.6)	72 (27.4)
Lacosamide	24 (27.6)	21 (23.6)	32 (36.8)	77 (29.3)
Lamotrigine	31 (35.6)	39 (43.8)	42 (48.3)	112 (42.6)
Levetiracetam	58 (66.7)	63 (70.8)	56 (64.4)	177 (67.3)
Perampanel	14 (16.1)	22 (24.7)	30 (34.5)	66 (25.1)
Rufinamide	35 (40.2)	38 (42.7)	44 (50.6)	117 (44.5)
Topiramate	45 (51.7)	46 (51.7)	60 (69.0)	151 (57.4)
Valproate[a]	45 (51.7)	54 (60.7)	52 (59.8)	151 (57.4)
Vigabatrin	34 (39.1)	33 (37.1)	36 (41.4)	103 (39.2)
Zonisamide	33 (37.9)	28 (31.5)	33 (37.9)	94 (35.7)

Table 6. Reason given in Case Report Form for discontinuation of a prior AED in Study 1601

Prior Failed AED	Number of Patients				
	Inadequate seizure control	Unsuitable tolerability	Both	Unknown	Other
CBD (all forms)	62/86 (72%)	7/86 (8%)	9/86 (10%)	5/86 (6%)	5/86 (6%)
CLB	116/148 (78%)	17/148 (11%)	9/148 (6%)	3/148 (2%)	6/148 (4%)
FLB	41/54 (76%)	5/54 (9%)	6/54 (11%)	2/54 (4%)	2/54 (4%)
LTG	96/131 (73%)	19/131 (15%)	8/131 (6%)	8/131 (6%)	4/131 (3%)
RUF	97/135 (72%)	14/135 (10%)	14/135 (10%)	7/135 (5%)	4/135 (3%)
TPM	125/180 (69%)	25/180 (14%)	21/180 (12%)	8/180 (4%)	6/180 (3%)
VPA (all forms)	127/187 (68%)	29/187 (16%)	11/187 (6%)	15/187 (8%)	11/187 (6%)

Table 7. Concomitant Antiepileptic treatments

Drug Class ATC Level 2 Preferred Term	Placebo (N=87)	ZX008 0.2 mg/kg/day (N=89)	ZX008 0.8 mg/kg/day (N=87)	All Subjects (N=263)
Subjects with ≥1 concomitant AED [a]	86 (98.9)	89 (100)	86 (98.9)	261 (99.2)
Acetazolamide	0	3 (3.4)	1 (1.1)	4 (1.5)
Brivaracetam	3 (3.4)	4 (4.5)	5 (5.7)	12 (4.6)
Carbamazepine	5 (5.7)	3 (3.4)	2 (2.3)	10 (3.8)
Clobazam	38 (43.7)	36 (40.4)	45 (51.7)	119 (45.2)
Clonazepam	9 (10.3)	12 (13.5)	8 (9.2)	29 (11.0)
Diazepam	1 (1.1)	1 (1.1)	2 (2.3)	4 (1.5)
Eslicarbazepine	0	1 (1.1)	0	1 (0.4)
Eslicarbazepine acetate	1 (1.1)	1 (1.1)	2 (2.3)	4 (1.5)
Ethosuximide	3 (3.4)	3 (3.4)	8 (9.2)	14 (5.3)
Felbamate	9 (10.3)	14 (15.7)	13 (14.9)	36 (13.7)
Gabapentin	1 (1.1)	2 (2.2)	0	3 (1.1)
Lacosamide	7 (8.0)	10 (11.2)	9 (10.3)	26 (9.9)
Lamotrigine	29 (33.3)	30 (33.7)	29 (33.3)	88 (33.5)
Levetiracetam	20 (23.0)	17 (19.1)	23 (26.4)	60 (22.8)
Lorazepam	2 (2.3)	0	1 (1.1)	3 (1.1)
Oxcarbazepine	2 (2.3)	5 (5.6)	3 (3.4)	10 (3.8)
Perampanel	7 (8.0)	5 (5.6)	6 (6.9)	18 (6.8)
Phenobarbital	5 (5.7)	2 (2.2)	4 (4.6)	11 (4.2)
Phenytoin	2 (2.3)	1 (1.1)	3 (3.4)	6 (2.3)
Phenytoin sodium	1 (1.1)	0	0	1 (0.4)
Rufinamide	18 (20.7)	17 (19.1)	18 (20.7)	53 (20.2)
Sultiame	0	2 (2.2)	2 (2.3)	4 (1.5)
Tiagabine hydrochloride	0	1 (1.1)	0	1 (0.4)
Topiramate	12 (13.8)	15 (16.9)	8 (9.2)	35 (13.3)
Valproate	49 (56.3)	52 (58.4)	46 (52.9)	147 (55.9)
Valproate magnesium	0	1 (1.1)	0	1 (0.4)
Valproate semisodium	17 (19.5)	14 (15.7)	10 (11.5)	41 (15.6)
Valproate sodium	8 (9.2)	3 (3.4)	11 (12.6)	22 (8.4)
Valproate sodium/valproic acid	7 (8.0)	4 (4.5)	6 (6.9)	17 (6.5)
Valproic acid	17 (19.5)	30 (33.7)	19 (21.8)	66 (25.1)
Vigabatrin	5 (5.7)	3 (3.4)	7 (8.0)	15 (5.7)
Zonisamide	7 (8.0)	6 (6.7)	7 (8.0)	20 (7.6)

It appears that most patients were on three AEDs with valproate+clobazam being used in combination with either lamotrigine, rufinamide or topiramate or felbamate. Although clobazam is not specifically indicated for the condition it is used in a large proportion of patients (81 patients) in combination with fenfluramine.

Fenfluramine is used in combination with lamotrigine as concomitant treatment in the trial (59 patients), followed by rufinamide (35 patients), felbamate (27 patients) and topiramate (24 patients). This would reflect a use of concomitant treatment in line with the recommendations made in the treatment algorithm (Cross 2017) where valproate is used first line in 98 patients. From the recommendations the sponsor cites that Cannabidiol is to be used in third line with clobazam.

In this highly treatment-refractory patient population, a statistically significant, clinically meaningful, and durable reduction in DSF compared with placebo was demonstrated when fenfluramine hydrochloride 0.8 mg/kg/day (Fintepla 0.7 mg/kg/day) was added to a subject's stable antiepileptic treatments (p = 0.0013). For the 0.8 mg/kg/day dose, the percentage change from baseline of DSF

was 26.5%, and the number of DSF from baseline as compared to placebo was 19 (95% Confidence Interval -31.02, -8.74).

This was also supported by key secondary endpoints of 50% responder rates of DSF and Percentage of Subjects with Improvement on the CGI-I (Clinical Global Impression by Investigator) Rating Scale.

Fintepla was also effective in reducing generalized tonic-clonic seizures (GTCs), with a reduction of 46-58% from Baseline in the fenfluramine treatment groups. This type of seizures is associated with SUDEP (sudden unexpected death in epilepsy). The treatment effects observed in Part 1 of the study were maintained in the open-label extension period of 12 months.

Post-hoc subgroup analyses of patients' refractory/intolerant to prior treatment with either CBD (n=27), FLB (n=30), LTG (n=68), RUF (n=61), TPM (n=68) and VPA (n=91) and CLB (n=80) all showed a statistically significant improvement versus placebo regarding seizure reduction (see figure 4 below). The clinical relevance of these findings was also supported by changes in CGI-I in these subgroups.

The sponsor envisioned that fenfluramine will be used as a later-line adjunctive therapy,, similarly to cannabidiol. The data from Study ZX008-1601 would indicate that the target patient population is indeed a late line.

In conclusion, Fintepla has shown a treatment effect as add-on therapy in patients who were extensively pre-treated and refractory/intolerant to multiple antiseizure medications.

4. COMP position adopted on 16 December 2022

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 Lennox-Gastaut syndrome (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 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 early-onset epileptic seizures, including tonic seizures, psychomotor delay and behavioural symptoms such as hyperactivity, aggressiveness and autistic behaviour;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Fintepla, the assumption that Fintepla may be of potential significant benefit to those affected by the orphan condition as defined in the granted therapeutic indication still holds. Clinical data has been submitted showing that Fintepla showed a treatment effect as add-on therapy in patients who were extensively pre-treated and refractory/intolerant to multiple antiseizure medications.

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 Lennox-Gastaut syndrome (EU/3/17/1836) is not removed from the Community Register of Orphan Medicinal Products.