

15 December 2022 EMA/CHMP/45762/2023 Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

# **Fintepla**

International non-proprietary name: fenfluramine

Procedure No. EMEA/H/C/003933/II/0012

# **Note**

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



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# List of abbreviations

AE adverse event
AED antiepileptic drug

API active pharmaceutical ingredient AR aortic (valvular) regurgitation

AS atonic seizure

AUC $_{0-24}$  area under the plasma concentration-time curve from time zero to 24 hours AUC $_{0-t}$  area under the plasma concentration-time curve from time 0 to the last measured

concentration

 $AUC_{0-inf}$  area under the plasma concentration-time curve from time 0 extrapolated to infinity

BID twice daily
BMI body mass index

BRIEF Behavior Rating Inventory of Executive Function

CBD Cannabidiol

CDC Centers for Disease Control and Prevention
CGI-I Clinical Global Impression – Improvement (scale)
CGI-S Clinical Global Impression – Severity (scale)

CI confidence interval

CL/F estimated geometric mean apparent clearance from plasma after oral administration

CLB Clobazam

C<sub>max</sub> peak plasma drug concentration

CMC chemistry, manufacturing, and controls C<sub>min</sub> minimum plasma drug concentration

COVID-19 coronavirus disease 2019

CSR clinical study report
CYP cytochrome P450
DCR Data Change Request
DDI drug-drug interaction

DSF drop seizure frequency per 28 days

ECG Electrocardiogram
ECHO Echocardiogram
eDiary electronic diary

EEG Electroencephalogram

eGFR estimated glomerular filtration rate

EMA European Medicines Agency

EOS End of Study

ESC Epilepsy Study Consortium

EU European Union

FDA Food and Drug Administration

GCP Good Clinical Practice
GI Gastrointestinal

GTC generalized tonic-clonic seizure

HADS Hospital Anxiety and Depression Scale

HCl Hydrochloride

HDPE high density polyethylene

HL Hodges-Lehmann

HR heart rate

ICPD Institute for Clinical Pharmacodynamics (US)
ISS-SAF Integrated Summary of Safety-Safety (Population)

KD ketogenic diet

LGS Lennox-Gastaut syndrome

mITT Modified Intent-to-Treat (Population)

MS myoclonic seizure

NDA New Drug Application (US)
OLE Open-Label Extension

PAH pulmonary arterial hypertension

PBPK physiologically based pharmacokinetic(s)

PK pharmacokinetic(s)

PopPK population pharmacokinetic(s)

QD once daily QoL quality of life

QOLCE Quality of Life in Childhood Epilepsy
QTc QT interval corrected for heart rate

QTcF heart rate-corrected QT interval calculated using Fridericia's formula

REMS Risk Evaluation and Mitigation Strategy

SAE serious adverse event SAP Statistical Analysis Plan SD standard deviation

SGTC secondarily generalized tonic-clonic seizure

SN Serial Number

sNDA supplemental New Drug Application (US)

SOC System Organ Class

STP Stiripentol

SUDEP sudden unexpected death in epilepsy

T+M combined Titration and Maintenance Periods

TA tonic/atonic seizure

TEE transesophageal echocardiogram

TS tonic seizure

TEAE treatment-emergent adverse event

UK United Kingdom
US United States

VHD valvular heart disease VNS vagus nerve stimulation

VPA Valproate

ZX008 fenfluramine hydrochloride oral solution

# 1. Background information on the procedure

# 1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Zogenix ROI Limited submitted to the European Medicines Agency on 17 December 2021 an application for a variation.

The following variation was requested:

Variation requested			Annexes affected
C.I.6.a	C.I.6.a C.I.6.a - Change(s) to therapeutic indication(s) - Addition		I and IIIB
	of a new therapeutic indication or modification of an approved one		

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. As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.3 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

# Information relating to orphan designation

Fintepla, was designated as an orphan medicinal product EU/3/17/1836 on 27 February 2017. Fintepla was designated as an orphan medicinal product in the following indication:

Treatment of Lennox-Gastaut syndrome

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Fintepla as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found here <u>Fintepla II-0012 - OD review summary report.docx (sharepoint.com)</u>.

# Information on paediatric requirements

Not applicable

# Information relating to orphan market exclusivity

# **Similarity**

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

# Protocol assistance

The MAH received Protocol Assistance from the CHMP on 14 December 2017 (EMEA/H/SA/2770/2/2017/PA/SME/II). The Protocol Assistance pertained to clinical aspects of the

dossier.

# 1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	17 December 2021
Start of procedure:	23 January 2022
CHMP Rapporteur Assessment Report	25 March 2022
PRAC Rapporteur Assessment Report	28 March 2022
PRAC members comments	31 March 2022
Updated PRAC Rapporteur Assessment Report	1 April 2022
PRAC Outcome	7 April 2022
CHMP members comments	13 April 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	13 April 2022
Request for supplementary information (RSI)	22 April 2022
CHMP Rapporteur Assessment Report	16 September 2022
PRAC Rapporteur Assessment Report	20 September 2022
PRAC members comments	21 September 2022
PRAC Outcome	29 September 2022
CHMP members comments	3 October 2022
Updated CHMP Rapporteur Assessment Report	7 October 2022
Request for supplementary information (RSI)	13 October 2022
CHMP Rapporteur Assessment Report	30 November 2022
CHMP members comments	7 December 2022
Updated CHMP Rapporteur Assessment Report	9 December 2022
Opinion	15 December 2022

# 2. Scientific discussion

#### 2.1. Introduction

## 2.1.1. Problem statement

#### Disease or condition

Lennox-Gastaut syndrome (LGS) is a rare, severe, paediatric-onset developmental and complex epileptic encephalopathy.

# State the claimed the 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.

# **Epidemiology**

Onset of LGS occurs most commonly before the age of 11 years, with a peak between 3 and 5 years of age (Arzimanoglou 2009; Hancock 2013). Patients with LGS account for 5% to 10% of children with seizures (Panayiotopoulos 2005).

# Clinical presentation, diagnosis and stage/prognosis

Lennox-Gastaut syndrome is a rare, paediatric-onset condition in which the epileptic activity itself may directly contribute additional cognitive and behavioural impairments over those expected from the underlying aetiology alone and that suppression of epileptic activity might minimize this additional impairment" (Scheffer 2017).

The diagnosis of LGS includes clinical signs combined with typical EEG features associated with LGS. The clinical presentation of LGS is heterogeneous. However, LGS is always characterized by a triad of symptoms: multiple seizure types, slow spike-and-wave EEG, and abnormal cognitive development. Tonic seizures (TS), atypical absence seizures, and "drop attacks," ie, seizures that result in sudden falls, are notable in this disorder and often result in serious injury. Patients with LGS also can experience milder seizures that do not result in falls, as well as many other seizure types, such as generalized tonic-clonic seizures (GTC), myoclonic seizures (MS), focal seizures, and nonconvulsive status epilepticus (Camfield 2011). Other comorbidities associated with LGS include speech, cognitive, neurobehavioral, and motor abnormalities, which are believed to be, at least in part, due to sequelae of repeated brain insult from poorly treated seizures. In addition to concerns about social integration and care, LGS is one of the most complex epileptic disorders to manage, both for the general or paediatric neurologist and for specialists in epilepsy (Arzimanoglou 2009).

Nearly all patients with LGS have treatment-resistant, lifelong epilepsy. Prognosis for LGS is very poor: approximately 5% of patients die, 80% to 90% continue having seizures into adulthood, and most patients have cognitive and behavioural problems (Panayiotopoulos 2005). In the setting of rare complete seizure freedom, behavioural and psychiatric disorders are nearly always present, language is frequently affected, and mental and psychiatric disorders tend to worsen with time (Hancock 2013).

Children and adults with LGS have an enormous disruptive impact on their families, and efforts to improve the quality of life for these patients are complex due to the severe lifelong limitations associated with drug-resistant epilepsy, intellectual disability, and other comorbidities (Camfield 2014).

# Management

Due to the heterogeneity in aetiology, pathophysiology, and type of seizures experienced by patients with LGS, many different treatments are currently tried (Verotti 2018), often with little success and a high rate of drug resistance. Due to the refractory nature of seizures in LGS, seizure freedom is an unlikely goal of treatment; a main objective is to improve the patient's QoL via a compromise between seizure control of the most severe seizures, avoidance of additional comorbidities, and tolerability (Cross 2017).

Currently, 7 antiepileptic drug (AED) products are approved for the treatment of LGS in the US: felbamate, topiramate, lamotrigine, rufinamide, clonazepam, clobazam (CLB), and cannabidiol (CBD). Nine AEDs are approved for the treatment of LGS in Europe: felbamate, topiramate, lamotrigine, rufinamide, clonazepam, CLB, valproate (VPA), nitrazepam, and CBD. Two AEDs are approved in Japan for the treatment of LGS: lamotrigine and rufinamide. Other pharmacologic (benzodiazepines, zonisamide) and nonpharmacologic treatments (ketogenic diet [KD], vagus nerve stimulation [VNS], surgery) also are prescribed based on clinical experience.

The use of carbamazepine, oxcarbazepine, eslicarbazepine, tiagabine, and phenytoin in LGS is not recommended due to the potential risk of aggravation of drop attacks with a myoclonic component (Cross 2017).

Initial treatment for LGS is usually monotherapy with 1 of the currently approved AEDs. If this is not successful, which is the most common case, a second agent is usually added, although some physicians will prescribe the second drug as monotherapy (Wheless 2007; Arzimanoglou 2009). The treatment of LGS frequently requires a combination of 2 or more AEDs with an individualized regimen; seizure control is suboptimal in most patients in the clinical population. The recommendation is to attempt to use drugs that have different mechanisms of action and the least amount of interaction with one another. After lack of response to 2 or more AEDs, nonpharmacological treatments such as KD, VNS, or surgery may be considered. A treatment that has been shown to be effective in certain common seizure types cannot be assumed to be effective in patients with LGS to treat that seizure type.

#### 2.1.2. About the product

Fintepla is an oral solution of fenfluramine hydrochloride (HCl), under development for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older. Fenfluramine is a racemic compound containing dexfenfluramine and levofenfluramine. The stereochemical configuration of the d or (+) isomer (also known as dexfenfluramine or dextrofenfluramine) corresponds to the S enantiomer, and the configuration of the l or (-) isomer (levofenfluramine) corresponds to the R enantiomer. The active pharmaceutical ingredient (API) in the ZX008 drug product is fenfluramine HCl.

Fenfluramine oral solution is approved in the United States (US), European Union (EU), and United Kingdom (UK) as a treatment for seizures associated with Dravet syndrome in patients 2 years of age and older. The approved dosage of fenfluramine is expressed in labelling as the free base (active moiety). Of note, during development of ZX008 (fenfluramine HCl), doses of ZX008 were expressed as the HCl salt in study reports and are provided as such in this submission.

The doses of fenfluramine HCl that have been evaluated in clinical studies and that are recommended for use are between 0.2 to 0.8 mg/kg/day administered orally as equal doses twice daily (BID), with a maximum total daily dose of 30 mg, regardless of weight.

# 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

As a result of the phase II POC study of fenfluramine for the treatment of seizures associated with LGS, a global clinical development program was launched to evaluate ZX008 for this use. US Food and Drug Administration (FDA) and European Medicines Agency (EMA) scientific advice regarding the design of the development program was sought.

The ZX008 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 comprises 2 parts analysed separately:
  - Study ZX008-1601 Part 1, a Phase 3, multicentre, randomized, double-blind, placebocontrolled, efficacy and safety evaluation in subjects with LGS
  - 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.

The MAH received Protocol Assistance from the CHMP on 14 December 2017 (EMEA/H/SA/2770/2/2017/PA/SME/II). The Protocol Assistance pertained to clinical aspects of the dossier

# 2.1.4. General comments on compliance with GCP

All studies were conducted with standard operating procedures that comply with the principles of Good Clinical Practice (GCP). All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects participating in these studies. Where required, regulatory approval was obtained from the relevant health authority.

# 2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

# 2.2.1. Ecotoxicity/environmental risk assessment

#### Phase I: Estimation of exposure

#### Screening for Persistence, Bioaccumulation and Toxicity (PBT)

A PBT screening was performed and assessed as part of the initial MAA, which did not indicate that fenfluramine hydrochloride presents a persistence, bioaccumulation or toxicity (PBT) risk.

Calculation of the Predicted Environmental Concentration (PEC) value for Fenfluramine Base

The PEC<sub>SURFACEWATER</sub> for fenfluramine base in EU has been calculated in the initial MAA ERA for Dravet syndrome to be  $0.00066 \, \mu g/L$ .

The following PEC<sub>SURFACEWATER</sub> calculation of fenfluramine base in EU is for Lennox-Gastaut syndrome:

In Phase I, the PEC calculation is restricted to the aquatic compartment. The calculation of the PEC in surface water ( $PEC_{SURFACEWATER}$ ) assumes that the predicted amount used per year is evenly distributed over the year and throughout the geographic area, the sewage system is the main route of entry, there is no biodegradation or retention of the drug substance in the sewage treatment plant (STP) and metabolism in the patient is not taken into account. Thus, the  $PEC_{SURFACEWATER}$  is only calculated for the drug substance.

An  $F_{pen}$  default value of 0.01 (1%) is proposed in the guideline. However, because data as confirmed by the Committee for Orphan Medicinal Products (COMP) are available to estimate a more accurate refined  $F_{pen}$  value in the EU for Lennox-Gastaut syndrome, these data, together with EU prevalence data from a recent literature search (conducted August 2021), have been utilised in the calculation of the PEC<sub>SURFACEWATER</sub>. Table 1 gives the value that has been used in the refined market penetration ( $F_{pen}$ ) calculation.

Table 1 Input value and source for calculation of refined market penetration factor (Fpen)

Input value	Abbreviation	Value
Prevalence for EU region: <2% in 10000 people with Lennox-Gastaut Syndrome	$P_{region} = refined F_{pen}$	0.0002

Since the indication is not linked to a specific time of the year, the predicted amount of fenfluramine hydrochloride used per year is assumed to be evenly distributed over the year and throughout the geographic area (EU Member States where drug product is to be used).

The worst-case (highest) calculation of the PEC<sub>SURFACEWATER</sub> in the EU is shown below with the values supporting the calculation provided in Table 2.

$$\mathsf{PEC}_{\mathsf{SURFACEWATER}} = \frac{{}_{DOSE_{AI}} \times {}_{Refined} \, {}_{Fpen}}{{}_{WASTEW_{inhab}} \times {}_{DILUTION}}$$

 $PEC_{SURFACEWATER} (mg/L) = \frac{26.4 \times 0.0002}{200 \times 10}$ 

PEC<sub>SURFACEWATER</sub> ( $\mu$ g/L) for fenfluramine base in EU = 0.00264  $\mu$ g/L

Table 2 Values supporting the worst-case (highest) calculation of PEC<sub>SURFACEWATER</sub> value in the EU for Fenfluramine base from use in treatment of Lennox-Gastaut Syndrome

Input Value	Abbreviation	Value	Unit
Maximum daily dose of fenfluramine hydrochloride with treatment daily	DOSE <sub>AI</sub>	30	mg/inhab/day
Maximum daily dose of fenfluramine base, with treatment daily	DOSE <sub>AI</sub>	26.4	mg/inhab/day

Refined market penetration factor for EU	Refined F <sub>pen</sub>	0.0002	-
Amount of waste water per inhabitant per day	$WASTEW_{inhab}$	200	L [default value]
Dilution from STP	DILUTION	10	[default value

The combined PEC<sub>SURFACEWATER</sub> for fenfluramine base in EU from its use in Dravet syndrome and Lennox-Gastaut syndrome is  $0.0033 \, \mu g/L$ .

A Phase II environmental fate and effects analysis is not applicable in view of the low environmental exposure to fenfluramine base, with the PEC<sub>SURFACEWATER</sub> (0.0033  $\mu$ g/L) > 3 times less than the action limit of 0.01  $\mu$ g/L.

# 2.2.2. Discussion on non-clinical aspects

The MAH has submitted an updated ERA as a part of a new indication application for use in Lennox-Gastaut syndrome (patients 2 years of age and older). The update consisted of a recalculation of  $PEC_{SURFACEWATER}$  including both indications (Dravet and Lennox-Gastaut syndrome), and led to a value below the action limit of  $0.01~\mu g/L$ .

# 2.2.3. Conclusion on the non-clinical aspects

Based on the available data, the new LGS indication does not lead to a significant increase in environmental exposure. The use of fenfluramine hydrochloride is not expected to pose a risk to the environment.

The CHMP agrees that the available non-clinical data are acceptable to support the new proposed LGS indication.

#### 2.3. Clinical aspects

#### 2.3.1. Introduction

#### **GCP**

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Table 3 ZX008 Clinical Studies Supporting the Marketing Application for Lennox-Gastaut Syndrome

Study Number	Design	Study Drug, Dosing Regimen	Duration of Treatment	Number of Subjects	Subject Population	Study Status
Clinical Studi	es in Lennox-Gastaut Sy	yndrome	•		•	•
ZX008-1601 Part 1 Cohort A	Phase 3, randomized, double- blind, placebo controlled, efficacy and safety study	Placebo, ZX008 0.2 mg/kg/day, ZX008 0.8 mg/kg/day <sup>a</sup> Administered orally BID in equal doses	16 weeks (2-week titration; 12-week maintenance; 2-week transition/tap er)	263 randomized (87 placebo, 89 ZX008 0.2 mg/kg/day, 87 ZX008 0.8 mg/kg/day)	Subjects 2-35 years of age with LGS with seizures that resulted in drops not completely controlled by current antiepileptic treatments	Complete
ZX008-1601 Part 2 Cohort A	Phase 3, open-label, long-term extension study	ZX008 0.2 mg/kg/day for 1 month, then flexibly dosed to maximum 0.8 mg/kg/day <sup>a</sup> Administered orally BID in equal doses	54 weeks	247	Subjects who satisfactorily completed Study 1601 Part 1 Cohort A	Ongoing
ZX008-1900	Phase 3, open-label, long-term extension study	ZX008 flexibly dosed to maximum 0.8 mg/kg/day <sup>a</sup> Administered orally BID in equal doses	up to 36 months	131 <sup>b</sup>	Subjects who successfully completed Study 1601 Part 2 <sup>b</sup>	Ongoing

BID = twice daily; CBD = cannabidiol; CLB = clobazam; DDI = drug-drug interaction; LGS = Lennox-Gastaut syndrome; QD = once daily; STP = stiripentol; THC = tetrahydrocannabinol; TQT = thorough QT; VPA = valproate

#### 2.3.2. Methods

#### **Bioanalysis**

A validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was used for quantitation of fenfluramine and norfenfluramine at KCAS, USA. The method utilized liquid/liquid extraction with derivatization of fenfluramine and norfenfluramine. Fenfluramine-d5 and norfenfluramine-d6 were used as internal standards. The method had a linear range of quantitation of 0.25 to 100 ng/mL for both analytes.

#### **Population PK analyses**

A previous Pop PK model was developed to describe the PK of fenfluramine and active metabolite norfenfluramine in patients with Dravet syndrome. A refined population PK model for fenfluramine/norfenfluramine identical in structure to the previous model with the lone exception being the estimation of the IIV in VcFEN, was used to fit the LGS data from Study 1601.

Study 1601 is a two-part study of ZX008 in children and adults with LGS. Part 1 included two cohorts: Cohort A included randomized subjects from North America, Europe, and Australia while Cohort B included randomized subjects from Japan. Data for the Pop PK model in LGS was obtained from Part 1, Cohort A. Part 2 is an ongoing long-term extension study.

A total of 250 subjects and 1920 plasma concentration records were available from the subjects enrolled in Cohort A of Study 1601, Part 1. Eighty-six subjects received standard-of-care treatment plus placebo and were excluded from the analysis dataset. A total of 4 fenfluramine concentrations were above the upper limit of quantification of the assay; none were BLQ. The final population PK dataset contained 164 subjects and 1260 concentration records (628 fenfluramine concentrations and 632 norfenfluramine concentrations).

The only covariates of significance in the previous Pop PK model were body weight and concomitant administration of stiripentol which were both included in the LGS model a priori. Concomitant medications received by subjects included in the population PK analysis were phenobarbital, VPA, CLB,

a Maximum dose of 30 mg/day

Study 1900 is conducted in subjects with epileptic encephalopathy, including Dravet syndrome and LGS. Only subjects with LGS who enter from Study 1601 Part 2 are included in the interim analysis

carbamazepine and various PPIs. Age, BMI, CLcr, sex, race, concomitant medications and indication (healthy subjects, DS, LGS) were evaluated as potential covariates.

Covariate analysis utilising forward selection and backward elimination resulted in the identification of one statistically significant relationship between CLNFEN and CLcr. The MAH considered the impact of renal function on CLNFEN to be modest in the 1601 Part 1 A dataset and unlikely of clinical relevance. The parameter estimates of the final model are shown in Table 4 with sampling-importance-resampling statistics (n=1000).

Table 4 Summary statistics of resampled population PK parametered in comparison to the model parameter estimates from the final population pharmacokinetic

	Final model			Resample	statistics (I	N=1000)
Parameter -	Final estimate	%SEE	Mean	Median	%CV <sup>a</sup>	90% CI
CL <sub>FEN</sub> (L/hr/70kg)	37.3	6.68	37.8	37.8	5.46	[34.5,41.1]
Vc <sub>FEN</sub> (L/70kg)	498	24.1	506	500	17.7	[376,660]
CLd <sub>FEN</sub> (L/hr/70kg)	118	21.3	121	119	18.8	[89.3,162]
Vp <sub>FEN</sub> (L/70kg)	500	_	500	500		_
CL <sub>NFEN</sub> (L/hr/70kg)	57.6	4.4	57.7	57.7	3.61	[54.3,61.3]
Vcnfen (L/70kg)	970	66.8	975	984	25.5	[596,1370]
CLd <sub>NFEN</sub> (L/hr/70kg)	150	274	175	152	63.9	[42.4,394]
Vpnfen (L/70kg)	500	_	500	500	_	_
Ka <sub>FEN</sub> (hr-1)	0.522	11.1	0.526	0.523	9.69	[0.444,0.611]
Ka <sub>NFEN</sub> (hr-1)	1.03	68	1.11	1.09	30	[0.624,1.67]
STP-CL <sub>FEN</sub>	0.458	_	0.458	0.458	_	_
CLcr-CL <sub>NFEN</sub>	0.581	27.3	0.599	0.596	22.6	[0.377,0.818]
ω <sup>2</sup> CL, FEN	0.230 (48.0 %CV)b	14.2	0.243	0.241	11.7	[0.201, 0.292]
$\omega^2$ Vc, FEN	0.813 (90.2 %CV)b	32.3	0.84	0.821	21.3	[0.577,1.17]
ω <sup>2</sup> CL, NFEN	0.232 (48.1 %CV)b	11.7	0.236	0.234	11.2	[0.198,0.282]
Covariance (ω <sup>2</sup> CL, FEN:ω <sup>2</sup> CL, NFEN)	0.115 (r <sup>2</sup> = 0.246)	21.7	0.122	0.12	17.4	[0.089,0.159]
σ <sup>2</sup> FEN, Proportional	0.0178 (13.3 %CV)°	7.90	0.0182	0.0182	10.3	[0.0153,0.0214]
σ <sup>2</sup> FEN, Additive	0.253 (0.503 ng/mL) <sup>c</sup>	67.4	0.262	0.241	67.2	[0.0243,0.598]
σ <sup>2</sup> NFEN, Proportional	0.00467 (6.83 %CV)c	4.64	0.0048	0.00481	8.77	[0.00409,0.0055]
σ <sup>2</sup> NFEN, Additive	0.0875 (0.296 ng/mL) <sup>c</sup>	42.9	0.0913	0.088	34	[0.0441,0.149]

Note: Abbreviations are provided in the Abbreviation Listing.

Based upon internal qualification diagnostics, the fit of the refined model was robust with minimal bias overall and the refined model was deemed qualified for estimation of exposure in the subjects with LGS from ZX008-1601 by the MAH.

#### **Estimation of exposure metrics**

Exposure metrics for Study 1601 were derived using individual predicted steady-state concentration-time profiles for each patient generated from the PK parameter estimates obtained from the final LGS PK model. The predicted mean AUC, Cmax and Cmin values with descriptive statistics are presented in Table 5.

a. Equivalent to the %SEE from the final model.

Shrinkage estimates were 1.93, 30.0, and 0.108% for IIV in CLFEN, VCFEN, and CLNFEN, respectively.

Shrinkage estimates were 18.1 and 15.6% for RV in FEN and NFEN concentrations, respectively.

Table 5 Summary [geometric mean(%CV)] of kye FEN, NFEN, and sum (FEN+NFEN) PK parameters, derived from the fit of the population PK model, stratified by dose and weight category for the higher dose group

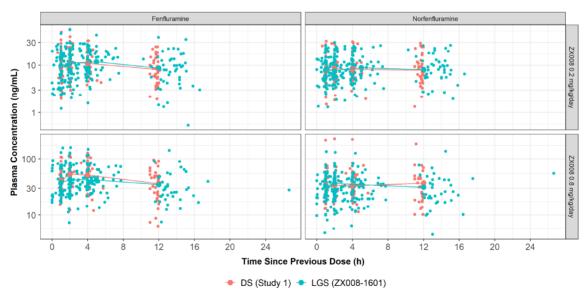
Parameter <sup>a</sup>	ZX008 0.2 mg/kg/day (n = 84)	ZX008 0.8 mg/kg/day Weight <37.5 kg (n = 38)	ZX008 0.8 mg/kg/day Weight ≥37.5 kg (n = 42) <sup>b</sup>
FEN			
AUC <sub>0-24</sub> (ng•h/mL)	246 (63.0)	1010 (56.2)	865 (47.7)
C <sub>max</sub> (ng/mL)	11.9 (56.1)	48.5 (49.7)	41.7 (43.7)
C <sub>min</sub> (ng/mL)	8.19 (75.6)	34.5 (66.5)	29.5 (54.8)
NFEN			
AUC <sub>0-24</sub> (ng•h/mL)	209 (56.3)	807 (50.6)	561 (53.8)
C <sub>max</sub> (ng/mL)	9.04 (53.4)	35.0 (47.8)	24.3 (51.9)
C <sub>min</sub> (ng/mL)	8.23 (61.3)	31.7 (55.6)	22.1 (57.1)
Sum (FEN+NFEN)			
AUC <sub>0-24</sub> (ng•h/mL)	468 (54.4)	1870 (48.2)	1470 (43.5)
C <sub>max</sub> (ng/mL)	21.4 (49.9)	85.7 (43.6)	67.6 (40.4)
C <sub>min</sub> (ng/mL)	17.0 (62.1)	68.7 (55.4)	53.3 (48.5)

Note: Abbreviations are provided in the Abbreviation Listing.

b. Subjects limited to daily doses of 30 mg/day (as per protocol)

Subjects with DS enrolled in Study 1 were chosen as the comparator group as they received the same doses as were administered in Study 1601 and no concomitant stiripentol. The geometric mean exposures were lower and the estimated geometric mean apparent oral systemic clearance (CL/F) was higher in subjects with LGS. While it is not possible to rule out that the observed differences geometric mean AUC0-24, Cmax, and CL/F for fenfluramine are due to the disease state (i.e., Dravet versus LGS), this is considered unlikely given that both disorders are paediatric epileptic encephalopathies that share clinical features and therapies. The differences are likely due to the relatively small sample sizes in each group.

Figure 1 Semi-log scattterplots of plasma concentrations verus time, stratified by treatment arm and study population and presented by analyte



Note: Abbreviations are provided in the Abbreviation Listing.

Subjects aged ≥18 yr and those receiving the maximum daily dose of 30 mg are excluded from the plots above. Squares with white fill and lines represent median concentrations over time

This hypothesis is supported by the comparison of the observed concentrations and distributions of fenfluramine exposures in subjects with LGS and DS (Figure 9) and by the comparability in the norfenfluramine exposures between the two populations, which exhibited nearly identical distributions and geometric means within  $\pm 10\%$ .

a. AUC<sub>0-24</sub>, C<sub>max</sub>, and C<sub>min</sub> calculated at steady-state.

Steady-state exposure metrics (AUC0-24, Cmax, Cmin) for fenfluramine and norfenfluramine derived in pediatric ( $\leq$  18 years of age) and adult (>18 years of age) subjects with Lennox-Gastaut syndrome from the fit of the population pharmacokinetic model to data from Study 1601 were shown and did not indicate relevant differences in exposure between the two age groups. Slightly higher mean exposures were observed for  $\leq$ 18 year at the 0.8 mg/kg dose compared to adults.

#### **Exposure-response analyses**

A total of 251 subjects were available for the exposure-response analyses for efficacy; 164 received active fenfluramine of which 84 and 80 subjects received the 0.2 or 0.8 mg/kg/day dose, respectively, while 87 received placebo. The majority of subjects were ≤18 years of age (77%). With few exceptions, all subjects included in the E-R analyses for efficacy were also available for the safety E-R analyses.

The population PK model was used for the estimation of fenfluramine and norfenfluramine exposure in LGS subjects from Study 1601. The individual estimates of exposure were used in the E-R analyses. The primary PK exposures were steady-state Cmax, Cmin and AUC0-24.

The objectives of the E-R analyses were to explore the relationship between fenfluramine and norfenfluramine, and the sum of fenfluramine and norfenfluramine exposure and efficacy (as measured by percent change in drop seizure frequency) and several endpoints of potential interest from a safety perspective (blood glucose concentration, platelet count, weight loss, evidence of mitral valve regurgitation on echocardiogram, blood pressure, and heart rate) in subjects with LGS.

The primary component of the E-R analyses was the construction of univariable statistical models, which were applied to quantify potential relationships among exposure variables and outcome. For continuous endpoints, linear, log-linear, or non-linear regression techniques were used, as indicated by the exploratory graphical analyses. If necessary Emax models were attempted to relate PK exposure to response. For categorical outcomes, analysis of variance (ANOVA) or logistic regression models were applied. After the univariable screening process, multivariable models were constructed to identify all potential predictors of variability.

Table 6 List of covariates to be evaluated as potential predictors during multivariable PK-PD model development

Analysis	Dependent Variable(s)	Covariates
Efficacy	Primary: Drop seizure frequency Secondary: (Typical) drop seizure frequency	Baseline seizure frequency Time since first seizure (yr) Indication [LGS vs. Dravet syndrome (DS)] <sup>a</sup> Age (yr) Sex Body weight (kg) Body mass index (BMI) (kg/m²) Type and number of concomitant AEDs Number of seizure types
Blood Glucose	Maximum percent change in blood glucose during T+M	Baseline blood glucose Age (yr) Sex Baseline body weight (kg) Baseline BMI (kg/m²) Concomitant medications
Platelet Count	Maximum percent change in platelet count during T+M	Baseline platelet count Age Sex Baseline body weight (kg) Baseline BMI (kg/m²) Concomitant medications
Weight loss	Maximum percent change in body weight during T+M	Baseline body weight Baseline BMI Indication (LGS vs. DS) <sup>a</sup> Age Sex Concomitant medications <sup>b</sup> Ketogenic diet (Yes/No)

Table 7 List of covariates to be evaluated as potential predictors during multivariable PK-PD model development

Analysis	Dependent Variable(s)	Covariates
Mitral regurgitation	Occurrence of trace regurgitation on ECHO	Indication (LGS vs. DS) <sup>a</sup> Age Sex Body weight (kg) BMI (kg/m <sup>2</sup> )
Cardiovascular Endpoints	Maximum percent change in blood pressure or heart rate during T+M  Presence or absence of at least 2 post-baseline occurrences of an absolute change from baseline >20 mm Hg for systolic blood pressure and >10 mm Hg for diastolic blood pressure	Baseline blood pressure or heart rate Age Sex Baseline body weight (kg) Baseline BMI (kg/m²) Concomitant medications

#### E-R for efficacy

While linear and log-linear regression models to relate exposure to efficacy were attempted, none of the exposure metrics were significantly related to the primary efficacy endpoint, percent change in drop seizure frequency. Separate sigmoidal Emax models were fitted to the data using percent change from baseline in drop seizure frequency during T+M as the dependent variable and each of the nine PK

Note: Abbreviations are provided in the Abbreviation Listing.
a. Given that the analyses were confined to the data from Study 1601, indication was not evaluated as a

potential covariate in the exposure-response analyses.

b. Note that concomitant medications for body weight were evaluated as a general category (i.e., any drugs that might affect body weight) and change in body weight was specifically evaluated with concomitant topiramate use due to the known effects of topiramate on anorexia and weight loss.

exposure measures as independent variables. The resultant parameter values and goodness-of-fit (using AIC) are provided in Table 8.

Table 8 Results of  $E_{max}$  models relating percent change from baseline in drop seizure frequency during T+M to various PK exposure measures at steady-state

Variable	Analyte	E <sub>0</sub>	EC <sub>50</sub>	E <sub>max</sub> <sup>a</sup>	Hill	p-value <sup>b</sup>	AIC	r <sup>2</sup>
Stoody State ALIC	Fenfluramine	6.06	129	-26.8	15	0.00452	2850.7	0.0337
Steady-State AUC <sub>0-24</sub>	Norfenfluramine	7.62	68.2	-27.3	15	0.00377	2850.7	0.0338
(ng•h/mL)	Sum (FEN + NFEN)	6.78	259	-27.8	15	0.00305	2850.1	0.0361
Stoody State C	Fenfluramine	4.41	2.00	-39.2	0.100	0.993	2853.7	0.022
Steady-State C <sub>max</sub>	Norfenfluramine	6.7	4.53	-27.9	3.69	0.00903	2851	0.0326
(ng/mL)	Sum (FEN + NFEN)	6.83	11.6	-27.5	15	0.00348	2850.3	0.0352
Stoody State C	Fenfluramine	4.36	2.00	-39.7	0.100	0.989	2853.8	0.0219
Steady-State C <sub>min</sub>	Norfenfluramine	6.63	3.6	-27.8	3.13	0.0103	2851	0.0324
(ng/mL)	Sum (FEN + NFEN)	6.67	9.31	-27.8	15	0.00284	2850	0.0363

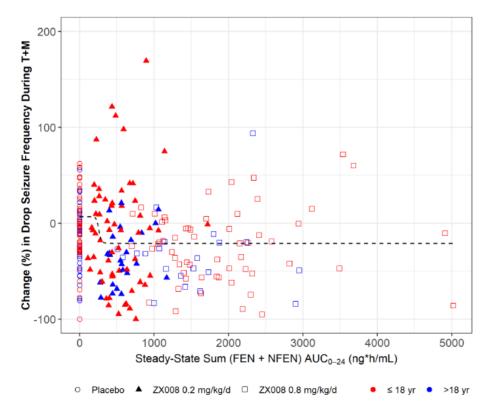
Note: Abbreviations are provided in the Abbreviation Listing.

Note: Parameter units are as follows: E<sub>0</sub> and E<sub>max</sub> are in units of the dependent variable (percent change in seizure frequency per 28 days during T+M), EC<sub>50</sub> is in the units of the independent variable (ng•h /mL or ng/mL), and the Hill coefficient does not have units. AIC is a measure of goodness of fit (lower values indicate better fit). The r<sup>2</sup> is the correlation between observed and predicted percent change in convulsive seizure frequency per 28 days during T+M.

- a. All Emax values are negative indicating that the effect of FEN, NFEN and Sum (FEN + NFEN) is to reduce convulsive seizure frequency.
- P-values are shown for the E<sub>max</sub> parameter. Values below 0.05 indicate that the effect of the exposure parameter is statistically significant.

The EC50 values were all below the geometric mean exposure of fenfluramine and norfenfluramine for the 0.2 mg/kg/day dose group, indicating that the population mean maximal effect was observed in most subjects randomized to the lower dose.

Figure 2 Scatterplot of percent change from baseline in drop seizure frequency during T+M versus steady-state sum (FEN+NFEN)  $AUC_{0-24}$  with fit of  $E_{max}$  model overlaid



Note: Abbreviations are provided in the Abbreviation Listing. Points are observations, solid line and shaded region represent the mean (90% confidence interval) predicted values from the E<sub>max</sub> model. Data for three subjects who received placebo (percent changes of +245, +400, and +557%), one subject receiving 0.2 mg/kg/day (+250%), and one subject receiving 0.8 mg/kg/day (+402%) are excluded from the above plot for visualization purposes.

#### E-R for safety

#### Blood glucose

Based upon the scatterplots, there does not appear to be a relationship between change in blood glucose concentration over time and PK exposure. None of the PK exposure measures are predictive of maximum change in blood glucose concentration during T+M as all of the p values were  $\geq 0.10$  (Table 9).

Table 9 Results of linear regression models relating maximum percent change in blood glucose concentration during T+M various PK exposure measures

Variable	Analyte	Intercept	Coefficient	Adjusted r <sup>2</sup>	p-value	AIC
		Exposure a	s Linear Variable	s		
04	Fenfluramine	5.11	0.00126	-0.00313	0.64	2302.6
Steady-State AUC <sub>0-24</sub>	Norfenfluramine	3.76	0.00582	0.00635	0.11	2300.3
(ng•h/mL)	Sum (FEN + NFEN)	4.43	0.00161	1.39E-06	0.32	2301.8
04	Fenfluramine	4.92	0.036	-0.00252	0.54	2302.5
Steady-State C <sub>max</sub>	Norfenfluramine	3.72	0.139	0.00657	0.10	2300.2
(ng/mL)	Sum (FEN + NFEN)	4.32	0.039	0.000561	0.29	2301.7
Steady-State C <sub>min</sub> (ng/mL)	Fenfluramine	5.33	0.0218	-0.00365	0.76	2302.8
	Norfenfluramine	3.83	0.14	0.006	0.11	2300.3
	Sum (FEN + NFEN)	4.57	0.038	-0.00066	0.36	2302
	E	xposure as Log	<sub>2</sub> -transformed Va	riables		
01 1 01 1 1110	Fenfluramine	3.84	0.336	0.000566	0.29	2301.7
Steady-State AUC <sub>0-24</sub>	Norfenfluramine	3.46	0.423	0.00272	0.20	2301.2
(ng•h/mL)	Sum (FEN + NFEN)	3.65	0.336	0.00133	0.25	2301.5
0	Fenfluramine	4.18	0.573	0.000494	0.29	2301.7
Steady-State C <sub>max</sub>	Norfenfluramine	3.72	0.861	0.00443	0.15	2300.7
(ng/mL)	Sum (FEN + NFEN)	3.87	0.577	0.00175	0.23	2301.4
011-01-1-0	Fenfluramine	4.36	0.578	2.45E-05	0.32	2301.8
Steady-State Cmin	Norfenfluramine	3.76	0.878	0.00448	0.15	2300.7
(ng/mL)	Sum (FEN + NFEN)	3.93	0.599	0.0017	0.23	2301.4

Note: Abbreviations are provided in the Abbreviation Listing.

#### Platelet count

Based upon the scatterplots, there does not appear to be a relationship between change in platelet count over time and PK exposure. None of the PK exposure measures are predictive of maximum change in platelet count during T+M as all of the p values are  $\geq 0.14$  (Table 10).

Table 10 Results of linear regression models relating maximum percent change in body weight during T+M to various PK exposure measures

Variable	Analyte	Intercept	Coefficient	Adjusted r <sup>2</sup>	p-value	AIC
		Exposure a	s Linear Variable	s		
04	Fenfluramine	-3.17	-0.00086	-0.00358	0.74	2281.7
Steady-State AUC <sub>0-24</sub>	Norfenfluramine	-1.87	-0.00514	0.00471	0.14	2279.6
(ng•h/mL)	Sum (FEN + NFEN)	-2.54	-0.00133	-0.00108	0.39	2281.1
Ct Ct-t- C	Fenfluramine	-3.11	-0.0215	-0.00346	0.71	2281.7
Steady-State C <sub>max</sub>	Norfenfluramine	-1.87	-0.12	0.00454	0.15	2279.7
(ng/mL)	Sum (FEN + NFEN)	-2.51	-0.0302	-0.00108	0.39	2281.1
Steady-State C <sub>min</sub> (ng/mL)	Fenfluramine	-3.25	-0.019	-0.00372	0.78	2281.7
	Norfenfluramine	-1.9	-0.127	0.00482	0.14	2279.6
	Sum (FEN + NFEN)	-2.57	-0.0343	-0.00106	0.39	2281.1
	E	cposure as Log	<sub>2</sub> -transformed Va	riables		
01	Fenfluramine	-2.18	-0.252	-0.00122	0.41	2281.1
Steady-State AUC <sub>0-24</sub>	Norfenfluramine	-2.13	-0.272	-0.00101	0.39	2281.1
(ng•h/mL)	Sum (FEN + NFEN)	-2.18	-0.227	-0.00138	0.42	2281.2
01 1 01 1 0	Fenfluramine	-2.3	-0.484	-0.00055	0.35	2281
Steady-State Cmax	Norfenfluramine	-2.22	-0.589	0.000259	0.30	2280.8
(ng/mL)	Sum (FEN + NFEN)	-2.24	-0.419	-0.00074	0.37	2281
0	Fenfluramine	-2.16	-0.617	0.000953	0.27	2280.6
Steady-State Cmin	Norfenfluramine	-2.14	-0.651	0.00103	0.26	2280.6
(ng/mL)	Sum (FEN + NFEN)	-2.13	-0.488	9.54E-05	0.31	2280.8

Note: Abbreviations are provided in the Abbreviation Listing.

#### **Body weight**

Univariable analyses were conducted using linear regression to assess the relationship between maximum percent change in body weight during T+M to the nine PK exposures. The resultant parameter values and goodness-of-fit (using AIC) are provided in Table 11. Overall, PK exposure is predictive of decreases in body weight in both linear and log2-linear regression models, regardless of which PK exposure is evaluated.

Table 11 Results of linear regression models relating maximum percent change in body weight during T+M to various PK exposure measures

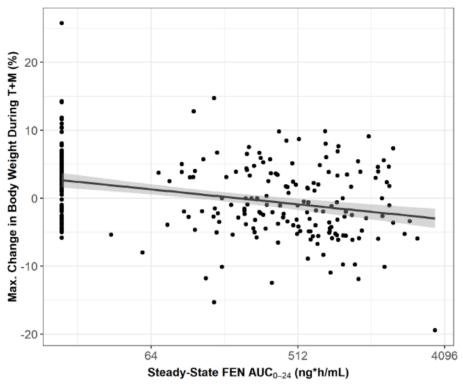
Variable	Analyte	Intercept	Coefficient	Adjusted r <sup>2</sup>	p-value	AIC
		Exposure a	s Linear Variable	s		
Ctoody Ctoto ALIC-	Fenfluramine	1.62	-0.00280	0.0754	<0.0001	1568.5
Steady-State AUC <sub>0-24</sub>	Norfenfluramine	1.41	-0.00311	0.0484	0.00026	1575.7
(ng•h/mL)	Sum (FEN + NFEN)	1.65	-0.00164	0.0700	< 0.0001	1569.9
Standy State C	Fenfluramine	1.68	-0.0626	0.0769	<0.0001	1568.1
Steady-State C <sub>max</sub>	Norfenfluramine	1.43	-0.0735	0.0485	0.00026	1575.7
(ng/mL)	Sum (FEN + NFEN)	1.69	-0.0374	0.0710	< 0.0001	1569.7
Steady-State C <sub>min</sub> (ng/mL)	Fenfluramine	1.54	-0.0730	0.0724	<0.0001	1569.3
	Norfenfluramine	1.39	-0.0758	0.0481	0.00027	1575.8
	Sum (FEN + NFEN)	1.59	-0.0417	0.0684	< 0.0001	1570.4
	E	xposure as Log	<sub>2</sub> -transformed Va	riables		
0	Fenfluramine	2.46	-0.379	0.0997	<0.0001	1561.8
Steady-State AUC <sub>0-24</sub>	Norfenfluramine	2.40	-0.384	0.0947	< 0.0001	1563.2
(ng•h/mL)	Sum (FEN + NFEN)	2.48	-0.346	0.0975	< 0.0001	1562.4
0 0 0	Fenfluramine	2.09	-0.653	0.100	<0.0001	1561.7
Steady-State Cmax	Norfenfluramine	1.95	-0.686	0.0913	< 0.0001	1564.1
(ng/mL)	Sum (FEN + NFEN)	2.19	-0.576	0.0981	< 0.0001	1562.2
04	Fenfluramine	1.95	-0.686	0.0974	<0.0001	1562.4
Steady-State Cmin	Norfenfluramine	1.90	-0.693	0.0902	< 0.0001	1564.4
(ng/mL)	Sum (FEN + NFEN)	2.13	-0.597	0.0972	< 0.0001	1562.5

Note: Abbreviations are provided in the Abbreviation Listing.

A full, multivariable model including all covariates, was then subjected to backward selection to identify any significant predictors of maximum percent change in body weight during T+M. Through this process, it was determined that the only significant predictor of maximum percent change in body weight during T+M was FEN AUC0-24. Based on the intercept value of 2.46, subjects receiving placebo would be expected to gain 2.46 kg during T+M. The coefficient term for the model (-0.379) indicates that a doubling in the steady-state FEN AUC0-24 would be expected to result in a relative loss of 0.379

kg during T+M, and the adjusted r2 value of 0.0997 indicates that FEN AUC0-24 explains approximately 10% in the variability in maximum change in body weight during T+M.

Figure 3 Scatterplot of maximum percent change in body weight during T+M versus steady-state fenfluramine  $AUC_{0-24}$ , with fit of the  $log_2$ -linear regression model of overlaid



Note: Abbreviations are provided in the Abbreviation Listing. Dark grey line and shaded region represent the fit of the linear regression model to the data (mean and 90% confidence interval).

# Mitral regurgitation

Across all three treatment groups, 45 of the 250 subjects (18%) had a reading of trace mitral regurgitation in a post-baseline ECHO. The incidence of trace mitral regurgitation was slightly higher in subjects randomized to placebo. There was no indication that subjects with higher exposure were more likely to exhibit trace mitral regurgitation. Given the lack of apparent exposure-response relationships, no further analyses were conducted for this outcome variable.

#### Blood pressure

Graphical displays indicated that for diastolic blood pressure, that there were no trends in the population overall but a suggestion of a relationship in adults in which diastolic blood pressure increases with increasing exposure. For systolic blood pressure, there appeared to be a trend for an overall decrease in systolic blood pressure with increasing exposure. However, all of the above trends appeared relatively weak. Univariable analyses were conducted using linear regression. None of the PK exposure measures were predictive of maximum absolute change in either diastolic or systolic blood pressure during T+M as all of the p values were  $\geq 0.13$  (Table 12).

Table 12 Results of linear regression models relating maximum absolute change in blood pressure during T+M to various PK exposure measures

Variable	Analyte	Analyte Intercept Coefficient A		Adjusted r <sup>2</sup>	p-value	AIC
		Diastolic	<b>Blood Pressure</b>			
Ot	Fenfluramine	1.35	-0.0407	-0.00386	0.85	2103.8
Steady-State AUC <sub>0-24</sub>	Norfenfluramine	1.41	-0.0553	-0.00375	0.80	2103.8
(ng•h/mL)	Sum (FEN + NFEN)	1.39	-0.0437	-0.00381	0.82	2103.8
C4	Fenfluramine	1.27	-0.056	-0.00392	0.88	2103.8
Steady-State C <sub>max</sub>	Norfenfluramine	1.36	-0.105	-0.00373	0.79	2103.8
(ng/mL)	Sum (FEN + NFEN)	1.33	-0.0676	-0.00384	0.83	2103.8
Steady-State C <sub>min</sub>	Fenfluramine	1.31	-0.0808	-0.00384	0.83	2103.8
	Norfenfluramine	1.41	-0.132	-0.00358	0.74	2103.7
(ng/mL)	Sum (FEN + NFEN)	1.39	-0.0916	-0.00371	0.78	2103.8
		Systolic	Blood Pressure			•
Ot	Fenfluramine	2.04	-0.363	0.00374	0.17	2217.5
Steady-State AUC <sub>0-24</sub>	Norfenfluramine	1.77	-0.328	0.00183	0.23	2217.9
(ng•h/mL)	Sum (FEN + NFEN)	1.97	-0.317	0.0029	0.19	2217.7
04	Fenfluramine	1.71	-0.636	0.00402	0.16	2217.4
Steady-State Cmax	Norfenfluramine	1.31	-0.553	0.00101	0.26	2218.1
(ng/mL)	Sum (FEN + NFEN)	1.7	-0.526	0.00291	0.19	2217.7
C4	Fenfluramine	1.71	-0.731	0.00533	0.13	2217.1
Steady-State Cmin	Norfenfluramine	1.31	-0.579	0.00133	0.25	2218.1
(ng/mL)	Sum (FEN + NFEN)	1.71	-0.568	0.00341	0.17	2217.5

Note: Abbreviations are provided in the Abbreviation Listing.

The multivariable models that were most predictive included FEN AUC0-24 (log2-transformed), either age category (for diastolic blood pressure) or age as a continuous variable (for systolic blood pressure), and the interaction between FEN AUC0-24 and the respective age variable. Despite statistical significance, neither of the models were considered informative as their adjusted r2 values were 0.0153 and 0.0242 for diastolic and systolic blood pressure, respectively (data not shown). These low r2 values indicate that the combination of age and exposure explains less than 2.5% of the variability in maximum absolute change in blood pressure in the study population.

Diastolic and systolic blood pressure were also evaluated as categorical variables defines as presence or absence of at least two post-baseline occurrences of an absolute change from baseline of >10 mm Hg for diastolic blood pressure and >20 mm Hg for systolic blood pressure. FEN AUC0-24 was used as an independent exposure variable in a recursive partitioning analysis. When the data were split at a FEN AUC0-24 value of 110 ( $\sim$ 5th percentile of active subjects), a substantial difference was seen in the incidence; 24% of placebo subjects and active subjects with FEN AUC0-24 <110 had elevated diastolic blood pressure as opposed to 34% of subjects with FEN AUC0-24  $\geq$ 110. This threshold was then tested using logistic regression. The coefficient for the AUC cut-off was of borderline significance p-value of 0.0877. Recursive partitioning was also conducted to identify if there were any threshold exposure values above and below which the incidence of elevated systolic blood pressure was significantly different. No thresholds could be identified.

#### Heart rate

The majority of subjects (238 of 251 or 94.8%) had three or more heart rate observations during T+M.

Graphical displays showed a slight trend for heart rate to decrease with increasing exposure in the pooled population and the paediatric subjects. Univariable analyses were conducted using linear regression. None of the PK exposure measures were predictive of maximum absolute change in heart rate as all of the p-values were  $\geq 0.43$  (Table 13). Results of multivariable models including potential effect of age were similar in that the p-values for the coefficients for all of terms in the model (i.e., exposure and age as continuous or categorical) were non-significant p > 0.5 (data not shown).

Table 13 Results of linear regression models relating maximum absolute change in heart rate during T+M to various PK exposure measures

Variable	Analyte	rte Intercept Coefficient Adjusted		Adjusted r <sup>2</sup>	p-value	AIC
		Exposure a	s Linear Variable	s		
0 0 4110	Fenfluramine	0.606	-0.00149	-0.00153	0.43	2141.1
Steady-State AUC <sub>0-24</sub>	Norfenfluramine	0.22	-0.00082	-0.00361	0.75	2141.6
(ng•h/mL)	Sum (FEN + NFEN)	0.491	-0.0007	-0.0025	0.54	2141.3
Ctd- Ct-t- C	Fenfluramine	0.62	-0.0325	-0.00161	0.44	2141.1
Steady-State C <sub>max</sub>	Norfenfluramine	0.22	-0.0191	-0.00362	0.75	2141.6
(ng/mL)	Sum (FEN + NFEN)	0.505	-0.016	-0.0025	0.54	2141.3
Steady-State C <sub>min</sub> (ng/mL)	Fenfluramine	0.575	-0.0399	-0.00149	0.43	2141.1
	Norfenfluramine	0.213	-0.0199	-0.00362	0.75	2141.6
	Sum (FEN + NFEN)	0.47	-0.018	-0.00252	0.54	2141.3
	E	cposure as Log	<sub>l2</sub> -transformed Va	riables		
01 1 01 1 1110	Fenfluramine	0.24	-0.0528	-0.00379	0.81	2141.7
Steady-State AUC <sub>0-24</sub>	Norfenfluramine	0.0218	-0.0133	-0.004	0.95	2141.7
(ng•h/mL)	Sum (FEN + NFEN)	0.145	-0.032	-0.00392	0.88	2141.7
01 1 01 1 0	Fenfluramine	0.408	-0.175	-0.00318	0.65	2141.5
Steady-State Cmax	Norfenfluramine	0.124	-0.0758	-0.00389	0.86	2141.7
(ng/mL)	Sum (FEN + NFEN)	0.285	-0.107	-0.00363	0.76	2141.6
04	Fenfluramine	0.482	-0.235	-0.0027	0.57	2141.4
Steady-State Cmin	Norfenfluramine	0.151	-0.0913	-0.00383	0.83	2141.7
(ng/mL)	Sum (FEN + NFEN)	0.334	-0.131	-0.00347	0.71	2141.6

Note: Abbreviations are provided in the Abbreviation Listing.

#### 2.3.3. Pharmacokinetics

The pharmacokinetics (PK) of fenfluramine were previously assessed in the initial MAA (for Dravet syndrome). In this extension of indication procedure, only part 1 of study 1601 was used to evaluate PK.

# **Absorption**

Fenfluramine is readily and completely absorbed from the gastrointestinal tract (Marchant 1992), and first-pass metabolism results in an oral bioavailability in the range of 68% to 83% (Bever 1997). Peak plasma drug concentrations are attained within 3 to 5 hours in humans (Study 1603; ICPD Report 00619-2; Redux US NDA 20-344; Bever 1997; Richards 1985).

Food does not affect the Cmax, time to peak plasma concentration (Tmax) or AUC of fenfluramine or norfenfluramine. The maximum dose of 15 mg BID of fenfluramine HCl (ie, 6 mL ZX008 oral solution) is fully soluble in the volume of the gastrointestinal (GI) tract over its entire pH range. Due to its high solubility, fenfluramine absorption is unlikely to be affected by the coadministration of agents that modify GI pH.

#### **Distribution**

Following dosing, fenfluramine is distributed throughout the body (Pinder 1975). Mean *in vitro* plasma protein binding of fenfluramine and norfenfluramine is about 50% and binding is not influenced by concentration.

# Elimination

Fenfluramine is metabolized to norfenfluramine, primarily by CYP1A2, CYP2B6, and CYP2D6. Enzymes CYP2C9, CYP2C19, and CYP3A4/5 are involved to a minor extent.

Norfenfluramine is deaminated and oxidized to inactive metabolites.

Over 90% of an oral dose of fenfluramine is excreted in the urine as fenfluramine, norfenfluramine, or other metabolites with fenfluramine and norfenfluramine accounting for less than 25% of the total; less than 5% is found in faeces.

As assessed in the initial MAA and reflected in the SmPC, the geometric mean (CV%) clearance (CL/F) of fenfluramine is 6.9 L/h (29%) and the half-life is 20 hours following oral administration of fenfluramine in healthy subjects. The elimination half-life of norfenfluramine is  $\sim$ 30 h.

# Dose proportionality and time dependencies

Fenfluramine PK is approximately dose proportional.

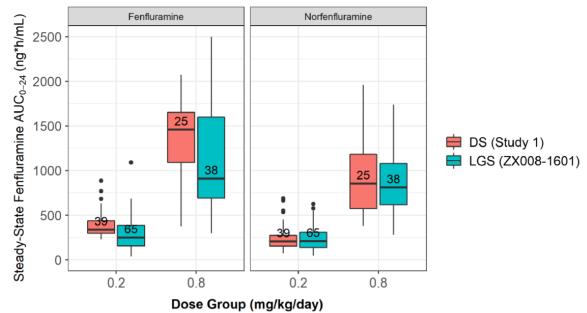
The relationship between ZX008 dose and weight was explored by PopPK analysis including subjects with LGS from Study 1601. When summary statistics are compared for the subjects randomized to ZX008 0.2 mg/kg/day with those randomized to ZX008 0.8 mg/kg/day who had body weight < 37.5 kg ie, subjects whose dose was not limited to the maximum of 30 mg/day), an approximately 4-fold increase in exposure is observed. This is consistent with a dose-proportional increase in exposure, indicating that exposures will change predictably between 0.2 mg/kg/day and 0.8 mg/kg/day when unconstrained by maximum daily dose.

# Special populations

Target population

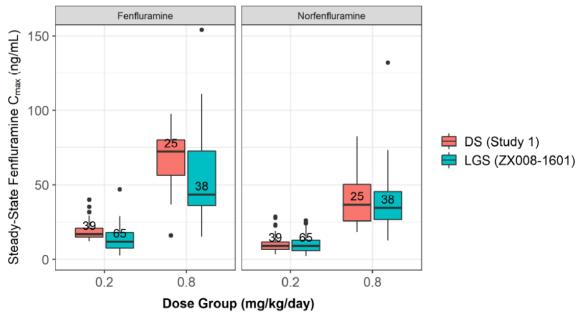
In subjects with LGS who received ZX008 0.8 mg/kg/day, up to a total maximum daily dose of 30 mg fenfluramine, the observed fenfluramine and norfenfluramine concentration-time profiles were similar and the steady-state exposures (Cmax and AUC0-24) overlapped with those in subjects with Dravet syndrome. Steady state systemic exposure (Cmax and AUC0-24) of fenfluramine in subjects with LGS was lower on average and estimated apparent clearance (CL/F) higher than in subjects with Dravet syndrome.

Figure 4 Box-and-whisker plots showing the distributions of estimated steady-state  $AUC_{0-24}$ , stratified by indication/study and dose regiment and presented by analyte



Note: Abbreviations are provided in the Abbreviation Listing. Subjects aged ≥18 yr and those receiving the maximum daily dose of 30 mg are excluded from the plots above. Numbers in each box show the count of subjects in the respective group. Only subjects with age less than 18 yr included; for the 0.8 mg/kg/day regimen, only subjects with body weight <37.5 kg are included.

Figure 5 Box-and-whisker plots showing the distributions of estimated steady-state  $C_{\text{max}}$ , stratified by indication/study and dose regiment and presented by analyte



Note: Abbreviations are provided in the Abbreviation Listing. Subjects aged ≥18 yr and those receiving the maximum daily dose of 30 mg are excluded from the plots above. Numbers in each box show the count of subjects in the respective group. Only subjects with age less than 18 yr included; for the 0.8 mg/kg/day regimen, only subjects with body weight <37.5 kg are included.

# 2.3.4. Pharmacodynamics

#### Mechanism of action

The combined results of binding studies, receptor functionality assays, and *in vivo* models previously reviewed suggest that fenfluramine is a selective serotonin-releasing agent and a positive modulator of sigma-1 receptor. Fenfluramine may reduce seizures by acting as an agonist at specific serotonin receptors in the brain, including the 5-HT1D, 5-HT2A, and 5-HT2C receptors, and also by acting as a positive modulator of the sigma-1 receptor. Fenfluramine may also act through other mechanisms not yet identified in reducing seizures.

# Primary and secondary pharmacology

#### 2.3.5. PK/PD modelling

Exposure-response relationships for both efficacy and safety were conducted. The primary efficacy endpoint was identical with that which was evaluated in the clinical trials: percent change in frequency of seizures that result in drops. Safety endpoints were selected for evaluation of potential relationships with PK exposure based on medical importance, utility of knowing the relationship to exposure, and observed frequency in the Phase 3 clinical program sufficient to support the analyses. The endpoints selected included laboratory values of interest (blood glucose concentration and platelet count), cardiovascular endpoints (blood pressure and heart rate), weight loss, and the occurrence of mitral regurgitation on echocardiogram.

Exposure-response analyses for efficacy: a statistically significant relationship was observed between PK exposure and percent reduction in drop seizure frequency during the T+M period.

Exposure-response analyses for safety: There were no relationships between any of the PK exposure variables and cardiovascular endpoints of blood pressure or heart rate, changes in blood glucose concentration or platelet count and the incidence of trace mitral regurgitation on echocardiogram during the T+M period.

A statistically significant relationship was observed between steady-state FEN AUC0-24 and maximum change in body weight during the T+M period. The relationship is relatively weak such that the mean predicted maximum percent change in body weight at the 90th percentile of FEN AUC0-24 (1,861 ng•h/mL) is a decrease in body weight of only 4.12% relative to placebo.

# 2.3.6. Dose finding

The initial rationale for the development of ZX008 for LGS was based on an ongoing Phase 2 open-label, pilot, dose-finding study (S58545) of fenfluramine HCl as an add-on therapy to conventional therapy in LGS (Lagae 2018). The study includes a 20-week Core period, in which the dose of ZX008 is titrated to a  $\geq$  50% response (ie,  $\geq$  50% reduction in major seizure frequency) and then maintained at that level until the end of the period, and an Extension period of up to 15 months, in which the dose is titrated to achieve maximum efficacy and tolerability.

The Core period, which was completed, was designed as a pilot dose-finding study; therefore, dose escalation from the starting dose of ZX008 0.2 mg/kg/day stopped when a subject's convulsive seizure frequency was reduced by  $\geq$  50% of baseline, with a maximum allowed dose of 30 mg/day. Thirteen subjects (9 males and 4 females) with a mean (standard deviation [SD]) age of 11.7 (4.4) years

(range: 3 to 17) were enrolled. All subjects received ZX008 treatment for at least 20 weeks, with the exception of 3 subjects, including 1 who discontinued due to both lack of efficacy and treatmentemergent adverse events (TEAEs) and 2 who discontinued due to TEAEs. For the subjects who completed the 20-week Core period, the seizure frequency was reduced from a median of 61 major seizures per month in the pre-ZX008 baseline period to a median of 22 major seizures per month at the end of the Core period. During the Core period, 8 of the 13 enrolled subjects (62%) had a  $\geq$  50% reduction in major seizures with ZX008 treatment, and 3 (23%) subjects had a ≥ 75% reduction. The median dose of ZX008 received in this period was 0.4 mg/kg/day (dose levels at which ≥ 50% improvement was achieved: n = 2, 0.2 mg/kg/day; n = 6, 0.4 mg/kg/day; n = 3, 0.8 mg/kg/day; n = 62, maximum 30 mg/day). Nine of the 13 subjects completed the Core period and entered the Extension period. At the time of each subject's most recent visit in the published 2018 interim analysis (Month 15 for 7 subjects and Month 3 for 2 subjects who discontinued), 6 of 9 subjects (67%) had a ≥ 50% reduction in major motor seizures and 3 of 9 (33%) had a  $\geq$  75% seizure reduction. For the study as a whole, a 58% median reduction was observed in seizure frequency compared with baseline. At 15 months, the median dose of ZX008 was 0.4 mg/kg/day (n = 5, 0.4 mg/kg/day; n = 1, 0.8 mg/kg/day; n = 3, maximum 30 mg/day). The most common TEAEs were decreased appetite (n = 4) and decreased alertness (n = 2). Sleep problems, fatigue, tiredness, and sleepiness were each reported in 1 subject. No valvular heart disease or pulmonary hypertension were observed in any subjects at the time of the report, nor have they been observed in this ongoing study to date.

# 2.3.7. Discussion on clinical pharmacology

The PK characteristics of fenfluramine have been defined in the initial MAA. Fenfluramine showed dose-proportional PK across the proposed dose range and age, sex or race did not influence the exposure (Cmax and AUC) of fenfluramine or norfenfluramine.

Compared to the population with Dravet syndrome studied for the initial MAA, the geometric mean exposures were lower and the estimated geometric mean apparent clearance from plasma after oral administration (CL/F) was higher in subjects with LGS with no mechanistical explanation for a difference caused by the disease itself. The MAH states that the differences in mean values are most likely due to the relatively small sample sizes in each group, which is accepted. The active metabolite norfenfluramine exposures are comparable between the 2 populations with distributions and geometric means within  $\pm$  10%.

For evaluation of dose-response relationship, weight loss and occurrence of mitral regurgitation on echocardiogram were selected as safety endpoints influenced by prior experience with fenfluramine treatment, which had been previously marketed as an appetite suppressant but was withdrawn from the US and EU markets due to post-marketing reports of cardiac valve disease and pulmonary hypertension. There was no relationship between any of the PK exposure variables and the incidence of trace mitral regurgitation on echocardiogram, cardiovascular endpoints of blood pressure or heart rate, changes in blood glucose concentration or platelet count. A statistically significant relationship was observed between steady-state AUC0-24 and maximum change in body weight. Decreased appetite and weight loss is reflected in section 4.4 of the SmPC, as well as aortic or mitral valvular heart disease and pulmonary arterial hypertension.

A statistically significant relationship was observed between PK exposure and percent reduction in drop seizure frequency during the T+M period.

No formal dose finding study for fenfluramine in the clinical development program was provided. Instead, reference was made to a prospective open-label, proof of concept study.

# 2.3.8. Conclusions on clinical pharmacology

The CHMP agrees that pharmacokinetics of fenfluramine are sufficiently described and support the proposed LGS extension of indication.

# 2.4. Clinical efficacy

# 2.4.1. Main study(ies)

The following clinical studies were provided to support the new LGS indication:

Table 14 Pahse 3 Clinical Studies of ZX008 in Lennox-Gastaut Syndrome Included in the Submission

Study Number/ Type	Design	Study Drug; Dosing Regimen	Duration of Treatment	Number of Subjects	Subject Population	Study Status
1601 Part 1 Cohort A/ Efficacy and Safety	Phase 3, randomized, double- blind, placebo- controlled	Placebo, ZX008 0.2 mg/kg/day, ZX008 0.8 mg/kg/day <sup>a</sup> administered BID in equal doses	16 weeks (2-week titration; 12-week maintenance; 2-week transition/taper)	263 randomized (87 placebo, 89 ZX008 0.2 mg/kg/day, 87 ZX008 0.8 mg/kg/day)	Subjects 2-35 years of age with LGS with seizures that resulted in drops not completely controlled by current antiepileptic treatments; ≥ 8 drop seizures in 4 weeks before Screening; receiving ≥ 1-4 concomitant AEDs	Complete
1601 Part 2 Cohort A/ Long-Term Safety	Phase 3, open-label extension	ZX008 0.2 mg/kg/day for 1 month, then flexibly dosed to maximum 0.8 mg/kg/day <sup>a</sup> administered BID in equal doses	54 weeks	247	Subjects who completed Study 1601 Part 1 Cohort A and are candidates for continued treatment for an extended period of time with ZX008	Ongoing
1900/ Long-Term Safety	Phase 3, open-label extension	ZX008 flexibly dosed to maximum 0.8 mg/kg/day <sup>a</sup> administered BID in equal doses	36 months	131	Subjects who completed Study 1601 Part 2 and remain candidates for continuous treatment for an extended period of time	Ongoing

AED = antiepileptic drug; BID = twice daily; LGS = Lennox-Gastaut syndrome

Study ZX008-1601: A Two-Part Study of ZX008 in Children and Adults with Lennox- Gastaut Syndrome (LGS); Part 1: A Randomized, Double-blind, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as Adjunctive Therapy for Seizures in Children and Adults with LGS

## Methods

Study ZX008-1601 is an international, multicenter, Phase 3 study. Part 1 is a randomized, double-blind, parallel-group, placebo-controlled study to assess the efficacy and safety of 2 dose levels of ZX008 (fenfluramine hydrochloride) as adjunctive therapy for seizures in subjects with LGS.

Up to approximately 80 study sites in North America, Europe, Japan, and Australia were planned to participate. Subjects in the study are divided into 2 cohorts: Cohort A includes subjects enrolled at sites in North America, Europe, and Australia; Cohort B includes subjects enrolled at sites in Japan only. The primary analysis for the study is based on Part 1 Cohort A data. Cohort A has completed Part 1.

Part 1 consisted of a 4-week Baseline, 2-week Titration Period (Titration), 12-week Maintenance, and 2-week Taper Period (Taper) or Transition Period (Transition). The 4-week Baseline consisted of the establishment of initial eligibility during a screening visit, followed by an observation period in which

Maximum dose 30 mg/day. Subjects receiving concomitant stiripentol received ZX008 0.5 mg/kg/day, maximum dose 20 mg/day.

subjects were assessed for baseline seizure frequency based on recordings of daily seizure activity entered into a diary.

Upon completion of Baseline, 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 or 0.8 mg/kg/day [maximum dose: 30 mg/day]) or placebo. Subjects receiving concomitant stiripentol (STP) were planned to be randomized to placebo or ZX008 0.5 mg/kg/day (maximum dose 20 mg/day; to be analyzed as part of the 0.8 mg/kg/day treatment group), with the ZX008 0.5 mg/kg/day dose being based on the predicted increase in fenfluramine plasma concentration with concomitant STP administration. However, no subjects receiving STP were randomized in the study.

Note that doses of ZX008 are expressed as the fenfluramine hydrochloride salt. The 0.2, 0.5, and 0.8 mg/kg/day doses are equivalent to 0.2, 0.4, and 0.7 mg/kg/day (rounded), respectively, of the fenfluramine free base (with a conversion factor of 0.864). The 20 and 30 mg/day maximum doses are equivalent to 17 and 26 mg/day of fenfluramine free base.

Randomization was stratified by weight (<37.5 kg, ≥37.5 kg) to ensure balance across treatment arms, with a target of at least 25% of subjects in each weight group. All subjects were titrated to their blinded randomized dose over the 2-week Titration. Following dose titration, subjects continued treatment at their randomly assigned dose over the 12-week Maintenance. Total treatment time from the beginning of Titration through the end of Maintenance was 14 weeks. Subjects had ECG and ECHO assessments midway during Maintenance (at Week 6) and at the End-of-Study (EOS) Visit (Week 14).

At the end of Maintenance (or early discontinuation), all subjects underwent the blinded 2-week Taper or Transition Period (Taper/Transition) depending on whether they exited the study or were enrolled in Part 2, the long-term open-label extension, respectively. Follow-up ECG and ECHO were performed 3 to 6 months after study drug discontinuation for early termination (ET), or for those subjects who completed the study but did not enter the open-label extension. If there were any findings at the 3-month post-dose follow-up, a second follow-up was repeated at 6 months and then every 3 months until resolved or stabilized.

Throughout the study, parents/caregivers used the diary every day to record information about subjects.

#### Study participants

A subject was required to meet all of the inclusion criteria and none of the exclusion criteria to be eligible to enroll in the study and enter Baseline, and after completion of Baseline was additionally required to meet the randomization criteria to be eligible for randomization.

The study population included pediatric and adult subjects with LGS 2 to 35 years of age who had a diagnosis of LGS with seizures that resulted in drops not completely controlled by current antiepileptic treatments. Because an accurate diagnosis of LGS is difficult in children younger than 2 years, and seizures that result in drops may not be accurately counted in this age group, children younger than 2 years were not included. Although seizures persist into adulthood, the primary seizure types and the treatment setting may differ; thus, adults older than 35 years were not included in the study. Subjects without a formal diagnosis could still be enrolled at Sponsor discretion if all other criteria were met.

Subjects must have met all of the following 4 criteria for LGS, as defined in the protocol:

a. Onset of seizures at 11 years of age or younger.

- b. Multiple seizure types (must have included TS or TA), including countable motor seizures that resulted in drops. Countable motor seizure types eligible for inclusion were: GTC, TS, CS, AS, FS, and MS that resulted in a drop.
- c. Abnormal cognitive development.
- d. Evidence of electroencephalogram (EEG) in the medical history that showed abnormal background activity accompanied by slow spike-and-wave pattern <2.5 Hz. (Acceptable evidence included a copy of the EEG trace, EEG report, or physician note that appropriately described the EEG findings.)

Subjects were required to have been receiving  $\geq 1$  to 4 concomitant AEDs. The ketogenic diet (KD) and vagal nerve stimulation (VNS) were permitted as concomitant therapies during the trial but did not count toward this requirement. Rescue medications for seizures were not counted towards the total number of AEDs. All medications or interventions for epilepsy, including KD and VNS, must have been stable for at least 4 weeks prior to Screening and were expected to remain stable throughout the study.

All subjects were required to have had  $\geq 8$  drop seizures in the 4 weeks immediately prior to Screening (minimum of 4 drop seizures in the first 2 weeks and 4 in the last 2 weeks before Screening) based on parent/guardian report or Investigator medical notes and  $\geq 8$  drop seizures during the 4-week Baseline ( $\geq 2$  drop seizures per week) as recorded in the eDiary. Eight or more drop seizures occurring at a consistent frequency represents subjects with uncontrolled seizures, excludes subjects whose seizures only occur in clusters or who have only intermittent infrequent seizures, and provides a sufficient baseline from which to measure meaningful change. Seizures that result in drops were of the type generalized tonic-clonic (GTC), secondarily generalized tonic-clonic (SGTC), tonic (TS), atonic (AS), and tonic/atonic (TA) that were reviewed and confirmed as drop seizures for each subject by the Epilepsy Study Consortium (ESC).

Female subjects of childbearing potential must have had a negative urine or serum pregnancy test at Screening. Subjects of childbearing or child-fathering potential must have been willing to use medically acceptable forms of birth control, which included abstinence, while receiving treatment and for 90 days after the last dose.

Exclusion criteria included but were not limited to: a degenerative neurological disease as aetiology of seizures; history of hemiclonic seizure (HS) in the first year of life; subject with only had drop seizure clusters where individual seizures could not be counted reliably; an anoxic episode requiring resuscitation within 6 months of the Screening Visit; pulmonary arterial hypertension (PAH); current or past history of cardiovascular or cerebrovascular disease such as cardiac valvulopathy, myocardial infarction or stroke, or clinically significant structural cardiac abnormality, including but not limited to mitral valve prolapse, atrial or ventricular septal defects, patent ductus arteriosus (note: patent foramen ovale or a bicuspid valve were not considered exclusionary); current or recent history of anorexia nervosa, bulimia, or depression within the prior year that required medical treatment or psychological treatment for a duration greater than 1 month; history of glaucoma; moderate or severe hepatic impairment (asymptomatic subjects with mild hepatic impairment, such as elevated liver enzymes <3 × upper limit of normal [ULN] and/or elevated bilirubin <2 × ULN, may have been enrolled after review and approval by the Sponsor); severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m2); concomitant therapy with centrally-acting anorectic agents, monoamine oxidase inhibitors, any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition, other centrallyacting noradrenergic agonists including atomoxetine, or cyproheptadine; positive result on urine or serum tetrahydrocannabinol panel or whole blood cannabidiol at the Screening Visit; felbamate for less than 1 year prior to Screening, or did not have stable liver function and hematology laboratory tests,

or the dose had not been stable for at least 60 days prior to the Screening Visit; HIV positive; active viral hepatitis B or C; institutionalized in a general nursing home (ie, a facility that does not provide skilled epilepsy care); a clinically significant condition, including chronic obstructive pulmonary disease, interstitial lung disease, or portal hypertension, or had clinically relevant symptoms or a clinically significant illness within 4 weeks prior to the Screening Visit other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject.

#### Randomization Inclusion Criteria

- 1. Subject had been approved for study inclusion by the ESC.
- 2. Subject did not have an exclusionary cardiovascular or cardiopulmonary abnormality based on ECHO, ECG or physical examination and was approved for entry by the central cardiac reader. Exclusionary abnormalities included but were not limited to:
- a. Trace or greater mitral or aortic valve regurgitation in a subject <18 years of age
- b. Mild or greater mitral or aortic valve regurgitation in a subject >18 years of age
- c. Possible signs of pulmonary hypertension with abnormal or greater than upper range of normal values
- d. Evidence of left ventricular dysfunction (systolic or diastolic)
- 3. Subject demonstrated a stable baseline with ≥2 seizures resulting in drops per week during the 4-week Baseline.
- 4. Subject's parent/caregiver had been compliant with electronic diary completion during Baseline, in the opinion of the Investigator and Sponsor.

#### **Treatments**

Subjects received ZX008 or matching placebo for up to approximately 16 weeks (Titration=2 weeks; Maintenance=12 weeks; Taper/Transition=up to 2 weeks).

Test Product: ZX008 was supplied as an oral solution in concentrations of 1.25, 2.5, and 5 mg/mL. Subjects were randomized to receive ZX008 0.2 mg/kg/day, ZX008 0.8 mg/kg/day (or 0.5 mg/kg/day if taking STP), or placebo. The maximum dose administered was 30 mg/day (or 20 mg/day for subjects taking STP). Study treatment was administered orally by the caregiver twice a day (BID) in equal divided doses.

Reference Product: Matching ZX008 placebo was supplied as an oral solution and dosed in the same manner as ZX008.

#### **Objectives**

The primary objective of Part 1 was the primary objective of the entire study.

• To evaluate the effect of ZX008 0.8 mg/kg/day versus placebo as adjunctive therapy for the treatment of uncontrolled seizures in children and adults with LGS based on the change in frequency of seizures that result in drops between baseline (ie, the Baseline Period [Baseline]) and the combined Titration + Maintenance Periods (T+M).

Seizures that result in drops were of the type generalized tonic-clonic (GTC), secondarily generalized tonic-clonic (SGTC), tonic (TS), atonic (AS), and tonic/atonic (TA) that were reviewed and confirmed

as drop seizures for each subject by the Epilepsy Study Consortium (ESC). These seizures may also be referred to as "seizures that result in drops (ESC-confirmed)," "ESC-confirmed drop seizures," or "drop seizures" for brevity.

The key secondary objectives of Part 1 were:

- To evaluate the effect of ZX008 0.2 mg/kg/day versus placebo as adjunctive therapy for the treatment of uncontrolled seizures in children and adults with LGS based on the change in frequency of seizures that result in drops between Baseline and T+M
- To evaluate the effect of ZX008 0.8 and 0.2 mg/kg/day (independently) versus placebo on the proportion of subjects who achieve a  $\geq$ 50% reduction from Baseline in the frequency of seizures that result in drops
- To evaluate the effect of ZX008 0.8 and 0.2 mg/kg/day (independently) versus placebo on the Clinical Global Impression Improvement (CGI-I) rating, as assessed by the Principal Investigator

# **Endpoints**

# **Primary efficacy endpoint**

Percent change from baseline in the frequency of seizures that result in drops (DSF) in the combined Titration and Maintenance Periods (T+M) in the ZX008 0.8 mg/kg/day group compared to the placebo group. Seizures that result in drops are GTC, SGTC, TS, AS, and TA confirmed for each subject as a drop seizure by the ESC.

#### Key secondary efficacy endpoints

- Change from baseline in DSF in T+M in the ZX008 0.2 mg/kg/day group compared to the placebo group.
- Proportion of subjects who achieve a ≥50% reduction from baseline in the frequency of seizures that result in drops comparing the ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo.
- Proportion of subjects who achieve improvement (minimally, much or very much improved) in the Clinical Global Impression Improvement as assessed by the Principal Investigator comparing the ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo.

#### Additional secondary efficacy endpoints

ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups compared independently versus placebo on the

- Change from baseline during T+M in frequency of all seizures that (typically) result in drops (i.e., GTC, SGTC, TS, AS, TA) whether ESC confirmed as drop or not.
- Change from baseline during T+M in frequency of all countable motor seizures (GTC, SGTC, TS, AS, TA, CS, FS, and HS).
- Change from baseline during T+M in frequency of all countable non-motor seizures (absence, myoclonic, focal without clear observable motor signs, infantile spasms, and epileptic spasms).
- Change from baseline during T+M in the frequency of all countable seizures (i.e., motor and non-motor).
- Change from baseline during M in the frequency of seizures that result in drops.
- Change from baseline during M in the frequency of seizures that typically result in drops.
- Change from baseline during M in the frequency of all countable motor seizures.
- Change from baseline during M in the frequency of all countable non-motor seizures.
- Change from baseline during M in the frequency of all countable seizures (i.e., motor and non-motor).

- Proportion of subjects who achieve a worsening from baseline (i.e.  $\leq$  0% reduction), or >0%,  $\geq$ 25%,  $\geq$ 50%,  $\geq$ 75%, or 100% reduction between baseline and T+M, and baseline and M, in seizures that result in drops (ESC confirmed), seizures that typically result in drops, all countable motor seizures, all countable non-motor seizures, and all countable seizures.
- Number of seizure-free days in the baseline, M and T+M period, defined as 1) days with no seizures that results in drops (ESC confirmed), and 2) days with no countable motor seizures.
- The longest interval (days) between seizures that result in drops (ESC confirmed) comparing the ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo Clinical Global Impression Improvement as assessed by the parent/caregiver

## Sample size

The sample size for Part 1 Cohort A was estimated under the assumption that adding ZX008 at 0.8 mg/kg/day to current therapy will lead to a mean decrease in drop seizures that is 30 percentage points greater than adding placebo to current therapy. For example, if adding placebo leads to a 10% decrease in seizures, then adding the high dose of ZX008 would be expected to decrease seizures by at least 40%.

The variability expected in the trial was estimated from a Phase 3 trial of clobazam for patients with Lennox-Gastaut syndrome leading to an assumption that the standard deviation (SD) is 50%. Other assumptions include an allowance for 20% dropouts between randomization and the start of the maintenance period. Under these assumptions, a sample size of 63 subjects per treatment group for a nonparametric analysis affords 90% power to detect a difference between the ZX008 0.8 mg/kg/day

and placebo groups that is significant at the  $\alpha$ =0.05 level. Assuming a 20% drop-out rate prior to the start of the maintenance period yields a requirement for an additional 14 subjects per group for a total of 79 subjects per treatment group for a nonparametric analysis. Similar calculations for the 0.2 mg/kg/day ZX008 group lead to a total required sample size of 237. The number of subjects randomized into Part 1 Cohort A is estimated to be approximately 250 due to the long baseline period.

#### Assessor's comments

The sample size calculations were based on the assumed mean decrease in drop seizures and dropout rates. The sample size calculation reflects the primary analysis, with estimated 90% power and a significance level of 5%. The sample size calculation is acceptable.

# **Randomisation**

Upon completion of the Baseline period in Part 1, subjects who qualify for the study will be 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; 30mg/day maximum [0.5 mg/kg/day; 20 mg/day maximum for subjects taking concomitant STP]) or placebo. The randomization will be stratified by weight (<37.5 kg,  $\ge37.5$  kg) to ensure balance across treatment arms, with a target of at least 25% in each weight group. Subjects will be assigned a randomization number by the IWR system upon confirmation that subject qualifies for enrollment in the Titration period. Once a randomization number is assigned to a subject, the site will record the subject's initials and identification number on the corresponding study drug bottles.

#### Assessor's comments

In ZX008-1601 part 1 Cohort A, eligible subjects were randomized (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 or placebo. The randomization was stratified by weight (<37.5 kg,  $\ge 37.5 \text{ kg}$ ) to ensure balance across treatment arms, with a target of at least 25% in each weight group. The randomization procedures in part 1 are agreed upon.

# Blinding (masking)

The blinding scheme instituted for this study will ensure that the volume of study medication taken cannot be associated with the dose group, thus unblinding the study. This is achieved by random assignment of different concentrations of the ZX008 oral solution (1.25 mg/mL, 2.5 mg/mL, and/or 5 mg/mL) by the IWR system. The IWR system will instruct site personnel to the volume of oral solution to be administered based on that subject's weight. (Dose will be recalculated by the system based on weight once at the midpoint of the study.) During the Titration, Maintenance, and Taper/Transition periods, the subjects and study personnel (Investigators, clinical staff, personnel involved in data collection and analysis, the Medical Monitor, and the Sponsor) will be blinded to the treatment allocation and to the concentration of ZX008 oral solution. If an Investigator feels the blind should be broken, he/she can do so when necessary for treatment decisions. However, the Investigator should endeavor to discuss with the

Medical Monitor or Sponsor's Medical Representative, if available. The blind should only be broken in the event the knowledge of whether the subject is on active study medication versus placebo is needed to determine course of medical treatment for the event. The subject will be discontinued from the clinical trial upon breaking of the blind and the decision whether the subject can enter Part 2 will rest with the Sponsor if the subject exited Part 1 prior to completion.

#### Statistical methods

# T+M Period:

The primary analysis will compare the ZX008 0.8 mg/kg/day group to the placebo group for Cohort A using a two-sided test at the  $\alpha$ =0.05 level of significance.

The primary endpoint will be analyzed using a non-parametric analysis of covariance (ANCOVA) model with treatment group (three levels; Placebo, 0.2 mg/kg/day, 0.8 mg/kg/day) and weight strata group ( $< 37.5 \text{ kg}, \ge 37.5 \text{ kg}$ ) as factors, rank of baseline DSFB as a covariate and rank of percent CDSFT+M as response. Treatment group mean differences from placebo will be estimated via least squares means from the analysis model along with 95% confidence intervals.

Rejection of the null hypothesis in favor of the alternative, in the presence of a statistically significantly smaller seizure frequency for the treatment group compared to the placebo group, (two-sided p-value <.05) will be regarded as evidence of a treatment benefit in favor of the 0.8 mg/kg group. A similar comparison of the location parameter for Z008 0.2 mg/kg/day vs. placebo will be regarded as evidence of a treatment benefit of the 0.2 mg/kg group. This is the 3rd key secondary endpoint.

Additional statements may be used to obtain estimates and associated 95% confidence intervals.

A second analysis of the primary endpoint will be completed using a parametric analysis of covariance (ANCOVA) model with treatment group (three levels; Placebo, 0.2 mg/kg/day, 0.8 mg/kg/day) and weight group (<37.5 kg,  $\ge37.5$  kg) as factors, log baseline DSFB as a covariate and log (CDSFT+M +1) as response. Treatment group mean differences from placebo will be estimated via least squares means from the analysis model along with 95% confidence intervals. Since the least square means and

confidence intervals will be on the log scale, these least square means and confidence intervals will be exponentiated back to the original scale.

Additional statements may be used to obtain estimates and associated 95% confidence intervals. Endpoints of the confidence interval (CIs) will be translated to the original scale using the ranks.

#### M Period only:

The primary endpoint analysis described above will be repeated using data from the Maintenance period only as response. For subjects who did not reach the Maintenance period, their Transition period data will be used to represent their M period data.

Similar non-parametric and parametric ANCOVA models will be used.

#### Treatment by baseline seizure category interaction:

Treatment by baseline seizure category interaction: The non-parametric and parametric analysis for the T+M and M period described above will be repeated with baseline seizure frequency as a categorical variable, rather than a covariate, and will include baseline seizure frequency by treatment

#### **Sensitivity Analyses**

#### Wilcoxon Rank-sum Test

The ZX008 0.8 mg/kg/day group will be compared to the placebo group on the percent change from baseline in seizures resulting in drops using a Wilcoxon rank-sum test. The median difference between the groups, and its 95% confidence interval, will be estimated using the Hodges-Lehmann estimator.

#### Impact of Antiepileptic Drugs (AED)

Subjects in the study are required to be on stable background therapy. Using the MITT population, an additional nonparametric ANCOVA analysis will be performed to assess the impact on the primary analysis of changes in dose or type of concomitant AED, which are protocol violations that may occur during the course of the study.

For this analysis, each subject will be classified according to the number of concomitant AEDs used during the T+M period. Fisher's exact tests will be used to compare the active dose groups with the placebo group on the percentage of subjects within each group who have a change in concomitant AEDs.

#### Per protocol Analysis

The primary efficacy ANCOVA will be repeated on the per protocol population (which excludes subjects with important protocol deviations that may affect the inference on efficacy such as a change in dose or type of concomitant AED).

#### **No Imputation for Seizure Clusters**

The primary efficacy ANCOVA will be repeated on the mITT population with no imputation for seizure clusters; i.e., seizure clusters will not be calculated in the frequency of seizures that result in drops.

#### **Exclusion of Outliers**

The distribution of the primary endpoint is inherently asymmetric since no subject can have more than a 100% decrease in seizures, but there is no reason a subject couldn't have a 200% or even 1000% increase. In fact, there is no theoretical upper bound to the possible magnitude of an increase in a percent change statistic. To assess the sensitivity of the primary analysis to extreme outliers in percent change in drop seizure frequency, the primary analysis will be repeated excluding any PCDSF value that satisfies Tukey's criterion for a "far out" outlier (Tukey, 1977).

#### **Imputation for Dropouts**

Two different methods for imputation of missing values due to subject drop out will be incorporated into the analysis of the primary efficacy endpoint. When referring to frequency in the paragraphs below, it refers to the number of seizure events per 28 days.

S1: Worst value substituted: In this analysis, for a subject who drops out of treatment, if the drop seizure frequency during T+M is lower than the baseline value, the baseline value will be substituted for the subject from the point of withdrawal to the end of the planned duration of T+M. However, if the seizure frequency during T+M is higher than the baseline value, there will be no substitution. The DSF for the planned duration of T+M will then be computed as a weighted mean of the value before dropout, and the imputed value after dropout. The weights will be the proportion of planned duration of T+M before and after dropout. The statistical analysis (nonparametric ANCOVA) described at the start of section 8.2.2 will then be performed on the resulting dataset.

Treatment comparisons will be based on the least squares means and standard errors obtained from the ANCOVA.

S2: Differential imputation method: In this analysis, subjects who dropout due to an adverse event, lack of compliance, loss to follow-up or subject choice will have their convulsive seizure frequency for the remainder of the time during the planned T+M period replaced with the worse of the observed value or the baseline value as described for S1. However, for other withdrawal reasons (e.g., "lack of efficacy") their observed DSF during T+M will be imputed for the remainder of the time between dropout and end

of planned T+M. The DSF for the planned duration of T+M will then be computed as a weighted mean of the value before dropout and the imputed value after dropout. The weights will be the proportion of time before and after dropout. The statistical analysis (nonparametric ANCOVA) described at the start of section 8.2.2 will then be performed on the resulting dataset. Treatment comparisons will be based on the least squares means and standard errors obtained from the ANCOVA.

# **Key Secondary Analysis of the Primary Efficacy Endpoint**

The first key secondary endpoint compares treatment groups on the percentage of subjects with at least a 50% reduction from baseline in seizures resulting in drops. That is, the proportion of subjects in the ZX008 0.8 mg/kg/day group who have a decrease in frequency of seizures resulting in drops of at least 50 percentage points will be compared to the analogous proportion in the placebo group. This the 1st key secondary efficacy endpoint.

The comparison of the percentage of subjects with at least a 50 percent drop from baseline between treatment groups will be made using a logistic regression model that incorporates the factors treatment and weight strata and the baseline seizure frequency. Separate models will be fit for ZX008 0.2 mg/kg/day vs. placebo and ZX008 0.8 mg/kg/day vs. placebo. Achievement of the 50 percentage point reduction or greater, yes or no) will be modeled as a function of treatment group (2 levels; ZX008 0.8 mg/kg/day (or ZX008 0.2 mg/kg/day) and placebo) and baseline weight strata group (<37.5 kg,  $\geq 37.5 \text{ kg}$ ). If the model with treatment and weight strata is not convergent (e.g. due to a 0 count in a treatment by weight strata combination, the model will be refit using treatment only and the baseline seizure frequency. If the model still does not converge, no odds ratio and p-value from the logistic regression will be reported.

The model estimated odds ratio (including a 95% confidence interval) and p-value for comparison of ZX008 0.8 mg/kg/day to placebo and ZX008 0.2 mg/kg/day to placebo will be provided. A supplementary Fisher's exact test comparing treatment groups will be provided.

Similarly, the number and percentage of subjects who have a worsening,  $\geq 0\%$  reduction,  $\geq 25\%$  reduction,  $\geq 50\%$  reduction,  $\geq 75\%$  reduction,  $\geq 100\%$  reduction, and near seizure-freedom will be

tabulated for each treatment. Near seizure-freedom will be defined as having 0 or 1 seizures leading to a drop in the T+M period. These are additional secondary endpoints.

## Multiplicity

The Part 1, Cohort A efficacy analyses will employ a serial gatekeeper strategy to maintain the Type 1 error rate at  $\alpha$ =0.05 across the family of analyses that support the primary and key secondary objectives.

The strategy specifies a hierarchy of significance tests where each test acts as a gatekeeper to the tests below it.

• The hierarchy starts with the primary analysis comparing ZX008 0.8 mg/kg/day to placebo on the change in number of seizures that results in drops from baseline.

The next steps in the hierarchy entail the comparisons for the key secondary endpoints.

- Change from baseline in frequency of seizures that result in drops in T+M in the ZX008 0.2 mg/kg/day group compared to placebo.
- Proportion of subjects who achieve a ≥50% reduction from baseline in the frequency of seizures that result in drops in the ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo.
- Proportion of subjects who achieve improvement (minimally, much, or very much improved) in the Clinical Global Impression Improvement (CGI-I) as assessed by the Principal Investigator comparing the ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo.

Below is a complete list of steps in the testing hierarchy in order:

- 1. Compare ZX008 0.8 mg/kg/day to placebo on the change in frequency in seizures that result in drops per 28 days between the Baseline and T+M periods.
- 2. Compare ZX008 0.8 mg/kg/day to placebo on the proportion of subjects who achieve a  $\geq$  50% reduction from baseline in the number of seizures that result in drops.
- 3. Compare ZX008 0.8 mg/kg/day to placebo on the CGI-I at Visit 12.
- 4. Compare ZX008 0.2 mg/kg/day to placebo on the change in frequency in seizures that result in drops per 28 days between the Baseline and T+M periods.
- 5. Compare ZX008 0.2 mg/kg/day to placebo on the proportion of subjects who achieve a  $\geq$  50% reduction from baseline in the number of seizures that result in drops.
- 6. Compare ZX008 0.2 mg/kg/day to placebo on the CGI-I at Visit 12

#### Results

## **Participant flow**

A total of 335 subjects were enrolled and screened for eligibility to participate in the study. Of these, 263 subjects were randomized in a 1:1:1 ratio to 1 of the 3 treatment groups: placebo: 87 subjects; ZX008 0.2 mg/kg/day: 89 subjects; ZX008 0.8 mg/kg/day: 87 subjects.

A total of 245 (93.2%) randomized subjects were considered Part 1 completers (completed the study through Visit 12 [n=242]; or completed through at least Visit 8 and then transferred to Part 2 [n=3]).

**Table 15 Subject Disposition (Enrolled Population)** 

	Placebo n (%)	ZX008 0.2 mg/kg/day n (%)	ZX008 0.8 mg/kg/day n (%)	All Subjects
Enrolled in Part 1	II ( /0)	H ( /0)	II ( /0)	335
Screen failures <sup>a</sup>				72 (21.5)
Reasons for screen failure <sup>b</sup>	_	_	_	72 (21.3)
Subject did not meet criteria for LGS diagnosis	_	_	_	13 (18.1)
Fewer than 8 drop seizures during the 4 weeks prior to Screening	_	_	_	≤11
Medications or interventions for epilepsy not stable for 4 weeks prior to Screening	_	_	_	≤11
Informed consent by caregiver not obtained	_	_	_	≤11
Caregiver unable to comply with study procedures	_	_	_	≤11
Subject has current or past history of cardiovascular or cerebrovascular disease <sup>c</sup>	_	_	_	32 (44.4)
Exclusionary anoxic episode	_	_	_	≤11
Exclusionary concomitant therapy at Screening	_	_	_	≤11
THC- or CBD-positive at Screening	_	_	_	≤11
Subject unwilling or unable to comply with study requirements	_	_	_	≤11
Exclusionary clinically significant condition	_	_	_	≤11
Subject participation not approved by ESC	_	_	_	≤11
Exclusionary seizure history during Baseline	_	_	_	≤11
Randomized	87	89	87	263
Part 1 Trial completers <sup>d</sup>	85 (97.7)	82 (92.1)	78 (89.7)	245 (93.2)
Part 1 Trial completers who transferred to Part 2 prior to Visit 12	≤11	≤11	≤11	≤11
Withdrawals by Period				
Double-blind Treatment Period	≤11	≤11	≤11	21 (8.0)
Titration Period	≤11	≤11	≤11	≤11
Maintenance Period	≤11	≤11	≤11	19 (7.2)
Taper/Transition Period	≤11	≤11	≤11	≤11
Reasons for withdrawal				
Adverse event	≤11	≤11	≤11	≤11
Death	≤11	≤11	≤11	≤11
Physician decision	≤11	≤11	≤11	≤11
Protocol Deviation	≤11	≤11	≤11	≤11
Withdrawal by subject	≤11	≤11	≤11	≤11
Withdrawal by subject Other <sup>e</sup>	≤11 ≤11	≤11 ≤11	≤11 ≤11	≤11 ≤11

Source: Table 14.1.1.1.1

Abbreviation: CBD=cannabidiol; ESC=Epilepsy Study Consortium; LGS=Lennox-Gastaut Syndrome;

THC=tetrahydrocannabinol

Screen failure includes those subjects who failed 1 or more Entry or Randomization criteria. A subject may have failed 2 or more of these criteria and therefore is counted in multiple categories.

Percentages are calculated using the number of screen failures as the denominator.

Subjects failed Exclusion criterion 6 or Randomization criterion 2. These criteria both relate to cardiovascular findings and were occasionally used interchangeably to refer to exclusionary regurgitation findings on the Visit 1 echocardiogram.

A Part 1 trial completer is a subject who completed Part 1 through Visit 12 or who completed through at least Visit 8 and then transferred to Part 2.

Subjects for whom an early transfer to Part 2 (prior to Visit 12) was reported as the primary reason for Part 1 discontinuation. A total of 7 subjects transferred to Part 2 early, but another primary reason for discontinuation was reported for 4 of these subjects.

#### Recruitment

Study Sites: Subjects in Part 1 Cohort A were enrolled at a total of 65 sites in North America (34), Europe (29), and Australia (2).

Studied Period: 27 November 2017 (first subject in Cohort A screened) to 25 October 2019 (last subject in Cohort A completed last Part 1 visit); database lock date of 30 January 2020.

# Conduct of the study

Major protocol deviations were summarized for the Safety Population. These included deviations that had the potential to impact subject safety, subject rights, GCP compliance, or analysis of efficacy or safety endpoints. Multiple deviations could occur in the same subject, and thus a subject could be counted in more than 1 deviation category. Major protocol deviations were presented in a subject data listing for the Enrolled Population, sorted by treatment and site.

≥1 major protocol deviation was reported for 138 subjects (52.5%).

**Table 16 Major Protocol Deviations (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 MPD	41 (47.1)	49 (55.1)	48 (55.2)	138 (52.5)
Type of MPD				
Concomitant Medications	13 (14.9)	10 (11.2)	11 (12.6)	34 (12.9)
Dosing	11 (12.6)	11 (12.4)	11 (12.6)	33 (12.5)
Enrollment Criteria	5 (5.7)	5 (5.6)	6 (6.9)	16 (6.1)
Informed Consent	10 (11.5)	14 (15.7)	16 (18.4)	40 (15.2)
Laboratory	12 (13.8)	20 (22.5)	15 (17.2)	47 (17.9)
Non-Compliance	2 (2.3)	1 (1.1)	0	3 (1.1)
Other	0	1 (1.1)	0	1 (0.4)
Visit Schedule	0	1 (1.1)	0	1 (0.4)
Visit/Procedure Required	12 (13.8)	10 (11.2)	15 (17.2)	37 (14.1)

Source: Table 14.1.1.2.1

Abbreviations: MPD=major protocol deviation

Note: Other deviations are those that do not fit into 1 of the prespecified deviation types.

Informed consent deviations were reported for 40 (15.2%) subjects overall.

Concomitant medication deviations affected 34 (12.9%) subjects overall, and were largely related to subjects taking prohibited behavioral medications (13 subjects: clonidine, guanfacine, quetiapine, aripriprazole, risperidone, methylphenidate, clozapine), antihistamines or cold preparations used >5 days (10 subjects), anti-nausea medication (3 subjects), or antidepressants (1 subject). Deviations

were also reported for an AED dose increase for 3 subjects, dose decrease for 3 subjects, and new concomitant medication initiated for 1 subject.

Dosing deviations were reported for 33 (12.5%) subjects overall and included calculated treatment compliance based on returned study drug bottles of >120% (15 subjects), treatment compliance of <80% (8 subjects), inability to perform compliance calculations due to missing study drug bottles (5 subjects), dosing intervals exceeding 12 hours (2 subjects), and errors made in blinded study drug bottle use during Titration (2 subjects) and Transition (2 subjects). Of the 15 subjects with deviations reported for treatment compliance of >120%, only 3 subjects experienced overdosing due to error.

#### **Baseline data**

# **Demographics**

The mean (SD) age was 13.7 (7.59) years, with the majority (187 [71.1%]) of subjects being <18 years of age. Overall, 55.5% of subjects were male. The ZX008 0.8 mg/kg/day group had a greater percentage of male subjects than the other groups. The majority of subjects were white, and the majority of subjects were not Hispanic or Latino. In all of the treatment groups, subjects were approximately evenly distributed between the 2 weight strata (<37.5 kg;  $\geq$ 37.5 kg). The 3 countries that enrolled the most subjects were the US (122 [46.4%]), Spain (25 [9.5%]), and Italy (19 [7.2%]).

Table 17 Demographic and Baseline Characteristics (Safety Population)

	Placebo (N=87)	ZX008 0.2 mg/kg/day (N=89)	ZX008 0.8 mg/kg/day (N=87)	All Subjects (N=263)
	n (%)	n (%)	n (%)	n (%)
Age (years)				
Mean	14.4	13.4	13.4	13.7
SD	7.71	7.79	7.28	7.59
Median	13.0	13.0	13.0	13.0
Min	2	3	2	2
Max	35	35	35	35
Age Group				
2 to <6 years	≤11	17 (19.1)	12 (13.8)	38 (14.4)
6 to <12 years	23 (26.4)	24 (27.0)	25 (28.7)	72 (27.4)
12 to <18 years	29 (33.3)	23 (25.8)	25 (28.7)	77 (29.3)
2 to <18 years	61 (70.1)	64 (71.9)	62 (71.3)	187 (71.1)
18 to 35 years	26 (29.9)	25 (28.1)	25 (28.7)	76 (28.9)
Sex				
Male	46 (52.9)	46 (51.7)	54 (62.1)	146 (55.5)
Female	41 (47.1)	43 (48.3)	33 (37.9)	117 (44.5)
Race				
White	71 (81.6)	67 (75.3)	70 (80.5)	208 (79.1)
Black or African American	≤11	≤11	≤11	12 (4.6)
Asian	≤11	≤11	≤11	≤11
American Indian or Alaskan Native	≤11	≤11	≤11	≤11
Native Hawaiian or Other Pacific Islander	≤11	≤11	≤11	≤11

	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 (%)
Other	≤11	≤11	≤11	≤11
Not Reported	≤11	≤11	≤11	24 (9.1)
Unknown	≤11	≤11	≤11	≤11
Multiple	≤11	≤11	≤11	≤11
Ethnic Group				
Hispanic or Latino	16 (18.4)	21 (23.6)	14 (16.1)	51 (19.4)
Not Hispanic or Latino	65 (74.7)	58 (65.2)	66 (75.9)	189 (71.9)
Not Reported	≤11	≤11	≤11	23 (8.7)
Baseline Height (m)				
n	87	88	87	262
Mean	1.448	1.417	1.417	1.428
SD	0.21.70	0.2453	0.2480	0.2368
Median	1.500	1.475	1.470	1.480
Min	0.93	0.98	0.78	0.78
Max	1.80	1.91	1.88	1.91
Baseline Weight (kg)				
n	87	89	87	263
Mean	43.85	42.36	42.24	42.81
SD	20.673	20.979	21.399	20.951
Median	38.70	41.00	39.00	39.00
Min	12.4	13.0	11.0	11.0
Max	110.0	107.8	127.0	127.0
Baseline Weight, n (%)				
<37.5 kg	42 (48.3)	42 (47.2)	40 (46.0)	124 (47.1)
≥37.5 kg	45 (51.7)	47 (52.8)	47 (54.0)	139 (52.9)
Baseline BMI (kg/m²)				
n	87	88	87	262
Mean	19.74	19.60	19.71	19.68
SD	4.995	5.229	5.075	5.082
Median	18.40	18.90	18.50	18.60
Min	10.6	11.9	9.9	9.9
Max	36.3	47.3	37.2	47.3

Source: Table 14.1.2.1.1

 $Abbreviations:\ BMI=body\ mass\ index,\ where\ BMI=weight\ (kg)/height\ (m^2);\ Max=maximum;\ Min=minimum;\ SD=standard\ deviation$ 

Notes: Percentages are calculated based on the number of subjects with non-missing data in the Safety Population.

<sup>&</sup>quot;Not Reported" and Unknown" values shown for race and ethnicity were valid values on the eCRF.

**Table 18 Geographic Distribution (Safety Population)** 

Region/Country	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 (%)
North America	44 (50.6)	45 (50.6)	43 (49.4)	132 (50.2)
Europe	41 (47.1)	43 (48.3)	38 (43.7)	122 (46.4)
Australia	≤11	≤11	≤11	≤11

Source: Table 14.1.2.1.1

#### **Disease characteristics**

Subjects in this study had seizures that were difficult to control, and most had experienced multiple treatment failures. The enrolled subjects had failed a median of 7 AEDs (range: 1 to 20) and were stabilized on standard of care antiepileptic treatments (Table 14) but were still experiencing high seizure burden, ranging from a median of 53 to 85 drop seizures per 28 days across the treatment groups. In both ZX008 treatment groups, subjects had a greater median DSF in Baseline than did subjects in the placebo group (Table 19).

Table 19 Frequency of Seizures That Result in Drops per 28 Days During Baseline: Summary Statistics (mITT Population)

Frequency	Placebo (N=87)	ZX008 0.2 mg/kg/day (N=89)	ZX008 0.8 mg/kg/day (N=87)
Mean	164.37	223.00	194.99
SD	309.801	435.498	308.894
Median	53.00	85.00	83.00
Min <sup>a</sup>	2.0	4.1	6.5
Max	1761.0	2943.0	1803.0

Source: Table 14.2.1.1.1.1

Abbreviations: ESC=Epilepsy Study Consortium; Max=maximum; Min=minimum; mITT=Modified Intent-to-Treat; SD=standard deviation

The incidence of each type of drop seizure during Baseline is summarized in Table 20. The seizure types experienced by the most subjects during Baseline were TS, GTC, and AS.

a All subjects with <8 seizures that resulted in drops during Baseline were documented as major protocol deviations and omitted from the Per Protocol Population. Six subjects experienced <8 seizures that resulted in drops during Baseline.

Table 20 Incidence of Seizures That Result in Drops During Baseline (Mitt Population)

	Placebo	ZX008 0.2 mg/kg/day	ZX008 0.8 mg/kg/day	Total
	(N=87)	(N=89)	(N=87)	(N=263)
Subjects experiencing the seizure type, n (9	%)	•	•	•
Generalized tonic-clonic	40 (46.0)	38 (42.7)	39 (44.8)	117 (44.5)
Secondarily generalized tonic-clonic	8 (9.2)	6 (6.7)	9 (10.3)	23 (8.7)
Tonic	68 (78.2)	67 (75.3)	67 (79.3)	202 (76.8)
Atonic	31 (35.6)	34 (38.2)	36 (41.4)	101 (38.4)
Tonic/atonic	21 (24.1)	21 (23.6)	16 (18.4)	58 (22.1)

Source: Table 14.2.4.4.1.1

Abbreviations: ESC=Epilepsy Study Consortium; mITT=Modified Intent-to-Treat

Table 21 Number of Prior Antiepileptic Drugs Taken per Subject (Safety Population)

	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%)
Number of prior AEDs	•	·	•	•
Mean	6.68	6.77	7.58	7.01
SD	3.699	3.558	4.146	3.814
Median	6.00	7.00	7.00	7.00
Min	1	1	1	1
Max	19	18	20	20

Table 22 presents the most commonly used prior AEDs (≥25% of all subjects). Differences of >10% between any of the treatment groups in subject usage of prior AEDs were noted for the following: clobazam, lamotrigine, perampanel, rufinamide, and topiramate.

**Table 22 Prior Antiepileptic Drugs Taken ≥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 <sup>a</sup>	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)

## **Concomitant AEDs and other therapies**

Most subjects (98.9%) received between 1 and 4 concomitant AEDs, the median number of concomitant AEDs was 3. The most commonly used concomitant AEDs ( $\geq$  25% of subjects overall) were clobazam, lamotrigine, and valproate.

# Table 23 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 concomita	ant 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 24 Concomitant Antiepileptic Drugs Taken per Subject** 

# (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 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)

#### **AEDs**

Most subjects (231 [87.8%]) took  $\geq 1$  concomitant medication. The most common concomitant medications and therapies ( $\geq 15\%$  of subjects overall) included the following: VNS (82 subjects [31.2%]), paracetamol (57 subjects (21.7%]), and melatonin (51 subjects [19.4%]). Note that no subjects received concomitant STP.

# **Numbers analysed**

Planned: Approximately 340 subjects were planned for screening to obtain approximately 250 subjects randomized into Part 1 Cohort A.

Enrolled: A total of 335 subjects were screened and 263 subjects were randomized into Part 1 Cohort A. 247 subjects were enrolled in Part 2.

Table 25 Study Populations (Part 1 Cohort A)

	Placebo	ZX008 0.2 mg/kg/day	ZX008 0.8 mg/kg/day	Total
Enrolled Population <sup>a</sup>	_	_	_	335
Modified ITT Population <sup>b</sup>	87	89	87	263
Per Protocol Population <sup>c</sup>	69	71	69	209
Safety Population d	87	89	87	263

Source: Table 14.1.1.3.1

Abbreviations: ITT=Intent-to-Treat

- a All subjects who gave informed consent/assent.
- b All randomized subjects who received at least 1 dose of ZX008 or placebo and for whom at least 1 week of eDiary data were available
- c All randomized subjects who received at least 1 dose of ZX008 or placebo, completed at least 4 weeks of Maintenance, and had no protocol deviations that would have a significant impact on clinical outcome.
- d All randomized subjects who received at least 1 dose of ZX008 or placebo.

## **Table 26 Study Populations**

		Part 1 Treatment			
	Placebo	ZX008 0.2 mg/kg/day	ZX008 0.8 mg/kg/day	Overall	
Part 1 Safety (DB SAF) Population <sup>a</sup>	87	89	87	263	
Open Label Safety (OLE Safety) Population <sup>b</sup>	86	83	78	247	
Open Label mITT (OLE mITT) Population <sup>c</sup>	85	78	78	241	
Long Term Safety (LT SAF) Population <sup>d</sup>	86	89	87	262	

Source: Table 14.1.1.3.3.

DB = double-blind, LT SAF = long-term safety, mITT = Modified Intent-to-Treat, OLE = Open-Label Extension, SAF = safety.

- a DB SAF Population: All randomized subjects who receive at least one dose of ZX008 or placebo in Part 1.
- b OLE Safety Population: All subjects who receive at least one dose of ZX008 during the open-label extension.
- c OLE mITT Population: All randomized subjects who receive at least one dose of ZX008 and have a valid estimate of the frequency of seizures that result in drops from Part 1 and at least one month (30 days) of valid seizure data during the openlabel extension.
- d LT SAF Population: All subjects who received at least one dose of ZX008 during Part 1 or Part 2. For subjects treated with Placebo in Part 1 and who were treated with ZX008 in Part 2, the first dose of active ZX008 would occur in the Part 1 transition period

## **Outcomes and estimation**

Results from the statistical analysis of the primary and key secondary efficacy endpoints and other clinically meaningful data are summarized for the mITT Population in Table 20.

Table 27 Summary of Statistical Results: Primary and Key Secondary Efficacy Endpoints and Other Clinically Meaningful Data (Mitt Population)

-	-	-	-	•
	Comparison	Analysis	Table Reference	p-value
Primary Efficacy Endpoint				
Percentage change from BL in DSF during T+M	ZX008 0.8mg/kg/day vs placebo	Nonparametric ANCOVA	14.2.1.2.1.1	0.0013
Key Secondary Efficacy Endpoints			•	
<ol> <li>Percentage of subjects with ≥50% reduction from BL in DSF during T+M</li> </ol>	ZX008 0.8 mg/kg/day vs placebo	Logistic regression	14.2.1.4.1.1	0.0150
Percentage of subjects with improvement <sup>a</sup> on CGI-I, Investigator rating at Visit 12	ZX008 0.8 mg/kg/day vs placebo	Cochran-Mantel- Haenszel	14.2.2.1.1.1	0.0567
4) Percentage change from BL in DSF during T+M	ZX008 0.2 mg/kg/day vs placebo	Nonparametric ANCOVA	14.2.1.2.1.1	0.0939
5) Percentage of subjects with ≥50% reduction from BL in DSF during T+M	ZX008 0.2 mg/kg/day vs placebo	Logistic regression	14.2.1.4.1.1	0.0051 b
Percentage of subjects with improvement <sup>a</sup> on CGI-I, Investigator rating at Visit 12	ZX008 0.2 mg/kg/day vs placebo	Cochran-Mantel- Haenszel	14.2.2.1.1.1	0.1565
Percentage of subjects with clinically meaningful improvement <sup>c</sup> on CGI-I, Investigator rating at Visit 12	ZX008 0.8 mg/kg/day vs placebo	Cochran-Mantel- Haenszel	14.2.2.1.1.1	0.0007
Percentage of subjects with clinically meaningful improvement <sup>c</sup> on CGI-I, Investigator rating at Visit 12	ZX008 0.2 mg/kg/day vs placebo	Cochran-Mantel- Haenszel	14.2.2.1.1.1	0.0100

Abbreviations: ANCOVA=analysis of covariance; BL=Baseline Period; CGI-I=Clinical Global Impression – Improvement; DSF=drop seizure frequency; mITT=Modified Intent-to-Treat; T+M=Titration + Maintenance Periods

# Primary endpoint and Third key secondary endpoint: Change from Baseline in Drop Seizure Frequency

Results of the primary nonparametric ANCOVA analysis of this endpoint are presented for the mITT Population in Table 8. These results demonstrated a statistically significant benefit for ZX008 0.8 mg/kg/day compared with placebo on the percentage change in DSF between the 4-week Baseline and the 14-week T+M (26.5% vs 7.6%, respectively, p = 0.0013). Median percentage changes from Baseline in DSF during T+M in the mITT Population are shown in Figure 6.

As third key secondary endpoint, the change from Baseline in DSF during T+M for the ZX008 0.2 mg/kg/day group was compared with the placebo group (p=0.0939).

a Minimally, much, or very much improved

b Although nominally significant, this p-value was not of statistical significance due to the serial gatekeeper strategy employed to maintain the Type 1 error rate at α=0.05.

Much or very much improved

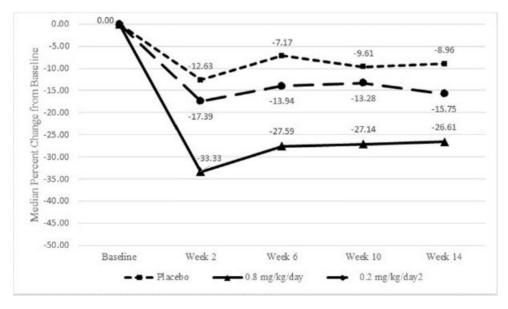
Table 28 Drop Seizure Frequency: T+M, Nonparametric Analysis (Mitt Population)

Drop Seizure Frequency	Placebo (N=87)	ZX008 0.2 mg/kg/day (N=89)	ZX008 0.8 mg/kg/day (N=87)
BL Summary Statistics <sup>a</sup>	•		•
Mean (SD)	164.37 (309.801)	223.00 (435.498)	194.99 (308.894)
Median	53.00	85.00	83.00
Min, Max	2.0, 1761.0	4.1, 2943.0	6.5, 1803.0
T+M Summary Statistics <sup>a</sup>		•	
Mean (SD)	145.20 (263.158)	247.30 (608.984)	162.60 (285.294)
Median	46.85	61.82	54.57
Min, Max	0.0, 1683.8	0.0, 5110.9	0.3, 1562.0
Percentage Change from BL <sup>a</sup>		•	
Mean (SD)	4.57 (85.948)	33.69 (363.836)	-21.11 (59.610)
Median	-7.59	-14.16	-26.49
Min, Max	-100.0, 557.1	-100.0, 3307.3	-925.2, 402.1
Nonparametric Model <sup>b</sup>			
p-value for comparison with placebo	_	0.0939	0.0013
HL Estimate for Median Difference (A-P)			
Estimate (Std Err)	_	-10.50 (7.391)	-19.88 (5.684)
95% CI	_	-24.99, 3.99	-31.02, -8.74

Source: 1601 Part 1 CSR Table 21

ANCOVA = analysis of covariance; A-P = active group-placebo group; BL = Baseline Period; CI = confidence interval; HL = Hodges-Lehmann; Max=maximum; Min = minimum; mITT = Modified Intent-to-Treat; SD = standard deviation; Std Err = standard error; T+M = Titration + Maintenance Periods

Figure 6 Median Percentage Change in Drop Seizure Frequency (Mitt Population)



First and fourth key secondary endpoints: Percentage of Subjects with ≥50% Reduction from Baseline in Drop Seizure Frequency

a BL, T+M, and percentage change from BL in T+M values for seizure frequency per 28 days are presented in original scale.

b Results are based on a nonparametric ANCOVA model with treatment group (3 levels) and weight strata (< 37.5 kg, ≥ 37.5 kg) as factors, rank of BL seizure frequency as a covariate, and rank of percentage change from BL in seizure frequency during treatment period (T+M) as response.</p>

The percentage of subjects with a  $\geq$ 50% reduction from Baseline in DSF (50% responder rate) during T+M in the ZX008 0.8 mg/kg/day group compared with the placebo group was the first key secondary endpoint.

Table 29 Percentage of Subjects Who Achieved a ≥50% Reduction from Baseline in DSF (mIIT Population)

	Placebo (n=87)	ZX008 0.2 mg/kg/day (n=89)	ZX008 0.8 mg/kg/day (n=87)
T+M		·	
≥50% reduction in DSF, n (%)	9 (10.3)	25 (28.1)	22 (25.3)
Odds ratio (95% CI)		3.30 (1.43, 7.59)	2.87 (1.23, 6.70)
p-value for comparison with placebo a		0.0051	0.0150
Maintenance		•	•
≥50% reduction in DSF, n (%)	11 (12.6)	28 (31.8)	27 (31.4)
Odds ratio (95% CI)		3.13 (1.44, 6.82)	3.12 (1.43, 6.84)
p-value for comparison with placebo a		0.0041	0.0044

Source: Table 14.2.1.4.1.1

Abbreviations: CI=confidence interval; DSF=drop seizure frequency; mITT=Modified Intent-to-Treat; T+M=Titration + Maintenance Periods

# Second and fifth key secondary endpoints: Percentage of Subjects Rated as Improved on Clinical Global Impression – Improvement - Investigator Rating

The number and percentage of subjects who were rated by the Investigator as improved at the EOS Visit (Week 12, Day 99) were numerically greater in the ZX008 0.8 mg/kg/day group (39 [48.8%]) compared with the placebo group (27 [33.8%]) (p=0.0567) (Table 30).

Based on a logistic regression model that included a categorical response variable (achieved percentage point reduction, yes or no), weight group strata (<37.5 kg, ≥37.5 kg), and Baseline DSF as a covariate.</p>

Table 30 Investigator Ratings of Improvement on the Clinical Global Impression – Improvement Scale at Visit 12 (mITT Population)

Summary Description	Placebo (N=87)	ZX008 0.2 mg/kg/day (N=89)	ZX008 0.8 mg/kg/day (N=87)
Visit 12, Day 99 Summary Statistics	·		•
n	80	85	80
Mean	3.69	3.45	3.38
Std Err	0.081	0.118	0.128
Median	4.00	4.00	4.00
Min, Max	2.0, 5.0	1.0, 6.0	1.0, 7.0
Subjects with CGI-I scores at Visit 12, Da	y 99, n (%)		•
1=Very much improved	0	4 (4.7)	2 (2.5)
2=Much improved	5 (6.3)	13 (15.3)	19 (23.8)
3=Minimally improved	22 (27.5)	21 (24.7)	18 (22.5)
4=No change	46 (57.5)	37 (43.5)	33 (41.3)
5=Minimally worse	7 (8.8)	8 (9.4)	5 (6.3)
6=Much worse	0	2 (2.4)	2 (2.5)
7=Very much worse	0	0	1 (1.3)
Clinically Meaningful Improvement	•	•	•
Subjects with score 1 or 2, n (%)	5 (6.3)	17 (20.0)	21 (26.3)
Odds ratio vs placebo (95% CI) a		3.73 (1.31, 10.65)	5.30 (1.89, 14.87)
p-value vs placebo <sup>b</sup>		0.0100	0.0007
Improvement	<del></del> -		•
Subjects with score 1, 2, or 3, n (%)	27 (33.8)	38 (44.7)	39 (48.8)
Odds ratio vs placebo (95% CI) <sup>a</sup>		1.58 (0.84, 2.97)	1.86 (0.98, 3.52)
p-value vs placebo <sup>b</sup>		0.1565	0.0567

Source: Table 14.2.2.1.1.1

Abbreviations: CGI-I=Clinical Global Impression – Improvement; CI=confidence interval; Max=maximum; Min=minimum; mITT=Modified Intent-to Treat; Std Err=standard error

# **Ancillary analyses**

## **Supplemental Analyses of the primary endpoint**

# - Change from Baseline in Drop Seizure Frequency: Maintenance

A supplemental analysis of the change from Baseline in DSF during Maintenance alone was performed for the mITT Population using the same nonparametric model as was used for the primary analysis of the change during T+M.

a Estimated Cochran-Mantel-Haenszel odds ratio adjusting for weight strata

b p-value from Cochran-Mantel-Haenszel test comparing active treatment with placebo, after adjusting for weight strata

Table 31 Drop Seizure Frequency: Maintenance, Nonparametric Analysis (mITT Population)

	Placebo	ZX008 0.2 mg/kg/day	ZX008 0.8 mg/kg/day
Drop Seizure Frequency	(N=87)	(N=89)	(N=87)
BL Summary Statistics (n)	87	88	86
Mean (SD)	164.37 (309.801)	225.19 (437.504)	190.99 (308.431)
Median	53.00	87.00	82.00
Min, Max	2.0, 1761.0	4.1, 2943.0	6.5, 1803.0
M Summary Statistics <sup>a</sup>	•	•	•
Mean (SD)	141.75 (253.093)	203.23 (342.336)	157.68 (280.125)
Median	47.33	59.17	55.73
Min, Max	0.0, 1588.1	0.0, 1844.0	0.0, 1527.1
Percentage change from BL	•	•	•
Mean (SD)	4.56 (88.422)	-0.70 (122.506)	-18.61 (83.534)
Median	-7.28	-18.63	-27.16
Min, Max	-100.0, 516.7	-100.0, 964.0	-100.0, 643.3
Nonparametric model <sup>b</sup>			
p-value for comparison with placebo	_	0.0764	0.0018
HL Estimate for Median Difference (A-P)			
Estimate (Std Err)	_	-11.48 (7.543)	-20.25 (5.795)
95% CI	_	(-26.26, 3.31)	(-31.61, -8.89)

Source: Table 14.2.1.2.1.1, Table 14.2.1.8.1

Abbreviations: ANCOVA=analysis of covariance; A-P=active group-placebo group; BL=Baseline Period; CI=confidence interval; ESC=Epilepsy Study Consortium; HL=Hodges-Lehmann; M=Maintenance Period; Max=maximum; Min=minimum; mITT=Modified Intent-to-Treat; SD=standard deviation; Std Err=standard error

# - Change from Baseline in Drop Seizure Frequency: T+M and Maintenance, Parametric Analysis

Another supplemental analysis compared the change from Baseline in DSF during T+M and during Maintenance between the ZX008 and placebo groups using a parametric ANCOVA model (1601 Part 1 CSR Table 32).

a BL and percentage change from BL in Maintenance values for seizure frequency per 28 28 days are presented in original scale.

b Results are based on a nonparametric ANCOVA model with treatment group (3 levels) and weight strata (<37.5 kg, ≥37.5 kg) as factors, rank of BL seizure frequency as a covariate, and rank of percentage change from BL in seizure frequency during treatment (Maintenance) as response.</p>

# Table 32 Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A - North America, Europe, Australia) mITT Population

Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A - North America, Europe, Australia) mITT Population

	Placebo (N-87)	ZX008 0.2 mg/kg/day (N-89)	ZX008 0.8 mg/kg/day (N-87)
Titration and Maintenance (T+M) Period Analysis	(11 31)	(11 00)	(1. 51)
Baseline Summary Statistics n Mean (SD) Median Min, Max	87 164.37 (309.801) 53.00 2.0, 1761.0	89 223.00 (435.498) 85.00 4.1, 2943.0	87 194.99 (308.894) 83.00 6.5, 1803.0
T+M Period Summary Statistics Observed			
n Mean (SD) Median Min, Max	87 145.20 (263.158) 46.85 0.0, 1683.8	89 247.30 (608.984) 61.82 0.0, 5110.9	87 162.60 (285.294) 54.57 0.3, 1562.0
Change from Baseline n Mean (SD) Median Min, Max	87 -19.17 (129.267) -2.57 -907.4, 270.4	89 24.30 (577.941) -7.03 -1565.4, 4960.9	87 -32.39 (145.341) -16.96 -854.5, 385.0
Percentage Change from Baseline n Mean (SD) Median Min, Max	87 4.57 (85.948) -7.59 -100.0, 557.1	89 33.69 (363.836) -14.16 -100.0, 3307.3	87 -21.11 (59.610) -26.49 -95.2, 402.1
T+M Period: Parametric Model [1] Results on log scale [1] Least Squares Mean (SE) [1] 95% CI for Least Squares Mean [1] Difference from Placebo: Estimate of A-P(95% CI) [1] p-value for comparison with Placebo [2]	4.33 (0.073) (4.19, 4.48)	4.18 (0.073) (4.04, 4.32) -0.15(-0.36, 0.05) 0.1430	4.03 (0.073) (3.88, 4.17) -0.30(-0.51, -0.10) 0.0038
Original scale Loast Squares Mean (SE) [3] Comparison with Placebo: Estimate of Ratio (95% CI)[3] Estimate of % Difference from Placebo (95% CI)[4]	76.10 (1.076)	65.37 (1.075) 0.86(0.70, 1.05) 14.10 (-5.31, 29.93)	56.13 (1.076) 0.74(0.60, 0.91) 26.24 (9.46, 39.91)
Maintenance (M) Period	\· /	<i>()</i>	\··/
Baseline Summary Statistics			
n Mean (SD) Median Min, Max	87 164.37 (309.801) 53.00 2.0, 1761.0	88 225.19 (437.504) 87.00 4.1, 2943.0	86 190.99 (308.431) 82.00 6.5, 1803.0
Maintenance Period Summary Statistics Observed			
n Mean (SD) Median Min, Max	87 141.75 (253.093) 47.33 0.0, 1588.1	88 203.23 (342.336) 59.17 0.0, 1844.0	86 157.68 (280.125) 55.73 0.0, 1527.1
Change from Baseline	07	00	0.0
n Mean (SD) Median Min, Max	87 -22.62 (156.603) -2.41 -1112.4, 415.6	88 -21.96 (297.757) -8.50 -1765.3, 1446.0	86 -33.32 (152.486) -17.96 -910.0, 350.1
Percentage Change from Baseline n Mean (SD) Median Min, Max Maintenance Period: Parametric Model [1]	87 4.56 (88.422) -7.28 -100.0, 516.7	88 -0.70 (122.506) -18.63 -100.0, 964.0	86 -18.61 (83.534) -27.16 -100.0, 643.3
Maintenance Perfor. Transmetric Model [1] Results on log scale [1] Least Squares Mean (SE) [1] 95% CI for Least Squares Mean [1] Difference from Placebo: Estimate of A-P(95% CI) [1] p-value for comparison with Placebo [2]	4.31 (0.081) (4.15, 4.47)	4.09 (0.080) (3.94, 4.25) -0.22(-0.44, 0.01) 0.0564	3.96 (0.081) (3.80, 4.12) -0.35(-0.58, -0.13) 0.0023
Original scale Least Squares Mean (SE) [3] Comparison with Placebo: Estimate of Ratio (95% CI)[3] Estimate of % Difference from Placebo (95% CI)[4]	74.64 (1.084)	59.97 (1.084) 0.80(0.64, 1.01) 19.66 (-0.61, 35.84)	52.40 (1.085) 0.70(0.56, 0.88) 29.79 (11.97, 44.00)

ESC - Epilepsy Study Consortium, mITT - Modified intent-to-treat, CI - Confidence Interval, ANCOVA - Analysis of Covariance, M - Maintenance, T+M - Titration + Maintenance, SE - Standard Error, A-P - Active arm - Placebo arm.

Note: The seizure types included in the count are: atonic, tonic, tonic/atonic, generalized tonic-clonic, and secondarily tonic-clonic seizures resulting in drops.

resulting in drops.

[1]Baseline, M, and T+M period values were log transformed prior to analysis. The M and T+M values have + 1 added prior to transform.

[2]Results are based on an ANCOVA model with treatment group (three levels) and weight strata (< 37.5 kg, >- 37.5 kg) as factors, log baseline seizure frequency as a covariate and log (seizure frequency + 1) for the Titration + Maintenance or Maintenance period as response. The p-value is obtained from this ANCOVA model.

[3]The LSMean and A-P difference and CI on the log scale were exponentiated.

[4]This is obtained from the LSMeans on the log scale as follows: 100 x [1 - exp(1s mean active - 1s mean placebo)].

Program: t-14-02-01-03-01.sas Output: 16.1.9.2.1.3.1.1.rtf Data Source: Listing 16.2.6.1.2.1 Date: 02JUL2021 11:37

# - Change from Baseline in Drop Seizure Frequency: Treatment by Baseline Seizure Frequency Category Interaction

Additional supplemental nonparametric and parametric analyses evaluated the treatment-by- Baseline drop seizure frequency category interaction for the change from Baseline in DSF during T+M and during Maintenance alone. Baseline DSF was categorized using tertiles; that is, subjects were divided into 3 equally sized groups based on their DSF during Baseline. The lowest tertile contained 87 subjects who had a DSF between 2 and 43 during Baseline. The middle tertile contained 88 subjects with Baseline DSF between 44 and 122, while the highest tertile contained 88 subjects with Baseline DSF of 124 or greater.

The nonparametric analysis suggested that the difference between both ZX008 0.8 and 0.2 mg/kg/day and placebo was most pronounced among the subjects with the lowest frequency of seizures during Baseline. However, neither the effect due to Baseline tertile, nor the interaction between treatment and Baseline tertile were statistically significant in the model (p = 0.1981 and p = 0.2131, respectively).

Table 33 Percentage Change from Baseline in Drop Seizure Frequency: T+M, Analysis with Categorized Baseline Seizure Frequency (mITT Population)

Percentage Change in Drop Seizure Frequency	Placebo (N=87)	ZX008 0.2 mg/kg/day (N=89)	ZX008 0.8 mg/kg/day (N=87)
BL-DSF=2-43	•	•	•
n	37	27	23
Mean (SD)	23.56 (116.811)	9.34 (155.454)	-12.18 (97.397)
Median	-3.88	-30.53	-31.71
Min, Max	-100.0, 557.1	-100.0, 700.9	-95.2, 402.1
p-value for comparison with placebo <sup>a</sup>		0.0152	0.0067
BL-DSF=44-122	•	•	•
n	25	29	34
Mean (SD)	-7.45 (59.154)	-25.91 (39.556)	-30.17 (39.268)
Median	-19.23	-36.54	-29.33
Min, Max	-78.7, 244.8	-84.2, 41.4	-86.0, 93.8
p-value for comparison with placebo <sup>a</sup>		0.2665	0.0561
BL-DSF=124-2943	•	•	•
n	25	33	30
Mean	-11.50 (39.101)	106.00 (577.858)	-17.70 (37.617)
Median	-11.21	-7.37	-19.98
Min, Max	-80.8, 58.0	-78.8, 3307.3	-84.1, 71.8
p-value for comparison with placebo a		0.3669	0.6928

p-value for the effect of Baseline tertile: 0.1981

p-value for the interaction between treatment and Baseline tertile: 0.2131

Source: Table 14.2.1.2.1.3

Abbreviations: ANCOVA=analysis of covariance; BL-DSF=Baseline Period drop seizure frequency; Max=maximum; Min=minimum; mITT=Modified Intent-to-Treat; SD=standard deviation; T+M=Titration + Maintenance Periods

Results of the analysis for the change from Baseline in DSF during Maintenance and the results of the parametric analyses were similar to those of the nonparametric analysis.

## - Change from Baseline in Drop Seizure Frequency: T+M, Sensitivity Analyses

Several sensitivity analyses of the primary endpoint during T+M and during Maintenance (M) alone were performed. When the primary nonparametric ANCOVA analysis was repeated excluding extreme outliers, not imputing for seizure clusters, and using 2 different methods for imputation of missing data due to subject dropout, the results were similar to those of the primary analysis in each case on the mITT Population. An additional analysis that used the Wilcoxon rank-sum test in place of the nonparametric ANCOVA had results similar to those of the primary analysis.

Results of analyses repeated using the PP Population rather than the mITT Population also were similar to the primary analysis results.

#### - Change from Baseline in Drop Seizure Frequency: by Seizure Type

At a subject level, the most common seizures during Baseline in the mITT Population were TS (76.8% of subjects overall [78.2% placebo, 79.3% ZX008 0.8 mg/kg/day]), GTC (44.5% [46.0%, 44.8%]), and AS (38.4% [35.6%, 41.4%]).

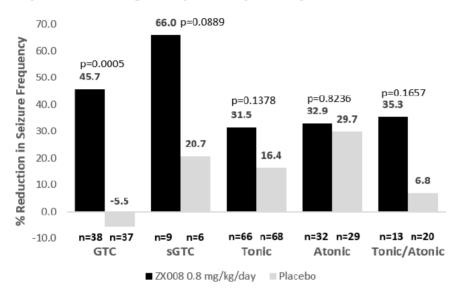
The median percentage change from Baseline in the frequency per 28 days of each of the 5 types of drop seizures during T+M was analyzed for the mITT Population using pairwise Wilcoxon rank-sum tests for comparisons between the ZX008 and placebo groups (Figure 7). The frequency of each seizure type in the ZX008 0.8 mg/kg/day group was reduced from Baseline to a greater or similar extent compared with the placebo group. ZX008 0.8 mg/kg/day had the greatest magnitude of effect

Based on a nonparametric ANCOVA model with treatment group (3 levels) and weight strata (<37.5 kg, ≥37.5 kg), and BL seizure frequency as a covariate, and rank of percent change from BL in seizure frequency during treatment (T+M) as

in reducing GTC frequency relative to placebo (p = 0.0005), with a median percentage change from Baseline of -45.7%, compared with 5.5% for the placebo group. Improvements in GTCs are clinically significant because this seizure type is associated with increased injuries and hospitalizations and are a major risk factor for SUDEP; the SUDEP risk increases in association with increasing frequency of GTC (Harden 2017; Sveinsson 2020).

Similar results were observed for the changes from Baseline during Maintenance in the frequency per 28 days of each of the 5 types of drop seizures. ZX008 0.8 mg/kg/day also had the greatest magnitude of effect in reducing GTC frequency relative to placebo (p = 0.0005).

Figure 7 Median Percentage Reduction from Baseline in Frequency per 28 Days of Each Type of Drop Seizure During T+M (mITT Population)



Source: 1601 Part 1 CSR Figure 2

GTC = generalized tonic-clonic seizure; mITT = Modified Intent-to-Treat; SGTC = secondarily generalized tonic-clonic seizure;

T+M = Titration + Maintenance Periods

Note: Treatment groups were compared using pairwise Wilcoxon rank-sum tests.

# - Responder Analyses of the Percentage of Subjects Achieving Reductions or Worsening from Baseline in Drop Seizure Frequency

A statistically significantly lower percentage of subjects in the ZX008 0.8 mg/kg/day group experienced worsening (increases) or no change from Baseline in DSF during T+M compared with the placebo group (p = 0.0229).

Table 34 Percentage of Subjects Who Achieved ≥50% Reduction from Baseline in Drop Seizure Frequency per 28 Days and Additional Reduction Thresholds (mITT Population)

	Placebo (N = 87)	ZX008 0.2 mg/kg/day (N = 89)	ZX008 0.8 mg/kg/day (N = 87)
T+M Distribution of Percentage Change from I	BL DSF	·	
n	87	89	87
Worsening or No Change (≤ 0%), n (%)	33 (37.9)	31 (34.8)	19 (21.8)
Odds ratio (95% CI)		0.90 (0.48, 1.68)	0.46 (0.23, 0.90)
p-value <sup>a</sup>		0.7411	0.0229
> 0%, n (%)	54 (62.1)	58 (65.2)	68 (78.2)
Odds ratio (95% CI)		1.11 (0.60, 2.07)	2.19 (1.11, 4.30)
p-value <sup>a</sup>		0.7411	0.0229
≥ 25%, n (%)	27 (31.0)	42 (47.2)	45 (51.7)
Odds ratio (95% CI)		1.91 (1.02, 3.57)	2.39 (1.28, 4.49)
p-value <sup>a</sup>		0.0417	0.0065
≥ 50%, n (%)	9 (10.3)	25 (28.1)	22 (25.3)
Odds ratio (95% CI)		3.30 (1.43, 7.59)	2.87 (1.23,6.70)
p-value <sup>a</sup>		0.0051	0.0150
≥ 75%, n (%)	4 (4.6)	9 (10.1)	7 (8.0)
Odds ratio (95% CI)		2.68 (0.78, 9.21)	1.97 (0.55, 7.09)
p-value <sup>a</sup>		0.1174	0.2971
= 100%, n (%)	1 (1.1)	1 (1.1)	0
Odds ratio (95% CI)	2 (212)	1.84 (0.06, 58.39)	NA
p value <sup>a</sup>		0.7303	NA
Near seizure free (0 or 1 observed seizure), n (%)	1 (1.1)	2 (2.2)	1 (1.1)
Odds ratio (95% CI)		8.23 (0.21, 317.92)	NA
p value <sup>a</sup>		0.2583	NA
Maintenance Distribution of Percentage Chang	e from BL DSF		
n	87	88	86
Worsening or No Change (≤ 0%), n (%)	35 (40.2)	31 (35.2)	18 (20.9)
Odds ratio (95% CI)		0.84 (0.45, 1.57)	0.39 (0.20, 0.78)
p-value <sup>a</sup>		0.5917	0.0077
> 0%, n (%)	52 (59.8)	57 (64.8)	68 (79.%)
Odds ratio (95% CI)		1.18 (0.64, 2.20)	2.53 (1.28, 5.02)
p-value <sup>a</sup>		0.5917	0.0077
≥ 25%, n (%)	29 (33.3)	41 (46.6)	46 (53.5)
Odds ratio (95% CI)		1.68 (0.91, 3.11)	2.30 (1.23, 4.29)
p-value <sup>a</sup>		0.0998	0.0090
≥ 50%, n (%)	11 (12.6)	28 (31.8)	27 (31.4)
Odds ratio (95% CI)		3.13 (1.44, 6.82)	3.12 (1.43, 6.84)
p value <sup>a</sup>		0.0041	0.0044
≥ 75%, n (%)	3 (3.4)	10 (11.4)	12 (14.0)
Odds ratio (95% CI)	Ç/	4.22 (1.10, 16.21)	4.62 (1.25, 17.09)
p-value a		0.0358	0.0217
= 100%, n (%)	1 (1.1)	3 (3.4)	2 (2.3)
Odds ratio (95% CI)	- \/	12.69 (0.36, 450.56)	3.83 (0.26, 56.75)
p value <sup>a</sup>		0.1629	0.3289
Near seizure free (0 or 1 observed seizure), n (%)	1 (1.1)	4 (4.5)	2 (2.3)
Odds ratio (95% CI)		NA	3.83 (0.26, 56.75)
p value <sup>a</sup>		NA	0.3289

BL = Baseline; CI = confidence interval; DSF = drop seizure frequency; mITT = Modified Intent-to-Treat; T+M = Titration + Maintenance Periods

Based on a logistic regression model that included a categorical response variable (achieved percentage point reduction, yes or no), weight group strata (< 37.5 kg, ≥ 37.5 kg), and Baseline DSF as a covariate. If the logistic model with treatment and Baseline seizure frequency was not convergent, then NA is presented for the odds ratio, 95% confidence interval, and p-value.</p>

#### - Number of seizure free days

The comparison of drop seizure-free days between the ZX008 0.8 mg/kg/day and placebo groups was statistically significant (p = 0.0293). The median percentage increase from Baseline in the number of drop seizure free days in the ZX008 0.8 mg/kg/day group was 38.9%, with a median absolute change of 1.4 days (range: -10.4 to 20.3), compared with a median percentage increase of 13.8%, with a median absolute change of 0.6 days (range: -11.3 to 14.7) in the placebo group. When the number of monthly drop seizure-free days during Maintenance alone was analyzed in the same manner, the comparisons between each of the ZX008 groups and the placebo group were not statistically significant (p = 0.1741).

#### **Per Protocol Efficacy Analyses**

The analyses of changes from Baseline in DSF during T+M, the 50% responder rate during T+M, and the percentages of subjects rated by the Investigator as improved and as clinically meaningfully improved on the CGI-I at Week 12 were repeated for the PP Population. Results of these analyses are summarized in Table 35. The results mirrored the mITT Population results, with the exception that for the PP Population, the percentage of subjects in the ZX008 0.8 mg/kg/day group who achieved a  $\geq$ 50% reduction from Baseline in DSF during T+M was not significantly greater than in the placebo group (p=0.0643).

Table 35 Per-Protocol Population Analyses: Primary, Key Secondary, and Select Additional Secondary Efficacy Endpoints and Other Clinically Meaningful Data

	Placebo N=69	ZX008 0.2 mg/kg/day N=71	ZX008 0.8 mg/kg/day N=69
Percentage change from BL in DSF during T+M	11-09	N-/1	14-09
Median (min, max)	-8.43 (-80.8, 400.2)	-10.85 (-89.0, 249.9)	-26.49 (-91.9, 402.1)
p-value <sup>a</sup>		0.1101	0.0120
Percentage of subjects with ≥50% reduction from BL in DSF during T+M			
n (%)	7 (10.1)	20 (28.2)	15 (21.7)
p-value <sup>b</sup>		0.0112	0.0643
Percentage of subjects with improvement <sup>c</sup> on CGI-I, Investigator rating at Visit 12	,		
n (%)	23 (35.9)	27 (39.1)	34 (54.0)
p-value <sup>d</sup>		0.7157	0.0424
Percentage of subjects with clinically meaningful improvement * on CGI-I, Investigator rating at Visit 12			
n (%)	4 (6.3)	10 (14.5)	18 (28.6)
p-value <sup>d</sup>		0.1273	0.0010

Source: Table 14.2.1.2.2.1, Table 14.2.1.4.2.1, Table 14.2.2.1.2.1

Abbreviations: ANCOVA=analysis of covariance; BL=Baseline Period; CGI-I=Clinical Global Impression – Improvement; DSF=drop seizure frequency; Max=maximum; Min=minimum; T+M=Titration + Maintenance Periods

- a Based on a nonparametric ANCOVA model with treatment group (3 levels) and weight strata (<37.5 kg, ≥37.5 kg) as factors, rank of BL seizure frequency as a covariate, and rank of percentage change from BL in seizure frequency during treatment (T+M) as response.</p>
- b Based on a logistic regression model that included a categorical response variable (achieved percentage point reduction, yes or no), weight group strata (<37.5 kg, ≥37.5 kg), and BL DSF as a covariate.</p>
- c Minimally, much, or very much improved
- d Based on Cochran-Mantel-Haenszel test comparing active treatment with placebo, after adjusting for weight strata
- e Much or very much improved

#### Other seizure types

The change from Baseline in all countable motor seizures, which include all seizures of the types GTC, SGTC, TS, AS, TA, CS, HS, and FS with observable motor signs, per 28 days during T+M was analyzed

for the mITT Population as a secondary endpoint using the same nonparametric ANCOVA model as used for the primary endpoint. ZX008 0.8 mg/kg/day had a statistically significant benefit in reducing countable motor seizures compared with placebo (p = 0.0025). The median percentage changes in the frequencies of GTC, SGTC, TS, AS, and TA are presented above. FS with clearly observable signs were experienced by approximately 20.2% of subjects during Baseline. The comparisons between 0.8 mg/kg/day and placebo groups did not reach statistical significance (p = 0.1833). Clonic seizures were experienced by few subjects during Baseline ( $\leq$  6 subjects per treatment group) and did not show an apparent response for 0.8 mg/kg/day group relative to the placebo group (p = 0.8528). Also, few subjects experienced HS ( $\leq$  3 subjects per treatment group).

The change from Baseline in all countable nonmotor seizures, which include all seizures of the types absence, myoclonic, focal without clear observable motor signs, infantile spasms, and epileptic spasms, per 28 days during T+M were analyzed for the mITT Population as a secondary endpoint using the same nonparametric ANCOVA model as used for the primary endpoint. Nonmotor seizures were experienced by approximately 66% to 72% of subjects in each treatment group during Baseline and no significant effect was observed in reducing countable nonmotor seizures during T+M compared placebo (p = 0.8027).

## **New-Onset Seizure Types**

The incidence of new-onset seizure types during T+M was assessed for the mITT Population in a posthoc analysis. Few subjects (9 [3.4%]) subjects experienced  $\geq$  1 new seizure type during T+M, with the subject incidence rate of new seizures being similar in all treatment groups (3 subjects in placebo, 4 subjects in ZX008 0.8 mg/kg/day group). Due to the low number of subjects who experienced new seizures, it was not possible to assess whether a relationship existed between treatment group and the type of new seizure experienced.

## **Incidence of Status Epilepticus**

The incidence and frequency of SE when reported as an AE, when analyzed as a seizure reported in the eDiary as lasting > 10 minutes in duration, or when defined as a comprising both of these criteria was summarized for each treatment group during Baseline and T+M. Regardless of how SE was defined, no significant differences were observed between each ZX008 group and the placebo group.

A posthoc sensitivity analysis further explored the incidence of SE. The subset of seizure types officially recognized as SE by the ILAE, including GTC, SGTC, focal with clear observable signs, focal without clear observable signs, or absence/atypical absence with duration > 10 minutes were identified as SE for this analysis. This subset of SE events was further assessed based on increasing emergency, ie, requirement for 0, 1, or > 1 rescue medication. Again, no notable differences were observed between each ZX008 group and the placebo group.

#### **Subgroups**

The following subgroups were utilized for some efficacy analyses and adverse event summarizations:

- Age: 2-<6 years, 6-<12 years, 12-<18, 2-<18 years,  $\ge 18-35$  years.
- Sex: Male, Female
- Baseline Weight: <37.5 kg vs. ≥ 37.5 kg
- Number of concomitant Antiepileptic Medications Used: ≤2, 3, ≥4 medications
- Number of prior Antiepileptic Medications Used: 0-3, 4-6, 7-9, ≥10 medications
- Baseline Frequency of Seizures that Result in Drops (events/28 days): based on observed tertiles

Usage of a specific concomitant medication(s) (top 3 concomitant AEDs to be determined by data review) (Yes / No)

All subgroup analyses were exploratory, and any estimates of treatment differences are considered nominal. Interpretability of the observed results is limited due to the relatively small sample size of many of the subgroups and the high variability in seizure frequency often observed in this population.

Age:

Table 36 Percentage Change from Baseline in Drop Seizure Frequency by Age: T+M, **Nonparametric Analysis (mITT Population)** 

Percentage Change in Drop Seizure Frequency	Placebo (N = 87)	ZX008 0.2 mg/kg/day (N = 89)	ZX008 0.8 mg/kg/day (N = 87)
2 to ≤ 18 years			_
n	61	64	62
Mean (SD)	14.45 (98.675)	58.60 (426.806)	-15.51 (66.257)
Median	-4.85	-7.19	-20.30
Min, Max	-100.0, 557.1	-100.0, 3307.3	-95.2, 402.1
p-value for comparison with placebo		0.3268	0.0106
≥ 18 years			
n	26	25	25
Mean (SD)	-18.59 (35.321)	-30.07 (36.203)	-35.01 (35.955)
Median	-17.76	-33.13	-36.34
Min, Max	-80.8, 55.7	-77.8, 74.3	-84.1, 93.8
p-value for comparison with placebo		0.1777	0.0877

Source: 1601 Part 1 CSR Table 29

ANCOVA = analysis of covariance; Max = maximum; Min = minimum; mITT = Modified Intent-to-Treat; SD = standard

deviation: T+M = Titration + Maintenance Periods

P-values are based on a nonparametric ANCOVA model with treatment group (3 levels) and weight strata (< 37.5 kg, ≥ 37.5 kg) as factors, rank of Baseline seizure frequency as a covariate, and rank of percentage change from Baseline in seizure frequency during treatment period (T+M) as response.

## Table 37 Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Age Subgroup: Nonparametrix Analysis (Cohort A - North America, Europe, Australia) mITT Population

Table 14.2.1.6.1 Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Age Subgroup: Nonparametric Analysis (Cohort A - North America, Europe, Australia) mITT Population

Age Group: 2 - <18 years

	Placebo	ZX008 0.2 mg/kg/day	ZX008 0.8 mg/kg/day
	(N=61)	(N=64)	(N=62)
Titration and Maintenance (T+M) Period Analysis			
Baseline Summary Statistics [1] n Mean (SD) Median Min, Max	61 196.83 (362.204) 49.54 2.0, 1761.0	64 279.64 (501.069) 115.00 5.0, 2943.0	62 207.16 (309.042) 87.50 6.5, 1803.0
T+M Period Summary Statistics [1]: Observed n Mean (SD) Median Min, Max	61	64	62
	181.37 (305.759)	317.09 (703.316)	188.04 (319.248)
	47.71	78.34	64.25
	0.0, 1683.8	0.0, 5110.9	0.3, 1562.0
Change from Baseline	61	64	62
n Mean (SD)	-15.46 (150.385)	37.45 (681.578)	-19.12 (132.789)
Median	-1.88	-4.63	-15.11
Min, Max	-907.4, 270.4	-1565.4, 4960.9	-665.8, 385.0

Percentage Change from Baseline n Mean (SD) Median Min, Max	61 14.45 (98.675) -4.85 -100.0, 557.1	64 58.60 (426.806) -7.19 -100.0, 3307.3	62 -15.51 (66.257) -20.30 -95.2, 402.1
T+M Period: Nonparametric Model [2] Results on rank scale Least Squares Mean (SE) 95% CI for Least Squares Mean Difference from Placebo(A-P): Estimate (95% CI) p-value for comparison with Placebo	104.91 (7.052) (91.00, 118.82)	95.37 (6.789) (81.98, 108.77) -9.54(-28.68, 9.60) 0.3268	79.79 (6.916) (66.14, 93.43) -25.12(-44.32, -5.93) 0.0106
Maintenance (M) Period			
Baseline Summary Statistics [1] n Mean (SD) Median Min, Max	61 196.83 (362.204) 49.54 2.0, 1761.0	63 283.59 (504.090) 118.00 5.0, 2943.0	61 201.72 (308.599) 86.00 6.5, 1803.0
Maintenance Period Summary Statistics [1]: Observed n Mean (SD) Median Min, Max	61 176.70 (293.578) 47.36 0.0, 1588.1	63 258.21 (385.715) 84.70 0.0, 1844.0	61 183.02 (315.247) 66.33 0.0, 1527.1
Change from Baseline n Mean (SD) Median Min, Max	61 -20.13 (183.489) -1.67 -1112.4, 415.6	63 -25.38 (351.323) -4.46 -1765.3, 1446.0	61 -18.70 (137.141) -13.04 -699.0, 350.1
Percentage Change from Baseline n Mean (SD) Median Min, Max	61 14.42 (101.405) -7.14 -100.0, 516.7	63 12.61 (141.183) -4.69 -100.0, 964.0	61 -11.62 (95.148) -22.49 -100.0, 643.3
Maintenance Period: Nonparametric Model [2] Results on rank scale Least Squares Mean (SE) 95% CI for Least Squares Mean Difference from Placebo(A-P): Estimate (95% CI) p-value for comparison with Placebo	103.67 (6.988) (89.89, 117.46)	94.12 (6.777) (80.75, 107.49) -9.55(-28.63, 9.52) 0.3242	79.63 (6.901) (66.01, 93.25) -24.04(-43.13, -4.96) 0.0138

Sex:

# Table 38 Percentage Change from Baseline in Drop Seizure Frequency by Sex: T+M, Nonparametric Analysis (mITT Population)

Percentage Change in Drop Seizure Frequency	Placebo (N=87)	ZX008 0.2 mg/kg/day (N=89)	ZX008 0.8 mg/kg/day (N=87)
Males	,	,	•
n	46	46	54
Mean	4.64 (98.573)	78.91 (501.676)	-26.11 (34.691)
Median	-7.84	-10.45	-25.31
Max, Min	-100.0, 557.1	-94.7, 3307.3	-89.5, 71.8
p-value for comparison with placebo a		0.6766	0.0344
Females			
n	41	43	33
Mean (SD)	4.50 (70.364)	-14.68 (55.402)	-12.94 (86.287)
Median	-7.59	-30.48	-30.08
Min, Max	-80.8, 400.2	-100.0, 121.6	-95.2, 402.1
p-value for comparison with placebo	ı	0.0598	0.0260

Source: Table 14.2.1.6.2

Abbreviations: ANCOVA=analysis of covariance; Max=maximum; Min=minimum; mITT=Modified Intent-to-Treat; SD=standard deviation; T+M=Titration + Maintenance Periods

Results are based on a nonparametric ANCOVA model with treatment group (3 levels) and weight strata (<37.5 kg, ≥37.5 kg) as factors, rank of BL seizure frequency as a covariate, and rank of percentage change from BL in seizure frequency during treatment (T+M) as response.</li>

# Weight:

Table 39 Percentage Change from Baseline in Drop Seizure Frequency by Age: T+M, Nonparametric Analysis (mITT Population)

Percentage Change in Drop Seizure Frequency:	Placebo (N=87)	ZX008 0.2 mg/kg/day (N=89)	ZX008 0.8 mg/kg/day (N=87)
BL Weight <37.5 kg			•
n	42	42	40
Mean (SD)	14.03 (99.833)	16.40 (130.445)	-16.91 (41.365)
Median	-6.49	-13.95	-16.32
Min, Max	-77.4, 557.1	-100.0, 700.9	-95.2, 71.8
p-value for comparison with placebo <sup>a</sup>		0.3435	0.1225
BL Weight ≥37.5 kg	•		
n	45	47	47
Mean (SD)	-4.25 (70.615)	49.15 (487.399)	-24.69 (71.862)
Median	-11.21	-14.16	-35.29
Min, Max	-100.0, 400.2	-94.7, 3307.3	-91.9, 402.1
p-value for comparison with placebo a		0.2718	0.0079

Source: Table 14.2.1.6.3

Abbreviations: ANCOVA=analysis of covariance; BL=baseline; Max=maximum; Min=minimum; mITT=Modified Intent-to-Treat; SD=standard deviation; T+M=Titration + Maintenance Periods

## AED:

Table 40 Percentage Change from Baseline in Drop Seizure Frequency by Number of Concomitant AEDs: T+M, Nonparametric Analysis (mITT Population)

Percentage Change in Drop Seizure Frequency	Placebo (N=87)	ZX008 0.2 mg/kg/day (N=89)	ZX008 0.8 mg/kg/day (N=87)
Concomitant AEDs ≤2			•
n	32	35	29
Mean (SD)	2.68 (53.142)	102.53 (562.618)	-1.71 (91.348)
Median	-5.25	-5.33	-20.28
Min, Max	-64.6, 244.8	-100.0, 3307.3	-84.1, 402.1
p-value for comparison with placebo <sup>a</sup>		0.8962	0.1694
Concomitant AEDs=3			
n	34	30	32
Mean (SD)	28.26 (121.198)	4.61 (138.546)	-29.73 (31.588)
Median	-2.66	-21.14	-28.97
Min, Max	-100.0, 557.1	-94.7, 700.9	-95.2, 47.3
p-value for comparison with placebo <sup>a</sup>		0.0535	0.0008
Concomitant AEDs ≥4		•	•
n	21	24	26
Mean	-30.89 (29.497)	-30.33 (42.000)	-32.14 (31.340)
Median	-30.40	-42.95	-26.75
Min, Max	-80.8, 11.8	-85.9, 78.3	-91.9, 32.7
p-value for comparison with placebo <sup>a</sup>		0.5853	0.7960

Results are based on a nonparametric ANCOVA model with treatment group (3 levels) and weight strata (<37.5 kg, ≥37.5 kg) as factors, rank of BL seizure frequency as a covariate, and rank of percentage change from BL in seizure frequency during treatment (T+M) as response.

Table 41 Percentage Change from Baseline in Drop Seizure Frequency by Number of Prior AEDs: T+M, Nonparametric Analysis (mITT Population)

	-		-
Percentage Change in Drop Seizure Frequency	Placebo (N=87)	ZX008 0.2 mg/kg/day (N=89)	ZX008 0.8 mg/kg/day (N=87)
Prior AEDs=0-3	•	•	•
n	18	18	16
Mean (SD)	0.23 (104.109)	19.47 (178.275)	9.12 (110.177)
Median	-23.15	-8.72	-6.93
Min, Max	-78.7, 400.2	-100.0, 700.9	-86.0, 402.1
p-value for comparison with place	cebo <sup>a</sup>	0.8896	0.4097
Prior AEDs=4-6		•	-
n	27	25	19
Mean (SD)	14.86 (113.024)	118.22 (666.215)	-22.22 (38.612)
Median	-4.38	-3.97	-21.10
Min, Max	-80.8, 557.1	-85.9, 3307.3	-95.2, 65.6
p-value for comparison with place	cebo <sup>a</sup>	0.1767	0.0422
Prior AEDs=7-9		,	,
n	28	27	28
Mean	2.85 (59.532)	-12.65 (56.179)	-32.77 (41.052)
Median	-4.81	-17.84	-36.22
Min, Max	-100.0, 244.8	-89.0, 169.2	-91.9, 93.8
p-value for comparison with pla	cebo <sup>a</sup>	0.1274	0.0029
Prior AEDs ≥10		•	•
n	14	19	24
Mean	-6.24 (37.515)	1.82 (79.936)	-26.78 (37.269)
Median	-3.58	-17.57	-33.58
Min, Max	-69.4, 62.4	-94.7, 249.9	-71.0, 71.8
p-value for comparison with pla	cebo <sup>a</sup>	0.8044	0.1641

Baseline Drop Seizure Frequency:

Table 42 Percentage Change from Baseline in Drop Seizure Frequency by Baseline Frequency of Drop Seizures Subgroup: T+M, Nonparametric Analysis (mITT Population)

Percentage Change in Drop Seizure Frequency	Placebo (N=87)	ZX008 0.2 mg/kg/day (N=89)	ZX008 0.8 mg/kg/day (N=87)
BL-DSF=2-43		•	
n	37	27	23
Mean (SD)	23.56 (116.811)	9.34 (155.454)	-12.18 (97.397)
Median	-3.88	-30.53	-31.71
Min, Max	-100.0, 557.1	-100.0, 700.9	-95.2, 402.1
p-value for comparison with placebo a		0.0426	0.0151
BL-DSF=44-122		•	•
n	25	29	34
Mean (SD)	-7.45 (59.154)	-25.91 (39.556)	-30.17 (39.268)
Median	-19.23	-36.54	-29.33
Min, Max	-78.7, 244.8	-84.2, 41.4	-86.0, 93.8
p-value for comparison with placebo <sup>a</sup>		0.2524	0.0723
BL-DSF=124-2943	•	•	
n	25	33	30
Mean	-11.50 (39.101)	106.00 (577.858)	-17.70 (37.617)
Median	-11.21	-7.37	-19.98
Min, Max	-80.8, 58.0	-78.8, 3307.3	-84.1, 71.8
p-value for comparison with placebo a		0.2407	0.9696

Region:

Table 43 Percentage Change from Baseline in Drop Seizure Frequency by Region: T+M,
Nonparametric Analysis (mITT Population)

Percentage Change in Drop Seizure Frequency	Placebo (N=87)	ZX008 0.2 mg/kg/day (N=89)	ZX008 0.8 mg/kg/day (N=87)
North America			
n	44	45	43
Mean	16.25 (115.383)	59.16 (498.888)	-22.68 (37.115)
Median	-6.49	-17.84	-24.13
Max, Min	-100.0, 557.1	-100.0, 3307.3	-95.2, 65.6
p-value for comparison with placebo <sup>a</sup>		0.0913	0.0434
Europe			
n	41	43	38
Mean (SD)	-6.63 (34.925)	9.47 (122.737)	-15.53 (79.728)
Median	-10.30	-10.05	-26.75
Min, Max	-77.4, 62.4	-94.7, 700.9	-91.9, 402.1
p-value for comparison with placebo <sup>a</sup>		0.5504	0.0222
Australia			
n	≤11	≤11	≤11
Mean (SD)	-22.77 (37.363)	-70.59 (NA)	-45.20 (39.432)
Median	-22.77	-70.59	-49.75
Min, Max	-49.2, 3.7	-70.6, -70.6	-86.0, 16.4
p-value for comparison with placebo <sup>a</sup>		0.3748	0.4881

Source: Table 14.2.1.6.8

Abbreviations: ANCOVA=analysis of covariance; Max=maximum; Min=minimum; mITT=Modified Intent-to-Treat; NA=not applicable; SD=standard deviation; T+M=Titration + Maintenance Periods

# Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 44 Summary of Efficacy for Study ZX008-1601

Title: Study ZX008-1601: A Two-Part Study of ZX008 in Children and Adults with					
Lennox-Gastaut					
	rt 1: A Randomized, Double-blind, Placebo-controlled Trial of Two				
	8 (Fenfluramine Hydrochloride) Oral Solution as Adjunctive Therapy				
for Seizures in Child	ren and Adults with LGS				
Study identifier	ZX008-1601				
	EudraCT 2017-002628-26				

a Results are based on a nonparametric ANCOVA model with treatment group (3 levels) and weight strata (<37.5 kg, ≥37.5 kg) as factors, rank of BL seizure frequency as a covariate, and rank of percentage change from BL in seizure frequency during treatment (T+M) as response.

Design	Study ZX008-1601 is an international, multicenter, Phase 3 study being conducted in 2 parts. Part 1 is a randomized, double-blind, parallel-group placebo-controlled study to assess the efficacy and safety of 2 dose levels of ZX008 (fenfluramine hydrochloride) as adjunctive therapy for seizures in subjects with LGS. Subjects in Cohort A were enrolled at sites in North America, Europe, and Australia. Part 1 consisted of a 4-week Baseline, 2-week Titration Period (Titration) 12-week Maintenance (Maintenance), and 2-week Taper Period (Taper) of Transition Period (Transition). The 4-week Baseline period consisted of the establishment of initial eligibility during a screening visit, followed by an observation period in which subjects were assessed for baseline seizure frequency based on recordings of daily seizure activity entered into an electronic diary.  Upon completion of Baseline, 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 or 0.8 mg/kg/day [maximum dose: 30 mg/day]) or placebo. Randomization was stratified by weight at screening (<37.5 kg, ≥37.5 kg) to ensure balance across treatment arms, with a target of at least 25% of subjects in each weight group.  All subjects were titrated to their blinded randomized dose over the 2-week Titration. Following dose titration, subjects continued treatment with study drug at their randomly assigned dose over the 12-week Maintenance under blinded conditions. Total treatment time from the beginning of Titration through the end of Maintenance was 14 weeks. Subjects had ECG and ECHO assessments midway during Maintenance (a Week 6) and at the End-of-Study (EOS) Visit (Week 14) in Part 1. At the end of Maintenance (or early discontinuation), all subjects underwent the blinded 2-week Taper or Transition Period (Taper/Transition) depending on whether they exited the study or were enrolled in Part 2, the long-term open-label extension, respectively. Parents/caregivers used the electronic diary every day			
	Duration of main phase:  16 weeks in Part 1 (Titration=2 weeks)  Maintenance=12 weeks;  Taper/Transition=up to 2 weeks).			
Hypothesis	(drop seizure freq	baseline in the uency (DSF))	Not applicable frequency of seizures that result in drops per 28-days for the ZX008 0.8 mg/kg atly different from the placebo group.	
Treatments groups	Placebo  ZX008 0.2 mg		Subjects randomised to receive placebo for up to approximately 16 weeks in Part 1 (Titration Period (T) =2 weeks; Maintenance Period (M) =12 weeks; Taper/Transition=up to 2 weeks).  Subjects randomised to receive ZX008 0.2 mg/kg/day for up to approximately 16 weeks in Part 1 (Titration Period (T) =2 weeks;	
	Maintenance Period (M) =12 weeks Taper/Transition=up to 2 weeks).  ZX008 0.8 mg Subjects randomised to receive ZX0 0.8 mg/kg/day for up to approxima 16 weeks in Part 1 (Titration Period =2 weeks; Maintenance Period (M) =12 weeks Taper/Transition=up to 2 weeks).			
Endpoints and definitions	Primary endpoint	DSF per 28 days	Percent change from Baseline in the frequency of seizures that result in drops (i.e., drop seizure frequency [DSF]) in T+M in the ZX008 0.8 mg/kg/day group compared with the placebo group	

	Key secondary endpoint #1	Proportion of subjects who achieved a ≥50% reduction from Baseline in DSF	Proportion of subjects who achieve a ≥50% reduction from Baseline in the DSF, comparing the ZX008 0.8 mg/kg/day group versus placebo
	Key secondary endpoint #2	Improveme nt in the CGI-I	Proportion of subjects who achieve improvement (minimally, much, or very much improved) in the CGI-I as assessed by Principal Investigator, comparing the ZX008 0.8 mg/kg/day group versus placebo
	Key secondary endpoint #3	DSF per 28 days	Change from Baseline in DSF in T+M in the ZX008 0.2 mg/kg/day group compared with the placebo group
	Key secondary endpoint #4	Proportion of subjects who achieved a ≥50% reduction from Baseline in DSF	Proportion of subjects who achieve a ≥50% reduction from Baseline in the DSF, comparing the ZX008 0.2 mg/kg/day group versus placebo
	Key secondary endpoint #5	Improveme nt in the CGI-I	Proportion of subjects who achieve improvement (minimally, much, or very much improved) in the CGI-I as assessed by Principal Investigator, comparing the ZX008 0.2 mg/kg/day group versus placebo
Database lock	30 January 2020		

# **Results and Analysis**

A	I Deliver and American	• -			
Analysis	Primary Analysis				
description		<u> </u>			
Analysis population and time point description	The Modified Intent-to-Treat (mITT) Population was defined as all randomized subjects who received at least 1 dose of study drug and for whom at least 1 week of eDiary data were available. Subjects were analyzed according to the treatment group to which they were randomized. Analyses of the primary efficacy and key secondary endpoints were performed on data from the mITT Population.				
	The Per Protocol (PP) Population was defined as all randomized subjects who received at least 1 dose of study drug; who completed at least 4 weeks of eDiary data in the Maintenance period; who had no major protocol deviations that would have a significant impact on clinical outcome in Part 1; and who met the inclusion criterion for Baseline drop seizure count. The primary efficacy endpoint and key secondary endpoint analyses were repeated on the PP Population.				
Descriptive	Treatment	Placebo	ZX008 0.2	ZX008 0.8	
statistics and	group		mg/kg/day	mg/kg/day	
estimate variability (Source: Study 1601	Number of subjects	N=87	N=89	N=87	
CSR Table 14.2.1.1.1)  Mean baseline DSF per 28 Days  164.37 223.00 194.99					

	Standard deviation	309.80	435.50	308	.90
	Modian	F2.00	05.00	02.4	20
	Median Min. may	53.00	85.00	83.0	
	Min, max Mean T+M DSF	2.0, 1761.0 4.1, 2943.0			, 1803.0
	per 28 days	145.20	247.30	162	60
	Standard deviation	263.16	608.99	285	.29
	Median	46.85	61.82	54.	57
	Min, max	0, 1683.8	0, 5110.9	0.3	, 1562.0
Effect estimate per	Primary	Comparison gro	oups	0.8 mg/kg	g/d vs Placebo
comparison	endpoint	Median Percent from BL During	age Change	-26.49%	-
		Estimate of % [		-19.88%	(Hodges-
		from Baseline in	n DSF	Lehmann estimate)	[HL]
		95% CI		-31.02, -8	3.74
		P-value		· · · · · · · · · · · · · · · · · · ·	onparametric
				ANCOVA)	p : 233
	Key secondary	Comparison gro	oups		g/d vs Placebo
	endpoint #1	% Achieving a ≥50% reduction from Baseline in DSF		25.3% vs	10.3
		Odds ratio (95% CI)		2.87 (1.23, 6.70)	
		P-value		0.0150 (logistic	
		Valde		regression)	
	Key secondary endpoint #2	Comparison groups  % With improvement on CGI-I, Investigator rating at visit 12		0.8 mg/kg	g/d vs Placebo
				48.8% vs	33.8%
		P-value		0.0567 (C Mantel-Ha	
	Key secondary	Comparison groups		0.2 mg/kg	g/d vs Placebo
	endpoint #3	Median Percentage Change from BL During T+M		-14.16%	
		Estimate of % Difference from Baseline in DSF		-10.50% (HL estimate)	
		95% CI		-24.99, 3 estimate)	
	Key secondary	Comparison gro	oups	0.2 mg/kg	g/d vs Placebo
	endpoint #4	% Achieving a reduction from DSF		28.1% vs	10.3
		Comparison gro	oups	0.2 mg/kg	g/d vs Placebo
	Key secondary endpoint #5	% With improvement on CGI-I, Investigator rating at visit 12		44.7% vs 33.8%	

The efficacy analyses employed a serial gatekeeper strategy to control the type 1 error rate for pairwise comparisons between the ZX008 and placebo groups among the primary and key secondary outcomes. The hierarchy started with the comparison of ZX008 0.8 mg/kg/day with placebo for the primary and key secondary endpoints #1 and #2 above in that order (Steps 1 through 3), followed by the comparison of ZX008 0.2 mg/kg/day with placebo for the key secondary endpoints #3, #4, and #5 above in that order (Steps 4 through 6). Once a p-value of > 0.05 was obtained for statistical comparison between the specified treatment groups for an endpoint, formal hypothesis testing of the remaining endpoints would stop.

# Supportive study(ies)

## Persistence of efficacy or tolerance

#### **Study 1601 Part 2**

Study 1601 Part 2 was designed to evaluate the long-term safety (primary objective) and effectiveness (secondary objective) of ZX008 for up to 1 year in the subjects who successfully completed Part 1.

<u>Treatment:</u> During the OLE Treatment Period, all subjects were transitioned from their blinded daily dose to be treated initially with ZX008 0.2 mg/kg/day for 1 month to assess effectiveness of this dose (Table 3). After 1 month at this dose, the Investigator could adjust the ZX008 dose for each subject based on effectiveness, safety, and tolerability.

#### **Efficacy Endpoints:**

The efficacy endpoints for Part 2 of the study are:

- The change from baseline in the frequency of seizures that result in drops (ESC-confirmed).
- The change in frequency of all seizures that (typically) result in drops (i.e., GTC, SGTC, TS, AS, TA) between baseline and the OLE Treatment Period whether ESC confirmed as drop or not.
- The change from baseline in the frequency of all countable motor seizures (GTC, sGTC, TS, CS, AS, TA, FS, and HS)
- The change from baseline in frequency of all countable non-motor seizures (absence, myoclonic, focal without clear observable motor signs, infantile spasms, and epileptic spasms).
- The change from baseline in the frequency of all countable seizures (ie, motor and non-motor)
- The proportion of subjects who achieve a worsening from baseline (ie, ≤ 0% reduction), or > 0%,
  - $\geq$  25%,  $\geq$  50%,  $\geq$  75%, 100% reduction, and "near seizure freedom" (ie, 0 or 1 seizures) from
  - baseline in frequency of seizures that result in drops (ESC-confirmed), seizures that typically result in drops, all countable motor seizures, all countable non-motor seizures, and all countable
  - seizures
- Number of seizure-free days, defined as 1) days with no seizures that result in drops (ESC confirmed) and 2) days with no countable motor seizures.
- Longest interval between seizures that result in drops (ESC-confirmed).
- Clinical Global Impression Improvement rating, as assessed by the Principal Investigator.
- Clinical Global Impression Improvement rating, as assessed by the parent/caregiver.

#### **Randomisation:**

Part 2 is an open-label, long-term safety study of ZX008 for subjects who have successfully completed 14

weeks of treatment (Titration + Maintenance) in Part 1 and are candidates for continuous treatment for

an extended period of time; subjects who have not completed the entire 14 weeks of treatment in Part 1 may be eligible to participate in Part 2 on a case-by-case basis and only following sponsor approval. Part 2 consists of a 12-month Open-Label Extension (OLE) Treatment Period and a 2-week Post-Dosing Period. Thus, subjects who were randomized to ZX008 during Part 1 and complete Part 2 will have been

treated with ZX0008 for at least 70 weeks (including their participation in both Part 1 and Part 2). Analysis sets:

#### **OLE Safety Population (OLE SAF)**

Safety analyses for Part 2 will be performed on the OLE Safety (SAF) Population, defined as all subjects

who receive at least one dose of ZX008 during the open label extension.

#### **OLE mITT Population**

The OLE Modified Intent-to-Treat (mITT) Population is defined as all subjects who receive at least one dose of ZX008 and have a valid estimate of the frequency of seizures that result in drops from Part 1 and

at least one month (30 days) of valid seizure data during the open label extension. Effectiveness analyses, such as evaluating the change in the frequency of drop seizures, will be performed on the OLF

mITT Population.

#### Safety Population for Part 1 (DB SAF)

The SAF Population for Part 1 is defined as all randomized subjects who received at least one dose of ZX008 or Placebo in Part 1, regardless of entry into Part 2.

## Long Term Safety (LT SAF)

This population will include subjects who received at least one dose of ZX008 during Part 1 or Part 2. For

subjects treated with Placebo in Part 1 and who were treated with ZX008 in Part 2, the first dose of  $7\times008$ 

would occur in the Part 1 transition period.

#### Participant flow:

A total of 247 Cohort A subjects enrolled in Part 2. At the time of the data cutoff date (19 October 2020), a total of 143 subjects had completed the study, 19 subjects were ongoing, and 85 subjects had withdrawn.

Table 5 shows that 122 subjects had completed and 83 subjects had withdrawn. The discrepancy of the 21 and 2 subjects, respectively, is due to delays in completion of the final disposition eCRFs as a result of profound restrictions and precautions related to COVID-19 for onsite personnel in-person availability and data monitoring.

As of the data cutoff date, 195 (78.9%) of the subjects had completed  $\geq$  6 months of the study, 150 (60.7%) of whom had completed  $\geq$ 1 year. (Some subjects remained in the study longer than the planned duration of 1 year due to COVID-19 related restrictions and precautions imposed on their EOS visit.) Throughout their study participation, subjects used the eDiary to record daily seizure activity, and assessments of efficacy and safety, including cardiovascular safety, were performed according to the schedule in Table 4. Of the 150 subjects who completed  $\geq$  1 year in the study, 117 (78.0%) had a Month 12 ECHO performed.

Table 45 Overall Subject Disposition (OLE Safety Population and Open-Label Extension mITT Population)

	Placebo (N = 86)	ZX008 0.2 mg/kg/day (N = 83)	ZX008 0.8 mg/kg/day (N = 78)	Overall (N =2 47)
Open Label Safety Population	86	83	78	247
Completed 6 Months in Part 2, n (%) <sup>a, b</sup>	71 (82.6%)	62 (74.7%)	62 (79.5%)	195 (78.9%)
Completed One Year in Part 2, n (%) <sup>b</sup> , c	60 (69.8%)	47 (56.6%)	43 (55.1%)	150 (60.7%)
Completed Part 2, n (%) b	47 (54.7%)	39 (47.0%)	36 (46.2%)	122 (49.4%)
Discontinued Part 2, n (%) b	24 (27.9%)	30 (36.1%)	29 (37.2%)	83 (33.6%)
Reason for Discontinuation from Part 2, n (%) <sup>b</sup>	•			
Adverse Event	5 (5.8%)	5 (6.0%)	3 (3.8%)	13 (5.3%)
Death	0	1 (1.2%)	0	1 (0.4%)
Lack of Efficacy	13 (15.1%)	20 (24.1%)	22 (28.2%)	55 (22.3%)
Rollover into Zogenix 1900 d	1 (1.2%)	0	0	1 (0.4%)
Withdrawal by Subject	5 (5.8%)	4 (4.8%)	4 (5.1%)	13 (5.3%)
Open Label mITT Population, n (%) <sup>e</sup>	85 (98.8%)	78 (94.0%)	78 (100%)	241 (97.6%)
Completed 6 Months in Part 2, n (%) a, e	71 (83.5%)	61 (78.2%)	62 (79.5%)	194 (80.5%)
Completed One Year in Part 2, n (%) <sup>c, e</sup>	60 (70.6%)	47 (60.3%)	43 (55.1%)	150 (62.2%)
Completed Part 2, n (%) e	47 (55.3%)	39 (50.0%)	36 (46.2%)	122 (50.6%)
Discontinued Part 2, n (%) e	23 (27.1%)	25 (32.1%)	29 (37.2%)	77 (32.0%)
Reason for Discontinuation from Part 2, n (%) e				
Adverse Event	5 (5.9%)	3 (3.8%)	3 (3.8%)	11 (4.6%)
Death	0	1 (1.3%)	0	1 (0.4%)
Lack of Efficacy	13 (15.3%)	18 (23.1%)	22 (28.2%)	53 (22.0%)
Rollover into Zogenix 1900 d	1 (1.2%)	0	0	1 (0.4%)
Withdrawal by Subject	4 (4.7%)	3 (3.8%)	4 (5.1%)	11 (4.6%)

mITT = Modified Intent-to-Treat, OLE = Open-Label Extension

Percentages are calculated using the number of subjects in the OLE mITT Population.

Note: Two subjects are not counted toward the number of discontinuations and 21 subjects are not counted toward the number of Part 2 completers due to delays in completion of the final disposition electronic case report forms (the source for this table), which occurred as a result of profound restrictions and precautions related to COVID-19 for onsite personnel in-person availability and data monitoring

#### **Recruitment:**

Study centers: Subjects in Part 2 Cohort A were enrolled at a total of 63 sites in North America (32) Europe (29), and Australia (2).

Studied period: 18 April 2017 (Date first subject enrolled in Part 2) to interim database cutoff date (19 October 2020).

#### Baseline data:

The interim analysis for Study 1601 Part 2 included 247 Cohort A subjects who had participated in double-blind Study 1601 Part 1. The subjects had a mean (SD) duration of exposure to ZX008 of 298.9 (122.88) days as of the data cutoff date of 19 October 2020. (Note that due to precautions and restrictions related to COVID-19, some subjects delayed their EOS Visit and remained in Part 2 for longer than  $365 \pm 4$  days [range: 370-542 days]).

a Completed treatment through at least 180 days in Part 2.
b Percentages are calculated using the number of subjects in the OLE Safety Population.

Completed treatment through at least 361 days (Study day 365 – 4) or later in Part 2.

 Study ZX008-1900 is a ZX008 open-label extension study available for subjects who complete Study 1601 Part 2. This discontinuation was entered erroneously by the site; the subject completed Part 2 as planned (data on file).

Of the 241 subjects in the OLE mITT Population (ie, subjects who received  $\geq 1$  dose of ZX008 and had a valid estimate of drop seizure frequency from Part 1 and  $\geq 1$  month of valid seizure data during the OLE), 194 (80.5%) subjects had completed  $\geq 6$  months of the study, 150 (60.7%) of whom had completed  $\geq 1$  year. Nearly half the subjects in the mITT Population, 113 subjects, received a mean daily dose of ZX008 of 0.4 to < 0.6 mg/kg/day during the study; 68 received a mean daily dose of > 0 to < 0.4 mg/kg/day and 60 received a mean daily dose of  $\geq 0.6$  mg/kg/day.

The demographic and baseline characteristics of the Study 1601 Part 2 mITT Population were similar to the overall characteristics for the mITT Population in Study 1601 Part 1. The mean (SD) subject age at entry to Part 2 Cohort A was 14.3 (7.60) years (range: 2 to 36). The majority of subjects (68.5%) were < 18 years of age; 31.5% were  $\geq$  18 year of age. Fifty-six percent of subjects were male. The majority of subjects (80.5%) were white. Slightly over half the subjects (53.9%) were  $\geq$  37.5 kg. Most (98.4%) subjects were receiving between 1 and 5 concomitant AEDs during the study. Two subjects received > 5 concomitant AEDs. The most commonly used ( $\geq$  25% of subjects) AEDs were valproate (all forms), clobazam, and lamotrigine.

#### Outcomes and estimation:

The first effectiveness outcome was the change from Baseline (Part 1) in DSF during the OLE Treatment Period (Table 31). Both the change in DSF for the entire OLE Treatment Period (Part 2 Day 1 to EOS) compared with Baseline (Part 1) and the change in DSF for Month 2 to EOS (Part 2 Day 31 to EOS) compared with Baseline (Part 1) were analyzed. The latter endpoint excluded the first month of open-label treatment, in which each subject was held on a dose of ZX008 0.2 mg/kg/day and in which some subjects may have still been adjusting to the dose transition from Part 1. Both endpoints included subjects who were randomized to placebo and subjects randomized to ZX008 treatment during Part 1. Note that for this analysis, "EOS" refers to either EOS, ET, or last visit as of the interim analysis data cutoff date, whichever occurred first, for each subject.

Table 46 Change from Baseline in Frequency of Seizures Resulting in Drops per 28 Days (OLE mITT Population)

		ZX008 Mean Daily Dose (mg/kg/day) <sup>a</sup>			
	> 0 - < 0.4 (N=68)	0.4 - < 0.6 (N=113)	≥ 0.6 (N=60)	Any ZX008 OLE Dose (N=241)	
Baseline (Part 1) DSF <sup>b</sup>					
n	68	113	60	241	
Mean	159.60	193.84	212.01	188.70	
SD	372.899	372.303	330.905	361.677	
Median	60.50	71.00	89.00	75.00	
Min	13.0	4.1	4.0	4.0	
Max	2943.0	2289.0	1680.0	2943.0	
Part 2, Day 1-EOS DSF	•				
n	68	113	60	241	
Mean	266.47	155.55	163.02	188.71	
SD	1076.931	333.828	323.020	635.472	
Median	58.26	43.73	52.61	48.89	
Min	0.0	0.1	2.7	0.0	
Max	8828.0	1953.5	1941.3	8828.0	
Part 2, Day 1-EOS: % Change in DSF from Baseline (Part 1)					
n	68	113	60	241	
Mean	55.56	-10.08	-14.78	7.27	
SD	370.397	80.484	90.786	210.411	
Median	-17.31	-31.34	-37.56	-28.57	
Min	-100.0	-99.5	-94.0	-100.0	
Max	2625.3	402.3	351.5	2625.3	
p-value <sup>c</sup>	0.1995	0.0016	< 0.0001	< 0.0001	
Part 2, Month 2-EOS DSF			-	1	
n	67	113	60	240	
Mean	294.43	153.69	162.43	195.17	
SD	1169.031	343.246	331.174	680.829	
Median	59.17	42.08	52.28	49.40	
Min	0.0	0.1	1.8	0.0	
Max	9490.1	2152.8	1958.3	9490.1	
Part 2, Month 2-EOS: % Change in DSF from Baseline (Part 1)					
n	68	113	60	240	
Mean	114.09	-11.09	-14.90	22.91	
SD	783.189	84.285	95.574	422.146	
Median	-20.11	-34.65	-38.91	-30.46	
Min	-100.0	-99.7	-94.7	-100.0	
	<del> </del>		<b>I</b>		
Max	6200.0	453.6	372.4	6200.0	

Source: 1601 Part 2 CSR Table 14

DSF = drop seizure frequency (per 28 days); ESC = Epilepsy Study Consortium, Max = maximum, Min = minimum, mITT = Modified Intent-to-Treat, OLE = Open-Label Extension, SD = standard deviation.

a The mean daily dose is calculated over the complete treatment duration in Part 2, using the sum of doses in mg/kg on each

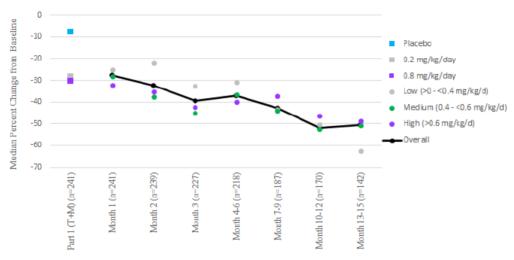
The median percentage reduction from Baseline in DSF during the overall OLE Treatment Period (ie, Day 1 to EOS) was 28.6% (p < 0.0001). The median percentage reduction from Baseline for Month 2 to EOS was 30.5% (p < 0.0001). Median percentage reductions in DSF were greatest at the  $\geq$  0.6 mg/kg/day mean daily dose level of ZX008.

day and dividing by the duration of treatment in Part 2.

b Baseline (Part 1) = Baseline = 28 days prior to double-blind treatment in Part 1.
c p-value is from a Wilcoxon signed-rank test that the median % change from baseline is significantly different from 0. Notes: The seizure types included in the count are: atonic, tonic, tonic/atonic, generalized tonic-clonic, and secondarily generalized tonic-clonic seizures resulting in drops.

As shown in Figure 8, median percentage reductions from Baseline in DSF were observed at Month 1 and maintained through Month 15.

Figure 8 Median Percentage Change from Baseline in Drop Seizures Frequency During the OLE Treatment Period (OLE mITT Population)



Source: 1601 Part 2 CSR Figure 1

mITT = modified Intent-to-Treat; OLE = Open-Label Extension

When analyzed by Part 1 randomized treatment, median percentage changes from Baseline in DSF during the overall OLE Treatment Period were similar for subjects originally randomized to the placebo, ZX008 0.2 mg/kg/day, and ZX008 0.8 mg/kg/day groups: -28.0%, 25.9%-, and 30.0%-, respectively.

Analyses by age subgroup demonstrated that both pediatric (2 to < 18 years [n = 171]) and adult ( $\geq$  18 years [n = 70]) subjects had statistically significant median percentage reductions from Baseline in DSF during the Month 2 to EOS period (25.9% [p < 0.0001] and 40.0% [p = 0.0011], respectively). All pediatric age groups experienced median percentage reductions from Baseline in DSF, though reductions were variable between the subgroups. No relationship between age and the percentage reduction in DSF was apparent during the OLE.

Table 47 Change from Baseline in Drop Seizure Frequency per 28 Days by Part 1 Age Subgroup (OLE mITT Population)

	Percentage Change from Baseline in Seizure Frequency						
Part 1 Age (years)	Day 1 to EOS			Month 2 to EOS			
	n	Median	P-value <sup>a</sup>	n	Median	P-value <sup>a</sup>	
≥ 18 to 35	70	-38.96	< 0.0001	70	-40.00	< 0.0001	
2 to < 18	171	-25.63	0.0037	170	-25.91	0.0011	
2 to < 6	37	-44.76	0.2476	37	-42.14	0.2122	
6 to < 12	63	-15.45	0.0923	63	-17.37	0.0183	
12 to < 18	71	-23.78	0.0646	70	-27.64	0.0870	

Source: Table 14.2.1.11.1.1.3.

 $EOS = End-of-Study, ESC = Epilepsy\ Study\ Consortium,\ mITT = Modified\ Intent-to-Treat,\ OLE = Open-Label\ Extension.$ 

Analyses by Part 1 baseline weight subgroup demonstrated that both subjects < 37.5 kg (n = 114) and  $\geq 37.5 \text{ kg}$  (n = 127) had statistically significant median percentage reductions in DSF during OLE from Month 2 to EOS period (28.2% [p = 0.0034] and 31.1% [p < 0.0001], respectively).

a P-value is from a Wilcoxon signed-rank test that the median percentage change from Baseline is significantly different from 0.

The percentage of subjects in the OLE mITT Population who achieved a  $\geq 50\%$  reduction from Baseline in DSF (50% responder rate) during the OLE Treatment Period is analyzed. Nearly one-third of subjects, 31.7%, achieved a clinically meaningful  $\geq 50\%$  reduction in DSF from Month 2 to EOS (ie, after the mandatory 1 month of ZX008 dosing at 0.2 mg/kg/day).

No subjects in the OLE mITT Population had an AE of SE during Baseline. During the longer Part 2 period, the number of subjects who had  $\geq 1$  AE of SE increased to 9 (3.7%) subjects. The mean (SD) number of AEs of SE per 28 days was 0.02 (0.178) (range: 0-2.4). When SE events were assessed based on seizure data from the eDiary alone (ie, seizures with duration > 10 mins), 104 (43.2%) subjects had  $\geq 1$  episode of SE during Baseline, and the mean (SD) number of episodes was 3.84 (9.243) per 28 days (range: 0-82). During the Part 2 period, 136 (56.4%) subjects had  $\geq 1$  episode of SE and the mean (SD) number of episodes was 5.22 (19.942) per 28 days (range: 0-216.5). The sampling time for the Part 2 treatment period – 1 year – was considerably longer than the Part 1 4-weeks Baseline, so the increase in episodes per 28 days during the OLE Treatment Period is likely attributable to the sampling duration. Of note, the mean number of episodes per 28 days in a 1-year trial (5.22) is not large and underscores the severity of LGS.

#### **Study 1900**

Study 1900 was designed to evaluate the long-term safety (primary objective) and the effectiveness of ZX008 (secondary objective) for up to 3 years (2 years in Denmark) in subjects with LGS, Dravet syndrome, or other epileptic encephalopathies. The interim analysis of this ongoing study included only subjects who entered this study from Study 1601 Part 2 Cohort A. As in Study 1601 Part 2, an openlabel, flexible dosing scheme for ZX008, up to 0.8 mg/kg/day (maximum 30 mg/day), was used in this study.

Study 1900 data are limited to data for 60 subjects from Study 1601 Part 2 Cohort A who received  $\geq 1$  dose of ZX008 in Study 1900 and had a valid efficacy assessment after Visit 1 during the OLE (the mITT Population). The mean (SD) subject age at entry to Study 1900 for subjects in the mITT Population was 15.2 (7.7) years of age (range: 4 to 37). The majority of subjects (66.7%) were < 18 years of age; 33.3% were  $\geq 18$  year of age. Approximately 47% of subjects were male. The majority of subjects (75.0%) were white. The median weight was 38.4 kg (range: 14 to 91). The majority of subjects (70.0%) were rated by the Investigator on the CGI-S as moderately ill or worse relative to the Investigator's total clinical experience within this patient population. The majority of subjects (70.0%) were rated by the parent/caregiver on the CGI-S as moderately ill or worse relative to expectations for age and development.

At the last assessment in Study 1900 for each subject in the mITT Population as of the data cutoff date, the majority (> 78%) in the mITT Population were rated on the CGI-I by the Investigator and by the parent/caregiver as having an improved or stable overall condition relative to the CGI-S rating at Visit 1 (Study Day 1), ie, as having minimal, much, or very much improvement or no change. Sixty percent and 62.0% of subjects were rated by the Investigator and parent/caregiver, respectively, as having improvement (ie, minimal, much, or very much improved), and 41.8% and 40.0% of subjects, respectively, were rated as having clinically meaningful improvement (ie, much or very much improved).

## 2.4.2. Discussion on clinical efficacy

Phase 3 Study 1601 Part 1 is considered main proof of efficacy in patients with LGS. The long-term extension study (Study 1601 Part 2) is considered as supportive study only.

# Design and conduct of clinical studies

## Study 1601 Part 1:

Part 1 is a randomized, double-blind, parallel-group, placebo-controlled study to assess the efficacy and safety of 2 dose levels of ZX008 (fenfluramine hydrochloride, 0.2 or 0.8 mg/kg/day [maximum dose: 30 mg/day]) as adjunctive therapy for seizures associated with LGS in children and adults (subjects 2 to 35 years of age). The study design is aligned with the standard placebo-controlled design recommended in epilepsy guideline for add-on therapies. Because an accurate diagnosis of LGS is difficult in children younger than 2 years, and seizures that result in drops may not be accurately counted in this age group, children younger than 2 years were not included.

Subjects were required to have been receiving  $\geq 1$  to 4 concomitant AEDs. The ketogenic diet (KD) and vagal nerve stimulation (VNS) were permitted as concomitant therapies during the trial but did not count toward this requirement. Changes to background therapies were not allowed.

All subjects were required to have had  $\geq 8$  drop seizures in the 4 weeks immediately prior to Screening (minimum of 4 drop seizures in the first 2 weeks and 4 in the last 2 weeks before Screening) based on parent/guardian report or Investigator medical notes and  $\geq 8$  drop seizures during the 4-week Baseline ( $\geq 2$  drop seizures per week) as recorded in the eDiary. Eight or more drop seizures occurring at a consistent frequency represents subjects with uncontrolled seizures, excludes subjects whose seizures only occur in clusters or who have only intermittent infrequent seizures, and provides a sufficient baseline from which to measure meaningful change. Seizures that result in drops were generalized tonic-clonic (GTC), secondarily generalized tonic-clonic (SGTC), tonic (TS), atonic (AS), and tonic/atonic (TA) seizures.

The exclusion criteria were acceptable.

After a 4-week Baseline, upon randomization (1:1:1), subjects entered a 2-week Titration followed by a 12-week Maintenance for a total of 14-weeks treatment. The duration of treatment is acceptable.

It is critical to note that doses of ZX008 are expressed as the fenfluramine hydrochloride salt. So, the 0.2 and 0.8 mg/kg/day doses are equivalent to 0.2 and 0.7 mg/kg/day (rounded), respectively, of the fenfluramine free base (with a conversion factor of 0.864) which is used in clinic and expressed in SmPC. The 30 mg/day maximum dose is equivalent to 26 mg/day of fenfluramine free base. SmPC presents all data in fenfluramine free base doses only. 0.8 mg/kg/day dose (30 mg max) is the dose approved for Dravet syndrome.

The comparison between the ZX008 0.8 mg/kg/day and placebo groups for the change from Baseline in DSF during T+M was the primary efficacy outcome measure; the comparison between the ZX008 0.2 mg/kg/day and placebo groups was a key secondary outcome measure. Two other key secondary efficacy outcome measures were evaluated for both groups independently: 1) the percentage of subjects who achieved a  $\geq$ 50% reduction from Baseline DSF, and 2) the percentage of subjects who were rated by the Investigator as improved on the CGI-I.

The efficacy analyses employed a serial gatekeeper strategy to maintain the Type 1 error rate at a=0.05 across the family of analyses that supported the primary and key secondary objectives. The hierarchy started with the comparison of ZX008 0.8 mg/kg/day with placebo for primary and key secondary outcomes, followed by comparison of ZX008 0.2 mg/kg/day with placebo in the same sequence of outcomes. The SAP and protocol, clinical summaries do not agree on the hierarchy of tests, but the Section 8.1 of the SAP v2.0 provides the right sequence. Further, the MAH provided some clarifications on the predefined analysis, estimand strategy, missing data, absolute changes for DSF and distribution of data.

#### Part 2:

Study 1601 Part 2 was designed to evaluate the long-term safety (primary objective) and effectiveness (secondary objective) of ZX008 for up to 1 year in the subjects who successfully completed Part 1.

Upon transition to Part 2, all subjects were transitioned from their blinded daily dose in Part 1 to be treated initially with ZX008 0.2 mg/kg/day for 1 month to assess effectiveness of this dose and all efficacy analysis used month 1 values as baseline. This creates confusion and issues with analysis regarding maintenance of effect as the treatment is blindly down titrated for all patients and started again at 0.2 mg/kg/day. For patients on active arms, this might have caused worsening of seizures or carry over effects from the high dose. Due to tapering and dosing transition between study parts, high discontinuation, and flexible dosing (most patients were treated with 0.4-0.6 mg/kg/day dose) the conclusion in Part 2 may be biased. It is highly uncertain if efficacy results beyond 14 weeks could form the basis of maintenance of efficacy.

# Efficacy data and additional analyses

#### Part 1:

A total of 335 subjects were enrolled and screened, 263 of these subjects were randomized (placebo: 87 subjects; ZX008 0.2 mg/kg/day: 89 subjects; ZX008 0.8 mg/kg/day: 87 subjects). A total of 245 (93.2%) randomized subjects were considered Part 1 completers. The study population included 187 (71.1%) pediatric subjects < 18 years of age and 76 (28.9%) adult subjects  $\geq$  18 years of age with LGS. Approximately half of the subjects (46.4%) were from Europe which gives a good representation of EU population. The baseline population was mostly <18 years of age (71.1%), 55.5% male, majority of white race. The enrolled subjects had failed a median of 7 AEDs (range: 1 to 20) and were stabilized on standard of care antiepileptic treatments but were still experiencing high seizure burden, ranging from a median of 53 to 85 drop seizures per 28 days across the treatment groups. Most subjects (98.9%) received between 1 and 4 concomitant AEDs, the median number of concomitant AEDs was 3. The most commonly used concomitant AEDs ( $\geq$  25% of subjects overall) were clobazam (45.2%), lamotrigine (33.5%), and valproate (55.9).

Study 1601 Part 1 met its primary objective with the ZX008 0.8 mg/kg/day dose and it was supported by p-value for 50% responders for this dose. A 26.5% median percentage reduction in DSF was observed between Baseline and the 14-week T+M in the ZX008 0.8 mg/kg/day group, compared with a reduction of 7.6% in the placebo group (p = 0.0013). The percentage of subjects achieving a clinically meaningful  $\geq$  50% reduction from Baseline in DSF during T+M (ie, 50% responder rate) was 25.3% in ZX008 0.8 mg/kg/day group, compared with 10.3% for placebo (p = 0.0150). CGI-I showed a supportive trend only.

As the third key secondary endpoint (the fourth endpoint in the testing hierarchy), the change from Baseline in DSF during T+M for the ZX008 0.2 mg/kg/day group was compared with the placebo group. The median percentage reduction from Baseline for the ZX008 0.2 mg/kg/day group was 14.2%. The difference between ZX008 0.2 mg/kg/day and placebo was not significant (p=0.0939). 0.2 mg/kg/day is not considered an effective dose.

Supplementary or sensitivity analyses of primary endpoint provided mostly supportive results (during maintenance period only, using PP population, excluding extreme outliers, not imputing for seizure clusters, and using 2 different methods for imputation of missing data due to subject dropout, using Wilcoxon rank-sum test, by seizure type). As maintenance period is recommended to be used for primary analysis in the epilepsy guideline, the primary analysis was used to compare the change from Baseline in DSF during Maintenance only. The results of this analysis for the ZX008 0.8 mg/kg/day

group (-27.2%) compared with the placebo group (-7.3%) (p=0.0018) were similar to those of the analysis for the T+M.

Additionally, no significant increases in any individual seizure types, no notable difference in new seizure types or incidence of status epilepticus are reassuring.

Due to small subgroups, some imbalances were observed. Most of the subgroups showed consistent favouring of 0.8 mg/kg/day treatment over placebo. Subgroups with uncertain effect were subjects using 4 or more concomitant AEDs, subjects with very high baseline seizure frequency, and subjects who had less than 4 AED use in the past. So, heavily treated subjects with highest baseline seizure frequency and subjects who have not failed many therapies in the past were the two extremes who had uncertain benefit of treatment with Fintepla. Of course, small numbers and no statistical power to detect differences in small subgroups is acknowledged. The most commonly used concomitant antiepileptic therapies did not seem to have an effect on the efficacy analysis.

#### Part 2:

247 subjects were enrolled in Part 2. A total of 83 subjects are reported as having discontinued during Part 2 as of the data cut-off date for the report. For the recommended dose, the claim of durable efficacy could be questionable, however the efficacy analyses (resembling primary analysis and responder analysis from Part 1) were supportive. Nearly one-third of subjects, 30.8%, experienced worsening or no change in DSF from Month 2 to EOS (ie, after the mandatory 1 month of ZX008 dosing at 0.2 mg/kg/day).

# 2.4.3. Conclusions on the clinical efficacy

The CHMP agrees that efficacy on reduction in drop of seizure frequency was demonstrated in a study of adequate design (Study 1601 Part 1) for the 0.8 mg/kg/day dose.

The recommended posology and the relevant data are correctly reflected in the SmPC.

## 2.5. Clinical safety

#### Introduction

Fintepla is approved in the United States (US), European Union (EU), and United Kingdom (UK) for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older. The New Drug Application (NDA) for fenfluramine for this indication (NDA 212102) was approved in the US in June 2020. The marketing authorization application for this indication in the EU and UK was approved in December 2020.

Fenfluramine was previously approved in Europe in the 1960s and the US (Pondimin NDA 16-618) in the 1970s as an appetite suppressant at a dose of 60 to 120 mg/day for the treatment of adult obesity. Fenfluramine was withdrawn from all world-wide markets by 1997 due to its reported association with cardiac valve abnormalities in adult patients who were receiving the drug, most often in combination with phentermine, to treat adult obesity (Centers for Disease Control and Prevention [CDC] 1997; Connolly 1997; Wong 1998). The maximum ZX008 dose studied in the LGS clinical program is 30 mg/day, which is the same as that studied and approved in Dravet syndrome and is 2 to 4 times lower than the daily doses prescribed in the past to treat adult obesity.

The date cut-off date for safety in the LGS development program was 19 Oct 2020. The clinical studies that evaluated the safety of ZX008 in subjects with LGS include the following:

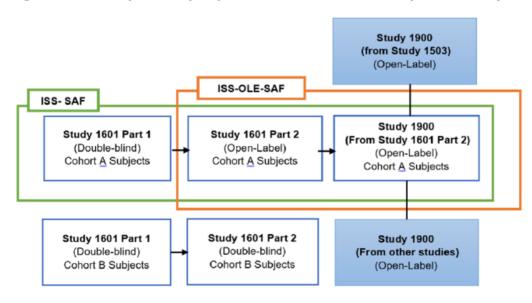
**Table 48 Summary of Clinical Studies Providing Safety Information** 

Study Identifier	Number of Subjects	Study Design and Type of Control	Test Product(s): Regimen, Route of Administration	Age Range	Duration of Treatment and Follow-up
Completed Randomized,	Double-Blind, Pl	acebo-controlled Study (Lennox	Gastaut syndrome)	•	
ZX008-1601 Part 1 Cohort A	263	Randomized, double-blind, placebo controlled to assess efficacy and safety	ZX008 0.2 mg/kg/day, 0.8 mg/kg/day; maximum 30 mg/day twice daily oral administration	2-35 years	2 weeks titration, 12 weeks maintenance, 2 weeks taper/transition 3 to 24 months cardiac follow-up
Ongoing Open-label Exte	nsion Studies as	of the data cutoff date of 19 Oct	2020 (Lennox Gastaut syndrome)		
ZX008-1601 Part 2 Cohort A	247	Open-label long-term safety and tolerability of ZX008 in subjects completing ZX008- 1601 Part 1	ZX008 flexible dosing up to 0.8 mg/kg/day; maximum 30 mg/day twice daily oral administration	2-36 years	12 months (52 weeks), 2 weeks taper 3 to 24 months cardiac follow-up
ZX008-1900	131	Open-label long-term safety and tolerability of ZX008 in subjects who participated in ZX008-1601 Part 2	ZX008 flexible dosing up to 0.8 mg/kg/day; maximum 30 mg/day twice daily oral administration	4-37 years	up to 36 months (156 weeks), 2 weeks taper 3 to 24 months cardiac follow-up

The following populations were defined for safety assessments (Figure 9):

- The Study 1601 Part 1 Safety Population was defined as all randomized subjects who received at least one dose of ZX008 or placebo in Study 1601 Part 1 (N=263).
- The ISS Safety Population (ISS-SAF) consists of all randomized subjects in Study 1601 Cohort A, who received  $\geq 1$  dose of ZX008 or placebo throughout their participation in Study 1601 Part 1, Part 2, or Study 1900 (N=263). One subject randomized to placebo in Part 1 did not continue into Part 2; thus 262 subjects were treated with ZX008 in the double-blind and open-label extension (OLE) treatment periods.
- The ISS Open-label Safety Population (ISS-OLE-SAF) consists of all subjects in the ISS Safety Population who received  $\geq 1$  dose of ZX008 in the Study 1601 Part 2 treatment period, regardless of whether they entered Study 1900 (N=247). The OLE period starts on the date of first open-label ZX008 dose in Study 1601 Part 2. Subjects in Study 1601 Part 1 who did not continue into Part 2 are not included in this population.

Figure 9 Summary of Study Populations at Interim Cut-off (19 Oct 2020)



# Patient exposure

#### **Table 49 Subject Disposition**

	Overall n (%)
Enrolled in Study 1601 Part 1	335
Randomized in Study 1601 Part 1	263
ISS Safety Population <sup>a</sup>	263
Completed 1601 Part 1, n (%) <sup>b</sup>	245 (93.2%)
Discontinued 1601 Part 1, n (%)	21 (8.0%)
Reason for Discontinuation from Part 1, n (%)	•
Adverse event	10 (3.8%)
Death	1 (0.4%)
Other	3 (1.1%)
Physician decision	2 (0.8%)
Protocol deviation	1 (0.4%)
Withdrawal by subject	4 (1.5%)
Enrolled in Study 1601 Part 2, n (%)	247 (93.9%)
ISS OLE Safety Population, n (%) <sup>c</sup>	247 (93.9%)
Completed Study 1601 Part 2, n (%)d	122 (46.4%)
Ongoing in Study 1601 Part 2, n (%)e	42 (16.0%)
Discontinued Study 1601 Part 2, n (%)	83 (31.6%)
Reason for Discontinuation from Study 1601 Part 2, n (%)	-
Adverse event	13 (4.9%)
Death	1 (0.4%)
Lack of efficacy	55 (20.9%)
Rollover into Zogenix 1900	1 (0.4%)
Withdrawal by subject	13 (4.9%)
Enrolled in Study 1900, n (%)	131 (49.8%)
Dosed in Study 1900, n (%)	131 (49.8%)
Completed Study 1900, n (%)f	0
Ongoing in Study 1900e	129 (49.0%)
Discontinued Study 1900, n (%)	2 (0.8%)
Reason for Discontinuation from Study 1900, n (%)	•
Subject switching to commercial ZX008	1 (0.4%)

Source: ISS Table 14.1.1

Withdrawal by subject

ISS = Integrated Summary of Safety, OLE = Open-Label Extension.

Note: Percentages are calculated based on the number of subjects with non-missing data in the ISS Safety Population.

- The ISS Safety Population consists of all randomized subjects in Study 1601 Cohort A who received at least one dose of ZX008 or placebo. Study 1601 Cohort B (Japan) subjects are not included.
- b Study 1601 Part 1 trial completers include randomized subjects who either, a) did not discontinue prior to Visit 12 (n=242), or
- b) completed at least through Visit 8 and enrolled into the Study 1601 Part 2 open label extension (n=3).

  The ISS OLE Safety Population consists of all subjects in the ISS Safety Population who received at least one dose of study drug in the OLE period. The Open-label treatment period starts from Study 1601 Part 2. Subjects in 1601 Part 1 who did not continue into Part 2 are not included in this population.

  d Completed Part 2 of the study through Visit 22; ie, did not early terminate.
- Ongoing as of the data cut-off for ISS analysis, which is 19 Oct 2020.
- A subject is defined as completed Study 1900 when they have received study drug for 3 years (2 years in Denmark) in Study 1900 or until ZX008 is approved in the subject's country of residence and listed on the subject's health plan formulary, or other transition to Fintepla (eg. Expanded Access Program), and the subject has completed the End of Study Visit in

The overall mean duration of exposure to ZX008 for the ISS-SAF Population at the time of the interim data cut-off was 454.13 (239.030) days overall. Overall, 262 subjects in the ISS-SAF Population received ≥ 1 dose of ZX008 by the interim cut-off, including a total of 219 (83.6%) subjects who

1 (0.4%)

received ZX008 for 6 months or longer, and 172 (65.6%) subjects who received ZX008 for 1 year or longer (Table 50).

A total of 186 study subjects 2 - < 18 years of age had a mean exposure of 450.88 (245.807) days while 76 subjects  $\geq$  18 years of age had a mean exposure of 462.11 (222.941) days.

The majority of subjects treated for  $\geq$  12 months had received a mean daily dose of ZX008 of 0.4 to <0.6 mg/kg/day.

Table 50 Duration of ZX008 Exposure During Double-Blind Through Open-label Extension Treatment Periods by Mean Daily Dose (mg/kg/dau); ISS-SAF Population

	A	Actual ZX008 Mean Daily Dose (mg/kg/day) <sup>a</sup>				
	>0 to <0.4 (N=81)	0.4 to <0.6 (N=113)	≥ 0.6 (N=68)	Any ZX008 (N=262)		
Duration of ZX008 Ex	xposure (days) <sup>b</sup>					
n	81	113	68	262		
Mean	339.40	479.04	549.41	454.13		
SD	235.267	216.613	227.752	239.030		
Median	298.00	503.00	529.50	471.00		
Min, Max	9, 945	15, 976	46, 991	9, 991		
≥ 1 Month	77 (95.1%)	111 (98.2%)	68 (100%)	256 (97.7%)		
≥ 3 Months	69 (85.2%)	111 (98.2%)	65 (95.6%)	245 (93.5%)		
≥ 6 Months	56 (69.1%)	101 (89.4%)	62 (91.2%)	219 (83.6%)		
≥ 9 Months	42 (51.9%)	87 (77.0%)	62 (91.2%)	191 (72.9%)		
≥ 12 Months	34 (42.0%)	80 (70.8%)	58 (85.3%)	172 (65.6%)		
≥ 15 Months	27 (33.3%)	67 (59.3%)	46 (67.6%)	140 (53.4%)		
≥ 18 Months	18 (22.2%)	46 (40.7%)	33 (48.5%)	97 (37.0%)		
≥ 21 Months	10 (12.3%)	28 (24.8%)	25 (36.8%)	63 (24.0%)		
≥ 24 Months	6 (7.4%)	15 (13.3%)	18 (26.5%)	39 (14.9%)		
≥ 27 Months	3 (3.7%)	7 (6.2%)	11 (16.2%)	21 (8.0%)		
≥ 30 Months	2 (2.5%)	5 (4.4%)	3 (4.4%)	10 (3.8%)		
≥ 33 Months	0	0	1 (1.5%)	1 (0.4%)		

Source: ISS Table 14.1.5.1

ISS = Integrated Summary of Safety, DB = Double-Blind, OLE = Open-Label Extension, SD = Standard Deviation, Min = Minimum, Max = Maximum.

#### Adverse events

#### Overview:

The number and percentage of subjects for whom  $\geq 1$  treatment emergent adverse event (TEAE) was reported during the 14-week double-blind combined T+M periods are presented for the 1601 Part 1 Safety Population by treatment group in Table 51.

<sup>&</sup>lt;sup>a</sup> The mean daily dose is calculated over the complete ZX008 duration during DB through OLE Treatment Periods. The calculation is using the weighted average of the daily dosages assigned by the investigator and the number of days at each dosage. For Study 1601, the assigned daily dosage is prorated by, and duration of treatment is derived from, subject-reported compliance in a medication diary. For Study 1900, assigned daily dosage and duration of treatment are derived directly from

Table 51 Overview of the Number of Sujects with Treatment-Emergent Adverse Events – T+M; Part 1 Safety Population

Placebo ZX008 0.2 mg ZX008 0.8 mg All Subjects (N=87%)(N=89%) N=87%) (N=263%) Subjects with: n (%%) n (%%) n (%%) n (%%) ≥1 TEAE 65 (74.7%) 69 (77.5%) 78 (89.7%) 212 (80.6%) > 1 treatment-related TEAE 34 (39.1%) 31 (34.8%) 48 (55.2%) 113 (43.0%) ≥ 1 treatment-emergent SAE 4 (4.6%) 4 (4.5%) 10 (11.5%) 18 (6.8%) ≥ 1 treatment-related treatment-0 1 (1.1%) 1 (1.1%) 2 (0.8%) emergent SAE ≥ 1 severe TEAE 1 (1.1%) 1 (1.1%) 3 (3.4%) 5 (1.9%) ≥ 1 treatment-related severe TEAE 1 (1.1%) 1 (1.1%) 2 (0.8%) 0 ≥ 1 TEAE leading to death 0 1 (1.1%) 1 (0.4%) ≥ 1 TEAE leading to premature 0 4 (4.5%) 5 (5.7%) 9 (3.4%) discontinuation of study treatment ≥ 1 TEAE leading to discontinuation 1 (1.1%) 4 (4.5%) 5 (5.7%) 10 (3.8%) from study ≥ 1 TEAE of special interest 1 (1.1%) 0 3 (3.4%) 4 (1.5%)

Source: 1601 Part 1 CSR Table 14.3.1.1.1.1

SAE=serious adverse event; T+M=Titration + Maintenance Periods; TEAE=treatment-emergent adverse event

Note: An adverse event is classified as treatment-emergent if it started on or after the date of the first dose of study treatment.

The number and percentage of subjects for whom  $\geq 1$  TEAE was reported during the double-blind through OLE periods are presented for the ISS-SAF Population by ZX008 mean daily dose (mg/kg/day) in Table 52.

Table 52 Overview of Number of Subjects with TEAE During Double-blind Through Openlabel Treatment Periods; ISS-SAF Population

	Actual ZX00	8 Mean Daily Dose	(mg/kg/day) <sup>a</sup>	
Number of Subjects with	>0 to <0.4 (N = 81) n (%)	0.4 to <0.6 (N = 113) n (%)	≥ 0.6 (N = 68) n (%)	Overall (N = 262) n (%)
At least one TEAE	70 (86.4%)	109 (96.5%)	63 (92.6%)	242 (92.4%)
At least one Related TEAE	47 (58.0%)	75 (66.4%)	36 (52.9%)	158 (60.3%)
At least one Serious TEAE	13 (16.0%)	22 (19.5%)	18 (26.5%)	53 (20.2%)
At least one Related Serious TEAE	4 (4.9%)	8 (7.1%)	1 (1.5%)	13 (5.0%)
At least one Severe TEAE	3 (3.7%)	11 (9.7%)	7 (10.3%)	21 (8.0%)
At least one Related Severe TEAE	0	5 (4.4%)	1 (1.5%)	6 (2.3%)
At least one TEAE Leading to Death	1 (1.2%)	0	1 (1.5%)	2 (0.8%)
At least one TEAE Leading to Premature Discontinuation of Study and/or Treatment	13 (16.0%)	7 (6.2%)	4 (5.9%)	24 (9.2%)

#### Common Adverse Events:

Table 53 provides a summary of TEAEs reported for  $\geq$  5% subjects in any treatment group during T+M by System Organ Class (SOC) and Preferred Term (PT) for the 1601 Part 1 Safety Population.

The most common TEAEs occurring during T+M in subjects in the ZX008 groups (≥10% of subjects in either group) were decreased appetite, fatigue, somnolence, diarrhea, vomiting, and pyrexia.

Decreased appetite was the most commonly reported TEAE in the ZX008 treatment groups; decreased appetite and pyrexia were the most commonly reported TEAEs in the placebo group. Decreased appetite was the only TEAE reported with a >10% difference in incidence between treatment groups; these events were reported for >10% more subjects in the ZX008 0.8 mg/kg/day group than in the placebo and 0.2 mg/kg/day group.

System organ classes in which TEAEs were commonly reported in either ZX008 group ( $\geq$  25% of subjects) that were reported with a  $\geq$  10% greater incidence than in the placebo group included Gastrointestinal disorders, Infections and infestations, and Metabolism and nutrition disorders.

Table 53 Study 1601 Part 1 Treatment-Emergent Adverse Events Occurring in ≥ 5% of Subjects in Any Treatment Group by System Organ Class and Preferred Term – T+M Period; Part 1 Safety Population

MedDRA System Organ Class Preferred Term	Placebo (N=87) n (%)	ZX008 0.2 mg/kg/day (N=89) n (%)	ZX008 0.8 mg/kg/day (N=87) n (%)
Subjects with any TEAE	65 (74.7%)	69 (77.5%)	78 (89.7)
Gastrointestinal disorders	20 (23.0%)	30 (33.7%)	31 (35.6%)
Constipation	5 (5.7%)	5 (5.6%)	8 (9.2%)
Diarrhoea	4 (4.6%)	10 (11.2%)	11 (12.6%)
Vomiting	5 (5.7%)	12 (13.5%)	7 (8.0%)
General disorders and administration site conditions	24 (27.6%)	21 (23.6%)	27 (31.0%)
Asthenia	3 (3.4%)	4 (4.5%)	5 (5.7%)
Fatigue	9 (10.3%)	8 (9.0%)	16 (18.4%)
Pyrexia	10 (11.5%)	9 (10.1%)	7 (8.0%)
Infections and infestations	19 (21.8%)	26 (29.2%)	34 (39.1%)
Nasopharyngitis	8 (9.2%)	3 (3.4%)	6 (6.9%)
Upper respiratory tract infection	3 (3.4%)	7 (7.9%)	6 (6.9%)
Investigations	15 (17.2%)	9 (10.1%)	16 (18.4%)
Weight decreased	2 (2.3%)	2 (2.2%)	7 (8.0%)
Metabolism and nutrition disorders	10 (11.5%)	20 (22.5%)	31 (35.6%)
Decreased appetite	10 (11.5%)	18 (20.2%)	31 (35.6%)
Nervous system disorders	27 (31.0%)	26 (29.2%)	30 (34.5%)
Lethargy	2 (2.3%)	2 (2.2%)	5 (5.7%)
Seizure	6 (6.9%)	8 (9.0%)	4 (4.6%)
Somnolence	9 (10.3%)	9 (10.1%)	15 (17.2%)
Psychiatric disorders	16 (18.4%)	15 (16.9%)	17 (19.5%)
Irritability	5 (5.7%)	7 (7.9%)	3 (3.4%)

Table 54 provides a summary of TEAEs reported for  $\geq 5\%$  subjects in any ZX008 mean daily dose group or overall, during the double-blind through OLE periods by MedDRA SOC and PT for the ISS-SAF Population. The most common TEAEs reported in  $\geq 10\%$  of subjects overall were decreased appetite, somnolence, seizure, nasopharyngitis, pyrexia, fatigue, diarrhea, vomiting, upper respiratory tract infection, constipation, and change in seizure presentation. Decreased appetite, vomiting, fatigue, pyrexia, nasopharyngitis, somnolence, and seizure were each reported for  $\geq 10\%$  of subjects at all mean daily dose levels of ZX008. TEAEs that were reported for  $\geq 10\%$  of subjects at any mean daily dose level and that appeared to have a dose relationship included pyrexia and nasopharyngitis, each of which was most common at the ZX008  $\geq 0.6$  mg/kg/day mean daily dose level.

The most common TEAEs by SOC ( $\geq$  25% of subjects) were nervous system disorders, infections and infestations, general disorders and administration site conditions, metabolism and nutrition disorders, and gastrointestinal disorders.

In the ISS-SAF Population, the TEAEs with incidence rates of  $\geq$  10 per 100 subject years of exposure include decreased appetite (26.4/100 subject years), fatigue (16.3/100 subject years), somnolence (15.0/100 subject years), seizure (13.2/100 subject years), nasopharyngitis (12.6/100 subject years), pyrexia (12.3/100 subject years), and diarrhea (10.4/100 subject years).

Table 54 Treatment-Emergent Adverse Events During Duoble-blind Through Open-label Treatment Periods in ≥ 5% of Subjects by MedDRA System Organ Class and Preferred Term; ISS-SAF Population

	Actual ZX00	8 Mean Daily Dose	(mg/kg/day)a	
MedDRA System Organ Class and Preferred Term	>0 to <0.4 (N = 81) n (%)	0.4 to <0.6 (N = 113) n (%)	≥ 0.6 (N = 68) n (%)	Overall (N = 262) n (%)
Subjects with any TEAE	62 (76.5%)	100 (88.5%)	59 (86.8%)	221 (84.4%)
Gastrointestinal disorders	17 (21.0%)	34 (30.1%)	22 (32.4%)	73 (27.9%)
Diarrhea	7 (8.6%)	16 (14.2%)	11 (16.2%)	34 (13.0%)
Vomiting	9 (11.1%)	14 (12.4%)	7 (10.3%)	30 (11.5%)
Constipation	5 (6.2%)	14 (12.4%)	10 (14.7%)	29 (11.1%)
General disorders and administration site conditions	25 (30.9%)	43 (38.1%)	24 (35.3%)	92 (35.1%)
Fatigue	14 (17.3%)	30 (26.5%)	9 (13.2%)	53 (20.2%)
Pyrexia	9 (11.1%)	17 (15.0%)	14 (20.6%)	40 (15.3%)
Asthenia	5 (6.2%)	7 (6.2%)	5 (7.4%)	17 (6.5%)
Infections and infestations	23 (28.4%)	46 (40.7%)	30 (44.1%)	99 (37.8%)
Nasopharyngitis	10 (12.3%)	17 (15.0%)	14 (20.6%)	41 (15.6%)
Upper respiratory tract infection	6 (7.4%)	15 (13.3%)	9 (13.2%)	30 (11.5%)
Gastroenteritis viral	1 (1.2%)	5 (4.4%)	6 (8.8%)	12 (4.6%)
Pneumonia	3 (3.7%)	4 (3.5%)	5 (7.4%)	12 (4.6%)
Urinary tract infection	2 (2.5%)	8 (7.1%)	2 (2.9%)	12 (4.6%)
Ear infection	1 (1.2%)	5 (4.4%)	4 (5.9%)	10 (3.8%)
Injury, poisoning and procedural complications	5 (6.2%)	19 (16.8%)	9 (13.2%)	33 (12.6%)
Laceration	3 (3.7%)	8 (7.1%)	5 (7.4%)	16 (6.1%)
Contusion	1 (1.2%)	7 (6.2%)	6 (8.8%)	14 (5.3%)
Fall	2 (2.5%)	8 (7.1%)	2 (2.9%)	12 (4.6%)
Investigations	7 (8.6%)	23 (20.4%)	13 (19.1%)	43 (16.4%)
Weight decreased	5 (6.2%)	11 (9.7%)	6 (8.8%)	22 (8.4%)
Echocardiogram abnormal <sup>b</sup>	2 (2.5%)	7 (6.2%)	3 (4.4%)	12 (4.6%)
Blood prolactin increased	0	7 (6.2%)	4 (5.9%)	11 (4.2%)
Metabolism and nutrition disorders	21 (25.9%)	45 (39.8%)	20 (29.4%)	86 (32.8%)
Decreased appetite	21 (25.9%)	45 (39.8%)	20 (29.4%)	86 (32.8%)
Nervous system disorders	38 (46.9%)	55 (48.7%)	36 (52.9%)	129 (49.2%)
Somnolence	13 (16.0%)	25 (22.1%)	11 (16.2%)	49 (18.7%)
Seizure	15 (18.5%)	17 (15.0%)	11 (16.2%)	43 (16.4%)
Change in seizure presentation	6 (7.4%)	13 (11.5%)	10 (14.7%)	29 (11.1%)

Lethargy	5 (6.2%)	10 (8.8%)	6 (8.8%)	21 (8.0%)
Status epilepticus	3 (3.7%)	5 (4.4%)	5 (7.4%)	13 (5.0%)
Tremor	4 (4.9%)	6 (5.3%)	1 (1.5%)	11 (4.2%)
Drooling	2 (2.5%)	3 (2.7%)	4 (5.9%)	9 (3.4%)
Headache	1 (1.2%)	7 (6.2%)	1 (1.5%)	9 (3.4%)
Psychiatric disorders	11 (13.6%)	15 (13.3%)	12 (17.6%)	38 (14.5%)
Irritability	5 (6.2%)	10 (8.8%)	3 (4.4%)	18 (6.9%)
Insomnia	4 (4.9%)	5 (4.4%)	5 (7.4%)	14 (5.3%)
Aggression	4 (4.9%)	1 (0.9%)	4 (5.9%)	9 (3.4%)
Respiratory, thoracic and mediastinal disorders	7 (8.6%)	8 (7.1%)	2 (2.9%)	17 (6.5%)
Cough	7 (8.6%)	8 (7.1%)	2 (2.9%)	17 (6.5%)

Table 55 summarizes TEAEs that started in the first month of ZX008 treatment in  $\geq$  5% of subjects by mean daily dose.

Table 55 Treatment-Emergent Adverse Events Starting in the First Month of ZX008 Treatment in ≥ 5% of Subjects by Preferred Term; ISS-SAF Population

	Actual ZX00	Actual ZX008 Mean Daily Dose (mg/kg/day) <sup>a</sup>				
MedDRA Preferred Term	>0 to <0.4 (N = 81) n (%)	0.4 to <0.6 (N = 113) n (%)	≥ 0.6 (N = 68) n (%)	Overall (N = 262) n (%)		
Subjects with any TEAE	41 (50.6%)	77 (68.1%)	36 (52.9%)	154 (58.8%)		
Diarrhea	3 (3.7%)	10 (8.8%)	5 (7.4%)	18 (6.9%)		
Vomiting	4 (4.9%)	7 (6.2%)	3 (4.4%)	14 (5.3%)		
Fatigue	6 (7.4%)	15 (13.3%)	6 (8.8%)	27 (10.3%)		
Decreased appetite	11 (13.6%)	30 (26.5%)	5 (7.4%)	46 (17.6%)		
Somnolence	6 (7.4%)	11 (9.7%)	5 (7.4%)	22 (8.4%)		

Source: ISS Table 14.3.1.7.1

The most common TEAE occurring after 6 months of treatment was seizure (6.9%).

#### **Treatment-related AEs:**

For the Study 1601 Part 1 Safety Population, the subject incidence of treatment-related TEAEs occurring during T+M was higher in the ZX008 0.8 mg/kg/day group (55.2%) than in the placebo (39.1%) and ZX008 0.2 mg/kg/day (34.8%) groups. The most common treatment-related TEAEs in the ZX008 groups ( $\geq$  10% of subjects in either group) were decreased appetite, fatigue, and somnolence. Decreased appetite and fatigue were the only common treatment-related TEAEs reported with a >10% difference in incidence between treatment groups.

Table 56 Study 1601 Part 1 Treatment-Related Treatment-Emergent Adverse Events Occurring in ≥ 5% of Subjects in Any Treatment Group by System Organ Class and Preferred Term – T+M; Part 1 Safety Population

MedDRA System Organ Class Preferred Term	Placebo (N=87%) n (%%)	ZX008 0.2 mg/kg/day (N=89%) n (%)	ZX008 0.8 mg/kg/day (N=87%) n (%)
Subjects with any treatment-related TEAE	34 (39.1%)	31 (34.8%)	48 (55.2%)
General disorders and administration site condition	ns		_
Fatigue	5 (5.7%)	6 (6.7%)	15 (17.2%)
Investigations	•	•	•
Weight decreased	2 (2.3%)	2 (2.2%)	6 (6.9%)
Metabolism and nutrition disorders			-
Decreased appetite	7 (8.0%)	13 (14.6%)	26 (29.9%)
Nervous system disorders	•		•
Lethargy	2 (2.3%)	0	5 (5.7%)
Seizure	1 (1.1%)	5 (5.6%)	3 (3.4%)
Somnolence	7 (8.0%)	7 (7.9%)	13 (14.9%)

Overall, 46.9% of subjects in the ISS-SAF Population experienced at least 1 treatment-related TEAE. Somnolence was reported for  $\geq 10\%$  of subjects with similar incidences at all mean daily dose levels of ZX008. Decreased appetite and fatigue were each reported for  $\geq 10\%$  of subjects with a higher incidence in the ZX008 0.4 to < 0.6 mg/kg/day group. The most common treatment-related TEAEs by SOC ( $\geq 25\%$  of subjects) was metabolism and nutrition disorders.

Table 57 Treatment-Related Treatment-Emergent Adverse Events Occurring in ≥ 5% of Subjects in Any Dose Group or Overall During Double-blind Through Open-label Treatment Periods by MedDRA System Organ Class and Preferred Term; ISS-SAF Population

	Actual ZX00	8 Mean Daily Dose	(mg/kg/day) <sup>a</sup>	
MedDRA System Organ Class and Preferred Term	>0 to <0.4 (N = 81) n (%)	0.4 to <0.6 (N = 113) n (%)	≥ 0.6 (N = 68) n (%)	Overall (N = 262) n (%)
Subjects with any treatment- related TEAE in ≥ 5% of Subjects	35 (43.2%)	62 (54.9%)	26 (38.2%)	123 (46.9%)
General disorders and administration site conditions	10 (12.3%)	24 (21.2%)	8 (11.8%)	42 (16.0%)
Fatigue	10 (12.3%)	24 (21.2%)	8 (11.8%)	42 (16.0%)
Investigations	4 (4.9%)	8 (7.1%)	4 (5.9%)	16 (6.1%)
Weight decreased	4 (4.9%)	8 (7.1%)	4 (5.9%)	16 (6.1%)
Metabolism and nutrition disorders	16 (19.8%)	40 (35.4%)	14 (20.6%)	70 (26.7%)
Decreased appetite	16 (19.8%)	40 (35.4%)	14 (20.6%)	70 (26.7%)
Nervous system disorders	21 (25.9%)	27 (23.9%)	12 (17.6%)	60 (22.9%)
Somnolence	10 (12.3%)	17 (15.0%)	8 (11.8%)	35 (13.4%)
Seizure	8 (9.9%)	5 (4.4%)	3 (4.4%)	16 (6.1%)
Lethargy	4 (4.9%)	6 (5.3%)	3 (4.4%)	13 (5.0%)
Tremor	1 (1.2%)	6 (5.3%)	0	7 (2.7%)
Psychiatric disorders	3 (3.7%)	2 (1.8%)	4 (5.9%)	9 (3.4%)
Insomnia	3 (3.7%)	2 (1.8%)	4 (5.9%)	9 (3.4%)

#### Treatment Emergent Adverse Events by Severity:

In Study 1601 Part 1, 5 subjects (3 in the ZX008 0.8 mg/kg/day group and 1 in each of the other treatment groups) had TEAEs during T+M that were graded as severe. The TEAE somnolence in the ZX008 0.8 mg/kg/day group and the TEAE for abnormal behavior in the placebo group were assessed as possibly related to the study drug by the Investigators.

Table 58 Treatment-Emergent Adverse Events Reported as Severe in Any Treatment Group, by System Organ Class and Preferred Term – T+M; Part 1 Safety Population

MedDRA System Organ Class Preferred Term	Placebo (N=87%) n (%%)	ZX008 0.2 mg/kg/day (N=89%) n (%%)	ZX008 0.8 mg/kg/day (N=87%) n (%%)
Subjects with severe TEAE	1 (1.1%)	1 (1.1%)	3 (3.4%)
Gastrointestinal disorders	_		
Gastritis	0	0	1 (1.1%)
General disorders and administration site conditions	·		
SUDEP	0	0	1 (1.1%)
Injury, poisoning and procedural complications			
Humerus fracture	0	0	1 (1.1%)
Nervous system disorders	_		
Change in seizure presentation	0	1 (1.1%)	0
Somnolence	0	0	1 (1.1%)
Psychiatric disorders			
Abnormal behavior	1 (1.1%)	0	0

For the ISS-SAF Population, severe TEAEs were reported for 21 (8.0%) subjects. Three (3.7%) subjects who received ZX008 >0 to < 0.4 mg/kg/day, 11 (9.7%) subjects who received ZX008 0.4 to < 0.6 mg/kg/day, and 7 (10.3%) subjects who received ZX008  $\geq$  0.6 mg/kg/day had severe TEAEs. Severe TEAEs reported for  $\geq$  2 subjects overall were: status epilepticus, somnolence, change in seizure presentation, decreased appetite, and seizure. Two severe TEAEs for somnolence, and 1 severe TEAE for status epilepticus, abnormal behavior, and lethargy in the ZX008  $\geq$  0.6 mg/kg/day group, and 1 severe TEAE for decreased appetite, and asthenia in the ZX008 0.4 - <0.6 mg/kg/day group were assessed as possibly related to the study drug by the Investigators.

Table 59 Severe Treatment-Emergent Adverse Events Occurring in ≥ 2 Subjects During Double-blind Through Open-label Treatment Periods by MedDRA Preferred Term; ISS-SAF Population

	Actual ZX008	se (mg/kg/day)ª		
MedDRA Preferred Term/Maximum Severity	>0 to <0.4 (N = 81)	0.4 to <0.6 (N = 113)	$\geq 0.6$ (N = 68)	Overall (N = 262)
Subjects with any TEAE	70 (86.4%)	109 (96.5%)	63 (92.6%)	242 (92.4%)
Mild	30 (37.0%)	53 (46.9%)	21 (30.9%)	104 (39.7%)
Moderate	37 (45.7%)	45 (39.8%)	35 (51.5%)	117 (44.7%)
Severe	3 (3.7%)	11 (9.7%)	7 (10.3%)	21 (8.0%)
Severe TEAEs occurring in ≥ 2 subjects				
Status epilepticus	2 (2.5%)	2 (1.8%)	2 (2.9%)	6 (2.3%)
Somnolence	0	2 (1.8%)	1 (1.5%)	3 (1.1%)
Change in seizure presentation	0	1 (0.9%)	1 (1.5%)	2 (0.8%)
Decreased appetite	1 (1.2%)	1 (0.9%)	0	2 (0.8%)
Seizure	1 (1.2%)	0	1 (1.5%)	2 (0.8%)

# Serious adverse event/deaths/other significant events

#### Deaths:

There were 2 deaths that occurred during Studies 1601 Part 1, 1601 Part 2, and 1900 as of the data cut-off date.

One death occurred during Study 1601 Part 1. One subject, a 6 to 12 year-old male randomized to the ZX008 0.8 mg/kg/day treatment group, experienced suspected SUDEP (MedDRA term: Sudden unexplained death in epilepsy) on Study Day 87. The subject had a relevant medical history including developmental delay, epilepsy, gastrostomy, and seizures. Concomitant antiepileptic medications and therapies included phenobarbital, levetiracetam, ethosuximide, valproate semisodium, and ketogenic diet (2014 – ongoing). The subject began dosing with study drug on Study Day -1 with ZX008 at 0.2 mg/kg/day, titrated to a dose of 0.8 mg/kg/day over Titration, and entered Maintenance at this dose on Study Day 14. The subject was found unresponsive on the morning of Study Day 87; he was well when put to bed the night before. He had no fever and had been seizure free in the previous 48 hours. Despite 55 minutes of resuscitation, he could not be revived. The Investigator assessed the SUDEP as not related to the study drug.

One death occurred during Study 1601 Part 2. One subject, a 30 - 40 year-old female randomized to the ZX008 0.2 mg/kg/day treatment group in Part 1 on Study Day -1 and entered Part 2 on Study Day 127. On Study Day 159, the dose was increased to 0.4 mg/kg/day, and on Study Day 246, the dose was increased to 0.6 mg/kg/day. On Study Day 350, the subject experienced convulsive status epilepticus (MedDRA preferred term: Status epilepticus). On Study Day 350, the subject experienced an increase of seizures with a generalized tonic clonic convulsion every ten minutes and was admitted to the hospital. The subject was treated with rectal diazepam 40 mg once for convulsive status epilepticus. During the hospitalization, the subject experienced several seizures and was treated with intermittent intravenous (IV) valproic acid, intermittent levetiracetam, and lacosamide. Lacosamide 300 mg IV was added once for convulsive status epilepticus, due to lack of response to treatment. The seizures were successfully controlled after IV lacosamide administration, but the subject suffered from a decreased level of consciousness. On Study Day 351, a chest x-ray performed showed she experienced the event of aspiration pneumonia (MedDRA preferred term: Pneumonia aspiration) and developed respiratory failure. The subject received amoxicillin and clavulanic acid, methylprednisolone, bronchodilators, and oxygen therapy as treatment for aspiration pneumonia. An electroencephalogram performed on Study Day 351 showed interactive epileptiform abnormalities in front of the temporal area. On Study Day 352, the subject's condition was noted to be clinically worsening and palliative sedation measures were taken. An electrocardiogram performed on Study Day 353 showed asystole. The outcome of the event of pneumonia aspiration was reported as death on Study Day 353. The Investigator assessed the pneumonia aspiration and death as not related to ZX008.

#### Other Serious Adverse Events:

For the Study 1601 Part 1 Safety Population, at least 1 treatment-emergent SAE was reported during T+M for 18 subjects (6.8%): 4 subjects (4.6%) in the placebo group, 4 subjects (4.5%) in the ZX008 0.2 mg/kg/day group, and 10 subjects (11.5%) in the ZX008 0.8 mg/kg/day group.

Two subjects had treatment-emergent SAEs during T+M considered by the Investigator as related to treatment, including somnolence of moderate severity in a subject in the ZX008 0.8 mg/kg/day group (reported during Titration), which resolved after withdrawal of study drug; and change in seizure presentation of moderate severity in a subject in the ZX008 0.2 mg/kg/day group (reported during Maintenance), which resolved with an IV levetiracetam treatment and no change to study drug dosing.

Table 60 Study 1601 Part 1 Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – T+M Period; Safety Population

MedDRA System Organ Class Preferred Term	Placebo (N=87%) n (%%)	ZX008 0.2 mg/kg/day (N=89%) n (%)	ZX008 0.8 mg/kg/day (N=87%) n (%)
Subjects with Any Serious TEAEs	4 (4.6%)	4 (4.5%)	10 (11.5%)
Endocrine disorders	1 (1.1%)	0	0
Thyroid mass	1 (1.1%)	0	0
Eye disorders	1 (1.1%)	0	0
Eye movement disorder	1 (1.1%)	0	0
Gastrointestinal disorders	0	2 (2.2%)	2 (2.3%)
Constipation	0	1 (1.1%)	0
Diarrhoea	0	0	1 (1.1%)
Gastritis	0	0	1 (1.1%)
Vomiting	0	1 (1.1%)	0
General disorders and administration site conditions	0	0	1 (1.1%)
SUDEP	0	0	1 (1.1%)
Infections and infestations	0	1 (1.1%)	3 (3.4%)
Infection	0	0	1 (1.1%)
Pneumonia	0	1 (1.1%)	1 (1.1%)
Subcutaneous abscess	0	0	1 (1.1%)
Injury, poisoning and procedural complications	0	0	1 (1.1%)
Humerus fracture	0	0	1 (1.1%)
Metabolism and nutrition disorders	0	0	1 (1.1%)
Dehydration	0	0	1 (1.1%)
Nervous system disorders	2 (2.3%)	2 (2.2%)	3 (3.4%)
Change in seizure presentation	0	2 (2.2%)	0
Seizure	2 (2.3%)	0	0
Somnolence	0	0	1 (1.1%)
Status epilepticus	1 (1.1%)	0	2 (2.3%)
Psychiatric disorders	0	1 (1.1%)	1 (1.1%)
Irritability	0	1 (1.1%)	0
Stereotypy	0	0	1 (1.1%)
Respiratory, thoracic, and mediastinal disorders	0	0	1 (1.1%)
Lung disorder	0	0	1 (1.1%)
Skin and subcutaneous tissue disorders	0	0	1 (1.1%)
Rash	0	0	1 (1.1%)

Overall, 20.2% of subjects in the ISS-SAF Population reported at least 1 treatment-emergent SAE.

Table 61 Serious TEAEs During Double-blind through Open-label Treatment Periods by MedDRA System Organ Class and preferred Term; ISS-SAF Population

•	-			-
	Actual ZX008	Mean Daily Dose	(mg/kg/day) <sup>a</sup>	
	>0 to <0.4	0.4 to <0.6	≥ 0.6	Overall
MedDRA System Organ Class	(N = 81)	(N = 113)	(N = 68)	(N = 262)
and Preferred Term	n (%)	n (%)	n (%)	n (%)
Subjects with any Serious TEAE	13 (16.0%)	22 (19.5%)	18 (26.5%)	53 (20.2%)
Blood and lymphatic system disorders	0	1 (0.9%)	0	1 (0.4%)
Hemolytic uremic syndrome	0	1 (0.9%)	0	1 (0.4%)
Congenital, familial and genetic disorders	0	0	1 (1.5%)	1 (0.4%)
Pyloric stenosis	0	0	1 (1.5%)	1 (0.4%)
Eye disorders	0	1 (0.9%)	0	1 (0.4%)
Keratoconus	0	1 (0.9%)	0	1 (0.4%)
Gastrointestinal disorders	1 (1.2%)	2 (1.8%)	5 (7.4%)	8 (3.1%)
Vomiting	1 (1.2%)	1 (0.9%)	1 (1.5%)	3 (1.1%)
Constipation	0	0	1 (1.5%)	1 (0.4%)
Diarrhea	0	0	1 (1.5%)	1 (0.4%)
Gastritis	0	0	1 (1.5%)	1 (0.4%)
Intestinal obstruction	0	0	1 (1.5%)	1 (0.4%)
Tooth loss	0	1 (0.9%)	0	1 (0.4%)
General disorders and administration site conditions	0	1 (0.9%)	4 (5.9%)	5 (1.9%)
Asthenia	0	1 (0.9%)	0	1 (0.4%)
Complication of device insertion	0	0	1 (1.5%)	1 (0.4%)
Gait inability	0	0	1 (1.5%)	1 (0.4%)
Pyrexia	0	0	1 (1.5%)	1 (0.4%)
Sudden unexplained death in epilepsy	0	0	1 (1.5%)	1 (0.4%)
Infections and infestations	3 (3.7%)	9 (8.0%)	4 (5.9%)	16 (6.1%)
Pneumonia	2 (2.5%)	3 (2.7%)	3 (4.4%)	8 (3.1%)
Influenza	0	1 (0.9%)	1 (1.5%)	2 (0.8%)
Urinary tract infection	0	2 (1.8%)	0	2 (0.8%)
Cellulitis of male external genital organ	0	1 (0.9%)	0	1 (0.4%)
Corona virus infection	0	1 (0.9%)	0	1 (0.4%)
Dengue fever	1 (1.2%)	0	0	1 (0.4%)
Gastroenteritis	0	1 (0.9%)	0	1 (0.4%)
Gastroenteritis viral	0	0	1 (1.5%)	1 (0.4%)
Infection	0	1 (0.9%)	0	1 (0.4%)
Pneumonia mycoplasmal	0	1 (0.9%)	0	1 (0.4%)
Respiratory syncytial virus bronchiolitis	0	0	1 (1.5%)	1 (0.4%)
Subcutaneous abscess	0	1 (0.9%)	0	1 (0.4%)
Injury, poisoning and procedural complications	0	2 (1.8%)	2 (2.9%)	4 (1.5%)
Humerus fracture	0	2 (1.8%)	0	2 (0.8%)
Foreign body in respiratory tract	0	0	1 (1.5%)	1 (0.4%)

Upper limb fracture	0	0	1 (1.5%)	1 (0.4%)
Investigations	0	0	2 (2.9%)	2 (0.8%)
Blood prolactin increased	0	0	1 (1.5%)	1 (0.4%)
Weight decreased	0	0	1 (1.5%)	1 (0.4%)
Metabolism and nutrition disorders	1 (1.2%)	3 (2.7%)	2 (2.9%)	6 (2.3%)
Dehydration	0	1 (0.9%)	2 (2.9%)	3 (1.1%)
Decreased appetite	1 (1.2%)	1 (0.9%)	0	2 (0.8%)
Failure to thrive	0	0	1 (1.5%)	1 (0.4%)
Hypoalbuminaemia	0	1 (0.9%)	0	1 (0.4%)
Nervous system disorders	10 (12.3%)	10 (8.8%)	8 (11.8%)	28 (10.7%)
Change in seizure presentation	2 (2.5%)	6 (5.3%)	2 (2.9%)	10 (3.8%)
Status epilepticus	3 (3.7%)	3 (2.7%)	4 (5.9%)	10 (3.8%)
Seizure	3 (3.7%)	0	1 (1.5%)	4 (1.5%)
Somnolence	1 (1.2%)	2 (1.8%)	1 (1.5%)	4 (1.5%)
Generalized tonic-clonic seizure	1 (1.2%)	1 (0.9%)	0	2 (0.8%)
Cerebral hemorrhage	0	0	1 (1.5%)	1 (0.4%)
Seizure cluster	0	1 (0.9%)	0	1 (0.4%)
Tonic convulsion	0	0	1 (1.5%)	1 (0.4%)
Psychiatric disorders	0	0	3 (4.4%)	3 (1.1%)
Agitation	0	0	1 (1.5%)	1 (0.4%)
Hallucination	0	0	1 (1.5%)	1 (0.4%)
Irritability	0	0	1 (1.5%)	1 (0.4%)
Stereotypy	0	0	1 (1.5%)	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	2 (2.5%)	0	3 (4.4%)	5 (1.9%)
Pneumonia aspiration	1 (1.2%)	0	2 (2.9%)	3 (1.1%)
Lung disorder	1 (1.2%)	0	0	1 (0.4%)
Pleurisy	0	0	1 (1.5%)	1 (0.4%)
Pneumonitis	0	0	1 (1.5%)	1 (0.4%)
Skin and subcutaneous tissue disorders	0	1 (0.9%)	0	1 (0.4%)
Rash	0	1 (0.9%)	0	1 (0.4%)
Vascular disorders	0	1 (0.9%)	0	1 (0.4%)
Distributive shock	0	1 (0.9%)	0	1 (0.4%)

# Adverse events of special interest:

Adverse events of special interest were specified as an elevated prolactin level  $\geq 2 \times ULN$ ; hypoglycemia < 3.0 mmol/L or 54 mg/dL, whether that level is associated with symptoms or not; and suicidal thoughts, ideation, or gestures.

For the Study 1601 Part 1 Safety Population, 1 subject (1.1%) in the placebo group and 3 subjects (3.4%) in the ZX008 0.8 mg/kg/day group had  $\geq$  1 treatment-emergent AESI during T+M. The subject in the placebo group had hypoglycemia. All 3 subjects in the ZX008 0.8 mg/kg/day group had either hyperprolactinemia or blood prolactin increased; only 1 of these events was considered by the Investigator as possibly related to treatment. All AESIs were mild in severity. None of the events were SAEs or led to discontinuation of treatment. All events resolved in Part 1 or after the subject began open-label treatment in Part 2, with no action taken during Part 1 or Part 2.

In ISS-SAF Population, a total of 9 (3.4%) subjects had  $\geq$  1 AESI. A total of 8 subjects had a single event of hyperprolactinemia (reported as either hyperprolactinemia or blood prolactin increased) and 1 subject had 2 separate blood prolactin increased events. Hypoglycemia was also reported for 1 of these subjects. Only 1 event (blood prolactin increased) was reported as related to treatment. Two subjects had events (blood prolactin increased) of moderate severity; the remainder of the subjects

had events of mild severity. Of the 9 subjects with hyperprolactinemia or blood prolactin increased, 7 subjects had experienced seizures within the prior 2 days of the elevated serum prolactin blood test results. None of the AESI led to discontinuation of treatment. The AESIs were resolved with no action taken for all but 1 subject (who had blood prolactin increased of mild severity) as of the data cutoff date. For 1 subject, who had blood prolactin increased of mild severity, the event was an SAE ("other medically important serious event"). The elevated prolactin level was first observed on Day 295 while the subject was receiving ZX008 0.7 mg/kg/day, resolved on Day 380, and was not associated with an increase in seizure activity.

#### Analysis of Adverse Events by Organ System or Syndrome:

A review of AEs reported in the double-blind study (Study 1601 Part 1) suggests a potential increased occurrence with higher ZX008 doses for decreased appetite, weight decreased, fatigue, and sompolence

- Decreased Appetite and Weight Loss

Table 62 Study 1601 Part 1 Treatment-Emergent Adverse Events of Weight Decreased and Decreased Appetite During Double-blind Treatment Period by MedDRA Preferred Term; Part 1 Safety Population

MedDRA Preferred Term	Placebo (N=87)	ZX008 0.2 mg (N=89)	ZX008 0.8 mg (N=87)	All Subjects (N=263)
Decreased appetite	13 (14.9%)	18 (20.2%)	32 (36.8%)	63 (24.0%)
Weight decreased	2 (2.3%)	3 (3.4%)	7 (8.0%)	12 (4.6%)

Table 63 Treatment-Emergent Adverse Events of Weight Decreased and Decreased Appetite During Double-blind Treatment Period by MedDRA Preferred Term (ISS-SAF Population)

	. ,				
	Actual ZX00	Actual ZX008 Mean Daily Dose (mg/kg/day)			
MedDRA Preferred Term	> 0 to < 0.4 (N = 81) n (%)	0.4 to < 0.6 (N = 113) n (%)	≥ 0.6 (N = 68) n (%)	Overall (N = 262) n (%)	
Decreased appetite	21 (25.9%)	45 (39.8%)	20 (29.4%)	86 (32.8%)	
Weight decreased	5 (6.2%)	11 (9.7%)	6 (8.8%)	22 (8.4%)	

Weight loss is a known effect of ZX008 (fenfluramine). Decreased appetite and weight loss TEAEs were reported in more subjects randomized to the ZX008 treatment groups than the placebo groups during T+M. This is not unexpected given the known anorectic effects of fenfluramine. Subjects who reported decreased appetite did not necessarily report weight loss. The protocols did not mandate recording of the TEAE of weight loss upon certain thresholds. Rather, evaluation was conducted on observed weight loss  $\geq$  7% over the double-blind and open-label studies with body weight recorded on the vital signs case report form.

#### - Lethargy, Somnolence, and Fatigue

Taken together, lethargy, somnolence, and fatigue were reported more commonly in the ZX008 groups compared with the placebo group in Study 1601 Part 1. These 3 TEAEs were also commonly reported in the ISS-SAF population during the double-blind through OLE periods.

# Laboratory findings

Few clinically significant abnormalities were observed in hematology, serum chemistry, and urinalysis laboratory results.

Mean platelet counts decreased slightly from baseline for both ZX008 treatment groups and the placebo group during double-blind treatment, although the mean and median values remained within the normal range. Valproate is associated with decreased platelet counts (Depakene® USPI 2020), and decreased platelet counts were observed during T+M in some subjects taking concomitant VPA in clinical studies of ZX008 in Dravet syndrome. A similar observation was made in Study 1601 Part 1. At Visit 8 among 130 subjects with platelet counts within the normal reference range at baseline and using VPA, 5/40 (12.5%) in the ZX008 0.8 mg/kg/day had platelet decreases from baseline of  $\geq$  25% during T+M as did 3/46 (6.5%) in the ZX008 0.2 mg/kg/day and 3/44 (6.8%) in the placebo groups. At Visit 12 among 136 subjects with platelet counts within the normal reference range at baseline and using VPA, 5/42 (11.9%) in the ZX008 0.8 mg/kg/day and 6/51 (11.8%) in the ZX008 0.2 mg/kg/day groups had platelet decreases from baseline of  $\geq$  25% during T+M as did 2/43 (4.7%) in the placebo group. This difference was not observed in subjects not using VPA.

Few abnormalities observed in growth, precocious puberty, and thyroid function parameters were considered clinically significant changes. Treatment-emergent AEs during T+M were: blood prolactin increased or hyperprolactinemia (1 in the placebo group and 6 in the ZX008 0.8 mg/kg/day group); blood follicle stimulating hormone decreased (mild in severity, 1 subject in the ZX008 0.8 mg/kg/day group); blood testosterone decreased (mild in severity, 1 subject in the in the ZX008 0.8 mg/kg/day group); blood thyroid stimulating hormone increased (3 subjects in the placebo group and 1 subject in the ZX008 0.2 mg/kg/day group, mild in severity).

Elevation in prolactin level has been previously associated with fenfluramine (Delgado 1991, Van de Kar 1985) and also with seizures in epilepsy (Chen 2005). Therefore, the number of subjects with  $\geq$  25% increases from baseline in prolactin during T+M was evaluated, and the number of subjects who had a seizure event during T+M within 48 hours before a prolactin increase also was evaluated. Most increases from baseline in prolactin of  $\geq$  25%, which were more common in subjects in the ZX008 group, were preceded by a seizure event. Elevated prolactin level  $\geq$  2 × upper limit of normal was prespecified as an AESI in Study 1601 Part 1 and Part 2 and was observed in 9 subjects.

# Vital signs:

In ISS-SAF, treatment-emergent adverse events related to abnormal vital signs are presented in Table 64.

Table 64 Treatment-Emergent Adverse Events Due to Abnormal Vital Signs or Body Weight by Primary System Organ Class and Preferred Term; ISS-SAF Population

	Actual ZX00	Actual ZX008 Mean Daily Dose (mg/kg/day)a				
MedDRA Preferred Term	>0 to <0.4 (N = 81) n (%)	0.4 to <0.6 (N = 113) n (%)	≥ 0.6 (N = 68) n (%)	Overall (N = 262) n (%)		
Pyrexia	9 (11.1%)	17 (15.0%)	14 (20.6%)	40 (15.3%)		
Body height decreased	0	1 (0.9%)	0	1 (0.4%)		
Heart rate increased	1 (1.2%)	0	0	1 (0.4%)		
Tachycardia	0	1 (0.9%)	0	1 (0.4%)		
Failure to thrive	0	0	1 (1.5%)	1 (0.4%)		

#### Weight, Height, BMI:

The protocol did not mandate recording of the TEAE of weight loss upon certain thresholds. Body weight decrease  $\geq$  7% of baseline value at any visit in Study 1601 Part 1 during T+M was observed for

13 subjects (4.9%): 5 (5.6%) in the ZX008 0.2 mg/kg/day group and 8 (9.2%) in the ZX008 0.8 mg/kg/day group. An additional subject in the ZX008 0.2 mg/kg/day group had such a weight loss during the Taper/Transition Period. Of these subjects, 9 experienced loss of body weight  $\geq$  10% of the baseline value at  $\geq$  1 visit: 4 in the ZX008 0.2 mg/kg/day group and 5 in the ZX008 0.8 mg/kg/day.

Weight decrease was reported as a TEAE for 5 of the 14 subjects with body weight loss  $\geq$  7%: 1 in the ZX008 0.2 mg/kg/day group and 4 in the ZX008 0.8 mg/kg/day group. Decreased appetite or hypophagia was reported as a TEAE during the time of the weight loss for 8 of the subjects with a body weight decrease  $\geq$  7%: 2 in the ZX008 0.2 mg/kg/day group and 6 in the ZX008 0.8 mg/kg/day group. Decreased appetite was reported as a non-treatment-emergent AE (reported as occurring on Study Day -1 through Day 128) for an additional subject in the ZX008 0.2 mg/kg/day group with a body weight decrease  $\geq$  7%.

Body weight increase  $\geq$  7% of baseline value at any visit in T+M was reported for 23 (8.7%) subjects: 12 (13.8%) in the placebo group, 5 (5.6%) in the ZX008 0.2 mg/kg/day group, and 6 (6.9%) in the ZX008 0.8 mg/kg/day group. Of these, 10 subjects experienced body weight gain  $\geq$  10% of the baseline value at  $\geq$  1 visit: 8 (9.2%) in the placebo group, and 2 (2.2%) in the ZX008 0.2 mg/kg/day group.

No consistent differences in the percentages of subjects having body weight losses were noted between the various pediatric age subgroups.

Table 65 Summary of Body Weight Gain or Loss in Categories of ≥ 7% and ≥ 10% Change from Baseline by Age Group During the Double-blind Through Open-label Study Periods; ISS-SAF Population

	Change from DB Baseline	Change from OLE Baseline
OLE Baseline Age Subgroup: 2 to < 18 year	ars	
Baseline, n	187	
Any Visit Postbaseline, n	187	
Lost ≥ 7% of weight	33 (17.6%)	
Lost ≥ 10% of weight	23 (12.3%)	
Gain ≥ 7% of weight	90 (48.1%)	
Gain ≥ 10% of weight	68 (36.4%)	
OLE Month 12, n	92	92
Lost ≥ 7% of weight	11 (12.0%)	10 (10.9%)
Lost ≥ 10% of weight	5 (5.4%)	6 (6.5%)
Gain ≥ 7% of weight	40 (43.5%)	36 (39.1%)
Gain ≥ 10% of weight	33 (35.9%)	28 (30.4%)
OLE Baseline Age Subgroup: ≥ 18 years	·	
Baseline, n	76	
Any Visit Postbaseline, n	76	
Lost ≥ 7% of weight	26 (34.2%)	
Lost ≥ 10% of weight	14 (18.4%)	
Gain ≥ 7% of weight	11 (14.5%)	
Gain ≥ 10% of weight	4 (5.3%)	
OLE Month 12, n	45	45
Lost ≥ 7% of weight	11 (24.4%)	8 (17.8%)
Lost ≥ 10% of weight	8 (17.8%)	5 (11.1%)
Gain ≥ 7% of weight	3 (6.7%)	6 (13.3%)
Gain ≥ 10% of weight	2 (4.4%)	3 (6.7%)

ISS-SAF Population. After 12 months of treatment in the open-label period, the mean (SD) BMI in 136 subjects had slightly decreased from the double-blind baseline BMI by 0.580 (2.1012) kg/m2 and 137 subjects had slightly decreased from the open-label baseline BMI by 0.276 (1.8246) kg/m2.

The mean z-score for height at baseline in the double-blind treatment period was -0.890 SD and the mean z-score at Month 12 was -1.055 SD representing a decrease of 0.165 SDs in height over the double-blind through OLE period. For weight, the mean z-score was -0.607SD at baseline in the double-blind treatment period and the mean z-score at Month 12 was -1.179 SD representing a decrease of 0.572 SDs. Short stature is defined by individual height that is 2 SDs or more below the average height for age, sex, and ethnic group or more than 2 SDs below mid parental height (Barstow 2015).

#### Cardiac:

Based on fenfluramine's history, the ZX008 clinical development program was designed to ensure no subjects with pre-existing VHD or risk factors for such development entered the trials. In addition, to enhance safety measures, all subjects were monitored and administered only low doses of ZX008.

The ZX008 LGS and Dravet syndrome clinical development programs, including subjects being treated with fenfluramine for more than 12 months, incorporated a prospectively defined, long-term longitudinal cardiovascular study of the heart valves, as well as evaluation for signs of pulmonary arterial hypertension (PAH) by 2-D Doppler echocardiogram. No PAH or structural abnormalities consistent with VHD were observed in any subject at any time during the LGS and Dravet syndrome programs.

In Study 1601 Part 1, where trace mitral or aortic regurgitation were observed, the results were often transient; eg, findings at 1 visit were not always present at the following visit, with the exception of 2 subjects. This observation was also recorded in the serial ECHOs conducted in the Dravet.

The 2 subjects who exhibited greater than trace regurgitation in the mitral or aortic valves were: one 12-18 year old subject in the ZX008 0.8 mg/kg/day group exhibited mild MR at Visit 12 (also considered physiologic), and one 6-12 year old subject in the ZX008 0.2 mg/kg/day group exhibited mild AR at Visit 12, which was later downgraded to absent regurgitation following a subsequent diagnostic transesophageal ECHO. No abnormalities were noted in valve morphology for either subject.

For the ISS-SAF Population at the time of the data cutoff, a total of 1667 ECHOs performed on 262 subjects were included in the summary analyses, with the mean (SD) number of ECHOs included per subject being 6.4 (1.94). As described in the sections below, no VHD or PAH was observed in the ZX008 LGS Phase 3 development program. Where trace MR or AR was observed, the results were often transient.

#### Table 66 Number and Percenetage of Subjects Who Exhibited ≥ Trace (< 18 Years) or ≥ Moderate (≥ 18% Years) Mitral Regurgitation with < or ≥ Median Days of Exposure (471 Days); ISS-SAF Population

Parameter/Time Point	Pre-ZX008 Baseline	Any Post-Baseline				
Subjects < 18 Years Who Exhibited Trace or Greater Mitral Regurgitation						
≥ 471 days of exposure (N=92) n/m (%)	7/91 (7.7%)	34/92 (37.0%)				
< 471 days of exposure (N=94) n/m (%)	6/94 (6.4%)	24/89 (27.0%)				
Subjects ≥ 18 Years Who Exhibited Moderate or Greater Mitra	l Regurgitation					
≥ 471 days of exposure (N=40) n/m (%)	0/40 (0.0%)	0/40 (0.0%)				
< 471 days of exposure (N=36) n/m (%)	0/36 (0.0%)	0/35 (0.0%)				

Source: ISS CV Table 4.4.1.4, ISS CV Table 4.4.1.5, ISS CV Table 4.4.3.4, ISS CV Table 4.4.3.5

Note: All Post-Baseline visits except for follow-up visits are considered for 'Any Post-Baseline'. n = Number of subjects with the specified value, m = Number of subjects with non-missing value, % = n / m \* 100.

Table 67 Cumulative Incidence of Valvular Regurgitation - Aortic Valve; ISS Safety Population <18 Years of Age

		ZX008 Mean Daily Dose Across Studies 1601 Part 1, 1601 Part 2, and 1900				
Parameter/Category	> 0 - < 0.4 mg/kg/day (N=48) n (%)	0.4 - < 0.6 mg/kg/day (N=78) n (%)	≥ 0.6 mg/kg/day (N=60) n (%)	Total (N=186) n (%)		
Absent	45 (100.0%)	75 (97.4%)	57 (96.6%)	177 (97.8%)		
Trace	0	1 (1.3%)	2 (3.4%)	3 (1.7%)		
Mild	0	1 (1.3%)	0	1 (0.6%)		
Moderate	0	0	0	0		
Severe	0	0	0	0		
Total	45	77	59	181		

#### Table 68 Categorical Summary of ECHO Data - Any PASP Change from Baseline > 10, > 15, > 20 mmHg; ISS Safety Population

	ZX008 Mean Part			
Parameter	> 0 - < 0.4 mg/kg/day (N=81) n/m (%)	0.4 - < 0.6 mg/kg/day (N=113) n/m (%)	≥ 0.6 mg/kg/day (N=68) n/m (%)	Total (N=262) n/m (%)
Subjects with Change in PASP >10 mmF	Ig			
Any Post-Baseline	4 / 44 (9.1%)	7 / 58 (12.1%)	6 / 43 (14.0%)	17 / 145 (11.7%)
Subjects with Change in PASP >15 mmF	Ig			
Any Post-Baseline	1 / 44 (2.3%)	1 / 58 (1.7%)	2 / 43 (4.7%)	4 / 145 (2.8%)
Subjects with Change in PASP >20 mmF	Ig			
Any Post-Baseline	0 / 44	0 / 58	0 / 43	0 / 145

Source: ISS CV Table 4.5.2

ECHO = echocardiogram; ISS = Integrated Summary of Safety; PASP = pulmonary artery systolic pressure
Note: All Post-Baseline visits except for follow-up visits are considered for 'Any Post-Baseline'. n = Number of subjects with the specified value, m = Number of subjects with non-missing value, % = n / m \* 100.

## Safety in special populations

#### <u>Age:</u>

For subjects 2 to < 6 years of age (N=38), the most common TEAEs in the ZX008 groups ( $\ge$  10% of subjects in either group) were the same as the overall Safety Population: decreased appetite, diarrhea, fatigue, pyrexia, somnolence, and vomiting; however, constipation, dysphagia, irritability, nasopharyngitis, pneumonia, seizure, and upper respiratory tract infection were additional common TEAEs for this subgroup. Common TEAEs reported with a  $\geq$  10% higher incidence in either ZX008 group compared with the placebo group were as follows:

- Pneumonia was reported for  $\geq 10\%$  more subjects in the ZX008 0.8 mg/kg/day group than in the placebo and ZX008 0.2 mg/kg/day groups.
- Constipation, diarrhea, decreased appetite, and nasopharyngitis were reported for  $\geq$  10% more subjects in the ZX008 0.2 mg/kg/day group than in the placebo group but not the ZX008 0.8 mg/kg/day group.
- Dysphagia, upper respiratory tract infection, and vomiting were reported for ≥ 10% more subjects in the ZX008 0.2 mg/kg/day group than in the placebo and ZX008 0.8 mg/kg/day groups.

For subjects 6 to < 12 years of age (N=72), the most common TEAEs in the ZX008 groups ( $\geq$  10% of subjects in either group) were similar to the overall Safety Population: decreased appetite, diarrhea, fatigue, pyrexia, somnolence, and vomiting; however, constipation and upper respiratory tract infection were additional common TEAEs for this subgroup. Common TEAEs reported with a  $\geq$ 10% higher incidence in either ZX008 group compared with the placebo group were as follows:

- Decreased appetite was reported for  $\geq$  10% more subjects in the ZX008 0.8 mg/kg/day group than in the placebo group and ZX008 0.2 mg/kg/day groups.
- Diarrhea was reported for  $\geq 10\%$  more subjects in the ZX008 0.8 mg/kg/day group than in the placebo group but not the ZX008 0.2 mg/kg/day group.

For subjects 12 to <18 years of age (N=77), the most common TEAEs in the ZX008 groups ( $\geq$  10% of subjects in either group) were similar to the overall Safety Population: decreased appetite, fatigue, pyrexia, somnolence, and vomiting; however, asthenia, blood prolactin increased, and constipation were additional common TEAEs for this subgroup. Common TEAEs reported with a  $\geq$  10% higher incidence in either ZX008 group compared with the placebo group were as follows:

- Decreased appetite was reported for  $\geq$  10% more subjects in both ZX008 groups than in the placebo group.
- Fatigue and blood prolactin increased were reported for  $\geq 10\%$  more subjects in the ZX008 0.8 mg/kg/day group than in the placebo and ZX008 0.2 mg/kg/day groups.

For subjects  $\geq$  18 years of age (N=76), the most common TEAEs in the ZX008 groups ( $\geq$ 10% of subjects in either group) were a subset of those for the overall Safety Population: decreased appetite, diarrhea, and somnolence; weight decreased, and irritability were additional common TEAEs for this subgroup. The only common TEAEs reported with a  $\geq$  10% higher incidence in either ZX008 group compared with the placebo group were diarrhea, reported for  $\geq$  10% more subjects in both ZX008 groups than in the placebo group, and decreased appetite, reported for  $\geq$  10% more subjects in the ZX008 0.8 mg/kg/day group than in the placebo and ZX008 0.2 mg/kg/day groups.

For the ISS-SAF Population, the overall subject incidence of TEAEs was generally similar across the 3 pediatric age groups, ranging from 91.7% to 94.7%. The subject incidence of TEAEs for the adult age group, 92.1%, was similar to the pediatric age groups. Treatment-emergent AEs experienced by  $\geq$  10% of subjects in all age groups were: decreased appetite, nasopharyngitis, seizure, and somnolence.

• For subjects 2 to < 6 years of age (N = 38), the most common TEAEs (≥ 10% of subjects) were the same as for the overall ISS-SAF Population and also included pneumonia, lethargy, insomnia,

irritability, diarrhea, upper respiratory tract infection, weight decreased, pyrexia, vomiting, constipation, fatigue, and change in seizure presentation.

- For subjects 6 to < 12 years of age (N = 72), the most common TEAEs ( $\geq$  10% of subjects) were the same as for the overall ISS-SAF Population and also included diarrhea, upper respiratory tract infection, pyrexia, vomiting, constipation, fatigue, and change in seizure presentation.
- For subjects 12 to < 18 years of age (N = 76), the most common TEAE ( $\geq$  10% of subjects) were the same as for the overall ISS-SAF Population and also included asthenia, vomiting, constipation, fatigue, and change in seizure presentation.
- For subjects  $\geq$  18 years of age (N = 76), the most common TEAEs ( $\geq$  10% of subjects) were the same as for the overall ISS-SAF Population and also included diarrhea, upper respiratory tract infection, and irritability.

#### AEDs:

All TEAEs are presented by usage of the 3 most commonly used concomitant AEDs (ie, clobazam, lamotrigine, valproate).

In double blind period, the most common TEAEs in the ZX008 groups for each concomitant AED subgroup were the same as those for the overall Safety Population, with the exception that pyrexia was not common in the valproate subgroup, and constipation, upper respiratory tract infection, and irritability were additional common TEAEs for the both the clobazam and lamotrigine subgroups.

Decreased appetite was reported for >10% more subjects in the ZX008 0. 8 mg/kg/day group than in the placebo group for all concomitant AED subgroups.

For the clobazam subgroup:

- Decreased appetite was reported for >10% more subjects in both ZX008 groups than in the placebo group.
- Vomiting was reported for >10% more subjects in the ZX008 0.2 mg/kg/day group than in the placebo group but not the ZX008 0.8 mg/kg/day group.

For the lamotrigine subgroup:

- $\bullet$  Decreased appetite and fatigue were reported for >10% more subjects in the ZX008 0.8 mg/kg/day group than in the placebo group and ZX008 0.2 mg/kg/day group.
- Somnolence and diarrhea were reported for >10% more subjects in the ZX008 0.8 mg/kg/day group than in the placebo group but not the ZX008 0.2 mg/kg/day group.
- Upper respiratory tract infection was reported for >10% more subjects in the ZX008 0.2 mg/kg/day group than in the placebo group but not the ZX008 0.8 mg/kg/day group.

For the valproate subgroup:

- Decreased appetite and somnolence were reported for >10% more subjects in the ZX008 0.8 mg/kg/day group than in the placebo group and ZX008 0.2 mg/kg/day group.
- Diarrhea was reported for >10% more subjects in the ZX008 0.8 mg/kg/day group than in the placebo group but not the ZX008 0.2 mg/kg/day group.

# Table 69 Treatment-Emergent Adverse Events in Part 1 by MedDRA System Organ Class and Preferred Term by Most Commonly Used Anti-Epileptic Medications (Cohort A – North America, Europe, Australia) Safety Population

Treatment-Emergent Adverse Events in Part 1 by MedDRA System Organ Class and Preferred Term by Most Commonly Used Anti-Epileptic Medications (Cohort A - North America, Europe, Australia)

Safety Population

Part 1 Period: Complete Part 1 Period

Subgroup	MedDRA System Organ Class and Preferred Term	Placebo (N-38)	ZX008 0.2 mg/kg/day (N-36)	ZX008 0.8 mg/kg/day (N-45)	All Subjects (N-119)
CLOBAZAM	Metabolism and nutrition disorders Decreased appetite Dehydration Hypoglycaemia Hypophagia	6 (15.8%) 6 (15.8%) 0 1 (2.6%)	13 (36.1%) 11 (30.6%) 1 (2.8%) 0 1 (2.8%)	15 (33.3%) 15 (33.3%) 1 (2.2%) 0	34 (28.6%) 32 (26.9%) 2 (1.7%) 1 (0.8%) 1 (0.8%)
	Musculoskeletal and connective tissue disorders Plantar fasciitis Posture abnormal Scoliosis	1 ( 2.6%) 0 0 1 ( 2.6%)	0 0 0	2 ( 4.4%) 1 ( 2.2%) 1 ( 2.2%) 0	3 ( 2.5%) 1 ( 0.8%) 1 ( 0.8%) 1 ( 0.8%)
	Neoplasms benign, malignant and unspecified (incleysts and polyps) Pituitary tumour benign	0 0	0	1 (2.2%) 1 (2.2%)	1 ( 0.8%) 1 ( 0.8%)
	Nervous system disorders Action tremor	13 (34.2%) 0	14 (38.9%) 1 (2.8%)	19 (42.2%) 0	46 (38.7%) 1 ( 0.8%)
	Infections and infestations Acute sinusitis Bacterial infection Bronchitis Cystitis Ear infection Fungal skin infection Gastroenteritis Gastroenteritis Urial Hordeolum Infection Influenza Localised infection Nasopharyngitis Oral candidiasis Oral herpes	8 (21.1%) 1 (2.6%) 0 0 0 0 1 (2.6%) 1 (2.6%) 0 0 4 (10.5%) 0 0	15 (41.7%) 0 0 1 (2.8%) 0 0 0 0 1 (2.8%) 0 0 3 (8.3%) 0 2 (5.6%) 1 (2.8%) 0	19 (42.2%) 0 1 ( 2.2%) 2 ( 4.4%) 1 ( 2.2%) 1 ( 2.2%) 0 0 1 ( 2.2%) 1 ( 2.2%) 1 ( 2.2%) 1 ( 2.2%) 1 ( 2.2%) 1 ( 2.2%) 1 ( 2.2%) 1 ( 2.2%) 1 ( 2.2%) 1 ( 2.2%) 1 ( 2.2%) 1 ( 2.2%)	42 (35.3%) 1 (0.8%) 1 (0.8%) 3 (2.5%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 4 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%)
	Otitis media Parotitis Pharyngitis Pharyngitis streptococcal Pharyngotonsillitis Pneumonia Rhinitis Sinusitis Subcutaneous abscess Tooth abscess Upper respiratory tract infection Urinary tract infection Varicella Viral upper respiratory tract infection	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0 1 ( 2.8%) 1 ( 2.8%) 0 2 ( 5.6%) 1 ( 2.8%) 0 1 ( 2.8%) 0 4 (11.1%) 1 ( 2.8%) 1 ( 2.8%) 1 ( 2.8%)	1 ( 2.2%) 0 1 ( 2.2%) 0 2 ( 4.4%) 1 ( 2.2%) 0 1 ( 2.2%) 3 ( 6.7%) 1 ( 2.2%) 0 0	1 ( 0.8%) 1 ( 0.8%) 1 ( 0.8%) 1 ( 0.8%) 2 ( 1.7%) 3 ( 2.5%) 1 ( 0.8%) 1 ( 0.8%) 1 ( 0.8%) 1 ( 0.8%) 2 ( 1.7%) 2 ( 1.7%) 3 ( 2.5%) 1 ( 0.8%) 1 ( 0.8%) 1 ( 0.8%)

In ISS-SAF, the treatment-emergent AEs experienced by  $\geq$  10% of subjects in all 3 groups were: decreased appetite, diarrhea, fatigue, pyrexia, nasopharyngitis, somnolence, seizure, and change in seizure presentation.

#### Withdrawal and rebound:

A total of 254 subjects in the Study 1601 Part 1 Safety Population received study drug during Taper/Transition.

Three subjects (1.2%) experienced treatment-related TEAEs of seizure during Taper/Transition: 2 subjects in the ZX008 0.2 mg/kg/day group and 1 subject in the ZX008 0.8 mg/kg/day group. All events were non-serious and considered moderate in severity, and the events resolved for all 3 subjects.

One subject had a severe TEAE during Taper/Transition (status epilepticus, reported for one subject in the ZX008 0.8 mg/kg/day group). The event was not considered treatment related and resolved without a change in study drug.

A review of subjects who experienced TEAEs during the Study 1601 Part 2 open-label taper period for subjects who did not enroll and continue treatment in Study 1900 showed TEAEs possibly related to

ZX008 or the tapering of ZX008 in 5 subjects. 3 were assessed as related to study drug and 1 of them was severe.

• One subject was randomized to the placebo group in the double-blind treatment period and experienced an SAE of status epilepticus on Study Day 205, 4 days after the subject's last dose of ZX008 in Study 1601 Part 2. The subject had been treated with a mean daily dose of ZX008 0.2 mg/kg/day during the OLE period. On Study Day 198, the subject withdrew participation from the study, with the reason being reported as withdrawal by subject. The Investigator assessed the event of status epilepticus as severe and related to study drug withdrawal. The event resolved on Study Day 205.

#### Discontinuation due to adverse events

Table 70 Study 1601 Part 1 Treatment-Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – T+M; Safety Population

MedDRA System Organ Class Preferred Term	Placebo (N=87%) n (%%)	ZX008 0.2 mg/kg/day (N=89%) n (%)	ZX008 0.8 mg/kg/day (N=87%) n (%)
Subjects with TEAE leading to study discontinuation	1 (1.1%)	4 (4.5%)	5 (5.7%)
Gastrointestinal disorders			_
Vomiting	0	1 (1.1%)	0
Metabolism and nutrition disorders	•	•	•
Decreased appetite	0	1 (1.1%)	0
Nervous system disorders			
Change in seizure presentation	1 (1.1%)	0	0
Pleurothotonus	0	0	1 (1.1%)
Seizure	0	3 (3.4%)	0
Somnolence	0	0	3 (3.4%)
Psychiatric disorders			_
Aggression	0	0	1 (1.1%)
Agitation	0	1 (1.1%)	0
Respiratory, thoracic and mediastinal disorders	•		
Lung disorder	0	0	1 (1.1%)
	-	-	•

Table 71 Treatment-Emergent Adverse Events Leading to Premature Discontinuation from Study and/or Treatment During Double-blind Through Open-label Treatment Periods by MedDRA System Organ Class and Preferred Term; ISS-SAF Population

	Actual ZX008 Mean Daily Dose (mg/kg/day) <sup>a</sup>			
MedDRA System Organ Class and Preferred Term	>0 to <0.4 (N = 81) n (%)	0.4 to <0.6 (N = 113) n (%)	≥ 0.6 (N = 68) n (%)	Overall (N = 262) n (%)
Subjects with any TEAE	13 (16.0%)	7 (6.2%)	4 (5.9%)	24 (9.2%)
Gastrointestinal disorders	3 (3.7%)	0	2 (2.9%)	5 (1.9%)
Vomiting	3 (3.7%)	0	1 (1.5%)	4 (1.5%)
Gastritis	0	0	1 (1.5%)	1 (0.4%)
General disorders and administration site conditions	2 (2.5%)	2 (1.8%)	0	4 (1.5%)
Fatigue	2 (2.5%)	1 (0.9%)	0	3 (1.1%)
Gait disturbance	0	1 (0.9%)	0	1 (0.4%)
Infections and infestations	0	0	1 (1.5%)	1 (0.4%)
Pneumonia	0	0	1 (1.5%)	1 (0.4%)
Investigations	2 (2.5%)	1 (0.9%)	0	3 (1.1%)
Echocardiogram abnormal <sup>b</sup>	1 (1.2%)	1 (0.9%)	0	2 (0.8%)
Heart rate increased	1 (1.2%)	0	0	1 (0.4%)
Metabolism and nutrition disorders	3 (3.7%)	0	1 (1.5%)	4 (1.5%)
Decreased appetite	3 (3.7%)	0	1 (1.5%)	4 (1.5%)
Nervous system disorders	8 (9.9%)	5 (4.4%)	2 (2.9%)	15 (5.7%)
Seizure	5 (6.2%)	0	1 (1.5%)	6 (2.3%)
Somnolence	1 (1.2%)	2 (1.8%)	1 (1.5%)	4 (1.5%)
Change in seizure presentation	1 (1.2%)	2 (1.8%)	0	3 (1.1%)
Amnesia	1 (1.2%)	0	0	1 (0.4%)
Generalized tonic-clonic seizure	1 (1.2%)	0	0	1 (0.4%)
Headache	1 (1.2%)	0	0	1 (0.4%)
Pleurothotonus	0	1 (0.9%)	0	1 (0.4%)
Psychiatric disorders	2 (2.5%)	0	1 (1.5%)	3 (1.1%)
Aggression	0	0	1 (1.5%)	1 (0.4%)
Agitation	1 (1.2%)	0	0	1 (0.4%)
Hallucination	1 (1.2%)	0	0	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	1 (1.2%)	0	0	1 (0.4%)
Lung disorder	1 (1.2%)	0	0	1 (0.4%)

## Post marketing experience

Since the iMAA of Fintepla, the PRAC assessed the 2 first PSUSAs (PSUSA-10907-202112 and PSUSA-10907-202106) and considered that the risk-benefit balance of medicinal products containing fenfluramine remains unchanged.

The most recent PBRER for Fintepla was submitted to the EMA on 26 August 2022 and is under assessment (PSUSA-10907-202206). The MAH PBRER concluded: "During the reporting interval, no signals were newly identified, closed, under monitoring or awaiting evaluation. There have been no significant changes in the knowledge of risks or benefits of fenfluramine; therefore, the benefit-risk balance remains positive."

# 2.5.1. Discussion on clinical safety

The main evidence of safety for Fintepla in the proposed LGS indication comes from

- Study 1601 Part 1 Safety Population (N=263) and
- ISS Safety Population (ISS-SAF) that consists of Study 1601 Cohort A subjects who are followed through Study 1601 Part 1, Part 2, or Study 1900 (N=263).

Fenfluramine (Fintepla) is approved in the United States, European Union (EU), and United Kingdom (UK) for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older. The existing safety profile from this indication and post-marketing experience brings in supportive safety data.

219 subjects with LGS have received ZX008 for  $\geq$  6 months, and 172 subjects have received ZX008 for  $\geq$  12 months, with an overall range of ZX008 exposure from 9 to 991 days. This is considered satisfactory for safety assessment.

During double-blind period, the incidence of TEAEs, treatment related TEAEs, treatment emergent SAEs severe TEAEs and TEAEs leading to discontinuation were all notably higher in ZX008 0.8 mg/kg/day group. 5.7% of these events lead to discontinuation. On the other hand, during ISS-SAF, the subject incidence of TEAEs leading to discontinuation of study drug and/or the study was greatest at the lowest dose range group (>0 to 0.4 mg/kg/day mean daily doses) and this could be impacted by tapering and restarting on 0.2 mg/kg/day dose for all subjects (including ones on active arms) at the end of double-blind period.

Most important TEAEs reported in the double-blind and open-label studies are known AEs associated with fenfluramine such as loss of appetite, weight loss, lethargy, somnolence, and fatigue.

The most common TEAEs that occurred in ZX008-treated subjects in the double-blind Study1601 Part  $1 \geq 10\%$  of subjects in either group) were decreased appetite, fatigue, somnolence, diarrhoea, vomiting, and pyrexia. For ZX008 0.8 mg/kg/day group, decreased appetite 35.6%, fatigue 18.4%, somnolence 17.2%, diarrhoea 12.6%, constipation 9.2%, vomiting 8%, weight decreased 8%, upper respiratory tract infection 6.9%, lethargy 5.7% were most frequently observed TEAEs which were higher than placebo group in frequency.

In ISS-SAF, the most common TEAEs reported to date ( $\geq$  10% of subjects overall) were decreased appetite, somnolence, seizure, nasopharyngitis, pyrexia, fatigue, diarrhoea, vomiting, upper respiratory tract infection, constipation, and change in seizure presentation. TEAEs that were reported for  $\geq$  10% of subjects at any mean daily dose level and that appeared to have a dose relationship included pyrexia and nasopharyngitis, each of which was most common at the ZX008  $\geq$  0.6 mg/kg/day mean daily dose level. By SOC, infections (nasopharyngitis, gastroenteritis viral, pneumonia, ear infection) and gastrointestinal disorders showed a tendency to increase in frequency with increased dose in ISS-SAF Population. The gastrointestinal events were also commonly observed during the first month of ZX008 treatment.

The most common treatment-emergent SAEs (all reported in  $\leq 10$  [3.8%] of subjects) in the double-blind through open-label treatment periods were change in seizure presentation (3.8%), status epilepticus (3.8%), pneumonia (3.1%), pneumonia aspiration (3.1%), seizure (1.5%), somnolence (1.5%), vomiting (1.1%), and dehydration (1.1%). For the double-blind period, a significantly higher percentage of patients experienced treatment-emergent SAEs in ZX008 0.8 mg/kg/day group (10 patients, 11.5%) in comparison to 4 subjects (4.6%) in the placebo group, 4 subjects (4.5%) in the ZX008 0.2 mg/kg/day group. Especially gastrointestinal disorders and infections were more common in

active groups. For the ISS-SAF Population, percentage of patients who experienced treatmentemergent SAEs increased with higher mean dose (16%, 19.5%, 26.5%).

2 deaths have occurred, 1 due to SUDEP and 1 due to aspiration pneumonia and respiratory failure (both were considered not related to study drug by the Investigators).

In Study 1601 Part 1, a total of 21 TEAEs leading to study discontinuation in the 9 subjects in the ZX008 groups included somnolence, seizure, pleurothotonus, decreased appetite, vomiting, aggression, agitation, and lung disorder, of which 18 events were considered to be treatment-related.

In the ISS-SAF Population, 24 (9.2%) subjects were reported as having withdrawn from treatment due to  $\geq 1$  TEAE. Events leading to treatment withdrawal that occurred in  $\geq 2$  subjects were seizure, somnolence, change in seizure presentation, decreased appetite, vomiting, fatigue, and echocardiogram abnormal (non-pathologic trace/physiologic regurgitation). Although rare, gait disturbance was one of the TEAEs leading to discontinuation. "Falls" was a previously identified signal in Dravet Syndrome.

No subject has developed VHD or PAH throughout the program (important risks in RMP). Out of 262 subjects monitored, 2 observations of mild MR/AR were noted during the program, but neither had any other echocardiographic signs of VHD nor any symptoms of VHD. Cardiac safety is monitored in ongoing Study 1900, however still limited with 3 years maximum follow up. Cardiac effects could occur in a longer exposure as they are related to cumulative exposure. The long-term safety is listed as missing information in RMP.

Few abnormalities observed in growth, precocious puberty, and thyroid function parameters were considered clinically significant changes. Among these, growth retardation is an important potential risk in RMP, as growth scores for weight and height represented a decrease over treatment period but were not affected above 2SDs.

Decreased appetite, weight loss, lethargy, somnolence, fatigue, ECG abnormal, prolactin increased are among identified signals. Weight loss, as an important identified risk, can be mitigated with routine event monitoring and medication guide/ educational materials to inform and educate prescribers and patients.

## 2.5.2. Conclusions on clinical safety

Based on the available safety data, the CHMP concludes that the safety profile of Fintepla in the proposed LGS indication is acceptable.

The highlighted safety concerns are appropriately reflected in the SmPC and will continue to be managed through the agreed RMP and monitored via the PSURs.

#### 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

# 2.6. Risk management plan

The MAH submitted an updated RMP version in this application.

The PRAC considered that the updated risk management plan is acceptable.

The CHMP endorsed the Risk Management Plan version 2.11 with the following content:

# Safety concerns

Summary of safety concerns		
Important identified risks	None	
Important potential risks	Valvular heart disease Pulmonary arterial hypertension Suicidal ideation and behaviour Growth retardation	
Missing information	Long-term safety Off-label use (in wider paediatric epilepsies; obesity) Patients with Hepatic Impairment	

# Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates	
	<b>Category 1</b> - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
A Registry of Subjects Treated with Fenfluramine Planned	Primary objective	Valvular heart disease  Pulmonary arterial hypertension  Long-term safety  Growth retardation	Protocol submission  Annual Progress reports  Final report	Marketing approval + 2 months PBRER*  Q1 2034	

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	posed mandatory additional pharn context of a conditional marketing circumstances			
None				
Category 3 - Red	quired additional pharmacovigilanc	e activities		
ZX008-1503: 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.	Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome.	Valvular heart disease  Pulmonary arterial hypertension  Suicidal ideation and behaviour  Long-term safety in Dravet syndrome patients	Progress report Final report	Q2 2022 Q4 2023

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
A Drug Utilisation	Primary objective	Off-label use (in	Protocol	Marketing
Study of	Describe fenfluramine use	wider paediatric	submission	approval
Fenfluramine in	in routine clinical practice	epilepsies;		+2 months
Europe	with a focus on its use in	obesity)		
	epilepsies other than	,,,	Final report	August
Planned	Dravet syndrome if any	Valvular heart disease		2025
	Secondary objectives			
	1. Describe the dose, frequency and duration of fenfluramine treatment 2. Describe the demographic characteristics (e.g., age, sex, weight) of patients treated with fenfluramine in routine clinical practice 3. Describe the extent and frequency of echocardiographic monitoring	Pulmonary arterial hypertension		
	Exploratory objective: Identify and describe prescriptions of fenfluramine for weight management			

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
A European Study of the Effectiveness of Risk Minimisation Measures for Fenfluramine in Dravet Syndrome  Planned	Primary objectives:  1. Assess the awareness and knowledge of physicians routinely prescribing fenfluramine regarding the educational material on echocardiogram follow-up.  2. Assess the self-reported compliance of physicians routinely prescribing fenfluramine with the recommendations provided in the educational materials  Secondary objectives:  1. Assess the physician-reported distribution of educational material to patients/carers by physicians routinely prescribing fenfluramine.  2. Assess the awareness, knowledge and self-reported compliance of physicians routinely prescribing fenfluramine regarding the physician-specific educational material to prevent off-label use for weight management	Valvular heart disease  Pulmonary arterial hypertension  Off-label use in wider paediatric epilepsies; obesity	Protocol submission  Interim report  Final report	Marketing approval + 6 months Q3 2023 Q3 2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
ZX008-1903: A Phase 1, Open- Label, Single- Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of ZX008 (Fenfluramine Hydrochloride) in Subjects With Varying Degrees of Hepatic Impairment  Ongoing		Use in patients with hepatic impairment	Final report	Q2 2022

<sup>\*</sup>Registry progress reports will be provided with the scheduled PBRER.

# Risk minimisation measures

# Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Valvular heart disease	<ul> <li>Routine risk minimisation measures:</li> <li>SmPC sections 4.3, 4.4 and 4.8</li> <li>PL sections 2, 4</li> <li>Contraindications to fenfluramine treatment in SmPC section 4.3</li> <li>Direction for echocardiogram assessment to confirm absence</li> </ul>	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:  None  Additional pharmacovigilance activities:

#### Safety concern **Risk minimisation measures** Pharmacovigilance activities ZX008-1503: An Open-Label of cardiac valve disease prior to Extension Trial to Assess the Longfenfluramine initiation in SmPC section 4.4. Term Safety of ZX008 Direction for echocardiogram (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy monitoring during use of fenfluramine in SmPC section in Children and Young Adults with 4.4. Dravet Syndrome. Recommendations for actions to (Progress report due date: Q2 2022 take with fenfluramine if Final study report due date: Q4 regurgitation is detected on A Registry of Subjects Treated with echocardiogram in SmPC section 4.4. Fenfluramine. Guidance that fenfluramine (Final study report due date: Q1 should not be used in patients 2034) with valve disease in PL section A European Study of the Effectiveness of Risk Minimisation Guidance that doctors should Measures for Fenfluramine in perform echocardiogram Dravet Syndrome. monitoring prior to starting (Interim report due date: Q3 2023 fenfluramine and during Final study report due date: Q3 treatment in PL section 2. 2025). Guidance on signs of heart A Drug Utilisation Study of problems which should be Fenfluramine in Europe. reported to the doctor (Final study report due date: immediately in PL section 2. August 2025). Legal status: Prescription only medicine, restricted medical prescription Additional risk minimisation measures: Guide for healthcare professionals Patient/carer guide CAP Pulmonary arterial Routine risk minimisation measures: Routine pharmacovigilance activities SmPC sections 4.3, 4.4 hypertension beyond adverse reactions reporting and PL sections 2, 4 signal detection: Contraindications to None fenfluramine treatment in SmPC section 4.3 Direction for echocardiogram Additional pharmacovigilance activities: assessment to confirm absence ZX008-1503: An Open-Label Extension Trial to Assess the Longof pulmonary hypertension prior to fenfluramine initiation in Term Safety of ZX008 SmPC section 4.4. (Fenfluramine Hydrochloride) Oral Direction for echocardiogram Solution as an Adjunctive Therapy monitoring during use of in Children and Young Adults with fenfluramine in SmPC section Dravet Syndrome. (Progress report due date: Q2 2022 Recommendations for actions to Final study report due date: Q4 take with fenfluramine if PAH is 2023) Registry of Subjects Treated with Fenfluramine. (Final study report due date: Q1 2034) A European Study of the Effectiveness of Risk Minimisation

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	detected on echocardiogram in SmPC section 4.4  Guidance that fenfluramine should not be used in patients with PAH in PL section 2.  Guidance that doctors should perform echocardiogram monitoring prior to starting fenfluramine and during treatment in PL section 2.  Guidance on signs of heart problems which should be reported to the doctor immediately in PL section 2.  Legal status: Prescription only medicine, restricted medical prescription  Additional risk minimisation measures:  Guide for healthcare professionals Patient/carer guide CAP	Measures for Fenfluramine in Dravet Syndrome. (Interim report due date: Q3 2023 Final study report due date: Q3 2025).  • A Drug Utilisation Study of Fenfluramine in Europe. (Final study report due date: August 2025).
Suicidal ideation and behaviour	Routine risk minimisation measures:  SmPC section 4.4  PL section 2  Guidance on monitoring of patients for signs of suicidal behaviour and ideation which should be reported to the doctor immediately in SmPC section 4.4.  Warning in PL section 2 to patients with prior history of suicidal thoughts or behaviours to contact their healthcare professional.  Legal status: Prescription only medicine, restricted medical prescription  Additional risk minimisation measures:  None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:  Targeted questionnaire  Additional pharmacovigilance activities:  ZX008-1503: 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.  (Progress report due date: Q2 2022 Final study report due date: Q4 2023).
Growth retardation	Routine risk minimisation measures:  SmPC sections 4.2, 4.4 and 4.8  PL section 4  Guidance for off-label use for weight loss in SmPC section 4.2  Recommendations for weight and height monitoring in SmPC section 4.4  Legal status: Prescription only medicine, restricted medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:  None  Additional pharmacovigilance activities:  Registry of Subjects Treated with Fenfluramine. (Final study report due date: Q1 2034)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	
Long-term safety	Routine risk minimisation measures: Legal status: Prescription only medicine, restricted medical prescription  Additional risk minimisation measures:  None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:  None  Additional pharmacovigilance activities:  ZX008-1503: 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. (Progress report due date: Q2 2022 Final study report due date: Q4 2023).  A Registry of Subjects Treated with Fenfluramine. (Final study report due date: Q1 2034)
Off-label use (in wider paediatric epilepsies; obesity)	Routine risk minimisation measures:  SmPC sections 4.1, 4.2 and 4.4  PL sections 1 and 2  Legal status: Prescription only medicine, restricted medical prescription  Additional risk minimisation measures:  CAP	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:  • Assessment of Fintepla sales patterns and patient exposure data  Additional pharmacovigilance activities:  • A Registry of Subjects Treated with Fenfluramine.  (Final study report due date: Q1 2034)  • A Drug Utilisation Study of Fenfluramine in Europe.  (Final study report due date: August 2025).  • A European Study of the Effectiveness of Risk Minimisation Measures for Fenfluramine in Dravet Syndrome.  (Interim report due date: Q3 2023 Final study report due date: Q3 2025).

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in patients with hepatic impairment	Routine risk minimisation measures:  • SmPC sections 4.2 and 5.2  Legal status: Prescription only medicine, restricted medical prescription  Additional risk minimisation measures:  • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:  None  Additional pharmacovigilance activities:  ZX008-1903: A Phase 1, Open-Label, Single-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of ZX008 (Fenfluramine Hydrochloride) in Subjects With Varying Degrees of Hepatic Impairment. (Final study report due date: Q2 2022)

# 2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. The due date of the final PASS Registry report as approved in the procedure EMEA/H/C/PSP/S/0093.3 has been reflected in Annex II.

Please see attachment 1 for full information.

#### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The justification for not testing with target patient group is that the package leaflet is essentially the same as the successfully tested Fintepla Package Leaflet for Dravet syndrome (DS) with the addition of the new indication, and the target audience is also very similar to that of DS, i.e. parents and carers of children and adults with a rare, severe and intractable epileptic syndrome.

## 3. Benefit-Risk Balance

# 3.1. Therapeutic Context

#### 3.1.1. Disease or condition

Lennox-Gastaut syndrome is a rare, severe, paediatric-onset developmental and complex epileptic encephalopathy. Onset of LGS occurs most commonly before the age of 11 years, with a peak between 3 and 5 years of age. Patients with LGS account for 5% to 10% of children with seizures. LGS can be subdivided into cases of known origin (genetic, structural, metabolic, immune and infectious) and idiopathic cases. The epileptic activity itself may directly contribute additional cognitive and behavioural impairments over those expected from the underlying aetiology alone and that suppression of epileptic activity might minimize this additional impairment.

LGS is always characterized by a triad of symptoms: multiple seizure types, slow spike-and-wave EEG, and abnormal cognitive development. Tonic seizures (TS), atypical absence seizures (AS), and "drop

attacks," ie, seizures that result in sudden falls, are notable in this disorder and often result in serious injury. Patients with LGS also can experience milder seizures that do not result in falls, as well as many other seizure types, such as generalized tonic-clonic seizures (GTC), myoclonic seizures (MS), focal seizures, and nonconvulsive status epilepticus.

Nearly all patients with LGS have treatment-resistant, lifelong epilepsy. Prognosis for LGS is very poor: approximately 5% of patients die, 80% to 90% continue having seizures into adulthood, and most patients have cognitive and behavioural problems. Children and adults with LGS have an enormous disruptive impact on their families, and efforts to improve the quality of life for these patients are complex due to the severe lifelong limitations associated with drug-resistant epilepsy, intellectual disability, and other comorbidities.

## 3.1.2. Available therapies and unmet medical need

Due to the heterogeneity in aetiology, pathophysiology, and type of seizures experienced by patients with LGS, many different treatments are currently tried, often with little success and a high rate of drug resistance. Due to the refractory nature of seizures in LGS, seizure freedom is an unlikely goal of treatment; a main objective is to improve the patient's QoL via a compromise between seizure control of the most severe seizures, avoidance of additional comorbidities, and tolerability. A combination of 2 or more AEDs with an individualized regimen is common.

Currently, 9 AEDs are approved for the treatment of LGS in Europe: felbamate, topiramate, lamotrigine, rufinamide, clonazepam, clobazam, valproate), nitrazepam, and cannabidiol. Other pharmacologic (benzodiazepines, zonisamide) and nonpharmacologic treatments (ketogenic diet [KD], vagus nerve stimulation [VNS], surgery) also are prescribed based on clinical experience.

The use of carbamazepine, oxcarbazepine, eslicarbazepine, tiagabine, and phenytoin in LGS is not recommended due to the potential risk of aggravation of drop attacks with a myoclonic component (Cross 2017).

#### 3.1.3. Main clinical studies

The main proof of efficacy was based on a multinational, randomized, double-blind, placebo-controlled, Phase 3 Study 1601 Part 1 in subjects with LGS aged 2 to 35 years of age.

The long-term effectiveness and safety is based on supportive studies: ongoing open-label, long-term extension part of the study, Study 1601 Part 2, and ongoing long-term extension Study 1900.

### 3.2. Favourable effects

<u>The primary endpoint:</u> In pivotal Study 1601 Part 1, the median percentage reduction in DSF from Baseline during the 14-week T+M for subjects in the ZX008 0.8 mg/kg/day group was 26.5%, compared with 7.6% for placebo (p= 0.0013). The reduction in DSF with ZX008 treatment was observed within 2 weeks.

The first key secondary endpoint: The percentage of subjects achieving a clinically meaningful  $\geq 50\%$  reduction from Baseline in DSF during T+M (ie, 50% responder rate) was 25.3% in ZX008 0.8 mg/kg/day group, compared with 10.3% for placebo (p = 0.0150).

<u>The second key secondary endpoint:</u> CGI-I as another key secondary endpoint, did not show nominal significance for the ZX008 0.8 mg/kg/day group compared to placebo (p = 0.0567).

The third key secondary endpoint was the median percentage reduction from Baseline during the 14-week T+M for subjects in the ZX008 0.2 mg/kg/day group (14.2%), compared with placebo (7.6%) (nominal p = 0.0939).

The fourth and fifth key secondary endpoints: The results for the ZX008 0.2 mg/kg/day group did not reach nominal statistical significance compared with the placebo group.

The most common drop seizures by type on a subject basis during Baseline of Study 1601 Part 1 were TS, GTC, and AS. With ZX008 treatment, none of the 5 drop seizure types worsened from Baseline or relative to placebo, with each having a similar or greater median percentage reduction from Baseline in frequency during T+M, as necessary to support a positive outcome of the study. GTC seizure type had the largest percentage reduction from Baseline relative to placebo (> 50 percentage point difference  $[p \le 0.0005]$ ).

#### 3.3. Uncertainties and limitations about favourable effects

Due to the heterogeneity in aetiology, pathophysiology, and type of seizures experienced by patients with LGS, many different treatments are currently tried, often with little success and a high rate of drug resistance. Due to the refractory nature of seizures in LGS, seizure freedom is an unlikely goal of treatment; a main objective is to improve the patient's QoL via a compromise between seizure control of the most severe seizures, avoidance of additional comorbidities, and tolerability. A combination of 2 or more AEDs with an individualized regimen is common.

Currently, 9 AEDs are approved for the treatment of LGS in Europe: felbamate, topiramate, lamotrigine, rufinamide, clonazepam, clobazam, valproate), nitrazepam, and cannabidiol. Other pharmacologic (benzodiazepines, zonisamide) and nonpharmacologic treatments (ketogenic diet [KD], vagus nerve stimulation [VNS], surgery) also are prescribed based on clinical experience.

The use of carbamazepine, oxcarbazepine, eslicarbazepine, tiagabine, and phenytoin in LGS is not recommended due to the potential risk of aggravation of drop attacks with a myoclonic component (Cross 2017).

# 3.4. Unfavourable effects

219 subjects with LGS have received ZX008 for  $\geq$  6 months, and 172 subjects have received ZX008 for  $\geq$  12 months, with an overall range of ZX008 exposure from 9 to 991 days.

Decreased appetite, weight loss, lethargy, somnolence, fatigue, ECG abnormal, prolactin increased are among identified signals and are known AEs associated with fenfluramine or seizures.

Valvular heart disease and pulmonary arterial hypertension are important potential risks. With treatment up to 2.5 years, no VHD or PAH has been reported. Out of 262 subjects monitored, 2 observations of mild mitral regurgitation/aortic regurgitation were noted.

Growth retardation is an important potential risk in RMP, as growth scores for weight and height represented a decrease over treatment period but were not affected above 2SDs.

The most common TEAEs that occurred in ZX008-treated subjects in the double-blind period (≥ 10% of subjects in either group) were decreased appetite, fatigue, somnolence, diarrhoea, vomiting, and pyrexia.

In ISS-SAF Population, the most common TEAEs reported to date ( $\geq 10\%$  of subjects overall) were decreased appetite, nasopharyngitis, fatigue, and seizure.

The TEAEs with the highest incidence rates of  $\geq$  10 per 100 subject years of exposure in the double-blind through open-label treatment periods were the same TEAEs as reported in Study 1601 Part 1 and Part 2.

The most common treatment-emergent SAEs (all reported in  $\leq 10$  [3.8%] of subjects) in the double-blind through open-label treatment periods were change in seizure presentation, status epilepticus, pneumonia, pneumonia aspiration, seizure, somnolence, vomiting, and dehydration.

2 deaths have occurred, 1 due to SUDEP and 1 due to aspiration pneumonia and respiratory failure (both were considered not related to study drug by the Investigators).

In Study 1601 Part 1, a total of 21 TEAEs leading to study discontinuation in the 9 subjects in the ZX008 groups included somnolence, seizure, pleurothotonus, decreased appetite, vomiting, aggression, agitation, and lung disorder, of which 18 events were considered to be treatment-related.

In the ISS-SAF Population, 24 (9.2%) subjects were reported as having withdrawn from treatment due to  $\geq 1$  TEAE. Events leading to treatment withdrawal that occurred in  $\geq 2$  subjects were seizure, somnolence, change in seizure presentation, decreased appetite, vomiting, fatigue, and echocardiogram abnormal (non-pathologic trace/physiologic regurgitation).

### 3.5. Uncertainties and limitations about unfavourable effects

The majority of subjects treated for  $\geq$  12 months had received a mean daily dose of ZX008 of 0.4 to <0.6 mg/kg/day (although 0.8 mg/kg/day is the recommended dose and only tested dose with significant effect over placebo). During the double-blind period, the incidence of TEAEs, treatment related TEAEs, treatment emergent SAEs severe TEAEs and TEAEs leading to discontinuation were all notably higher in ZX008 0.8 mg/kg/day group. 5.7% of these events lead to discontinuation. On the other hand, during ISS-SAF, the subject incidence of TEAEs leading to discontinuation of study drug and/or the study was greatest at the lowest dose range group (>0 to 0.4 mg/kg/day mean daily doses) and this could be impacted by tapering and restarting on 0.2 mg/kg/day dose for all subjects (including ones on active arms) at the end of double-blind period.

Valvular heart disease and PAH were risks evaluated for ZX008 based on the previously reported cardiotoxicity associated with fenfluramine at doses of 60 to 120 mg/day when used to treat adult obesity, i.e., 2 to 4 times higher than the proposed maximum daily dose (30 mg) for treatment of seizures in LGS. Cardiac safety is monitored in Study 1900 which is ongoing, however still limited with 3 years maximum follow up. Cardiac effects could occur in a longer exposure as they are related to cumulative exposure. LGS population is usually young and require long term treatment.

## 3.6. Effects Table

Table 72 Effects Table for [insert product name and indication] <(data cut-off: ...)>.

Table 1. Eff ect	Short description	Uni t	ZX008	Placeb o	Uncertainties / Strength of evidence	Refer ences
Favourable	Effects					
Primary endpoint	DSF Percentage change from BL during T+M, 0.8 mg/kg/d	med ian	-26.49	-7.59	Estimate (Std Err) of % Difference from Baseline in DSF= -19.88 (5.684), (95% CI -31.02, -8.74) p=0.0013	Study 1601 Part 1 14.2.1 .2.1.1 and Table 14.2.1

Table 1. Eff	Short	Uni	ZX008	Placeb	Uncertainties /	Refer
ect	description	t		0	Strength of evidence	ences
Key secondary endpoint #1	Percentage of subjects who achieved a ≥50% reduction from Baseline in DSF (50% Responder Rate) during T+M,	n (%)	22 (25.3)	9 (10.3)	p=0.0150 Odds ratio (95% CI) 2.87 (1.23, 6.70)	.8.1 Study 1601 CSR Table 14.2.1 .4.1.1
Key secondary endpoint #2	Percentage of Subjects with Improvement d on CGI-I, Investigator Rating at Visit 12, 0.8 mg/kg/d	n (%)	39 (48.8)	27 (33.8)	Nominal p=0.0567 Subjects with score 1, 2, or 3. Odds ratio vs placebo (95% CI) 1.86 (0.98, 3.52)  Testing stops here, remaining key secondary endpoints for 0.2 mg/kg/d dose vs placebo has nominal and not significant results.	Study 1601 Part 1 CSR Table 14.2.2 .1.1.1
Key secondary endpoint #3	DSF Percentage change from BL during T+M, 0.2 mg/kg/d	med ian	-14.16	-7.59	Estimate (Std Err) of % Difference from Baseline in DSF= -10.5 (7.391), (95% CI -24.99, 3.99) nominal p=0.0939	
	DSF Percentage change from BL during Maintenance , 0.8 mg/kg/d	med ian	-27.16	-7.28	HL Estimate (Std Err) fpr median difference = -20.25 (5.795), (95% CI -31.61, -8.89) p=0.0018	Study 1601 Part 1 14.2.1 .2.1.1 and Table 14.2.1 .8.1
Unfavourab	le Effects					
Metabolism and nutrition disorders	Decreased appetite	%	0.8 mg/kg/d: 35.6 0.2 mg/kg/d: 20.2	11.5	Known AE	Study 1601 Part 1
Investigatio ns	Weight decrease	%	0.8 mg/kg/d: 8.0 0.2 mg/kg/d: 2.2	2.3	Known AE	Study 1601 Part 1

Table 1. Eff ect	Short description	Uni t	ZX008	Placeb o	Uncertainties / Strength of evidence	Refer ences
Gastrointes tinal disorders	Vomiting	%	0.8 mg/kg/d: 8.0 0.2 mg/kg/d:	5.7	Identified signal in Dravet syndrome.	Study 1601 Part 1
	Diarrhea	%	13.5 0.8 mg/kg/d: 12.6 0.2 mg/kg/d: 11.2	4.6	Identified signal in Dravet syndrome.	Study 1601 Part 1
	Constipation	%	0.8 mg/kg/d: 9.2 0.2 mg/kg/d: 5.6	5.7	Identified signal in Dravet syndrome.	Study 1601 Part 1
Nervous system disorders	Seizure	%	0.8 mg/kg/d: 4.6 0.2 mg/kg/d: 9.0	6.9	Identified signal in Dravet syndrome.	Study 1601 Part 1
	Status epilepticus	%	>0.6 mg/kg/d: 7.4 0.4-0.6 mg/kg/d: 4.4 <0.4 mg/kg/d: 3.7	NA	Increased frequency by increasing dose.	ISS- SAF Popula tion
	Somnolence	%	17.2 10.1	10.3	Known AE	Study 1601 Part 1
	Lethargy	%	5.7 2.2	2.3	Known AE	Study 1601 Part 1
General disorders	Fatigue	%	18.4 9.0	10.3	Known AE	Study 1601 Part 1
Infections/ infestastion s	Upper respiratory tract infection	%	6.9 7.9	3.4	Identified signal in Dravet syndrome.	Study 1601 Part 1
	Gastroenteriti s viral	%	>0.6 mg/kg/d: 8.8 0.4-0.6 mg/kg/d: 4.4 <0.4 mg/kg/d: 1.2	NA	Dose dependent increase in frequency in ISS-SAF.	ISS- SAF Popula tion
	Pneumonia	%	>0.6 mg/kg/d: 7.4 0.4-0.6 mg/kg/d: 3.5 <0.4 mg/kg/d: 3.7	NA	Pneumonia was observed as treatment emergent SAE in 3.1% of all exposed patients: 2 subjects (2.5%), 3 subjects (2.7%), 3 subjects (4.4%) with increasing dose levels respectively. In double blind population, in 2-6 yr age group, pneumonia	ISS- SAF Popula tion

Table 1. Eff ect	Short description	Uni t	ZX008	Placeb o	Uncertainties / Strength of evidence	Refer ences
					was common and observed only with 0.8 mg/kg/day as well as bronchitis, nasopharyngitis, rhinitis, tonsillitis, upper respiratory tract infection, urinary tract infection which were not seen in placebo arm and was seen in 2 or more patients in active arms.	
Injury	Falls	%	>0.6 mg/kg/d: 2.9 0.4-0.6 mg/kg/d: 7.1 <0.4 mg/kg/d: 2.5	NA	Identified signal in Dravet syndrome.	ISS- SAF Popula tion

## 3.7. Benefit-risk assessment and discussion

# 3.7.1. Importance of favourable and unfavourable effects

With 0.8 mg/kg/day dose, Study 1601 Part 1 (double-blind) met its primary objective and has shown 26.5% decrease in median change from baseline in drop seizure frequency during treatment and maintenance periods. It is considered a clinically relevant effect size. This was supported by key secondary endpoint testing the 50% responder rate for this dose during the same period, and 25.3% of patients in the fenfluramine group compared with 10.3% in the placebo group achieved this endpoint. This is considered as clinically significant. Both endpoints supporting the efficacy for ZX008 0.8 mg/kg/day dose is reassuring.

Results with 0.2 mg/kg/day group versus placebo were not significant for the change from baseline in DSF and this dose is not recommended for clinical use.

Supportive results for effect of 0.8 mg/kg/day were observed with supplemental or sensitivity analyses of primary objective (during maintenance period only [27.2% vs 7.3% for placebo], using PP population, excluding extreme outliers, not imputing for seizure clusters, and using 2 different methods for imputation of missing data due to subject dropout, using Wilcoxon rank-sum test, by seizure type, ...) and other secondary or exploratory endpoints such as percentage of subjects with improvement on CGI-I investigator rating. No significant increases in any seizure types, no notable difference in new seizure types or incidence of status epilepticus are reassuring.

Decreased appetite, weight loss, lethargy, somnolence, fatigue, ECG abnormal, prolactin increased are among identified signals and are known AEs associated with fenfluramine or seizures. Valvular heart disease, pulmonary arterial hypertension, and growth retardation remain as important potential risks. Further discussions are due on infections, gastrointestinal disorders, status epilepticus, falls.

#### 3.7.2. Balance of benefits and risks

Efficacy on reduction in drop seizure frequency for Fintepla 0.8 mg/kg/day (one of the two doses tested in Study 1601 Part 1) was demonstrated in a study of adequate design and Fintepla 0.8 mg/kg/day dose appears to have a manageable safety profile for treatment of LGS patients with a 5.7% discontinuation rate.

#### 3.8. Conclusions

The overall B/R of Fintepla for the extension of the indication for LGS is positive.

# 4. Recommendations

#### **Outcome**

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by a majority of 28 out of 29 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation a	Туре	Annexes				
			affected			
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition	Type II	I, II and IIIB			
	of a new therapeutic indication or modification of an					
	approved one					

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. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The due date of the final PASS Registry report as approved in the procedure EMEA/H/C/PSP/S/0093.3 has been reflected in Annex II. Version 2.11 of the RMP has also been agreed.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

## Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

## Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Fintepla is not similar to Epidyolex within the meaning of Article 3 of Commission Regulation (EC) No. 847/200 (See appendix 1).

# 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "steps after the authorisation" will be updated as follows:

# Scope

Please refer to the Recommendations section above.

# Summary

Please refer to Scientific Discussion 'Fintepla-H-C-003933-II-0012'

# **APPENDIX**

DIVERGENT POSITION DATED 15 DECEMBER 2022

#### **DIVERGENT POSITION DATED 15 December 2022**

## **Fintepla** EMEA/H/C/003933/II/0012

The undersigned member of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the following new indication for Fintepla oral solution to the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) as an add-on therapy to other antiepileptic medicines in children aged 2 years and older. The reason for divergent opinion was the following:

We consider the overall Benefit/Risk of fenfluramine negative in LGS because of limited efficacy results associated with a worrying cardiovascular safety profile, in such a longer term use setting.

## CHMP Member expressing a divergent position:

Alexandre Moreau (FR)