15 October 2020
EMA/639853/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fintepla

International non-proprietary name: fenfluramine

Procedure No. EMEA/H/C/003933/0000

Note

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

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List of abbreviations

Abbreviations	Definition
5-HT	5-hydroxytryptamine
ADHD	attention deficit and hyperactivity disorder
ADI	accepted daily intake
AE	adverse event
AED	antiepileptic drug
AESI	adverse event of special interest
API	active pharmaceutical ingredient
AUC	area under the plasma-concentration time curve
AUC_{0-24}	area under the plasma-concentration time curve from time 0 to 24 hours
AUC_{0-inf}	area under the plasma-concentration time curve from time 0 extrapolated to infinity
AUC_{0-t}	area under the plasma-concentration time curve from time 0 to the last measured concentration
AUC_{0-tau}	area under the plasma-concentration time curve over the dosing interval tau
BCRP	breast cancer resistance protein
BCS	Biopharmaceutical Classification System
BID	twice daily (in 2 divided doses)
BMI	body mass index
BRI	Behaviour Rating Inventory
BRIEF	Behaviour Rating Inventory of Executive Function – assessment tool
CAS	Chemical Abstract Service
CBD	cannabidiol
CGI-I	Clinical Global Impression – Improvement
CHMP	Committee for Medicinal Product for Human Use (EMA)
CLB	clobazam
C_{max}	peak plasma drug concentration
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COMP	Committee for Orphan Medicinal Products
CSF	convulsive seizure frequency
CSR	clinical study report
CV	coefficient of variation
CV ISS	Integrated Summary of Cardiovascular Safety
CYP	cytochrome P450
DB	double-blind
DDI	drug-drug interaction
DHHS	Department of Health and Human Services, US
DSC	Differential Scanning Calorimetry
EC	European Commission
ECG	electrocardiogram

Abbreviations	Definition
ECHO	echocardiogram
EMA	European Medicines Agency
EOS	end of study
EU	European Union
FDA	Food and Drug Administration
FT-IR	Fourier Transform Infrared Spectroscopy
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GRAS	generally recognized as safe
HCl	hydrochloride
HDPE	high density polyethylene
HPLC	High performance liquid chromatography
HS GC	Headspace gas chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICPD	Institute for Clinical Pharmacodynamics
ICP-MS	Inductively coupled plasma mass spectrometry
IIS	Investigator-initiated study
ILAE	International League Against Epilepsy
INN	international nonproprietary name
ISE	Integrated Summary of Efficacy
ISR	incurred sample reanalysis
ISS	Integrated Summary of Safety
IV	Intravenous
KD	ketogenic diet
KF	Karl Fischer titration
Kg	Kilogram
LDPE	Low density polyethylene
LEV	levetiracetam
LTE	long-term efficacy
LTS	long-term safety
MATE	multidrug and toxin extrusion protein
Max	maximum

Abbreviations	Definition
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
Min	minimum
mL	Millilitre
MS	Mass Spectrometry
µM	micromolar
NCBI	National Centre for Biotechnology Information
NDA	New Drug Application
Ng	nanogram
NHV	normal healthy volunteer
NLM	National Library of Medicine
NMR	Nuclear Magnetic Resonance
OAT	organic ion transporter
OATP	organic anion transporter protein
OCT	organic cation transporter
OLE	open-label extension
PAH	pulmonary artery hypertension
PBPK	physiologically-based pharmacokinetics
PDR	Physicians' Desk Reference
PedsQL	Pediatric Quality of Life assessment tool
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetics
PopPK	population pharmacokinetics
PP	Polypropylene
PT	preferred term
QPLCE	Quality of Life in Childhood Epilepsy assessment tool
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RH	Relative Humidity
S9 fraction	the product of an organ tissue homogenate used in biological assays to measure the metabolism of drugs and other xenobiotics

Abbreviations	Definition
SAE	serious adverse event
SAF	Safety Population
SAP	statistical analysis plan
SBA	summary basis of approval
SCNIA	gene for type 1 alpha subunit of the sodium channel
SD	standard deviation
SE	status epilepticus
SMEI	severe myoclonic epilepsy of infancy
SmPC	Summary of Product Characteristics
SOC	system organ class
SOP	standard operating procedure
STP	Stiripentol
SUDEP	sudden unexpected death in epilepsy
TC	tonic-clonic
TEAE	treatment-emergent adverse event
T+M	Treatment + Maintenance
T_{max}	time to peak concentration
TPM	topiramate
TQT	thorough QT interval prolongation (study)
TS	tonic seizure
US	United States
USAN	United States adopted name
USP	United States Pharmacopeia
UV	Ultraviolet
VHD	valvular heart disease
VNS	vagal nerve stimulation
VPA	valproic acid
XRPD	X-Ray Powder Diffraction
ZX008	fenfluramine hydrochloride oral solution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Zogenix GmbH submitted on 5 February 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Fintepla, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 January 2014. The applicant was subsequently changed to Zogenix ROI Limited on 23 January 2020.

Fintepla was designated as an orphan medicinal product EU/3/13/1219 on 18 December 2013 in the following condition: Treatment of Dravet syndrome.

The applicant applied for the following indication: *Treatment of seizures associated with Dravet syndrome in children aged 2 years to 17 years and adults.*

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

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. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/fintepla

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0354/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001990-PIP01-16 was not yet completed as some measures were deferred.

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 applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request(s) for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant indicated the active substance fenfluramine contained in the above medicinal product to be considered as a known active substance.

Protocol assistance

The applicant received the following Protocol Assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
24 July 2014	EMEA/CHMP/SAWP/343866/2014	Monique Wakelkamp, Mario Miguel Rosa, Kerstin Westermark
4 September 2014	EMEA/COMP/367491/2014	

The Protocol Assistance pertained to the following clinical aspects:

- Adequacy of the design of a planned placebo-controlled, double-blind clinical study to evaluate the efficacy of fenfluramine for the treatment of Dravet Syndrome, in particular with a view to the proposed primary efficacy endpoint, the sample size, the duration of treatment, the stratified design based on age with a cut-off of 6 years of age and the proposed safety monitoring assessments.
- Appropriateness a proposed patient registry to collect safety and efficacy data in treated children post-authorisation including a special focus on cardiac safety monitoring as the basis for a future Risk Management Plan
- Adequacy of the plans for PopPK analyses to characterise the PK profile in subjects with Dravet Syndrome.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kirstine Moll Harboe Co-Rapporteur: Johann Lodewijk Hillege

The application was received by the EMA on	5 February 2019
The procedure started on	28 February 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 May 2019

The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 May 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	3 June 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 June 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 January 2020
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Safety/Efficacy assessment of the product:	
A GCP inspection at two investigator sites in USA and Denmark and at the Sponsor site in USA, between 26 August and 18 October 2020. The outcome of the inspection carried out was issued on 29 November 2019.	29 November 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	6 March 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 March 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	20 March 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	26 March 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 May 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 June 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 June 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	14 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	3 September 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	14 September 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	17 September 2020

The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 September 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	1 October 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Fintepla on	15 October 2020
The CHMP adopted a report on similarity of Fintepla with Epidyolex on (Appendix 1)	15 October 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Fintepla (fenfluramine hydrochloride) is proposed for the treatment of seizures associated with Dravet Syndrome (DS) in patients from 2 years of age and older.

DS is a rare disease and sufficient seizure control may be difficult to achieve with existing therapies. There is therefore a need for new therapies with a different mode of action.

2.1.2. Epidemiology

Dravet Syndrome: Incidence approximately 1:20,000 births. Prevalence estimates uncertain possibly around 3/100,000. DS is believed to account for approximately 7% of all severe epilepsies starting before the age of 3 years.

2.1.3. Biologic features

Between 70% and 80% of DS patients carry sodium channel α1 subunit gene (SCN1A) abnormalities. Truncating mutations account for about 40%. Other SCN1A mutations comprise splice-site and missense mutations, most of which fall into the pore-forming region of the sodium channel. Mutations are randomly distributed across the SCN1A protein. Most mutations are de novo, but familial SCN1A mutations also occur. The aetiology of about 20% of DS patients remains unknown, and additional genes are likely to be implicated.

2.1.4. Clinical presentation, diagnosis

Dravet Syndrome, also known as severe myoclonic epilepsy in infancy, is characterised by a variety of seizures (febrile and afebrile, generalized and unilateral, clonic or tonic–clonic) that occur in the first year of life. The onset is usually between 4 and 8 months of age, and often triggered by fever. In addition to convulsive seizures, other seizure types appear between the ages of 1 and 4 years, including myoclonic seizures, focal seizures, and atypical absences. Status epilepticus (SE) may occur at initial presentation or later in the clinical course. By late childhood, the seizure profile will often have stabilised. Significant developmental delay becomes apparent from the second year onwards and associated neuropsychological disturbances, such as attention deficit/hyperactivity disorder, are common. Intellectual impairment affects nearly all patients and is severe in 50% of cases. Dependency in adulthood is common. Death during childhood is common and may be due to SE, drowning or accidents.

2.1.5. Management

Stiripentol (STP, trade name Diacomit), taken in conjunction with sodium valproate (VPA) or clobazam (CLB), is currently approved in the Europe for the treatment of DS. Since September 2019, Epidyolex (cannabidiol) taken with clobazam has been authorised throughout the Europe for the treatment of DS. Neither VPA nor CLB are approved for DS specifically, but both are approved for use in epilepsy in the EU, and widely used. VPA is often used to prevent the initial recurrence of convulsive seizures, and benzodiazepines (e.g. diazepam, midazolam, clonazepam, or CLB) are frequently co-administered to limit the duration of long-lasting seizures. Second line treatments and other options in DS typically include STP, topiramate, ketogenic diet, levetiracetam (LEV), bromides, and vagus nerve stimulation (VNS). Polytherapy is common. Of note, patients with DS may be prone to seizure exacerbation with sodium channel modulators such as carbamazepine, oxcarbazepine, LTG, phenytoin, and vigabatrin.

Sufficient seizure control may be difficult to achieve, and there is therefore a need for new therapies with a different mode of action.

About the product

Fenfluramine is a racemic compound containing dexfenfluramine and levofenfluramine. The active pharmaceutical ingredient (API) is fenfluramine hydrochloride (HCl). The intended commercial formulation is an oral, aqueous solution at a concentration of 2.5 mg/mL fenfluramine HCl (equivalent to 2.2 mg/mL fenfluramine). Fenfluramine HCl is a highly soluble substance and is expected to remain soluble in the gastrointestinal tract.

Fenfluramine was approved in Europe in the 1960s, and in the United States in the 1970s as an appetite suppressant at a dose of 60 to 120 mg/day for the treatment of adult obesity. Fenfluramine was used extensively in an off-label combination with phentermine. The d (or (+)) isomer of fenfluramine (dexfenfluramine) was also approved and marketed (Adifax®, Redux® and others) as an anorectic medication. Fenfluramine (racemate) was sold in 118 countries and was in clinical use for 20 to 30 years. Approximately 50 million Europeans were treated with fenfluramine for appetite suppression between 1963 and 1996 (Barceloux 2012) and the US Department of Health and Human Services estimated an exposure of over 61 million patient-months prior to its global withdrawal in 1997 (Lee/DHHS 1994).

In the late 1990s, fenfluramine was withdrawn from world-wide markets due to its association with cardiac valve abnormalities (CDC 1997; Connolly 1997; Wong 1998). In its review in 1999, the EMA considered the safety profile of fenfluramine for the treatment of obesity unacceptable under prescribed conditions of use and the benefit/risk balance unfavourable.

Subsequently, however, open-label long-term studies (representing up to approximately 30 years of daily treatment) in Belgium suggested efficacy of fenfluramine hydrochloride in controlling seizures in patients with Dravet Syndrome. A total of 21 patients from 6 months to 50 years of age were followed after the product's withdrawal from the market. The doses used were administered as fixed doses between 5 and 40 mg/day fenfluramine hydrochloride, most commonly 5 or 10 mg twice a day. These doses corresponded to approximately 0.8 to 1.0 mg/kg/day for young children, and 0.1 to 0.3 mg/kg/day for the older patients. The results were regarded as promising with respect to efficacy and safety.

The proposed indication for Fintepla is for the treatment, as an add-on therapy to other antiepileptic medicines, of seizures associated with Dravet syndrome in patients 2 years of age and older. The doses are 0.2 to 0.7 mg/kg/day fenfluramine administered orally in 2 divided doses (BID), with a maximum total daily

dose of 26 mg, regardless of weight. For patients concomitantly taking stiripentol (with clobazam and/or valproate), a modification in the maximum daily dose to 0.4 mg/kg/day, not to exceed a total daily dose of 17 mg, is recommended.

Type of Application and aspects on development

The applicant requested an accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004. The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest, for the following reasons:

Whilst the unmet medical need for the treatment of seizures associated with Dravet syndrome is acknowledged, the CHMP concluded that the strength of evidence presented in the request for accelerated assessment prevented the granting of a positive decision. In particular, the clinical evidence regarding the efficacy of fenfluramine in the clinical studies is not outstanding when compared to other available treatment options/standard of care including stiripentol. In addition, the safety profile of fenfluramine is known for the risk of valvular heart disease and pulmonary arterial hypertension. These risks are known to be cumulative and it is expected that the standard assessment time would be required to support the thorough assessment and discussions needed in the context of the new intended indication of treatment of Dravet syndrome.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as an oral solution containing 2.2 mg of fenfluramine. The product contains the hydrochloride salt.

Other ingredients are: sodium ethyl parahydroxybenzoate (E 215), sodium methyl parahydroxybenzoate (E 219), sucralose (E 955), hydroxyethylcellulose (E 1525), monosodium phosphate (E 339), disodium phosphate (E 339), cherry flavouring powder [consisting of: acacia (E 414), dextrose (maize), ethyl benzoate, natural flavouring preparations, natural flavouring substances, flavouring substances, maltodextrin (maize) and sulphur dioxide (E 220)], potassium citrate (E 332), citric acid monohydrate (E 330) and water for injections.

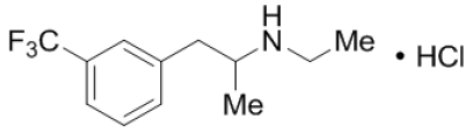
The product is available in high density polyethylene (HDPE) bottles with a child-resistant, tamper-evident cap (multilayer of HDPE/PP/LDPE), as described in section 6.5 of the SmPC. Four different bottle sizes may be used to package the drug product. These are: 60, 120, 250 and 360 mL. The finished product is co-packaged in a paperboard carton with a low density polyethylene (LDPE) press-in bottle adaptor and oral syringes [two of 3mL (0.1 mL increments) and two of 6 mL (0.2 mL increments and graduation between 0-3 mL erased)] used to administer the prescribed dose, as described in the SmPC. Both syringes consist of a polypropylene barrel with an HDPE plunger.

2.2.2. Active Substance

General information

The chemical name of fenfluramine hydrochloride is (*RS*)-ethyl(α-methyl-3-trifluoromethylphenethyl)amine hydrochloride corresponding to the molecular formula $C_{12}H_{16}F_3N$ • HCl. It has a molecular mass of 267.72 g/mol and the following structure:

Active substance structure



The chemical structure of fenfluramine hydrochloride was elucidated by a combination of Fourier transform infrared spectroscopy (FT-IR), nuclear magnetic resonance (NMR) spectroscopy, ultraviolet (UV) spectroscopy, mass spectrometry (MS) and elemental analysis.

The solid-state properties of the active substance were measured by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and hygroscopicity by vapor sorption.

Fenfluramine hydrochloride is a white to off-white crystalline powder. The active substance is non-hygroscopic. The active substance aqueous solubility varies moderately as a function of pH.

Fenfluramine exhibits stereoisomerism due to the presence of a single chiral centre. Fenfluramine hydrochloride has been developed as a racemic mixture and contains equal amounts of dexfenfluramine and levofenfluramine. The chiral carbon does not bear acidic protons and is therefore stable to racemization. The racemic mixture of *R*/*S* fenfluramine has been verified using chiral high-performance liquid chromatography (HPLC) analysis. The chiral stability of the active substance was also demonstrated by testing samples from active substance approximately 1-3 years after manufacture as well as forced degradation study samples.

Fenfluramine hydrochloride is a crystalline material that exists as a single form (Form 1) with a needle-like morphology. The active substance is chemically and physically stable in the solid state and no other polymorphs have been observed in a polymorph screening study or in the accelerated and long-term stability studies.

Manufacture, characterisation and process controls

Fenfluramine hydrochloride is obtained from a single manufacturer. The active substance is synthesized in four main steps followed by crystallisations and salt formation steps using a single well-defined commercially available starting material with acceptable specifications. Three synthesis intermediates are isolated.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Changes introduced have been presented in enough detail and have been justified. The quality of the active substance used in the various phases of the development is considered comparable with that produced by the proposed commercial process.

The active substance is packaged in heat-sealed linear-low-density polyethylene (LLDPE) film sleeves as the primary packaging which complies with the EC directive 2002/72/EC and EC 10/2011 as amended. The primary packaging is then placed inside a LDPE bag as secondary packaging which is secured with a cable tie. The double bags are placed inside a suitable size HDPE keg. The keg is sealed with a HDPE lid and rubber 'O' ring.

Specification

The active substance specification shown includes tests for: appearance, identification (FTIR, XRPD, of chloride), water content (KF), chloride content (titration), residue on ignition (Ph. Eur.), residual solvents (HS GC), impurities (HPLC) and assay (HPLC).

As described above, several polymorph screens have resulted in only one polymorph ever observed, and generation of amorphous material was not possible. The current proposed specifications use XRPD to identify the active substance crystalline form (Form 1), and potential polymorphism is monitored during stability. No changes are expected nor have any been observed under long-term and accelerated stability studies.

The proposed specification for 4-fenfluramine is supported by toxicology data.

The level of impurities in the active substance was found to be very low and the applicant was requested to tighten the proposed limit to reflect batch results. Since the number of batches manufactured at the time of opinion is very limited, the applicant committed to re-evaluate it post-approval (see recommendation below).

As indicated above, fenfluramine is a chiral racemic drug being developed as an equal mixture of (*R*) and (*S*) enantiomers.

Elemental impurity limits have been omitted from the active substance specification based on data from active substance and finished product batches, and the low content of active substance in the finished product.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on active substance batches manufactured by the development and clinical-stage manufacturer and the intended commercial manufacturer of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three production scale batches of active substance from the proposed commercial manufacturer stored in a container closure system representative of that intended for the market for up to 36 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

Supportive stability data on active substance manufactured by the development supplier and by the intended commercial supplier are also available for up to 48 months at 25°C/60%RH and 6 months at 40°C/75%RH.

The following parameters were tested: appearance, identification (XRPD), DSC, water content, impurities, assay and microbial testing. The analytical methods used were the same as for release and were stability indicating.

All tested parameters met the proposed specifications and no trends were observed. Additionally, there were no single impurities exceeding the ICH Q3A identification threshold of 0.10%, and none trending at the 0.05% reporting level observed at any time point.

Forced degradation studies have been performed under heat (7 days, 80°C), heat and humidity (7 days, 80°C / 80% RH), heat (solution for 48 hours, 80°C), photolytic stress (solid and in solution), acid (48 hours, 80°C, 2M HCl), base (48 hours, 80°C, 2M NaOH) and peroxide (14 days, ambient, 3% H_2O_2). The results suggest that fenfluramine is very stable to all stress conditions examined. Impurities were only formed under oxidative conditions (~3% peroxide, 25°C, 14 days), resulting in a 2% area loss of parent.

Photostability testing following the ICH guideline Q1B was performed on a single batch. The active substance is photostable.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 4 years with no special storage conditions in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Fintepla solution for oral administration is a clear, colourless, slightly viscous liquid, with a pH of 5. It contains 2.2 mg/mL fenfluramine (equivalent to 2.5 mg/mL fenfluramine hydrochloride) in aqueous vehicle. During the evaluation, a major objection was raised on the expression of strength of the product, proposed to be based on hydrochloride salt. As a result, the product information was amended during the procedure and the proposed posology in the SmPC is now based on the approved product strength of Fintepla, i.e. 2.2 mg/mL fenfluramine (the active moiety).

The aim of pharmaceutical development was to produce a liquid formulation for oral administration, with a single concentration of fenfluramine hydrochloride that is suitable for paediatric and adult use across the entire dosing range and is stored in a multi-use bottle at room temperature.

The physicochemical properties of fenfluramine hydrochloride active substance are summarized here.

As indicated in the active substance section, fenfluramine hydrochloride is a crystalline material that exists as a single form (Form 1). The active substance is chemically and physically stable in the solid state and no other polymorphs have been observed in a polymorph screening study or in the accelerated and long-term stability studies.

The active substance aqueous solubility varies moderately as a function of pH. At 25°C, the solubility ranges from approximately 25 mg/mL at pH 1.7 to over 50 mg/mL at pH 6.7. With solubility of more than 10-fold higher than its concentration in the finished product, precipitation of the active substance out of solution is

unlikely to occur under normal storage conditions, including long-term refrigeration Fenfluramine hydrochloride active substance is non-micronized.

Forced degradation studies indicated the active substance is very stable in aqueous solution. Thermal stability of buffered aqueous solutions of fenfluramine hydrochloride ranging from 0.5 mg/mL to 5 mg/mL concentration was investigated during early development. The data show that fenfluramine hydrochloride solution is stable for at least 6 months when stored at 60ºC at pH 6.8.

The excipients in fenfluramine oral solution formulation include preservatives, viscosity building agent, sweetener, buffering agents and a flavouring agent. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, when applicable. The applicant was requested to replace the proposed identification test included in the cherry flavouring specification by a more discriminative test. Since this has not been addressed at the time of opinion and does not constitute a major concern, the applicant is recommended to address this issue post-approval. He has committed to implement the new identification test no later than the end of 1st Quarter 2021.

The excipients levels in the formulation comply with the Annex to the European Commission guideline on 'Excipients in the labelling and packaging leaflet of medicinal products for human use' (EMA/CHMP/302620/2017) and Guideline on pharmaceutical development of medicines for paediatric use (EMEA/CHMP/QWP/805880/2012 Rev 2) via oral route. Natural flavouring preparations, a component of the cherry flavouring powder meets the definition for "Flavouring Preparations under EU Regulation (EC) No 1334/2008. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Methylparaben is a preservative commonly used in multiple-use oral, topical and injectable pharmaceutical formulations, both as free acid and sodium salt and exhibits its antimicrobial activity in the pH range of 4-8. Paraben preservatives are typically used in combination due to the known synergy in their antimicrobial effects. Methylparaben sodium is used in the formulation, in combination with ethylparaben sodium). These preservative levels were selected based on data from preservative efficacy testing. A lower concentration was also evaluated in the study. A weakness was consistently observed in the low-level preservative prototypes with respect to fungal species which suggested that these prototypes may not be able to retain adequate preservation efficacy by the end of their projected shelf-life or intended in-use period. This weakness continued on long-term stability of the low preservative prototypes, failing to meet Ph. Eur. 5.1.3 acceptance criteria after 6 months stability storage. Methylparaben concentration in Fintepla is within the range used in EU authorised oral pharmaceutical products.

Methylparaben sodium has a higher aqueous solubility than the free acid and was found to dissolve more rapidly in the finished product formulation.

Ethylparaben was selected for use as the second paraben preservative in fenfluramine oral solution due to its higher aqueous solubility compared to the more commonly used propylparaben, since the parabens' aqueous solubility decreases with the chain length.

The sodium salt of both parabens was selected to minimize the risk of preservative precipitation if the product is inadvertently stored at cold temperatures for an extended period of time. With the sodium salts of methyl- and ethylparaben (in combination), no sign of precipitation was observed in the finished product formulation after one month of storage at 5°C during early development.

The pH of the finished product formulation was optimized to minimize the preservative degradation (which was observed at high pH). The performance of the preservative system in the finished product formulation was confirmed using compendial preservative efficacy testing (Ph. Eur. 5.1.3) for oral products.

The guideline on pharmaceutical development of medicines for paediatric use was considered when selecting the dosage form and formulation components.

An aqueous oral solution is generally considered an acceptable dosage form for children as young as newborns. The liquid dosage form provides flexibility for age-based or weight-based dosing. The target range of dose volumes (0.5 mL to 6 mL) is small enough for administering to young children without compromising accuracy of dose measurement.

Compared to other paediatric oral dosage forms (suspensions, dispersible powders or granules and orally disintegrating tablets), oral solutions have the lowest risk of choking and aspiration due to the absence of solid particles.

An oral solution is also most likely to be compatible with gastric and naso-gastric tube administration.

Unlike oil-based formulations, aqueous solutions generally have acceptable mouth feel, similar to familiar water-based drinks.

Aqueous formulations in multi-dose containers require preservation against microbial growth.

Although the active substance is stable across a wide range of pH, a buffering system is required to maintain the pH at an adequate range for preservatives efficacy, solubility and stability.

The finished product is sweetened and flavoured to improve acceptability by paediatric patients by masking potential objectionable taste from the active and/or other formulation components, such as preservatives, and the saline taste from the buffering salt. The levels of flavour and sweetener are relatively low, sufficient to achieve the desired taste masking without making the product too attractive to children. This is supported by data from the palatability study.

A thickener is added to increase the viscosity of the liquid formulation and reduce the potential for accidental spillage, allow for accurate delivery using an oral syringe (no dripping), and potentially improve palatability of the formulation by reducing the contact area with the tongue.

With regards to the formulation development, fenfluramine hydrochloride concentrations between 0.5 and 5 mg/mL were initially evaluated. For accuracy of dose measurement and ease of administration, 2.2 mg/mL was selected as the target concentration for the intended commercial product since it results in dosing volumes of not less than 0.5 mL per dose and not more than 6 mL per dose.

Given the active substance aqueous stability, the development therefore focused on selecting functional excipients and on identifying suitable concentration ranges for these excipients.

In selecting the excipients, choices were intentionally limited to excipients that fit the constraints of a ketogenic diet, which some patients are put on to help control seizures. Short term stability studies of early prototype formulations were conducted to evaluate compatibility of the active substance with potential formulation excipients in aqueous solution. The stability was later confirmed in longer term stability studies in parallel with the clinical program.

The overall acceptability and palatability of the formulation was studied in children aged 2 to 18 years as part of a Phase 3 open-label clinical study using the intended commercial formulation (Study ZX008-1503).

Results from the study confirmed the palatability and overall acceptability of the formulation in the paediatric patient population.

Two formulation composition variations were used during clinical development:

i) A red colored clinical formula which included 1.25, 2.5 and 5 mg/mL fenfluramine hydrochloride as well as placebo, and was filled in amber glass bottles.

ii) A colorless clinical formulation included the same fenfluramine hydrochloride concentrations in a dye-free liquid filled in HDPE bottles.

The formulations are very similar (qualitatively and quantitatively) except for minor differences in the amounts of cherry flavoring and citric acid, as well as the removal of the red coloring. Therefore, they are considered representative of each other. The colorless clinical formulation used during clinical studies is the same as that intended for marketing.

Fintepla oral solution is a simple aqueous solution manufactured by addition of the solid ingredients to water and mixing at room temperature until completely dissolved. The bulk solution manufacture is followed by bottle filling and capping (primary packaging).

The product will be administered using a suitable size oral syringe that will be co-packaged with the finished product. Two 3 mL and two 6 mL oral dosing syringes and a press-in bottle adapter are included in the paperboard carton together with the finished product bottle. The 3 mL syringes are printed in green, with numbered graduations for 0.5, 1, 1.5, 2, 2.5, and 3 mL and unnumbered graduations in 0.1 mL increments. The 6 mL syringes are printed in purple, with numbered markings for 3, 4, 5, and 6 mL and unnumbered marking in 0.2 mL increments. Both syringes consist of a polypropylene barrel with an HDPE plunger; the markings utilize similar line thicknesses. The bottle adapter and syringes are CE marked and have been evaluated for performance and suitability. Following a major objection raised on the originally proposed graduation of the syringes and the dosing accuracy, the graduations were revised as described above, and the 3 mL syringes are proposed to be used for dosing volumes below and including 3 mL. The 6 mL syringe is proposed to be used for dosing volumes above 3 mL. To ensure this syringe cannot be used to dose volumes below 3.0 ml, the lowest part of the graduation scale is erased.

During the evaluation, detailed information on the graduation of the syringes and suitability of the device has been submitted. Dosing accuracy of the two syringes was evaluated at various dose levels starting at 0.5 mL. The provided dose accuracy study is considered representative of the worst-case scenario.

A study was performed to demonstrate the suitability of the in-use period for the dosing syringes. The cleaning study was conducted with two syringes that were supplied with the product during clinical studies (1.5 mL syringe and 6 mL). No deterioration to markings or numbering was observed for any of the syringe sizes after cleaning by the hand wash method. Similarly, no deterioration was seen for the 6 mL syringes from the dishwasher cleaning; however, a slight deterioration of the marking and numbering of the 1.5 mL syringe was observed from dishwasher cleaning. The extent of deterioration was not substantial enough to affect the visibility or readability of the markings and therefore it was concluded to have no impact upon accurate dosing.

The intended commercial adapter was selected to fit 30 mL – 360 mL finished product bottles and to remain in place with repeated use. A study was performed to evaluate the adapter for leakage, security of adapter placement within the bottle neck, and durability of the adapter-syringe fitting to repeated use. The correct placement of the closure was verified, and no interference between the cap and adapter were observed. No loss of the child-resistant feature was reported for any bottles upon opening. Based on the results of this

study, the finished product container-closure was demonstrated to be compatible with appropriately sized, commercially available press-in bottle adapters.

A comprehensive extractables-leachables risk assessment was conducted on the container closure components, including the label adhesive, and on the bottle adapter and dosing syringes. The assessment concluded that, based on materials of construction of the primary, secondary and associated packaging components, their food contact regulations and the criteria for safety discussed in the 1999 FDA Guidance Document for the Packaging of Human Drugs and Biologics for oral solutions / suspensions, the leachables risk is low for the packaging and delivery of the fenfluramine oral solution. Since the container-closure is made of compendial material and complies with Ph. Eur. 3.2.2 (Plastic Containers and Closures for Pharmaceutical Use), and the polymers and additives of the contact surfaces are suitable for use with foodstuffs according to the EU regulations, extractables and leachables studies are not required.

The primary packaging is HDPE bottle with a child-resistant, tamper-evident cap (multilayer of HDPE/PP/LDPE). The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps, presented in scheme 2: ethylparaben and methylparaben solution manufacturing, bulk solution manufacturing, filling of bottles and single unit carton packaging. The process is considered to be a standard manufacturing process.

The critical steps in the bulk manufacture are mixing of the buffer components and the mixing after final dilution. The critical step in the primary packaging (filling) operation is the bottle filling step.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications shown in Table 4 include appropriate tests for this kind of dosage form: appearance, identification (HPLC, UV), fenfluramine assay (HPLC), impurities (HPLC), methylparaben identity (HPLC), methylparaben assay (HPLC), ethylparaben identity (HPLC), ethylparaben assay (HPLC), preservatives degradation product (HPLC), pH (Ph. Eur.), viscosity (Ph. Eur.), uniformity of delivered doses (Ph. Eur.), and microbial limits (Ph. Eur.).

Residual solvents are not included in the product specification. All excipients, except for the cherry flavoring powder, are USP and Ph. Eur. grades. The cherry flavoring powder is food grade as there is no USP or Ph. Eur. grade available. The active substance and the excipients do not contain Class 1 residual solvents and conform to ICH Q3C limits for Class 2 and Class 3 residual solvents.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

Fenfluramine HCl is a chiral compound being developed as racemic mixture. Enantiomer composition was fully evaluated as part of active substance development. To assess the chiral stability of fenfluramine hydrochloride in the finished product formulation, several samples from the finished product registration batches were tested using the SFC method. The samples included long-term stored product and accelerated stability (40°C/75%RH) samples. Based on these data for the active substance and the finished product, it is concluded that there is no specification needed for chirality in the finished product.

Following a major objection, a nitrosamine risk evaluation has been completed for both the active substance and the finished product (excipients, finished product manufacturing process, packaging material and finished product storage). No risk of presence of nitrosamines was identified, and potential nitrosating agents are absent in the active substance and all excipients. Excipient hydroxyethyl cellulose may contain $\leq$ 0.2% sodium nitrate; however, a supplemental risk evaluation performed by the active substance manufacturer determined that the finished product formulation conditions prohibit either reduction of the nitrate to nitrite or subsequent nitrosation of the secondary amine in fenfluramine. The primary packaging materials for both the active substance and the finished product do not contain nitrocellulose, and therefore pose negligible risk of nitrosamines.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 18 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from four commercial scale batches of finished product (three unfiltered and one filtered) of different bottle sizes (30 mL, 60 mL, 120 mL, 360 mL, 500 mL) stored for up to 36 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Bottles were kept in in an upright and inverted position. The batches are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. The filtered batch was included to support the addition of the bulk filtration step to the commercial manufacturing process.

A bracketing approach was used with regards to bottle size and bottle orientation for the primary batch stability studies. Through this design, the full range of bottle sizes was studied on stability.

Samples were tested for appearance, fenfluramine assay, related impurities, methylparaben assay, ethylparaben assay, preservatives known degradation product, pH, viscosity and microbial limits. The analytical procedures used are stability indicating.

The data demonstrate that fenfluramine oral solution is stable over the proposed shelf-life. No significant changes or trends have been observed and all batches met acceptance criteria both at release and the available stability time points, except for the observation of the "barely visible" HEC particles in most samples at the 3-month time point and in a few samples at a subsequent time point (all manufactured using process A), that resulted in an investigation and implementation of the bulk filtration step in the manufacture of the finished product, as discussed earlier in the report.

To date, stability data from the filtered primary stability batch are available for 24 months at 25°C/60%RH and 6 months at 40°C/75%RH. No significant changes or trends were observed, and all samples met acceptance criteria both at release and the available stability time points. The data demonstrate that fenfluramine oral solution is stable over the proposed shelf life, and that the addition of in-line filtration to the manufacturing process does not have an impact on product quality, including long-term stability. The attribute-by-attribute comparison supports a conclusion that the filtered product is equivalent to the unfiltered product and that the primary stability batches from the unfiltered product are representative of the filtered product's stability and therefore can be used as registration batches for the filtered product.

Short-term temperature excursions (such as what might occur during shipping) are permitted based on temperature cycling studies between 5°C and 50°C, and ambient and -20°C.

Forced degradation studies have been performed on two batches under oxidative, acid, base, thermal, white light and UV light stress. Samples were tested for fenfluramine and parabens assay and their related impurities. The active substance in fenfluramine oral solutions was demonstrated to be very stable under stress conditions, and no new fenfluramine related impurities or degradation products were present at the level of or greater than the identification threshold (0.2%). The forced degradation results support the conclusion that the active substance in fenfluramine oral solutions is very stable.

The in-use studies have been performed in the upright position. Considering the same material for the insert is used as for the cap, the primary stability studies including bottles in the inverted position sufficiently justify that the quality of the product is not expected to be affected when the product is placed in inverted position with the insert present.

A 90-day in-use study was performed on the intended commercial formulation in 120 mL and 500 mL HDPE bottles. The 120 mL bottle is the smallest bottle that can hold a 90-day supply. The 500 mL bottle is not intended for EU market, but was included in the study as a bracketing size for the 250 mL and 360 mL bottles. The finished product was stored at long term conditions. Use was simulated by withdrawing 0.5 mL (120 mL bottle) and 1 mL (500 mL bottle) twice daily (working days) with additional withdraws on Monday and Friday or Bank holidays. After opening the bottle was kept open for 60 minutes. Testing was conducted on T0, 30 days, 60 days and 90 days.

A second study of 95-day in-use stability was conducted on the intended commercial product in 60 mL, 120 mL, and 360 mL HDPE bottles stored under the long-term conditions with simulated daily use resulting in diminishing amount of product in the bottles.

Samples were tested for appearance, pH, drug assay and impurities, preservative assay and impurities, viscosity, microbial limits and preservative efficacy initially and after 30, 60, 90 days or 95 days of simulated use.

The results show that the stability of the product throughout its in-use period remained stable over time, no specific trend or change was noted in any of the tested parameters.

A similar in-use study was conducted for the 2.2 mg/mL intended commercial product stored at 2 – 8°C for 30 days to support accidental refrigerated storage during the use period. 60 mL and 360 mL bottles were used in this study, with the 60 mL bottles being tested after 14 days of simulated use and the 360 mL bottles after 30 days of simulated use. The obtained data showed out of specification results for the preservatives assay after 14 days, indicating the product not to be kept in the refrigerator.

Although the studied in-use study period would not be sufficient to cover the clinical use of the product, it is also noted that in the primary stability study, photostability and forced degradation studies there is no indication

that the finished product may be susceptible to deterioration. As such, longer in-use stability studies are not considered necessary. However, the applicant is recommended to conduct an additional in-use stability study toward the end of shelf life once 48-month samples are available.

The results conform the stability of the product for a period of 90 days. This is reflected in section 6.3 of the SmPC: Use within 3 months of first opening the bottle.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Samples were tested for appearance, pH, drug assay and impurities, preservative assay and impurities, and viscosity. The results confirm that the finished product is photostable.

Based on available stability data, the proposed shelf-life of 4 years and no special storage conditions (the product should not be refrigerated or frozen) as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

The white child-resistant cap that is part of the finished product container-closure system may contain an additive (tallow) which is of bovine origin. The plastic containing this material is subjected to severe conditions during manufacture, thus ensuring inactivation of any agents present in the plastic material, regardless of the source and type of material. The manufacturer confirms adherence to current EU Legislation for Plastics and Articles in Contact with Food EC 10/2011, Current Packaging & Packing Waste Directive 94/62/EC, Commission Regulation EC No. 2023/2006 on GMP for materials and articles intended to come into contact with food.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The finished product manufacturing process was revised during the course of development to add an in-line filtration step for the bulk product through a 20µm filter. This change was intended to improve the product aesthetic appearance and avoid potential complaints resulting from observation of the HEC barely visible particles intrinsic to the formulation.

The product will be administered using a suitable size oral syringe that will be co-packaged with the product.

During the procedure the expression of strength was changed to be based on the active moiety in line with the SmPC guideline.

Extensive information on the suitability of dosing syringes has been provided.

Risk assessment on the presence of nitrosamines impurities identified no risk.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Three recommendations are agreed with the Applicant to re-evaluate the total impurities acceptance criteria for the active substance, to initiate an in-use study of a batch towards the end of shelf-life and to implementing of a GC identification method for the cherry flavouring.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendations for future quality development

1. The applicant is recommended and has committed to re-evaluate the total impurities acceptance criterion (active substance specification) after gathering more manufacturing experience.

2. The applicant is recommended and has committed to initiate an in-use study of a batch towards the end of shelf-life once 48-month samples are available.

3. The applicant commits to implementing a more discriminative identification method for the cherry flavouring. Since this method must be developed and validated, it will be implemented for receipt testing no later than the end of 1st Quarter 2021.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant provided an adequate non-clinical package, composed by the non-clinical programme conducted to support the DS indication, together with the non-clinical data on fenfluramine available in the published literature and in the context of the previous therapeutic use in obese adults at a higher dose range (60 to 120 mg/day).

2.3.2. Pharmacology

Primary pharmacodynamic studies

Fenfluramine is a racemic compound containing dexfenfluramine and levofenfluramine in equal amounts. The stereochemical configuration of the d or (+) isomer (also known as dexfenfluramine) corresponds to the S enantiomer, and the configuration of the l or (-) isomer (levofenfluramine) corresponds to the R enantiomer.

The choice to develop the racemate (±) fenfluramine in the Dravet Syndrome (DS) indication was driven by the efficacy clinical observation in a clinical study where the racemate was used (Ceulemans et al., 2012).

A well-known primary pharmacological activity of (±) fenfluramine and its metabolite (±) norfenfluramine is the release of serotonin. Studies in rats showed that complete depletion of serotonin prevented the anticonvulsant activity of fenfluramine, suggesting a role for serotonin in mediating the anticonvulsive effect of fenfluramine. The anticonvulsant activity of fenfluramine was shown in mice, rats and in a Zebrafish model.

Studies with Zebrafish models for DS suggest that fenfluramine acts on multiple receptors, including agonism of 5-HT2C, 5-HT1D, 5-HT1A and 5-HT2A. 5-HT2B appears not to be involved in the antiepileptic activity of

fenfluramine in this model. The (+) enantiomer of fenfluramine and norfenfluramine have the highest activity in the serotonin release assay when the locomotor activity is used as endpoint. The (-) enantiomer also displays significant activity, but less than the (+) enantiomer. When frequency and duration of abnormal epileptiform activity are taken as endpoints in the Zebrafish, the difference between the enantiomers is much less pronounced and the parent compound is more active than the nor-metabolites.

Evidence shows that activation of 5-HT2B receptors potentially underlies valvular heart disease associated with fenfluramine. Reference is made to a proprietary study (Study XS-0715) on the effects of the fenfluramine and norfenfluramine enantiomers on various receptors and to a publication on the involvement of 5-HT2B receptors in fenfluramine associated valvular heart disease. The data show that the (+) norfenfluramine enantiomer binds with higher affinity to the 5-HT2B receptor and that this enantiomer is more potent at activating the 5-HT2B receptor than the other enantiomers. It was noted that the unbound concentrations of (+) and (-) fenfluramine and (-) norfenfluramine in patients are lower than their potency for interaction with 5-HT2B receptors but that an interaction of (+) norfenfluramine with the 5-HT2B receptor cannot be ruled out. In fact, the ratio between the activation constant (K_{act}) in an *in vitro* assay for (+) norfenfluramine at the 5-HT2B receptor and the free plasma C_{max} is 0.5, suggesting that activation of this receptor at half maximal to maximal plasma concentrations appears likely. However, as they come from different assays and require extrapolation from *in vitro* to *in vivo* data, these observations need to be interpreted cautiously.

The studies in the Zebrafish model also suggest that fenfluramine acts as an antagonist at the σ1-receptor. However, in contrast, *in vitro* data suggested it acted as a positive modulator enhancing the activity of a σ1-receptor agonist. Data obtained in wild-type CD-1 mice suggested that 5-HT2A agonistic and the σ1-receptor antagonist activity of (+) fenfluramine and (+) norfenfluramine may confer part of the antiepileptic activity in a model of NMDA-induced seizures. The applicant presented additional literature data suggesting that positive modulators at the σ1 receptor have anticonvulsant activity. These data are, however, in contrast with the results from Rodriguez-Munoz 2018 obtained in mice that suggested that σ1-antagonism protects against seizures.

Secondary pharmacodynamic studies

Fenfluramine exerts secondary pharmacological effects through monoaminergic mechanisms. Neuroendocrinological effects (renin, prolactin) are mainly affected through serotonergic mechanisms, providing at least a potential for secondary effects in patients. 5-HT2C agonism is responsible for the anorexic effects of fenfluramine (see also section Safety pharmacology programme below).

Safety pharmacology programme

In animals, fenfluramine affects EEG, sleep and feeding behaviour, induced anxiogenic effects, motor activity, learning and memory, affects respiration, intestinal motility and urinary flow, heart rate and blood pressure. These effects were generally mild and of a transient nature and they are related to the primary and secondary pharmacological effects of fenfluramine, especially those related to the monoaminergic systems.

Fenfluramine can act on the hypothalamic-pituitary axis by causing an increase in ACTH, cortisol, and corticosterone secretion (Fuller 1992). It is a dose-dependent effect and it seems to be mediated by serotonin/serotonin agonists/serotonin transporter inhibitors (Fuller 1996). Fuller also described the

neuroanatomical links demonstrated in the rat, that are compatible with the observed increases in ACTH and cortisol. The effect is considered mediated through 5-HT1A receptor.

In a study in rats (Van de Kar 1985), fenfluramine induced a strong increase in plasma prolactin and corticosterone at 5 mg/kg. Referring to a study in healthy volunteers investigating the cortisol response to 60 or 180 mg divided in three doses of 20 or 60 mg over 24 hours of fenfluramine (Schürmeyer et al. 1996), it appears likely that the dose intended for DS patients (maximum total daily dose of 26 mg, regardless of weight) would not be expected to give rise to increased cortisol levels as observed in the rat (Van de Kar 1985). The dose of 20 mg every 8 hours over 24 hours did not increase cortisol levels above baseline in healthy volunteers, whereas 60 mg every 8 hours increased mean plasma ACTH and cortisol by 85 and 129%. Fenfluramine did not modulate the frequency but increased the amplitudes of ACTH and cortisol secretory episodes. Schürmeyer concludes that fenfluramine stimulates the activity of the hypothalamic-pituitary-adrenal axis at a suprapituitary level by modulating the amplitude of ACTH and cortisol secretory bursts.

Later publications indicated that fenfluramine increased cortisol at dose levels relevant for DS patients. Plasma cortisol decreased at 1 hour after oral doses of 15 or 30 mg and then increased to a peak at 4 hours in healthy volunteers (Bond 1995). Increases in cortisol were also found starting at 2 hours after administration of an oral dose of 60 mg to depressed and healthy volunteers (Mitchell 1990).

No data on hERG channel inhibition was provided and the cardiovascular safety pharmacology studies in animals predated the introduction of GLP requirements. However a thorough QTc clinical study (AX008-1603) was performed and showed no QTc prolongation. These results override the need for further non-clinical studies.

Pharmacodynamic drug interactions

No dedicated drug-drug interactions studies were performed.

Fenfluramine is a substrate of the serotonin transporter and causes a release of serotonin into the synapse. It may therefore interact with other serotonergic drugs (including SSRIs, SNRIs, tricyclic antidepressants, or triptans), with agents that impair metabolism of serotonin such as MAOIs, or with antipsychotics that may affect the serotonergic neurotransmitter systems. This interaction may potentiate the risk of serotonin syndrome, even though it is reassuring that literature does not report observations of serotonin syndrome in clinical practice (Richelson 1994). Similarly, the risk of coadministration with cyproheptadine, a serotonin antagonist, may block the beneficial effects of fenfluramine. The risk of serotonin syndrome is further discussed in the clinical pharmacology sections.

The clinical pharmacodynamic drug interaction data for fenfluramine with other drugs, including other AEDs used in combination for the treatment of DS, are described in clinical sections.

2.3.3. Pharmacokinetics

Single dose pharmacokinetics

Fenfluramine and norfenfluramine exhibited good permeation through Caco-2 cell monolayers with efflux ratios between 0.7 and 1.0 over a concentration range of 1 to 100 µM. Neither fenfluramine nor norfenfluramine is actively transported by P-glycoprotein (P-gp).

Data from published literature showed that (±) fenfluramine is rapidly absorbed in the gastrointestinal tract in mice, rats and dogs.

In mice, there were no differences in exposures between the enantiomers of fenfluramine. Cmax values were reached within 15 minutes and the plasma half-lives were about 4 hours.

In rats, (+) and (-) fenfluramine both reached Cmax within 30 minutes. Bioavailability was about 20% for the (-) enantiomer. Plasma concentrations increased linearly with the dose over the dose range 2.5 to 6.25 mg/kg for (-) fenfluramine. However, the (+) enantiomer was metabolised and excreted at a slower rate (T½ of 2.6 hours) than the (-) isomer (T½ of 1.1 hours), resulting in a larger area under the curve (AUC). These differences are consistent with stereo-selective N-deethylation of fenfluramine, where the formation of norfenfluramine from (-) fenfluramine occurs much faster than from (+) fenfluramine.

In dogs, there was no difference in the pharmacokinetics of the (+) and (-) enantiomers of fenfluramine. The Cmax occurred within 2 hours and the plasma half-life (T½) was 2.5 hours. The T½ and AUC for both enantiomers of norfenfluramine were higher than those for fenfluramine. The T½ and AUC of the (+) and (-)norfenfluramine were in the same range.

Toxicokinetics

The toxicokinetics of racemic fenfluramine has been evaluated in juvenile rats by an oral dose-range finding study and a pivotal 10-week oral, repeated dose toxicity study and in an oral, 13-week repeated dose toxicity study in adult rats. The (+) and (-) enantiomers were not separately measured in these studies

The studies in juvenile rats showed that the exposures of fenfluramine and norfenfluramine were similar from the first to the last day (76), with no differences between males and females. The increase in fenfluramine was greater than dose proportional, while the increase in norfenfluramine was close to dose proportional.

The 13-week repeated dose toxicity in adult rats, the exposure of fenfluramine was close to dose proportional over the dose range from 3.5 to 8 mg/kg/day, except for males from 3.5 to 5 mg/kg/day on Day 89 and for both genders from 8 to 13 mg/kg/day on Day 1, the systemic exposure (AUC(0-t)) was greater than dose proportional. There was some accumulation on Day 89 relative to Day 1, with accumulations ratios ranging from 2.64 to 15.7 for fenfluramine and 1.88 to 3.33 for norfenfluramine.

Plasma protein binding

The in vitro plasma protein binding is around 50% for fenfluramine and norfenfluramine over a concentration of 10 to 100 ng/mL.

Distribution to red blood cells

The in vitro blood-to-plasma ratio of fenfluramine and norfenfluramine was not investigated. Literature data indicate that fenfluramine and norfenfluramine tend to concentrate in the red cells rather than the plasma, to the extent of about 40% greater (Campbell, 1973).

Tissue distribution

The site of action of fenfluramine and norfenfluramine is the brain.

As determined in rats, fenfluramine is widely distributed throughout tissues (Vd=6-8 L/kg) and passes the blood-brain barrier. Fenfluramine and norfenfluramine distribute into brain tissue at concentrations much greater than the concentrations found in plasma, with the brain tissue concentration ranging from 15 to 60-fold that of plasma concentration.

The Applicant calculated a maximal concentration of 2.2 to 2.6 µM for the (+) and (-) enantiomers of fenfluramine and a maximal concentration of 1.4 to 1.7 µM for the (+) and (-) enantiomers norfenfluramine in human brain tissue, based on Cmax values reported in literature for animals and in literature and studies for humans. These calculations, however, did not consider the outcome of other literature that suggests that the (+) enantiomer of fenfluramine is more slowly metabolised than the (-) enantiomer.

Metabolism

The in-vitro metabolism of fenfluramine has been investigated in mice, rats, dogs and humans in vivo. From the metabolites of fenfluramine identified, a metabolic pathway has been proposed in human (Brownsill 1991). Fenfluramine is N-de-ethylated to norfenfluramine which possibly undergoes oxidative deamination to the fenfluramine ketone and C-oxidation to the fenfluramine hydroxyketone and fenfluramine diol. The fenfluramine hydroxyketone was further biotransformed to the trifluoromethylbenzoic acid, with phase II conjugation occurring for both components, the trifluoromethylbenzoic acid to trifluoromethylhippuric acid and the fenfluramine diol to fenfluramine diol glucuronide.

Interspecies comparisons show that there are no metabolites unique to humans. Norfenfluramine was found to be a major metabolite in rats and humans, with rats producing higher levels of norfenfluramine than humans. In addition, the unconjugated diol occurs at a lower fraction in rat plasma than in human plasma. In plasma, the diol metabolite was present at a level equal to 13% of fenfluramine in rats, and 45% of fenfluramine in humans. For this metabolite, the 13-week toxicology study provided a 3-fold margin of exposure for this metabolite relative to human exposure when rats were tested at the NOAEL of 20 mg/kg/day.

Placenta transfer

Both fenfluramine and norfenfluramine cross the placenta in monkeys and presumably, because of the drug's low molecular weight, in humans (Briggs et al 2011).

Transfer to milk

It is not known whether fenfluramine is excreted in human. However its lipophilic properties and low molecular weight probably allow the excretion of fenfluramine into milk. Because fenfluramine is readily absorbed from the gastrointestinal tract and has a long plasma half-life (about 20 hours), the nursing infant could be exposed to a potentially neurotoxic agent during a period of rapid brain development (Briggs et al 2011).

Excretion

Fenfluramine is excreted as parent compound or active metabolite; the remainder is non-active benzoic acid and alcohol derivatives.

In mouse, rat, dog and human, fenfluramine and metabolites are predominantly excreted in urine (>80%) via the kidney, with small amounts found in the faeces. This implies that the enterohepatic circulation of fenfluramine plays a minor role.

Marchant et al. (1992) investigated the metabolite profile in 24-hour urines of mice rats and dogs. Dependent on the species, 11 metabolites eleven in addition to fenfluramine (1-42%); U1 (2-22%), U2 (diol glucuronide, 4-24%), U3 (11-24%), U5 (hippurate, 3-21%), U6 (3-7%), U7 (1-8%) U8 (norfenfluramine, 4-31%), U10 (2-3%) and U11 (hydroxyketone, 2%).

Public information shows that fenfluramine is also excreted in saliva and sweat to a small extent.

2.3.4. Toxicology

Single dose and repeat dose toxicity

Results from non-GLP studies have shown that use of high fenfluramine doses in several animal species result in CNS signs (tremors, convulsions, salivation and mydriasis) and acute death, most likely due to respiratory failure. Lower, chronic doses were usually better tolerated and resulted in fenfluramine pharmacology-related effects, primarily decreased body weight gain and food consumption and decreased activity, which was shown consistently across species at all dose levels. Overall, clinical signs are quite similar between different animal species and between animals and humans.

Toxicity testing in young adults

The Applicant has conducted a GLP-compliant 13-week repeat-dose toxicity study (no. 8001991), administering 3.5 to 20 mg/kg fenfluramine per day via oral gavage to 6-week-old Sprague-Dawley rats. All observed fenfluramine-related effects (clinical signs, decreased body weight and food consumption, changes in blood parameters and olfactory epithelium) were considered pharmacological driven and most of these are known clinical effects in humans. No mortality or other unexpected events occurred in this toxicity study. No changes in the cardiac valves were observed. Macroscopic and microscopic changes observed in several tissues were sufficiently explained (i.e. mostly fenfluramine-related, but non-adverse effects) or did not appear to be associated with (irreversible) inflammation/degeneration.

Based on the study findings, the NOAEL is considered to be 20 mg/kg/day. Toxicokinetic evaluation shows that at this dose, the safety margin between animals and humans is at least 10-fold for fenfluramine and 23-fold for the main metabolite norfenfluramine.

Toxicity testing in juveniles

Since most available data was obtained in adults, the Applicant conducted two juvenile toxicity studies to be able to bridge non-clinical data to paediatric patients.

A GLP-compliant dose-range finding study (no. 9000468) was performed in juvenile Sprague-Dawley rats. They were administered 12 to 100/50 mg/kg fenfluramine per day (once or twice daily) via oral gavage starting at PND7.

In addition, a 10-week pivotal toxicity GLP study in juvenile Sprague Dawley rats (no. 9000406) was conducted, orally administering them 3.5 to 20 mg/kg fenfluramine per day, starting at PND7, including toxicokinetic investigations. The study was extended with a 4-week recovery period to determine reversibility of the findings.

In both studies, CNS-related clinical signs (e.g. salivation, tremors, incoordination), dehydration, reduced body weight and food consumption were present and dose-dependent in severity. Unscheduled mortality was related to poor condition, especially in the pre-weaning phase, but no concomitant inflammatory or degenerative lesions were found in any of the tissues analysed.

However, signs of potential fenfluramine toxicity were noted in 2 males in the 9 mg/kg/day group (no. 3022 with salivation, no. 3008 with decreased activity and muscle tone, tremors, dehydration). One animal was found dead, the other animal had bilateral ventricle dilatation at necropsy. In addition, 2 males in the 3.5 mg/kg/day group were euthanised at day 17 because of domed skulls, which appeared to be caused by bilateral ventricle dilatation (i.e. hydrocephalus) at necropsy. Since serotonin may be involved in regulation of

cerebrospinal fluid (CSF) production and fenfluramine impacts the serotonin pathway, this was further discussed. It was concluded that, even if both animals developed hydrocephalus, this may be spontaneous/congenital (based on the publications on spontaneous ventriculomegaly) and likely not directly related to fenfluramine.

Reproductive and developmental toxicity

The Applicant submitted six GLP-compliant Developmental and Reproductive Toxicology (DART) studies in two animal species. The overall conclusion from the studies is that all effects on fertility and on the offspring observed in the DART studies were related to maternal/paternal toxicity, which is in agreement with the sparse reproductive toxicity data from Pondimin and most pre-clinical literature studies. The DART studies did not show fenfluramine-related clinically relevant effects on the reproductive parameters of males. However, effects on female fertility may occur at clinically relevant exposures. It is generally agreed that maternal (F0) toxicity is most likely responsible for effects seen in the offspring and that translation of data to the clinic will therefore be difficult. However, in agreement with ICH S5 (R3), a direct relation between fenfluramine and the occurrence of malformations in rat offspring (F1) at 40 mg/kg/day cannot be excluded, considering that (nor)fenfluramine concentrations in foetuses were higher than in mothers (both rats and rabbits). Nevertheless, the fenfluramine dose in rats at which malformations were observed related to AUC exposures around 28-fold the human AUC at the highest clinical dose of 0.8 mg/kg/day.

Though the amount of data on use of fenfluramine or benfluorex (i.e. fenfluramine analogue) during human pregnancies is limited, these data do not indicate a fenfluramine-related safety concern for embryo-foetal development in humans upon use according to the indicated regimen.

Excipients, impurities and degradation product

Fintepla contains several excipients, including methyl- and ethylparabens. None of the excipients are novel and the amount of individual excipients at the maximum dose of 30 mg/kg are well below the acceptable daily intake of these compounds.

The proposed manufacturing process resulted in batches which contained the impurity 4-fenfluramine at lower levels than the juvenile toxicity batches. These batches have been used in the toxicology studies and the clinical trials. The assessment of the genotoxic potential of 4-fenfluramine was conducted according to ICH guideline M7 on genotoxic impurities and showed no genotoxic potential. No additional impurity studies are warranted.

Genotoxicity

Fenfluramine hydrochloride was tested in GLP-compliant genotoxicity studies in accordance with ICH Guideline S2 (R1).

Bacterial reverse mutation assays were conducted on the active moiety fenfluramine. The studies were performed to GLP with use of adequate positive and negative controls with and without rat S9 activation. Rat S9 activation is considered adequate, since the metabolism seemed similar between species and no unique human metabolite was identified. The study was performed with five strains of salmonella with a negative outcome, which is considered acceptable.

A GLP *in vivo* study (no. 9800312) was conducted to evaluate the genotoxicity of fenfluramine when given by oral gavage to Sprague-Dawley rats using the bone marrow micronucleus test and the Comet assay. Dose

levels for the main study was determined by an initial dose-range finding study to 17.5, 3 and 70 mg/kg, based on observed effects in the high dose groups.

In the main study, animals displayed clinical effects in line with effects observed in the other repeat dose studies, such as salivation, red staining of the fur at the muzzle, right pinnae, lower jaw, right periorbital and/or abdominal areas, yellow staining of the fur at urogenital area, wet fur at the lower jaw, muzzle, forelimbs, axillary, ventral cervical, ventral thoracic and/or abdominal areas, and/or red skin at the nasal mucosa (one animal). No mortalities occurred.

In the micronucleus test, the study was interpreted as negative for increase in frequency of micronucleated immature erythrocytes, indicating that fenfluramine did not induce chromosome damage. In addition, there were no substantial decreases in the proportion of immature erythrocytes, indicating that fenfluramine was non-toxic to the bone marrow at the dose levels tested.

In the Comet assay, animals treated with fenfluramine hydrochloride did not show any substantial increases in the tail DNA percentage in the liver tissue. Thus, there was no evidence of an increase in DNA damage in this assay.

Carcinogenicity

No GLP-compliant carcinogenicity studies have been performed on fenfluramine.

The CHMP noted that, in line with the BfArM Scientific Advice Meeting of 26 June 2013 and considering that no clinically relevant genotoxic potential is identified by fenfluramine, the Applicant proposed to provide two long-term carcinogenicity studies (a 2-year GLP-compliant carcinogenicity study in rats and a 26-week GLP-compliant carcinogenicity study in mice) as a post-marketing commitment.

Local Tolerance

No local tolerance studies have been conducted. Considering that no indication of local tolerance was found in other repeat-dose studies and as there is clinical experience in the adult and paediatric patient population, this is accepted.

Other toxicity studies

No studies for antigenicity, immunogenicity have been conducted. In agreement with the argumentation of the Applicant, this is accepted.

No new studies were conducted to investigate dependency. This was further discussed, and a literature search provided several investigations concerning self-administration, conditioned place preference and drug discrimination studies. In general toxicity studies, fenfluramine did not induce behavioural stereotypies like those produced by amphetamine, nor did it induce self-administration. Fenfluramine did however share discriminative stimulus properties with drugs that elevate serotonin levels, including MDMA (Ecstacy) and other serotonergic drugs, which corresponds with the pharmacological action of fenfluramine. However it did not produce the stimulant-like effects of MDMA. It was accepted the property shared between fenfluramine and MDMA is likely dysphoria, which is also consistent with the observations of no self-administration in tests and a general aversive reaction of the test animals in the studies. From these data, it was agreed that fenfluramine did not show potential for abuse or dependency.

2.3.5. Ecotoxicity/environmental risk assessment

The Applicant submitted a confirmatory experimental GLP study using the shake flask method (OECD 107) for determining log Kow, with the experimental value of 3.4 at pH 7. This value is lower than the cut-off value of 4.5. The test substance is considered not potentially PBT. Further PBT assessment is not necessary.

Phase I

The Applicant refined the F_{pen} by using the medicinal orphan drug designation for Dravet syndrome, with the prevalence for the EU region of 0.5 in 10,000 people, as adopted by the Committee for Orphan Medicinal Products (COMP). The refined Fpen was calculated to be 0.00005 for the EU region. The Applicant calculated the PEC_{sw}, resulting in a PEC_{sw} of 0.00066 µg/L.

The calculation of the maximum daily dose and the refinement of F_{pen} were considered acceptable. The refined $PEC_{surfacewater}$ is considered acceptable. PEC_{sw} is 0.00066 µg/L, which is below the action limit of 0.01 µg/L. Therefore, a risk to the environment is not anticipated based on the prescribed use of Fintepla. A further assessment is not deemed necessary

Summary of main study results

Substance (INN/Invented Name): Fenfluramine			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Literature	3.36	Not PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.36	not B
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00066	µg/L	Below trigger value

Considering the above data, fenfluramine is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The information on the fenfluramine primary pharmacodynamic activity of at relevant receptors in the brain is still limited.

The anticonvulsant activity of fenfluramine appears to be associated with serotonin release and agonistic activity at the serotonin receptors 5-HT2C, 5-HT1D, 5-HT1A and 5-HT2A. It is however unclear to which extent the agonistic activity at the receptors or the activation of the receptors via fenfluramine-mediated release of serotonin contribute to the activity.

The 5-HT2B receptor seems not to be involved in the mode of action regarding the anticonvulsive activity of fenfluramine, however it has been implicated as having a possible role in the valvular heart disease associated with the use of fenfluramine.

The potential role of the σ-1 receptor in the mode of action of fenfluramine regarding its anticonvulsant activity remains uncertain.

Fenfluramine exerts secondary pharmacological effects through monoaminergic mechanisms. Fenfluramine acts on the hypothalamic-pituitary axis, including increase in plasma prolactin and cortisol. Even though these observations were done at higher doses than the maximum daily dose for DS patients, an increase in cortisol induced by fenfluramine cannot be ruled out. However, it is also recognised that as DS patients are already in a physiologically stressful state due to repeated seizures and that fenfluramine has the potential to reduce seizures, this concern appears of limited clinical relevance. The impact of plasma prolactin increase has been further investigated and discussed in the Clinical sections.

The non-clinical data suggest that fenfluramine can affect sleep patterns. A potential effect of fenfluramine on sleep disturbances in Dravet patients cannot be excluded.

There was no data on hERG channel inhibition and the animal cardiovascular studies pre-dated the GLP requirements. A QTc clinical study has therefore been conducted and showed no QTc prolongation.

The clinical pharmacodynamic drug interaction data, including interaction with serotonergic drugs and potential risk of serotonin syndrome, are described in the clinical pharmacology sections.

Pharmacokinetics

Data from published literature showed that fenfluramine is rapidly absorbed in the gastrointestinal tract in mice, rats and dogs.

The (+) and (-) enantiomers of fenfluramine have different pharmacological properties and there is some indication that the pharmacokinetics of fenfluramine and norfenfluramine are different.

Comparison of the plasma concentrations time curve of fenfluramine showed a slower rate of elimination in man than in animals. The T½ of the (+) enantiomer ranged from about 2.5 hr in rat and dog, to about 4.4 hr in mouse and averaged 18 hr in man. The T½ of norfenfluramine was longer than that of fenfluramine in all of these species.

The site of action of fenfluramine and norfenfluramine is the brain. Although, the (+) enantiomer of fenfluramine is more slowly metabolised than the (-) enantiomer, there is sufficient evidence to assume that the concentration of the racemic mixture in the brain is pharmacologically effective for the release of serotonin.

In general, metabolism was adequately described, and no unique human metabolite was identified.

Toxicology

The toxicology package is in line with the requirements under the relevant guidelines and due consideration to the proposed Fintepla posology was taken.

Use of high fenfluramine doses in single and repeat dose studies in several animal species resulted in CNS signs and acute death, most likely due to respiratory failure. Lower, chronic doses were usually better

tolerated and resulted in fenfluramine pharmacology-related effects, primarily decreased body weight gain and food consumption and decreased activity, which was shown consistently across species at all dose levels.

Minimal cytoplasmic vacuolation and eosinophilic globules within the olfactory epithelium have been observed as a dose-response related effect at all dose levels in both the 13-week repeat dose GLP study in rats and in the 10-week GLP study in juvenile rats. It was not possible to conclude on the clinical relevance and the findings are not considered of toxicological concern.

Changes in skin and fur such as red staining was a common observation in the repeat-dose study, the in vivo genotoxicity study and the juvenile toxicity studies. A possible explanation of red staining is the secretion of porphyrins from the Harderian gland. Although this secretion is species-specific (i.e. not occurring in humans), it may be a sign of stress or illness. Fenfluramine is known to increase the stress-related hormone cortisol. However stress-related signs are also commonly observed in toxicology studies, due to frequent handling of the animals and sampling.

Few animals dosed with fenfluramine $\geq$ 5.0 mg/kg/day (repeat-dose study) or $\geq$ 3.5 mg/kg/day (pivotal juvenile toxicity study) showed changes in the retina, such as focal atrophy or folding. These findings were still present in the recovery period. The ocular changes in rats are however considered background findings and ocular abnormalities in humans using fenfluramine for obesity reasons are rare. Therefore, the retinal changes observed in rats do not indicate a clinical safety concern for fenfluramine in the DS indication.

Overall, clinical signs are similar between different animal species and between animals and humans. Findings in juvenile animals did overall not point toward greater susceptibility to fenfluramine-related effects than adult animals.

None of the studies indicated a genotoxic potential of fenfluramine.

Non-GLP studies did not show any carcinogenic findings. However, in order to confirm this and in line with the BfArM advice, two long-term carcinogenicity studies in two different species will be provided as a post-marketing commitment. Considering that there is no clinically relevant genotoxic potential and no major concern regarding the carcinogenic potential, this is acceptable.

Fenfluramine was shown to have effects on female fertility in a FEED study, and embryo-foetal toxicity was observed in rats and rabbits, however at dose levels that also resulted in maternal toxicity. Taking the patient population (DS patients) and the lack of clinical findings into account, the benefits for treatment with fenfluramine of this population is considered to outweigh the risks of reproductive toxicity. These findings are adequately reflected in section 5.3 and 4.6 of the SmPC.

From the available data, it was agreed that fenfluramine did not show potential for abuse or dependency.

Given the worldwide withdrawal of fenfluramine for cardiac valvular abnormalities in the late 90s, potential cardiotoxicity was specifically considered. An overview of primarily in vivo animal data of potential fenfluramine-related valvular heart disease was provided. Although no valvular heart disease was observed in the animal toxicology studies, in vitro receptor binding data suggest that especially (+) norfenfluramine has the potential to induce valvular heart disease (as the pEC50 is slightly higher than the EC50 for pergolide, associated with valvular heart disease). The lack of findings in the non-clinical studies could be due to the limited duration of the studies or the lack of a relevant/predictive animal model. The occurrence of valvular heart disease in some animal models was described in public literature in mice and rats, which showed an effect on thickening of the mitral and/or aortic valve following administration of (+) fenfluramine or (+) norfenfluramine. The mode of action was determined via 5-HT2B receptor agonism and further mobilisation of BM-derived CD34+CD31+ cells by 5-HT2B receptor stimulation as the initial steps of mitral

valve remodelling. Monitoring at a clinical level is therefore warranted. It is noted that investigations of mitral and aortic valves will be performed in the 2-year rat carcinogenicity study to be provided as a post-marketing commitment. The valvular heart disease is an identified risk adequately described in the Product Information, and managed through a number of risk management measures.

2.3.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, the application is considered approvable.

However, the applicant should submit the following post-authorisation non-clinical studies:

- a 2-year GLP-compliant carcinogenicity study in rats

- a 26-week GLP-compliant carcinogenicity study in mice

2.4. Clinical aspects

2.4.1. Introduction

GCP

A statement that clinical trials were carried out in accordance with GCP requirements was included in the dossier. However, one of the pivotal studies (study 1) was in fact a combined analysis of patients included in other studies, and the details of the exact conduct of the study were very scarce. A protocol for this study was not available and a clear description of data collection and analyses were lacking.

Consequently, the CHMP asked for an inspection to be carried out on the conduct of the Study 1, in accordance with Article 57 of Regulation (EC) No. 726/2004 and Article 15 of Directive 2001/20/EC. The scope of the inspection was to verify compliance with applicable regulations and GCP for selected efficacy and safety data reported in the Marketing Authorisation Application for a sample of patients.

At the inspection of one site, there were one (collective) critical, 20 (collective) major and 7 minor deviations. At the inspection of another site, there were no critical, 18 major and 6 minor deviations. At the inspection of the sponsor site, there were nine (collective) critical, 29 (collective) major and 14 minor deviations.

The impact of these deviations, including the impact on the reliability of trial data, the assessment and the benefit-risk evaluation of Fintepla, have thereafter been taken into consideration during the evaluation of the dossier.

The applicant 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

Study Number	Phase	Study Status	Description	Dose mg/kg/day*	Planned Number of Subjects	Duration of Exposure
Study 1[a]	3	Complete	Efficacy and Safety	Placebo, 0.2, 0.8	120	16 weeks
ZX008-1504 Cohort 2	3	Complete	Cohort 2: Efficacy and Safety	Placebo, 0.5	80	17 weeks
ZX008-1503	3	Ongoing	Open-label extension (for subjects from Study 1, Study 2[b], and Study 1504)	0.2, 0.4, 0.5, 0.6, 0.8[c]	340	3 years
Additional Clinical Studies						
ZX008-1504 Cohort 1	1	Complete	Cohort 1: PK/Safety	Cohort 1: 0.2, 0.4	Cohort 1: 20	Cohort 1: 2 to 24 weeks
ZX008-1505 Part 1	1	Complete	DDI-PK (ZX008 + STP/CLB/VPA)	0.8	26	7 days
Part 2	1	Complete	Food Effect	0.8	14	4 days
ZX008-1603	1	Complete	TQT Safety	Placebo, 15, 60 mg twice daily (BID)	180	1 to 8 days
ZX008-1604	1	Complete	DDI-PK (ZX008 + CBD)	0.4 mg/kg (2 doses only)	24	1 to 28 days
Study 2[b]	3	Ongoing	Safety and Efficacy	Placebo, 0.2, 0.8	120	16 weeks

Abbreviations: CBD=cannabidiol; CLB=clobazam; DDI-PK-drug-drug interaction/pharmacokinetic; PK=pharmacokinetics; STP=stiripentol; TQT=Thorough QT Interval Prolongation study; VPA=valproate

* unless indicated

[a] Study 1 represents the prospective merged analysis of the first 119 consecutive subjects enrolled 2 identical studies, ZX008-1501 conducted in North America and ZX008-1502 conducted in Europe, Australia.

[b] Study 2 includes the next 120 subjects from ZX008-1501 and ZX008-1502 randomized after database lock for Study 1, including subjects from Japan. Efficacy data for Study 2 are not included in this ISE as the study is still ongoing and remains blinded.

[c] Dosing in Study 1503 was flexible, ranging from 0.2 mg/kg/day to 0.8 mg/kg/day given as 2 daily doses up to a maximum of 30 mg/day, or 0.2 mg/kg/day to 0.5 mg/kg/day given as 2 daily doses up to a maximum of 20 mg/day when STP was present as a concomitant antiepileptic drug.

2.4.2. Pharmacokinetics

Fenfluramine is a racemic compound containing dexfenfluramine (S enantiomer or (+)) and levofenfluramine (R enantiomer or (-)). The clinical doses of fenfluramine hydrochloride are between 0.2 to 0.8 mg/kg/day administered orally in 2 divided doses (BID), with a maximum total daily dose of 30 mg, regardless of weight. For patients concomitantly taking stiripentol (with clobazam and/or valproate), a modification in the maximum daily dose of fenfluramine hydrochloride to 0.5 mg/kg/day, not to exceed a total daily dose of 20 mg, is recommended.

Three phase 1 clinical studies and the phase 3 Study 1 were the primary contributors of pharmacokinetic data in the development programme of fenfluramine for the treatment of Dravet Syndrome. Characterization was supplemented with data from *in vitro* studies and literature.

Absorption

For fenfluramine, the Cmax occurs ~3 h following a single oral dose and is 28.6 ng/mL following a dose of 0.4 mg/kg, and 59.3 ng/mL following a dose of 0.8 mg/kg fenfluramine HCl. The AUCinf is 673 ng × h/mL and 1660 ng × h/mL following 0.4 mg/kg and 0.8 mg/kg, respectively. For norfenfluramine, the Cmax occurs ~12 h following a single oral dose and is 11.7 ng/mL and 16.1 ng/mL following a dose of 0.4 mg/kg or 0.8 mg/kg, respectively. The AUCinf is 798 ng × h/mL and ~800 ng × h/mL following 0.4 mg/kg and 0.8 mg/kg, respectively. The metabolite-parent ratio is 0.26 to 0.41 for the Cmax and 0.5 to 1.2 for the AUCinf and decreases with increasing dose; the AUCinf of norfenfluramine is similar following a 0.4 mg/kg dose compared to a 0.8 mg/kg dose. The absolute bioavailability of fenfluramine in solution is approximately 75-83% based on literature data (no absolute oral bioavailability study was conducted. Fenfluramine is highly soluble and highly permeable. Food does not affect the Cmax, tmax or AUC of fenfluramine or norfenfluramine.

Distribution

The *in vitro* plasma protein binding of fenfluramine and norfenfluramine is ~50% using equilibrium dialysis. The *in vitro* blood-to-plasma ratio of fenfluramine and norfenfluramine was not investigated. Literature data indicates that fenfluramine and norfenfluramine tend to concentrate in the red cells rather than the plasma, to the extent of about 40% greater. After absorption fenfluramine is widely distributed throughout the body, with high concentrations in the brain, kidney, liver, bile, and urine (post-mortem data in a 13-year old boy who ingested 2000 mg fenfluramine HCl). The geometric mean (CV%) volume of distribution (Vz/F) of fenfluramine is 11.9 (16.5%) L/kg following oral administration of fenfluramine HCl in healthy subjects.

Elimination

Most of an orally administered, radiolabelled dose of fenfluramine is recovered in urine (>90%); little radioactivity is excreted in faeces. Absorbed fenfluramine is mainly excreted as metabolite. The geometric mean (CV%) clearance (CL/F) of fenfluramine is 6.9 (29%) L/h and the half-life is 20 hours following oral administration of fenfluramine HCl healthy subjects. The elimination half-life of norfenfluramine is ~30 h.

Dose proportionality and time dependencies

Dose-proportionality: Based on data from the studies 1604 and 1505, Cmax and AUCinf of fenfluramine appear dose proportional over the 0.4 to 0.8 mg/kg fenfluramine HCl dose range. However, the Cmax and AUCinf of norfenfluramine are not dose-proportional over the 0.4 to 0.8 mg/kg dose range. The AUCinf increase was 0.5-fold for the 0.8 mg/kg fenfluramine HCl dose compared to the 0.4 mg/kg dose. The Cmax increase was 0.7-fold for the 0.8 mg/kg dose compared to the 0.4 mg/kg dose.

Time dependency: The t½ of fenfluramine and norfenfluramine indicates that approximately 94% of steady-state would be reached in approximately 4 days for fenfluramine and 5 days for norfenfluramine (4 half-lives). The time to steady-state was supported by data from Study 1603, in which the increase in the

trough level of fenfluramine between Day 5 and Day 7 was approximately 6% (n=59) and 11% (n=60) for doses of 15 mg BID and 60 mg BID, respectively. Based on the PK data from studies 1505 and 1603, a Cmax accumulation ratio of 3.8- to 4.1-fold for fenfluramine may be expected and a Cmax accumulation ratio of 6.2- to 6.4-fold for norfenfluramine.

Inter- and intra-subject variability: No information was provided on the intra-individual variability, because individual PK profiles were only evaluated on single occasions in the studies. The inter-individual variability in healthy volunteers is 27-30% for fenfluramine and norfenfluramine at a dose in mg/kg without concomitant medication. The inter individual variability for fenfluramine and norfenfluramine increased to 34-43% in the presence of stiripentol, clobazam and valproic acid and decreases to 17-27% in the presence of cannabidiol. Greater variability was observed in patients with Dravet syndrome who participated in the Phase 3 trials. The variability ranged from 33% to 85% in fenfluramine PK parameters and from 43 to 56% in norfenfluramine PK parameters.

Pharmacokinetics in target population: Study 1501 and Study 1502 investigated fenfluramine in children and adolescents with DS. The study results were integrated in Study 1. In paediatric patients who received fenfluramine HCl 0.8 mg/kg/day, maximum 30 mg/day in divided doses twice daily, the geometric mean steady-state fenfluramine (coefficient of variation) for Cmax was 68.6 (41%) ng/mL and AUC0-24h was 1400 (44%) ng × h/mL. Norfenfluramine Cmax,ss was 37.8 (50%) ng/mL and AUCss,0-24 was 872 ng × h/mL. Fenfluramine has a time to maximum plasma concentration (tmax) of 3 hours at steady state. Norfenfluramine has a tmax of 4 to 4.5 hours. At a dose of 30 mg (maximum administered dose), the exposure appears higher in children compared to adults.

Special populations

Impaired renal function: Renal elimination is the predominant route of elimination of fenfluramine-related products, with more than 90% of the administered dose eliminated in the urine as parent or metabolites. There are no human clinical data on the effect of renal impairment on the PK of fenfluramine and norfenfluramine.

Impaired hepatic function: No studies on the effect of hepatic impairment on the PK of fenfluramine in adults or children were found. With hepatic metabolism of fenfluramine, plasma drug concentrations may be affected in patients with significant hepatic impairment. Subjects with moderate or severe hepatic impairment were excluded from the phase 3 clinical trials.

Gender: The PK of fenfluramine and norfenfluramine were consistent between males and females.

Race: The evaluation was limited by the small sample size of non-white subjects that no conclusion on the effect of race on the PK can be made. The genetic polymorphs of the enzymes that metabolize fenfluramine are similar across races, only their frequency differs. Thus, although the mean exposure may differ slightly depending on race, the range of exposure would be expected to be similar.

Weight/Body Mass Index: The results of the PopPK analysis indicate that fenfluramine and norfenfluramine PK parameters are related to patient body weight. However, as the dose is based on body weight, exposure is expected to be comparable in patients across a broad range of ages. Examination of the post-hoc PK parameter and exposure estimates in relationship to BMI, indicated that the drug clearance and PK exposure of fenfluramine and norfenfluramine (Cmax and AUC) increase with increasing BMI.

Elderly: Fintepla is indicated in children with Dravet syndrome aged 2 to older. No data in geriatric patients have been submitted.

Children: The exposure (Cmax and AUC) to fenfluramine and norfenfluramine increases with age for the 0.2 mg/kg dosing group. The exposure (Cmax and AUC) to fenfluramine and norfenfluramine appears independent of age for the 0.8 mg/kg dosing group.

Pregnancy and nursing: No information is currently available from the literature about fenfluramine in pregnant women. It is not known whether fenfluramine and/or norfenfluramine are excreted in human milk, although (+) fenfluramine is transferred into the milk of lactating rats. The use of fenfluramine during pregnancy or lactation is not recommended.

Pharmacokinetic interaction studies

Fenfluramine as victim: *In vitro*, fenfluramine is metabolised by CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4; with the involvement of CYP2C8 and 2C9 only at higher concentrations. Norfenfluramine is metabolised in vitro by CYP2A6, 2B6, 2C8, 2D6, 2E1, and 3A4. The contribution of the individual enzymes to the biotransformation of fenfluramine and norfenfluramine is unknown. Furthermore, the involvement of other enzymes (e.g. UGTs) in the metabolism of norfenfluramine is unknown. If norfenfluramine is glucuronidated to a significant extent, UGT inhibitors may lead to an increased exposure to norfenfluramine. Fenfluramine and norfenfluramine were not substrates of drug transporters.

Clinical DDI studies were performed with the combination of clobazam, valproic acid and stiripentol and with cannabidiol. Stiripentol is an inhibitor of CYP1A2, 2B6, 2C9, 2C19, 2D6 and 3A4. Clobazam is an inhibitor of CYP2D6. Valproic acid is an inhibitor of UGTs. Cannabidiol is an inhibitor of CYP1A2, 2B6, 2C9, 2D6, and 3A4. No clinical DDI studies were performed specifically investigating the individual DDI with clobazam, valproic acid and stiripentol. Concomitant administration of fenfluramine with stiripentol, clobazam and valproic acid compared to concomitant administration of fenfluramine with clobazam and valproic acid resulted in an increase for fenfluramine of 1.4-fold in AUC and 1.2-fold in Cmax and a decrease for norfenfluramine of 1.6-fold in AUC and 1.7-fold in Cmax. When cannabidiol was concomitantly administered with fenfluramine, the Cmax and AUC of fenfluramine increased 1.1-fold and 1.4-fold. In contrast, the Cmax and AUC of norfenfluramine decreased 1.4-fold and 1.5-fold. No dose adjustments were recommended with valproate, clobazam or cannabidiol. A fenfluramine HCl reduced dose of 0.4 mg/kg/day, with a maximum of 17 mg/day is recommended for patients taking concomitant stiripentol. If fenfluramine, cannabidiol and stiripentol were to be administered concomitantly, no further dose adjustment is required.

Given the lack of supportive clinical evaluation of induction of CYP1A2 or CYP2B6 and impact on fenfluramine PK, caution should be exercised when fenfluramine is co-administered with drugs that are known to induce CYP1A2, CYP2B6 or CYP3A4.

Fenfluramine as perpetrator: Based on *in vitro* data, fenfluramine is an inhibitor of CYP2D6. There have been reports of clinical drug-drug interactions with the concomitant administration of fenfluramine and CYP2D6 substrates such as tricyclic antidepressants (Fogelson 1997; Price 1990). Steady-state desipramine concentrations increased approximately 2-fold with concomitant administration of fenfluramine. of CYP2D6.

At clinically relevant systemic steady state concentrations, norfenfluramine is an inhibitor of MATE1.

Furthermore, fenfluramine may be an inducer of CYP3A4 at maximal intestinal concentrations. Based on *in vitro* data, it cannot be excluded that fenfluramine is an inducer of CYP2B6 at clinically relevant portal vein concentrations.

2.4.3. Pharmacodynamics

Fenfluramine pharmacodynamics (PD) were primarily studied in the open-label, proof-of concept study ZXIIS2015-004 as well as the dedicated QTc study AX008-1603. Further, the phase 1 studies contributed to exploratory PD data.

The mechanism of action of fenfluramine in the prevention of seizures in Dravet Syndrome has only been partially clarified. It appears that through stimulation of the release of serotonin, fenfluramine is able to have an agonistic effect on various 5-HT receptors resulting in overall 5-HT stimulation.

Fenfluramine may also have indirect inhibitory effect on NMDA receptors, possibly through interaction with both serotonin and sigma-1-receptors, but the pathology of Dravet is still incomplete and the mechanism of action of fenfluramine is still not fully understood.

Primary pharmacology: 14 study participants contributed to interim report of Study ZXIIS2015-004. The effective doses used in this cohort were administered as fixed doses between 5 and 40 mg/day, most commonly 5 or 10 mg BID (10-20mg daily). These doses corresponded to approximately 0.8 to 1.0 mg/kg/day for young children, and 0.1 to 0.3 mg/kg/day for the older patients. The median (min, max) number of major motor seizures per month during Baseline was 2.5 (0.4, 38.4). During treatment with fenfluramine, the median (min, max) monthly frequency of motor seizures was 2.0 (0.2, 9.1), a median reduction from baseline of -76.3%. 13/14 Patients achieved a ≥ 50% reduction from baseline in monthly major motor seizure frequency. A treatment response (≥ 75%) was achieved in 10/14 patients and 2 (14.3%) patients were seizure free for the duration of time in the study at the time of this interim report (1 to 12 months).

From this open-label treatment experience, the Applicant derived the 0.2 and 0.8 mg/kg/day doses used in the phase 3 clinical program. Since none of the 14 patients appeared to have reached the maximum dose of 0.8 mg/kg/day, the study results at interim data cut-off appeared to provide inadequate support for the dose recommendation carried forward in phase 3 studies. The MAH clarified that a maximum dose of 30 mg/day was selected to ensure a lower exposure than the exposure expected in treatment of obesity where cardiac toxicity led to withdrawal of the product. The maximum recommended dose in the SmPC for patients who are not taking stiripentol is 0.35 mg/kg twice daily. The rational for this dose is not clear but it is within the dosing range used in study ZXIIS2015-004 where fenfluramine was dosed between 0.1 and 1.0 mg/kg/day. The majority of patients experienced some degree of improvement.

Secondary pharmacology: Fenfluramine was originally approved and widely marketed as an appetite suppressant for the treatment of obesity in adults. The anorexic effect of fenfluramine and norfenfluramine is mediated through the 5-HT2C receptor (Vickers 2001). In the phase 3, placebo-controlled studies, more subjects treated with ZX008 compared with placebo-treated subjects experienced AEs of decreased appetite (42/122 [34.4%] vs 7/84 [8.3%]) and weight loss (11/122 [9.0%] vs 1/84 [1.2%]).

A dedicated QTc study was conducted (study ZX008-1603). The doses of fenfluramine tested produced plasma levels of fenfluramine relevant for comparison to clinical conditions. The study results demonstrate that fenfluramine did not exert QTc prolonging effects following neither therapeutic nor supratherapeutic dosing.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Three phase 1 clinical studies and the phase 3 Study 1 were the primary contributors of pharmacokinetic data in the development programme of fenfluramine for the treatment of Dravet Syndrome. Characterization was supplemented with data from *in vitro* studies and literature. A Pop PK model and a PBPK model were developed but they were not considered suitable to predict the exposure of fenfluramine and norfenfluramine. The provided PK information is too limited to allow a full evaluation in particular in terms of differential exposure of metabolites and enantiomers. There are indications in literature that the pharmacokinetics are different for the R and S enantiomers of fenfluramine and norfenfluramine and the R-enantiomer appears to be more slowly metabolised than the S-enantiomer. It cannot be excluded that R-norfenfluramine may interact with 5-HT2B receptors at clinically relevant concentrations.

The ADME parameters were established based on study data and literature. Fenfluramine is highly soluble and highly permeable with an absolute bioavailability above 70%. Fenfluramine pharmacokinetics is independent of food. The *in vitro* plasma protein binding of fenfluramine and norfenfluramine is ~50%. The volume of distribution is 11.9 L/kg.

A number of CYP systems contribute to the metabolism of fenfluramine. Fenfluramine is metabolised in vitro by CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4; with the involvement of CYP2C8 and 2C9 only at higher concentrations. Norfenfluramine is metabolised by CYP2A6, 2B6, 2C8, 2D6, 2E1, and 3A4 *in vitro*. No full biotransformation profile has been determined in plasma and urine. Primarily, *in vivo* metabolism is carried out via CYP1A2, CYP2B6 and CYP2D9. The first step of metabolism involves formation of the active metabolite, norfenfluramine. Further metabolism yields 4 inactive metabolites. The primary route of excretion is via urine. Clearance is an estimated 6.9 L/h and T½ is an estimated 20 hours in healthy subjects. Although fenfluramine undergoes hepatic metabolism, consequences of possible genetic polymorphism do not appear clinically relevant. This may in theory be due to the multiple possible pathways of metabolism. Literature data indicates that norfenfluramine may be glucuronidated to a significant extent.

Dose-proportionality across the therapeutic range of fenfluramine is overall present for fenfluramine after a single dose. For norfenfluramine exposure increased less than dose-proportionally across the 0.4 to 0.8 mg/kg dose range. Based on data from studies 1505 and 1603 accumulation was observed. The accumulation ratios for fenfluramine and norfenfluramine were 3.7 and 6.4 (Cmax) and 2.6 and 3.7 (AUC0-24), respectively.

The phase 1 studies overall demonstrated low inter-subject variability. The variability in Dravet patients were up to 85% in the phase 3 trials. In paediatric patients who received fenfluramin HCl 0.8 mg/kg/day, maximum 30 mg/day in divided doses twice daily, the geometric mean steady-state fenfluramine (coefficient of variation) for Cmax was 68.6 (41%) ng/mL with a Tmax of 3 hours and AUC0-24h was 1400 (44%) ng × h/mL.

No clinical studies were conducted in patients with renal or hepatic impairment. Renal and hepatic impairments are categorised as missing information in the RMP and the relevant statements are included in the SmPC. In order to characterise the effect of renal and hepatic impairments on the pharmacokinetic of fenfluramine, the Applicant will provide a PK study in subjects with renal impairment and a PK study in subjects with hepatic impairments post-marketing (category 3 studies, as detailed in the RMP).

Pharmacokinetic parameters of fenfluramine depend on bodyweight. Therefore, a weight-based dosing is recommended, and exposure is expected to be comparable across a broad age range. Fenfluramine

pharmacokinetics seem independent of gender, race and genotype. Fenfluramine PK was not studied in elderly for the claimed indication. Fenfluramine is not recommended in pregnant or lactating patients, primarily due to lack of data.

Clinical DDI studies were performed with the combination of clobazam, valproic acid and stiripentol and with cannabidiol. No dose adjustments were recommended with valproate, clobazam or cannabidiol. A reduced fenfluramine HCl dose of 0.4 mg/kg/day, with a maximum of 17 mg/day is recommended for patients taking concomitant stiripentol. If fenfluramine, cannabidiol and stiripentol were to be administered concomitantly, no further dose adjustment is required.

Fenfluramine and norfenfluramine were not substrates of drug transporters. If norfenfluramine is glucuronidated significantly, concomitant UGT inhibitors may lead to increased exposure of norfenfluramine.

Caution should be exercised when fenfluramine is co-administered with drugs that are known to induce CYP1A2, CYP2B6 or CYP3A4. In order to complete the available data and further investigate if fenfluramine is a clinically relevant inducer, the Applicant committed to provide a clinical DDI study (CYP2B6 at clinically relevant portal vein concentrations and CYP3A4 at maximal intestinal concentrations) and provide it as a post-authorisation measure. The relevant information is appropriately reflected in section 4.5 of the SmPC.

At clinically relevant systemic steady state concentrations, *in vitro* data indicated fenfluramine is an inhibitor of CYP2D6 and norfenfluramine of MATE1. In order to complete the available data and further investigate the clinical relevance of the effect, the Applicant commits to provide a clinical DDI study of norfenfluramine as a clinically relevant inhibitor of MATE1 and provide it as a post-authorisation measure. The relevant information is appropriately reflected in section 4.5 of the SmPC.

Pharmacodynamics and PK/PD

Pharmacodynamic data were derived from studies ZXIIS2015-004 (proof-of-concept study) and AX008-1603 (dedicated QTc study). Exploratory PD data were also derived from the phase 1 studies. Fenfluramine mediates its effects at least in part through invoking serotonergic agonism at 5-HT receptors. This is believed to reduce seizures. As the mechanism of action has not been completely clarified, it was considered acceptable to assess primary pharmacology on a more global level than simply 5-HT receptor agonism. A total of 14 patients in the proof-of-concept study provided data at the time of interim data cut-off. These patients contributed to documenting the starting dose recommended in the SmPC.

Regarding secondary pharmacology, anorexic effects were observed. These are also believed to be mediated through the 5-HT receptor agonism and are thus not unexpected. No effect on the QTc interval was observed in the dedicated QTc study.

Pharmacodynamic interactions may be experienced especially in the event of concomitant treatment with other medicinal products invoking serotonergic agonism. This may increase the risk of serotonin syndrome. It is however reassuring that literature has not reported events of serotonin syndrome in relation to treatment with fenfluramine (Richelson 1994). As a precautionary measure, the risk for serotonin syndrome when fenfluramine is administered with other serotonergic drugs (including SSRIs, SNRIs, tricyclic antidepressants, or triptans), with agents that impair metabolism of serotonin such as MAOIs, or with antipsychotics that may affect the serotonergic neurotransmitter systems, is addressed in section 4.4 of the SmPC. Similarly, the risk of coadministration with cyproheptadine, a serotonin antagonist which may block the beneficial effects of fenfluramine, is also addressed in section 4.4 of the SmPC.

Overall, a fragile concentration-effect relationship has been demonstrated.

The relevant PK and PD data are appropriately reflected in the SmPC.

2.4.5. Conclusions on clinical pharmacology

The CHMP was of the view that, even though the PK data package of fenfluramine is limited and the PK of the enantiomers of both fenfluramine and norfenfluramine have not been fully elucidated, the available data are acceptable to support the approval of fenfluramine in DS.

The CHMP considers the following measures necessary to address the uncertainties related to pharmacology:

- Clinical DDI study of norfenfluramine as a clinically relevant inhibitor of MATE1

- Clinical DDI study (CYP2B6 at clinically relevant portal vein concentrations and CYP3A4 at maximal intestinal concentrations)

- PK study in subjects with renal impairment (category 3 study, as detailed in the RMP)

- PK study in subjects with hepatic impairments (category 3 study, as detailed in the RMP)

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

No dedicated dose response study was performed.

The doses used in Study 1 were based on the data from an open label trial of fenfluramine as an add-on therapy to conventional therapy (Study ZXIIS2015-04). The effective doses used in Study ZXIIS2015-04 ranged between 0.1 and 1.0 mg/kg/day, administered as fixed doses between 5 and 40 mg/day, most commonly 5 or 10 mg BID. Doses in Study 1 were selected within the effective range used in Study ZXIIS2015-04, balancing a need to establish efficacy (0.8 mg/kg/day) as well as a desire to identify a minimally effective dose, especially in younger patients (0.2 mg/kg/day). The dosage of 0.5 mg/kg/day (maximum dose 20 mg/day) used in Study 1504c2 was selected based on data from the study Cohort 1, as well as from an already completed drug-interaction study (Study 1505 Part 1) and an early version of a physiologically-based pharmacokinetic model.

2.5.2. Main study(ies)

Clinical efficacy was evaluated in two double-blind randomised studies: Study 1 and Study 1504 Cohort 2. In Study 1, stiripentol (STP) use was an exclusion criterion, while in Study 1504 treatment with STP was an inclusion criterion. Both studies have almost identical methods.

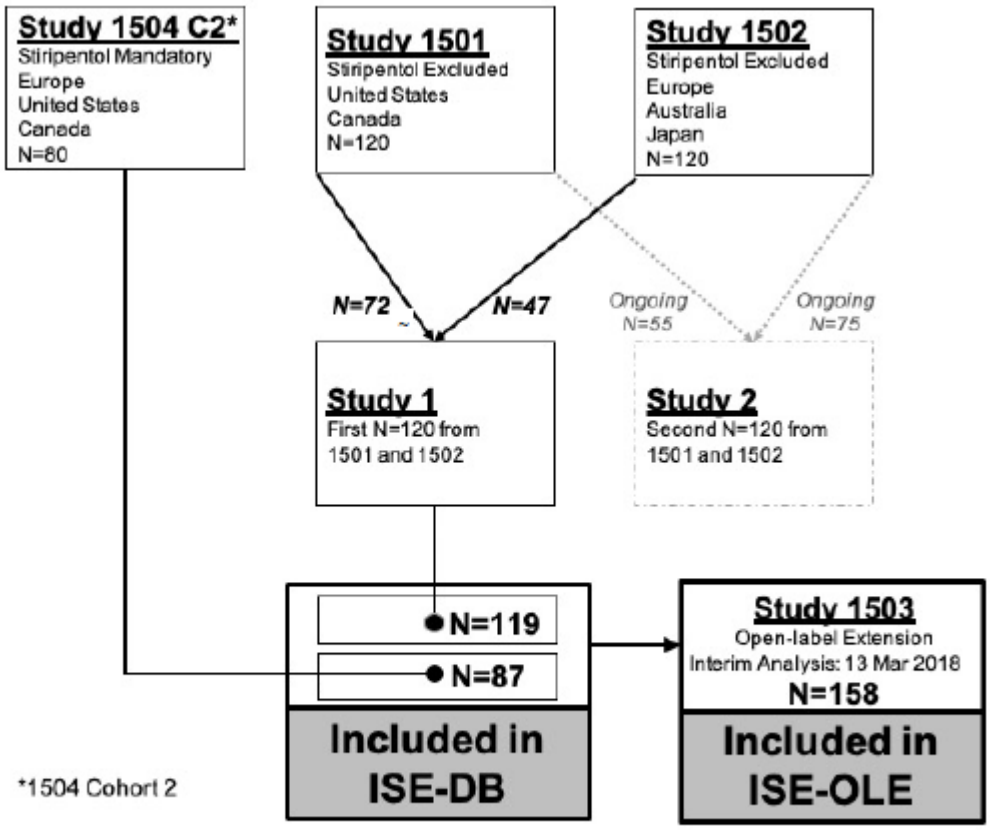
Table 5 Clinical development program in Marketing Authorisation Application

Study ID **No. of study centres/ locations** **Study period**	**Design** **Duration**	**Study Posology (mg/kg/day)** **Subjects by arm entered/ completed**	**Efficacy endpoints** CSF: convulsive seizure frequency

Objective			
Study 1[a] 38 centres: US, CAN, EUR, AUS, JAP Jan 2016-Aug 2017 Efficacy and safety	RD DB PC PA 6 wks BL + 2 wks T + 12 wks M	119/110 patients: PL (N=40/37) 0.2 (N=39/39) 0.8 (N=40/34) Next to standard of care AED, **excluding Stiripentol**	Δ from BL in the frequency of CSF (per 28 days) during the combined T+M periods Proportion of subjects with ≥50% reduction from BL in CSF Longest CS-free interval
ZX008-1504 28 centres: EUR, US and CAN Jan 2017-Jun 2018 Efficacy and safety	RD DB PC PA 6 wks BL+ 3 wks T+ 12 wks M	87/77 patients: PL (N=44/41) 0.5 (N=43/36) Next to stable standard of care AED (CLB and/or VPA) + **Stiripentol**	Δ from BL in the frequency of CSF (per 28 days) during the combined T+M periods Proportion of subjects with ≥ 50% reduction in CSF from BL to the T+M period Longest CS-free interval during the T+M period (days)
ZX008-1503 56 centres: US, CAN, EUR, AUS, JAP Jun 2016 - Ongoing cut off date: 13 Mar 2018 Long-term safety and tolerability	Prospective OLE-study subjects from Studies 1 and 1504 3 years	158 patients All subjects started at 0.2 dose and could flexibly titrate to 0.8mg/kg/day. Max. dose depends on concomitant Stiripentol - use	Δ in mean CSF per 28 days between the pre-ZX008 baseline and OLE period
ZXIIS2015-004 Belgian–cohort 1 centre: Antwerp (BE) Jan 2011 - Ongoing cut off date: 30 Apr 2018 Observational	Prospective OLE-study 7 years	14 patients Doses ranged from 0.1-1.0 mg/kg/day Next to standard of care AED	Δ in frequency of major motor seizures compared with the 3-month baseline period Δ in major motor seizure frequency at 3, 6, 9, and 12 months compared to the 3-month baseline period

[a] Study 1 represents the prospective merged analysis of the first 119 consecutive subjects enrolled two identical studies, ZX008-1501 conducted in North America and ZX008-1502 conducted in Europe, Australia.

AED = antiepileptic drugs, AUS = Australia, BL= baseline, CAN = Canada, CLB = clobazam, CS = convulsive seizure, CSF = convulsive seizure frequency, DB = double-blind, EUR = Europe, IA = interim analysis, JAP = Japan, M = maintenance period, OLE = open label extension, PA = parallel group, PC = placebo-controlled, PL = placebo, RD = randomised, T = titration period, US = United States, VPA = valproic acid, WKS = weeks, Δ = change



Source: ZX008 Integrated Summary of Efficacy (ISE)
Abbreviations: ISE-DB = ISE double blind; ISE-OLE = ISE open label extension (study)

Study 1

Methods

Study Participants

The main inclusion criteria were:

- Male or female, aged 2 to 18 years.
- Clinical diagnosis of Dravet syndrome, where convulsive seizures were not completely controlled by current antiepileptic drugs (AEDs).
- Subjects had to meet **all** the following 5 criteria:
    a. Onset of seizures in the first year of life in an otherwise healthy infant.
    b. A history of seizures that were either generalized tonic-clonic or unilateral clonic or bilateral clonic, and were prolonged.
    c. Initial development was normal.
    d. History of normal brain magnetic resonance imaging (MRI) without cortical brain malformation.
    e. Lack of alternative diagnosis.

- Subjects had to meet at least one of the following 3 criteria:
    a. Emergence of another seizure type, including myoclonic, generalized tonic-clonic, tonic, atonic, absence and/or focal developed after the first seizure type.
    b. Prolonged exposure to warm temperatures induced seizures and/or seizures were associated with fevers due to illness or vaccines, hot baths, high levels of activity, and sudden temperature changes, and/or seizures were induced by strong natural and/or fluorescent lighting, as well as certain visual patterns.
    c. Genetic test results consistent with a diagnosis of Dravet syndrome (pathogenic, likely pathogenic, variant of unknown significance, or inconclusive but unlikely to support an alternative diagnosis).
- Subject had ≥ 4 convulsive seizures (tonic, tonic-atonic, tonic-clonic, or clonic) per 4-week period for the past 12 weeks prior to Screening, reported by parent/guardian to investigator or investigator medical notes.
- All medications or interventions for epilepsy (including ketogenic diet [KD] and vagal nerve stimulator/stimulation [VNS]) were stable for at least 4 weeks prior to Screening and were expected to remain stable throughout the study.

Treatments

Study 1

Doses to be studied included 0.2 mg/kg/day and 0.8 mg/kg/day, divided into 2 daily (BID) doses, up to a maximum of 30 mg/day. Doses were administrated in the morning and in the evening. An intermediate dose of 0.4 mg/kg/day was used for titration.

Objectives

The primary objective of Study 1 was to demonstrate that ZX008 0.8 mg/kg/day is superior to placebo as adjunctive therapy in the treatment of DS in children and young adults based on change in the frequency of convulsive seizures between the Baseline Period and the combined Titration and Maintenance (T+M) Periods.

The secondary objectives were to demonstrate that ZX008 0.2 mg/kg/day to placebo, and to demonstrate the superiority to placebo for both doses (0.8 and 0.2 mg/kg/day) for the proportion of subjects who achieve a ≥ 50% reduction from Baseline in convulsive seizure frequency and for the longest convulsive seizure-free interval.

The study also included a PK objective with the characterisation of the PK of ZX008 0.2 and 0.8 mg/kg/day at steady state in subjects ages 2 to 6 years and > 6 to 18 years with DS.

Outcomes/endpoints

The main endpoints of Study 1 were:

Primary Endpoint

• Change in CSF (mean number of convulsive seizures per 28 days) from Baseline to the T+M period

Key Secondary Endpoints

• Proportion of subjects (n [%]) who achieved a ≥ 50% reduction in CSF from Baseline to the T+M period

• Duration of the longest convulsive seizure–free interval during the T+M period (days)

Additional secondary endpoints were number of convulsive seizure-free Days, proportion of subjects with ≥ 25% and ≥ 75% reduction from baseline in CSF, proportion of subjects achieving complete or nearly complete convulsive seizure freedom, total (convulsive + nonconvulsive) seizure frequency, change from baseline in CSF by seizure type, change from baseline in frequency of all nonconvulsive seizures, change from baseline in nonconvulsive seizure frequency by seizure type, rescue medication usage, incidence of hospitalization and other resource utilization, incidence of status epilepticus, duration of prolonged seizures, clinical global impression (CGT, assessed by the parent/caregiver and by the principal investigator, quality of life in childhood epilepsy (QOLCE) scale, paediatric quality of life inventory (PedsQL) parent report scale and family impact module, quality of life of the parent/caregiver (using EQ-5D-5L).

Sample size

Based on the stiripentol studies and assumptions regarding treatment difference and SD, the initial sample size for studies 1501 and 1502 was 105 subjects required to find a treatment difference of 40% at a 5% significance level with a 90% power. Following the presentation of the phase III Epidyolex study results, the sample size was recalculated, using a higher variation observed in the Epidyolex study. A sample size of approximately 120 subjects (40 per arm) affords 90% power to detect a difference in mean change from Baseline of 40 percentage points with 55% SD.

Randomisation and Blinding (masking)

Two randomisation schemes were implemented using a 2:2:1:1 scheme (0.2 mg/kg/day: 0.8 mg/kg/day: 0.2 placebo: 0.8 placebo): randomisation to dose group, and randomisation to study drug concentration.

The Titration, Maintenance, and Taper/Transition Periods of the study were double-blind. The ZX008 and placebo solutions were identical. The blinding scheme incorporated combinations of volume and concentration to ensure that the volume of study medication taken could not be associated with a specific dose group

Statistical methods

General considerations

The intent-to-treat (ITT) (randomized) set included all subjects randomised to receive study treatment.

The modified intent-to-treat (mITT) Population was defined as all randomised subjects who received at least 1 dose of ZX008 or placebo and for whom at least 1 week of diary data were available. Subjects were analysed according to the treatment group to which they were randomised. The primary comparison of ZX008 0.5 mg/kg/day to placebo, as well as key secondary analyses, were performed using the mITT Population.

All efficacy parameters were summarized by descriptive statistics. Two-sided statistical significance testing (alpha level = 0.05) comparing ZX008 to placebo were performed for the primary and secondary endpoints, unless otherwise noted.

Primary endpoint

The primary efficacy endpoint is the change in the mean convulsive seizure frequency (MCSF) per 28 days between the Baseline and T+M periods. For each subject, the convulsive seizure frequency (CSF) will be

calculated from all available data collected during the Baseline and T+M Periods, and the treatment group MCSF per 28 days (MCSF) will be calculated for the baseline and T+M period.

The baseline period is the 42 days immediately preceding the Randomization visit and the T+M period is planned for 15 weeks (including 3 weeks titration). Actual durations will be computed for each subject based on the individual subject's start and stop dates for each period with the exception that if the baseline period is longer than 42 days, the average for the baseline period will be the 42 days' data immediately preceding the Randomization date.

The CSF will be counted from the daily diary records provided by the Subject or Parent/Caregiver. For any individual subject, the convulsive seizure frequency per 28 days during the baseline period (CSFB) will be derived as follows:

CSFB = (28 × Total number of convulsive seizures during the Baseline Period) / Total number of days in the Baseline Period with non-missing diary data

For each treatment group, the mean is obtained by averaging over the subjects in the treatment group.

Similarly, for each subject, the convulsive seizure frequency per 28 days for the T+M period (CSFT+M) is derived.

The percentage change from baseline for any individual subject will be estimated by (CSFT+M - CSFB)*100/CSFB. The difference from baseline will be estimated by CSF$_{TT+MM}$ − CSF$_{BB}$.

The primary endpoint was analysed using a parametric ANCOVA model with treatment group (ZX008 dose or placebo) and age group (< 6 years, ≥ 6 years) as factors, log Baseline frequency (CSFB) as a covariate, and log CSFT+M + 1 as response. Treatment group means and difference from placebo were estimated with least squares means from the analysis model along with 95% confidence intervals (CIs) and associated 2-sided P values. Estimated treatment group means and CI endpoints were exponentiated for presentation. If distributional assumptions of the ANCOVA were not met, a nonparametric analysis was to be performed in its stead.

Supplementary and sensitivity analyses for the primary endpoint

Per-Protocol Analysis: The primary efficacy analysis was repeated on the PP Population.

Percentage Reduction from Baseline: An alternative approach calculates the percentage change in CSF from Baseline directly and uses that quantity as the response variable in an ANCOVA model. Specifically, the ANCOVA used the percentage change from the T+M period as the response variable, Baseline CSF as a covariate, and treatment and age stratum as classification factors.

The primary analysis described above was repeated with Baseline seizure frequency as a categorical variable, rather than a covariate. Baseline seizure frequency per 28 days was categorized as either < 10; 10 to 50; or > 50.

A nonparametric ANCOVA will be used to analyse the data, with ranks of the baseline CSFB as a covariate and ranks of CSFT+M as response

The primary analysis described above was repeated using data from the Maintenance period only as response. For subjects who did not reach the Maintenance period, data from the Transition were used to represent their Maintenance period data. A similar ANCOVA model was used, and if distributional assumptions were not met, a nonparametric analysis was performed.

Key secondary endpoints

Proportion of Subjects with ≥ 50% Reduction from Baseline in Convulsive Seizure Frequency (50% Responder Rate)

The comparison between the ZX008 group and placebo group was made using a logistic regression model that incorporated the same factors as the ANCOVA used in the primary analysis. This modelled a categorical response variable (achieved 50 percentage point reduction, yes or no) as a function of Treatment group (ZX008 and placebo), Baseline seizure frequency, and age group (< 6 years, ≥ 6 years).

Longest Convulsive Seizure–Free Interval

The longest convulsive seizure-free interval was summarized; summary statistics included median, mean, minimum, maximum, the 25th and 75th percentiles, and 95% confidence intervals on the difference in medians between groups (Hodges-Lehmann estimator). The Wilcoxon rank-sum test was used to test for differences between ZX008 and placebo, and the P values from this test were presented.

Handling of Dropouts and Missing Data

There will be no imputation of missing data for efficacy endpoints.

Seizure Diaries: Seizures are recorded in the Daily Seizure Diary (DSD), while the End of Day Diary (EDD) provides Yes/No confirmation that that seizures were experienced for a specific date, or that the date was seizure free.

• If no seizures are entered in the DSD and the EDD confirms seizure freedom, the number of seizures for that date is zero.

• If seizures are entered in the DSD and the EDD states seizure freedom, the seizures recorded for that date supersede the EDD stating seizure freedom.

• If no seizures are entered in the DSD and there is no response in the EDD, that day will be considered to have missing diary data.

• If no seizures are entered in the DSD and there is a Yes response in the EDD, that day will be considered to have missing diary data.

Unless specified otherwise in the relevant sections describing analyses for individual parameters, missing diary data will not be imputed for efficacy variables. Hence for subjects missing some of the daily measurements, the available data will be used. No explicit imputation will be performed for subjects who drop out prior to end of study (Visit 12).

Longest Interval Between Convulsive Seizures

For each subject, the longest interval between convulsive seizures was calculated over the entire T+M Period. This was derived as the maximum of the number of days between consecutive convulsive seizures. If a subject had 2 consecutive days of missing diary data, the current seizure-free period was ended on the first date of missing diary data, and a new one begun on the next date that diary data were available and no seizure occurred.

Type I error control for Study 1

A serial gatekeeping strategy was developed to control the type I error rate for pairwise comparisons between active and placebo groups, among the primary and key secondary efficacy parameters.

Results

Participant flow

A total of 173 subjects were screened for eligibility to participate in the study 1; of these, 119 subjects were randomized to study treatment in a 1:1:1 ratio (placebo: 40 subjects; ZX008 0.2 mg: 39 subjects; and ZX008 0.8 mg: 40 subjects). A total of 110 subjects (92.4%) completed the study (37 subjects, 92.5% placebo; 39 subjects, 100% ZX008 0.2 mg/kg/day, and 34 subjects, 85.0% ZX008 0.8 mg/kg/day).

The completion rate was highest in the ZX008 0.2 mg/kg/day group and lowest in the ZX008 0.8 mg/kg/day group. Of the 9 subjects who did not complete the study 3 were randomised to placebo and 6 were randomized to ZX008 0.8 mg/kg/day. Reasons for premature discontinuation for the 3 subjects randomized to placebo were withdrawal by subject (parent or legal guardian) (2 subjects [5.0%]), and lack of efficacy (1 subject [2.5%]). Reasons for premature discontinuation for the 6 subjects randomized to ZX008 0.8 mg/kg/day group were AEs (5 subjects [12.5%]), and withdrawal by subject (1 subject [2.5%]). AEs leading to withdrawal occurred only in the ZX008 0.8 mg/kg/day group. Three subjects who exited the study prematurely advanced to the open-label extension study (placebo: 1 subject; 0.8 mg/kg/day: 2 subjects).

Baseline data

The treatment groups were balanced for age, sex, and race. Overall, the mean (SD) age was 9.0 (4.65) years. In all groups, the majority of subjects were ≥6 years of age. The majority of subjects in all treatment groups were male and the majority of all treatment groups were white.

Summary of demographics and baseline characteristics (mITT population)

	Placebo (N=40)	ZX008 0.2 mg (N=39)	ZX008 0.8 mg (N=40)	Total (N=119)
Age (years)				
n	40	39	40	119
Mean (SD)	9.2 (5.10)	9.0 (4.52)	8.8 (4.41)	9.0 (4.65)
Median	8.5	8.0	8.5	8.0
Age Group n (%)				
<6 years	11 (27.5)	9 (23.1)	11 (27.5)	31 (26.1)
≥6 years	29 (72.5)	30 (76.9)	29 (72.5)	88 (73.9)
Sex				
Male	21 (52.5)	22 (56.4)	21 (52.5)	64 (53.8)
Female	19 (47.5)	17 (43.6)	19 (47.5)	55 (46.2)
Race				
White	31 (77.5)	33 (84.6)	34 (85.0)	98 (82.4)
Asian	4 (10.0)	2 (5.1)	1 (2.5)	7 (5.9)
American or Alaska Native	1 (2.5)	1 (2.6)	0	2 (1.7)
Other	2 (5.0)	1 (2.6)	1 (2.5)	4 (3.4)
Not Reported [*]	2 (5.0)	2 (5.1)	4 (10.0)	8 (6.7)
Ethnic Group				
Hispanic or Latino	4 (10.0)	4 (10.3)	3 (7.5)	11 (9.2)
Not Hispanic or Latino	29 (72.5)	32 (82.1)	32 (80.0)	93 (78.2)
Not Reported[1]	7 (17.5)	2 (5.1)	4 (10.0)	13 (10.9)
Unknown1	0	1 (2.6)	1 (2.5)	2 (1.7)
Baseline Height (m)				
n	40	38	40	118
Mean (SD)	1.29 (0.224)	1.31 (0.223)	1.28 (0.204)	1.29 (0.216)
Median	1.29	1.33	1.30	1.30
Baseline Weight (kg)				
n	40	39	40	119
Mean (SD)	31.7 (16.15)	35.1 (19.57)	31.8 (13.47)	32.9 (16.49)
Median	26.5	29.6	28.3	27.9
Baseline BMI (kg/m^2)				
n	40	38	40	118
Mean (SD)	17.96 (3.793)	19.32 (5.688)	18.47 (3.502)	18.57 (4.408)
Median	17.56	17.24	18.03	17.79

Source: Table 14.1.2.2

BMI=Body Mass Index, where BMI=weight (kg)/height (m^2); mITT= Modified Intention-to-Treat.

Note: Percentages are calculated based on the number of subjects with nonmissing data in the Safety population.

[1] Not reported, or missing: Privacy laws in some regions/countries preclude disclosure of certain personal information.

Summary of baseline convulsive seizure frequency

	Placebo (N=40)	ZX008 0.2 mg (N=39)	ZX008 0.8 mg (N=40)
Mean	46.1	47.2	33.0
SD	40.70	99.64	31.38
Median	31.4	17.5	21.2
Min, Max	3.3, 147.3	4.8, 623.5	4.9, 127.0

Source: Table 14.2.1.2

Prior Anti-Epileptic Medications/Therapies

All subjects received at least one prior AED. Overall, the most commonly used prior AEDs/therapies, were clobazam (83.2%), levetiracetam (79.0%), topiramate (68.9%), valproate semisodium/sodium (68.1%), stiripentol (48.7%), zonisamide (43.7%), phenobarbital (40.3%), ketogenic diet (37.8%), lamotrigine (27.7%), cannabidiol (26.9%), clonazepam (26.9%), and valproic acid (26.1%).

Concomitant Anti-Epileptic Medications/Therapies

All subjects were to be receiving at least one concomitant anti-epileptic treatment during the study. Most subjects (97.6%) received between 1 and 4 AEDs. In addition to AEDs, 9 subjects were on the ketogenic diet (1 on placebo, 4 on 0.2 mg/kg/day, and 4 subjects on 0.8 mg/kg/day), and 23 subjects had a vagal nerve stimulator implantation (9 subjects on placebo, 8 subjects on 0.2 mg/kg/day, and 6 subjects on 0.8 mg/kg/day). One subject in the 0.2 mg/kg/day treatment group did not receive any concomitant AED medication during the study but did have a vagal nerve stimulator implanted.

Numbers analysed

There were 5 study populations: the enrolled population, the ITT (randomised) Population, the mITT Population, the PP Population, and the Safety Population.

All 119 subjects who were randomised received at least 1 dose of ZX008 or placebo and had at least 1 week of diary data; therefore, the ITT and mITT Populations are identical. The primary comparison of ZX008 0.8 mg/kg/day to placebo, as well as key secondary analyses, were performed on the mITT Population. Subjects were analyzed according to the treatment group to which they were randomized. A total of 102 subjects were included in the PP population. Subjects excluded from the PP population are those with major protocol deviations that had the potential to impact clinical outcome (safety, efficacy, data integrity). All safety analyses were conducted using the Safety population, which included all 119 subjects.

Outcomes and estimation

Primary endpoint:

The primary endpoint was change from Baseline during T+M in the mean CSF per 28 days for the ZX008 0.8 mg/kg/day group compared with the placebo group.

The least squares mean CSF per 28 days was 7.9 and 21.8 for the 0.8 mg/kg/day and placebo dose groups, respectively. The model gives an estimate of the percent difference in baseline-adjusted CSF between the 0.8 mg/kg/day group and placebo (95% CI) of 63.9% (49.40, 74.22).

Convulsive Seizure Frequency per 28 days: T+M period

	Placebo (N=40)	ZX008 0.2 mg (N=39)	ZX008 0.8 mg (N=40)
Baseline Summary Statistics			
Mean (SD)	46.07 (40.704)	47.17 (99.636)	32.95 (31.480)
Median	31.39	17.50	21.17
Min, Max	3.3, 147.3	4.8, 623.5	4.9, 127.0
T+M Period Summary Statistics			
Mean (SD)	40.56 (39.748)	29.23 (40.169)	18.89 (32.080)
Median	26.03	14.33	5.42
Min, Max	3.2, 180.6	0.0, 202.11	0.0, 169.9
T+M Period: Parametric Model Summary[1] Results on Log Scale[1]			
Least Squares Mean (SE)	3.08 (0.127)	2.67 (0.130)	2.07 (0.126)
95% CI for Least Squares Mean	2.84, 3.33	2.42, 2.93	1.82, 2.31
Difference from Placebo:			
Estimate of A-P (95% CI) [1]		-0.41 (-0.75, 0.07)	-1.02 (-1.36, -0.68)
p-value for comparison with placebo[2]		0.019	<0.001
Original Scale			
Least Squares Mean3	21.8	14.5	7.9
Comparison with placebo			
Estimate of Ratio (95% CI) [3]		0.66 (0.47, 0.93)	0.36 (0.26, 0.51)
Estimate of % Difference from Placebo (95% CI)4		33.74 (7.06, 52.77)	63.89 (49.40, 74.22)

Source: Table 14.2.1.2

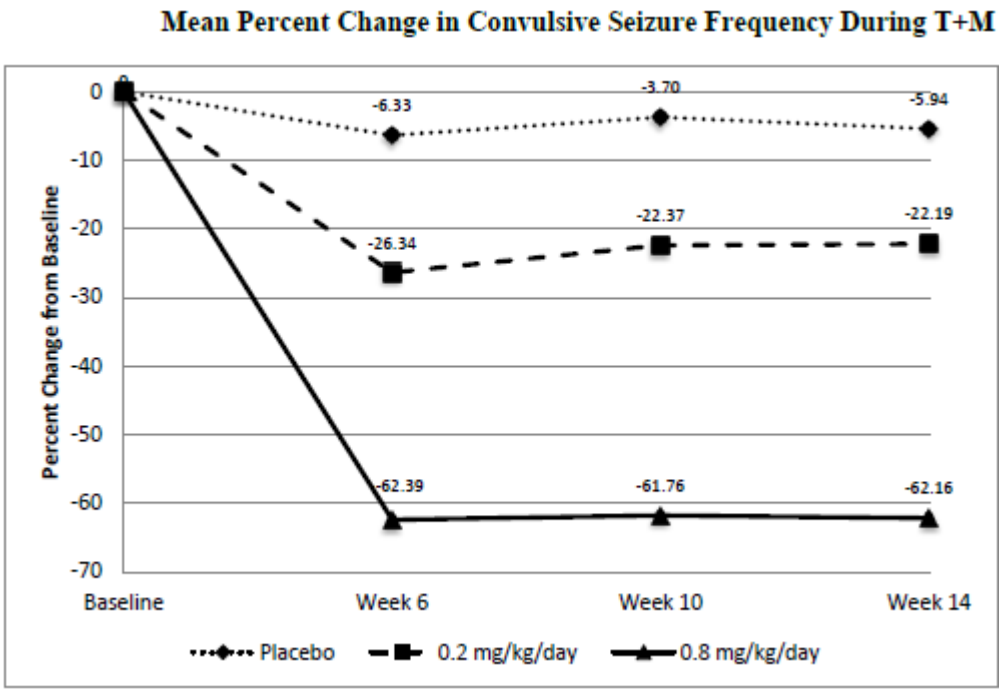
ANCOVA=Analysis of covariance; CI=confidence interval; M=Maintenance; mITT=modified intent-to-treat population; SD=Standard Deviation; SE=Standard error; T=Titration.

[1] Baseline, M, and T+M Period values were log transformed prior to analysis. To avoid taking log of 0, a value of 1 was added to the M, T+M Period values before log transformation.

[2] Results are based on an ANCOVA model with treatment group (3 levels) and age group (<6 years, ≥6 years) as factors, log baseline convulsive seizure frequency as a covariate and log convulsive seizure frequency (Titration + Maintenance, or Maintenance) period as response. The p-value was obtained from this ANCOVA model.

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

[4] This is obtained from the LS Means on the log scale as follows: 100 * [1 - exp (LS mean active –LS mean placebo)].



Key secondary endpoints:

Change from Baseline in Convulsive Seizure Frequency for ZX008 0.2 mg/kg/day Versus Placebo

Using the same methodology as for the primary endpoint, the least squares mean CSF per 28 days for the 0.2 mg/kg/day group was 14.5; the estimate of the percent difference between placebo (95% CI) and the 0.2 mg/kg/day dose group was 33.7% (7.06, 52.77). The mean (SD) CSF per 28 days for subjects randomized to the 0.2 mg/kg/day dose group during Baseline was 47.2 (99.64) and at the end of the T+M Period was 29.2 (40.17) which was statistically significant compared to placebo (p=0.019).

Proportion of Subjects with ≥50% Reduction from Baseline in Convulsive Seizure Frequency – Responder Analysis

Percentage Reduction in Convulsive Seizure Frequency (mITT Population)

	Placebo (N=40)	ZX008 0.2 mg (N=39)	ZX008 0.8 mg (N=40)
T+M Period Distribution of Percentage Change from Baseline in convulsive seizure frequency			
≥50%, n (%)	3 (7.5)	16 (41.0)	28 (70.0)
Odds ratio (95% CI)		10.095 (2.480, 41.100)	29.098 (7.182, 117.890)
p-value[1]		0.001	<0.001

Source: Table 14.2.2.1

CI=confidence interval; mITT=modified intent-to-treat population.

[1] Two separate logistic regression models that include a categorical response variable (achieved 50% percentage point reduction, yes or no) as a function of treatment group (Active or placebo), age group (< 6 years, ≥ 6 years), and baseline convulsive seizure frequency were used.

Longest Interval between Convulsive Seizures

Longest Interval (Days) between Convulsive Seizures (mITT Population)

	Placebo (N=40)	ZX008 0.2 mg (N=39)	ZX008 0.8 mg (N=40)
Median	9.00	14.00	20.50
Mean (SD)	9.53 (5.383)	22.00 (26.559)	27.53 (23.986)
Min	2.0	3.0	2.0
25th percentile	5.50	7.00	7.00
75th percentile	11.00	21.00	39.00
Max	23.0	104.0	97.0
Estimate of Median Treatment Difference		5.00	11.50
95% CI for Treatment Difference[1]		1.00, 9.00	5.00, 18.00
p-value[2]		0.011	<0.001

Source: Table 14.2.3.1

CI=confidence interval; Max=maximum; Min=minimum; mITT=modified intent-to-treat population; SD=standard deviation.

[1] Based on Hodges-Lehmann estimator of treatment difference.

[2] From Wilcoxon rank sum test comparing active with placebo.

Study 1504

Study 1504 consisted of 2 parts. The first part (Cohort 1) was an open-label study in 18 subjects with Dravet syndrome to assess pharmacokinetics (PK) and safety to define the dose of fenfluramine to be used in Cohort 2, when fenfluramine was added to a regimen that included stiripentol (STP). The second part (Cohort 2) was a double-blind, randomized, 2-arm, placebo-controlled study to evaluate ZX008 in combination with STP, valproate (VPA) and/or clobazam (CLB).

Methods

Study Participants

The inclusion and exclusion criteria in Study 1504 were similar to Study 1. The most important difference being the requirement of stable STP (plus CLB and/or VPA treatment) whereas STP treatment was an exclusion criterion in Study 1. A requirement in Study 1 of at least 4 convulsive seizures per 4 weeks was not a requirement in Study 1504c2.

Treatments

Dose to be studied included 0.5 mg/kg/day, divided into 2 daily (BID) doses, up to a maximum of 20 mg/day. Doses were administrated in the morning and approximately 12 hours later in the evening. An intermediate dose of 0.4 mg/kg/day was used for titration.

Objectives

The primary efficacy objective was to demonstrate that ZX008 is superior to placebo for the treatment of Dravet syndrome in children and young adults optimized on a STP regimen based on the change in convulsive seizure frequency (CSF) from Baseline to the combined Titration and Maintenance periods (T+M periods).

The secondary objectives were to demonstrate of ZX008 to placebo for the proportion of subjects who achieve a ≥ 50% reduction from Baseline in convulsive seizure frequency and for the longest convulsive seizure-free interval.

Outcomes/endpoints

Primary endpoint:

- Change from baseline in convulsive seizure frequency (CSF) to the T+M periods.

Key secondary endpoints:

- Proportion of subjects (n [%]) who achieved a ≥ 50% reduction in CSF from Baseline to the T+M period.
- Longest convulsive seizure-free interval during the T+M period (days)

Additional secondary endpoints were number of convulsive seizure-free days, proportion of subjects with ≥ 25% and ≥ 75% reduction from Baseline in CFS, proportion of subjects achieving complete or nearly complete convulsive seizure freedom, total (convulsive + nonconvulsive) seizure frequency, change from Baseline in CSF by seizure type, change from Baseline in frequency of all nonconvulsive seizures (all types

and by seizure type), rescue medication usage, incidence of hospitalization and other resource utilization, incidence of status epilepticus, duration of prolonged seizures, Clinical Global Impression (improvement rating by the parent/caregiver and by the principal investigator), Quality of Life in Childhood Epilepsy (QOLCE) Scale, Paediatric Quality of Life Inventory (PedsQL), Quality of Life of the Parent/Caregiver

Sample size

Similarly to study 1, the sample size calculation for study 1504 was derived from the stiripentol studies. This resulted in an initial sample size of 70 subjects required to find a treatment difference of 40% at a 5% significance level and with a 90% power. When the results of a phase III Epidyolex study came available the sample size was recalculated, using a higher SD. A sample size of approximately 80 subjects (35-40 per arm) was considered needed. The final determination was based on the results of Study 1 with a higher SD (58) and it was planned to include approximately 90 subjects (45 per arm).

Randomisation and Blinding (masking)

Subjects were randomized (1:1) in a double-blind manner to receive ZX008 (at a dose of 0.5 mg/kg/day; maximum dose of 20 mg/day) or placebo. The randomization was stratified by age (< 6 years, ≥ 6 years) to ensure balance across treatment regimens and approximately 25% of subjects were in each age group. Study drug was provided in one concentration: 2.5 mg/mL fenfluramine HCl.

The Titration, Maintenance, and Taper/Transition periods of the study were double-blind.

Statistical methods

The statistical analyses were similar to those for study 1.

Participant flow

A total of 115 subjects were screened for eligibility to participate in Study 1504 Cohort 2. Of these, 28 subjects (24.3%) were screen failures (18 subjects due to ECHO findings) and 87 subjects (75.7%) were randomized to study treatment in a 1:1 ratio (placebo: 44 subjects; and ZX008 0.5 mg/kg/day: 43 subjects). A total of 77 subjects (88.5%) completed the study: 41 subjects (93.2%) in the placebo group and 36 subjects (83.7%) in the ZX008 0.5 mg/kg/day group.

Of the 10 subjects who did not complete the study, 3 subjects were in the placebo group and 7 subjects were in the ZX008 0.5 mg/kg/day group (1 subject discontinued in the T+M period and 6 subjects discontinued in the Maintenance period). Reasons for premature discontinuation in the placebo group were given as an AE, subject with early termination due to worsening of seizures (approved by Medical Monitor and Sponsor to have early rollover into the open-label study), and uncontrolled seizures (1 subject [2.3%] each). Reasons for premature discontinuation in the ZX008 0.5 mg/kg/day group were as follows: 2 subjects (4.7%) due to AEs and 1 subject (2.3%) in each of the following: lack of efficacy, physician decision, subject early termination due to worsening seizures, and withdrawal by subject. One subject in the ZX008 0.5 mg/kg/day group discontinued early due to an ECHO finding per Sponsor request when an investigation of a mild mitral regurgitation (MR) report at Visit 8 revealed that mild mitral regurgitation had been present at an initial

Screening ECHO but was not identified at a subsequent rescreening ECHO, which allowed the subject to be inappropriately enrolled into the study.

Baseline data

The treatment groups were balanced for age, sex, and race. Overall, the mean (SD) age was 9.1 (4.80) years. In each group, the majority of subjects were ≥ 6 years of age. Over half of the subjects in each treatment group were male and, where reported, over half of the subjects in each group were white.

Summary of demographics and baseline characteristics

	placebo (n=44)	ZX008 0.5 mg/kg/day (n=43)	Total (N=87)
Age (years)			
Mean (SD)	9.4 (5.05)	8.8 (4.56)	9.1 (4.80)
Median	9.0	9.0	9.0
Min	2	2	2
Max	19	18	19
Age group, n (%)			
<6 years	12 (27.3)	12 (27.9)	24 (27.6)
≥6 years	32 (72.7)	31 (72.1)	63 (72.4)
Sex			
Male	27 (61.4)	23 (53.5)	50 (57.5)
Female	17 (38.6)	20 (46.5)	37 (42.5)
Race			
White	29 (65.9)	23 (53.5)	52 (59.8)
Black or African American	2 (4.5)	1 (2.3)	3 (3.4)
Asian	1 (2.3)	2 (4.7)	3 (3.4)
Other	1 (2.3)	3 (7.0)	4 (4.6)
Not Reported[a]	11 (25.0)	13 (30.2)	24 (27.6)
Unknown[a]	0 (0.0)	1 (2.3)	1 (1.1)
Ethnic group			
Hispanic or Latino	7 (15.9)	3 (7.0)	10 (11.5)
Not Hispanic or Latino	22 (50.0)	25 (58.1)	47 (54.0)
Not Reported[a]	12 (27.3)	14 (32.6)	26 (29.9)
Unknown[a]	3 (6.8)	1 (2.3)	4 (4.6)
Baseline Height (m)			
Mean (SD)	1.32 (0.253)	1.31 (0.235)	1.31 (0.243)
Median	1.33	1.32	1.32
Baseline Weight (kg)			
Mean (SD)	36.2 (21.08)	31.3 (14.85)	33.8 (18.32)
Median	30.5	27.9	28.6
Baseline BMI (kg/m^2)			
Mean (SD)	19.14 (4.890)	17.32 (2.715)	18.24 (4.049)
Median	17.51	16.58	17.13

Source: End-of-Text Table 14.1.2.2b.

Abbreviations: BMI = body mass index, where BMI = weight (kg)/height (m^2); kg = kilograms; m = meters; mITT = modified intent-to-treat; SD = standard deviation.

[a] Not reported or missing: Privacy laws in some regions/countries precluded disclosure of certain personal information.

Summary of baseline convulsive seizure frequency

Number of Seizures	placebo (n=44)	ZX008 0.5 mg/kg/day (n=43)
Mean	21.62	27.90
SD	27.650	36.939
Median	10.67	14.00
Min, Max	(2.7, 162.7)	(2.7, 213.3)

Source: End-of-Text Table 14.2.1.1.1b.
Abbreviations: Max = maximum; Min = minimum; mITT = modified intent-to-treat; SD = standard deviation.

Concomitant Antiepileptic Medications/Therapies

All subjects were to have been receiving at a minimum STP plus CLB and/or VPA during the study. Table 16 summarizes the number of concomitant AEDs taken by subjects by treatment group for the Safety Population. All subjects received at least 2 AEDs; most subjects received 3 or 4 AEDs (51.7% and 36.8%, respectively). There were more subjects in the ZX008 0.5 mg/kg/day group receiving 5 AEDs (7 subjects) compared to the placebo group (1 subject). This smaller cohort of subjects receiving such a level of polypharmacy of 5 AEDs could be considered as more refractory than the other subjects on fewer AEDs and were more heavily weighted toward the ZX008 0.5 mg/kg/day group.

Numbers analysed

There were 5 study populations: the enrolled population, the ITT (randomised) Population, the mITT Population, the PP Population, and the Safety Population.

A total of 115 subjects were included in the enrolled population. All 87 subjects who were randomized to receive ZX008 0.5 mg/kg/day or placebo received at least 1 dose of study drug and had at least 1 week of diary data; therefore, the ITT, Safety, and mITT Populations were identical. The primary comparison of ZX008 0.5 mg/kg/day to placebo, as well as key secondary analyses, were performed for the mITT Population. Subjects were analysed according to the treatment group to which they were randomized. A total of 73 subjects were included in the PP Population. Subjects excluded from the PP Population were those with MPDs that had the potential to impact clinical outcome (safety, efficacy, or data integrity) or those who did not complete at least 4 weeks of the Maintenance period. All safety analyses were conducted using the Safety Population.

Outcomes and estimation

Primary endpoint:

The primary objective of Study 1504 was to evaluate the efficacy of ZX008 0.5 mg/kg/day (maximum 20 mg/day) versus placebo in reducing convulsive seizures over the 15-week Treatment period. Seizure types contributing to the primary endpoint were GTC, secondarily GTC, clonic, drop seizures (tonic-atonic), hemiclonic, and focal seizures with a clear and observable motor component.

The primary analysis estimated that subjects randomized to ZX008 0.5 mg/kg/day achieved a 54.0% (95% CI: 35.6%, 67.2%) greater reduction in monthly CSF between the Baseline period and the T+M period than subjects randomised to placebo ($P < 0.001$).

Convulsive Seizure Frequency Per 28 Days in Study 1504 Cohort 2: T+M period - Parametric Analysis (mITT Population)

T+M Period Analysis	placebo (n=44)	ZX008 0.5 mg/kg/day (n=43)
Baseline Summary Statistics		
n	44	43
Mean (SD)	21.62 (27.650)	27.90 (36.939)
Median	10.67	14.00
Min, Max	(2.7, 162.7)	(2.7, 213.3)
T+M Period Summary Statistics		
n	44	43
Mean (SD)	20.97 (27.700)	24.72 (72.054)
Median	11.43	5.17
Min, Max	(2.2, 170.1)	(0.0, 458.6)
T+M Period: Parametric Model Summary[a]		
Results on log scale[a]		
Least Squares Mean (SE)[a]	2.72 (0.131)	1.94 (0.130)
95% CI for Least Squares Mean[a]	(2.46, 2.97)	(1.68, 2.19)
Difference from placebo:		
Estimate of A-P (95% CI)[a]		–0.78 (–1.12, –0.44)
P value for comparison with placebo[b]		<0.001
Original scale		
Least Squares Mean[c]	15.1	7.0
Comparison with placebo:		
Estimate of Ratio (95% CI)[c]		0.46 (0.33, 0.64)
Estimate of % Difference from placebo (95% CI)[d]		54.04 (35.55, 67.23)
P value for comparison with placebo[c]		<0.001

Source: End-of-Text Table 14.2.1.2b.
Abbreviations: ANCOVA = analysis of covariance; A-P = Active–placebo; CI = confidence interval; LS = least squares; Max = maximum; Min = minimum; SE = standard error; T+M = Titration plus Maintenance period.

[a] Baseline and T+M period values were log transformed prior to analysis. To avoid taking log of 0, a value of 1 was added to the M and T+M period values before log transformation.

[b] Results were based on an ANCOVA model with treatment group and age group (< 6 years, ≥ 6 years) as factors, log Baseline convulsive seizure frequency per 28 days as a covariate, and log convulsive seizure frequency per 28 days during T+M period or Maintenance period as response. The P value was obtained from this ANCOVA model.

[c] The LS Means and A-P difference and CI on the log scale were exponentiated.

[d] This was obtained from the LSMeans on the log scale as follows: 100 × [1-exp (ls mean active – ls mean placebo)].

Key secondary endpoints

Proportion of Subjects with ≥ 50% Reduction from Baseline in Convulsive Seizure Frequency – Responder Analysis (mITT Population)

Responders with ≥ 50% Reduction in Convulsive Seizure Frequency in Study 1504 Cohort 2 (mITT Population)

T+M Period	placebo (n=44)	ZX008 0.5 mg/kg/day (n=43)
Reduction in CSF from Baseline		
≥ 50%, n (%)	2 (4.5)	23 (53.5)
Odds ratio (95% CI)		26.037 (5.502, 123.214)
P value[a]		< 0.001

Source: End-of-Text Table 14.2.2.1.1b.
Abbreviations: CI = confidence interval; CSF = convulsive seizure frequency; mITT = modified intent-to-treat; T+M = Titration plus Maintenance period.
[a] A logistic regression model that included a categorical response variable (achieved 50% percentage point reduction, yes or no) as a function of treatment group (active or placebo), age group (< 6 years, ≥ 6 years), and Baseline convulsive seizure frequency was used.

Longest Interval Between Convulsive Seizures (mITT Population)

Longest Interval (Days) Between Convulsive Seizures in Study 1504 Cohort 2 (mITT Population)

	placebo (n=44)	ZX008 0.5 mg/kg/day (n=43)
Duration of longest interval, days		
Mean (SD)	13.43 (7.528)	29.70 (27.349)
Min	1.0	3.0
25th Percentile	8.50	11.00
Median	13.00	22.00
75th Percentile	17.00	44.00
Max	40.0	105.0
Estimate of treatment difference, days		
Median		8.50
95% CI for treatment difference[a]		2.000, 15.000
P value[b]		0.004

Source: End-of-Text Table 14.2.3.1b.
Abbreviations: CI = confidence interval; Max = maximum; Min = minimum; mITT = modified intent-to-treat; SD = standard deviation.
[a] Based on Hodges-Lehmann estimator of treatment difference.
[b] From Wilcoxon rank-sum test comparing active with placebo.

Summary of main studies

The following tables summarise the efficacy results from the two main studies (study 1 and study 1504). These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Please note that the summaries of efficacy results have been adjusted during the assessment with the re-analysed data. Therefore, there may be some deviations comparing to the raw data of the clinical reports as initially submitted.

Table 1 Summary of efficacy for Study 1

Title: A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome			
Study identifier	ZX008-Study 1 IND 125797 EudraCT 2015-004167-37		
Design	Study 1 is the prospective, merged analysis of 2 identical double-blind, placebo-controlled studies, ZX008-1501 and ZX008-1502. Study 1501 and Study 1502 are being conducted in parallel. After obtaining informed consent/assent, subjects entered a 6-week Baseline Period. This period consisted of the establishment of initial eligibility during a screening visit followed by an observation period when subjects were assessed for baseline seizure activity based on recordings of daily seizure activity entered into an electronic diary. Upon completion of the Baseline Period, subjects who qualified for the study were randomized (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; maximum dose: 30 mg/day) or placebo. Randomization was stratified by age (< 6 years, ≥ 6 years) to achieve balance across treatment arms, with the target of 25% of subjects in each age group. All subjects were titrated in a blinded fashion to their randomized dose over a 2-week Titration Period. Following titration, subjects continued treatment at their randomly assigned dose during a 12-week Maintenance Period. For subjects who completed the full Titration and Maintenance Periods (T+M) total treatment time was 14 weeks. At the end of the Maintenance Period (or early discontinuation), all subjects underwent a 2-week blinded taper or transition (Taper/Transition Period), depending on whether they exited the study or were enrolled in the subsequent long-term open-label extension study. Parents/caregivers used an electronic diary every day during study participation to record the number/type of seizures, dosing, and use of rescue medication.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		19 months First Patient Enrolled: 15 Jan 2016 Last Patient Last Visit: 14 Aug 2017 not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Placebo		Placebo throughout the 2-week Titration Period (T) and 12-week Maintenance Period (M); 40 randomized
	ZX008 0.2 mg/kg		ZX008 0.2 mg/kg/day throughout the 2-week Titration Period (T) and 12-week Maintenance Period (M); 40 randomized
	ZX008 0.8 mg/kg		Subjects randomized to be titrated from 0.2 mg/kg/day up to 0.8 mg/kg/day over the 2-week Titration Period (T) and then taking 0.8 mg/kg/day (up to a maximum dose of 30 mg/day) for the 12-week Maintenance Period (M); 40 randomized
Endpoints and definitions	Primary efficacy endpoint	CSF per 28 days	Change from Baseline during T+M in the mean convulsive seizure frequency (CSF) per 28 days for the ZX008 0.8 mg/kg/day group compared with the placebo group
	Key secondary endpoint #1	Proportion of subjects who achieved a ≥50%	The proportion of subjects with a ≥50% reduction from Baseline in convulsive seizure frequency for the 0.8 mg/kg/day group compared to placebo

		reduction from Baseline in CSF	
	Key secondary endpoint #2	Longest interval between convulsive seizures	The longest interval between convulsive seizures during the T+M Period for the 0.8 mg/kg/day group compared to placebo
	Key secondary endpoint #3	CSF per 28 days	Change from Baseline during T+M in the mean CSF per 28 days for 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 CSF	The proportion of subjects with a ≥50% reduction from Baseline in convulsive seizure frequency for the 0.2 mg/kg/day group compared to placebo
	Key secondary endpoint #5	Longest interval between convulsive seizures	The longest interval between convulsive seizures during the T+M Period for the 0.2 mg/kg/day group compared to placebo
Database lock	18 Sep 2017		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Convulsive Seizure Frequency Per 28 Days: Baseline and T+M Period – Parametric Analysis based on log transformation (mITT Population) A serial gatekeeping strategy was developed to control the type I error rate for pairwise comparisons between active and placebo groups, among the primary and key secondary efficacy parameters. Key secondary endpoints are listed below in order of testing.			
Descriptive statistics and estimate variability	Treatment group	Placebo	ZX008 0.2 mg	ZX008 0.8 mg
	Number of subjects	N=40	N=39	N=40
	Mean baseline CSF per 28 Days (SD)	46.07 (40.7)	47.17 (99.6)	32.95 (31.5)
	Median baseline CSF per 28 Days	31.39	17.50	21.17
	Min, Max	3.3, 147.3	4.8, 623.5	4.9, 127.0
	Mean T+M CSF per 28 Days (SD)	40.56 (39.7)	29.23 (40.2)	18.89 (32.1)
	Median T+M CSF per 28 Days	26.03	14.33	5.42
	Min, Max	3.2, 180.6	0.0, 202.1	0.0, 169.9
	Median CSF at end of M period (max,min)	25.7 (3.6, 204.7)	17.1 (0.0, 194.3)	4.9 (0, 105.5)

Effect estimate per comparison	Primary endpoint (M period only)	Comparison groups	0.8 mg/kg/d vs Placebo
		Estimate of % Difference from Baseline in CSF	67.3%
		95% CI	52.83, 77.28
		P-value *(ANCOVA)*	<0.001
	Median percent change in CSF from baseline	Comparison groups	0.8 mg/kg/d vs Placebo
		Placebo	-17.4% (-76.1, 73.9)
		0.8 mg/kg/d	-72.4% (-100, 196.4)

		P-value *(Wilcoxon rank-sum tests)*	<0.001	
	Key secondary endpoint #1 50% responder rate (M period only)	Comparison groups	Placebo	0.8 mg/kg/d
		% achieving a ≥50% reduction from Baseline CSF	10.3%	72.5%
		Relative Risk (95% CI)	7.07 (2.74, 18.24)	
		P-value	<0.001	
	Key secondary endpoint #2 Longest interval between convulsive seizures (T+M period)	Comparison groups	Placebo	0.8 mg/kg/d
		Median longest convulsive seizure-free interval (days)	9.5	25
		95% CI for Treatment Difference	6.00, 25.00	
		P-value	<0.001	
	Key secondary endpoint #3 CSF 0.2 mg/kg/d (M period only)	Comparison groups	0.2 mg/kg/d vs Placebo	
		Mean % change from Baseline in CSF	36.73%	
		95% CI	8.71, 56.15	
		P-value	0.016	
	Median percent change in CSF from baseline	Comparison groups	0.2 mg/kg/d vs Placebo	
		Placebo	-17.4% (-76.1, 73.9)	
		0.2 mg/kg/d	-37.6% (-100, 220.0)	
		P-value *(Wilcoxon rank-sum tests)*	0.017	
	Key secondary endpoint #4 50% responder rate (M period only)	Comparison groups	Placebo	0.2 mg/kg/d
		% achieving a ≥50% reduction from Baseline in CSF	10.3%	43.6%
		Relative Risk (95% CI)	4.25 (1.57, 11.49)	
		P-value	0.0018	
	Key secondary endpoint #5 Longest interval between convulsive seizures (T+M period)	Comparison groups	Placebo	0.2 mg/kg/d
		Median longest convulsive seizure-free interval (days)	9.5	15.0
		95% CI for Treatment Difference	0.00, 9.00	
		P-value	0.035	
Notes	A total of 173 subjects were screened for eligibility to participate in this study; of these, 119 subjects were randomized to study treatment in a 1:1:1 ratio (placebo: 40 subjects; ZX008 0.2 mg: 39 subjects; and ZX008 0.8 mg: 40 subjects). A total of 110 subjects (92.4%) completed the study (37 subjects, 92.5% placebo; 39 subjects, 100% ZX008 0.2 mg/kg/day, and 34 subjects, 85.0% ZX008 0.8 mg/kg/day). Of the 9 subjects who did not complete the study 3 were randomized to placebo and 6 were randomized to ZX008 0.8 mg/kg/day. Reasons for premature discontinuation for the 3 subjects randomized to placebo were withdrawal by subject (ie, parent or legal guardian) (2 subjects [5.0%]), and lack of efficacy (1 subject [2.5%]). Reasons for premature discontinuation for the 6 subjects randomized to ZX008 0.8 mg/kg/day group were AEs (5 subjects [12.5%]), and withdrawal by subject (1 subject [2.5%]). AEs leading to withdrawal occurred only in the ZX008 0.8 mg/kg/day group.			
Analysis description	**Secondary analysis (pre-specified)**			
Analysis population and time point description	M Period: Proportion of Subjects with ≥25%, ≥75%, and 100% Reduction from Baseline in Convulsive Seizure Frequency (mITT Population)			
Descriptive statistics	Treatment group	Placebo	0.2 mg/kg/d	0.8 mg/kg/d

and estimate variability	Number of subjects	N=40	N=39	N=40
	≥75% %	5.1	25.6	52.5
	=100% %	0	15.4	15
Analysis description	**Secondary analysis (pre-specified)**			
Analysis population and time point description	T+M Period: Investigator Ratings of Improvement on the Clinical Global Impression – Improvement (CGI-I) at Visit 12			
Descriptive statistics and estimate variability	Treatment group	Placebo	0.2 mg/kg/d	0.8 mg/kg/d
	Number of subjects	N=37	N=39	N=38
	Mean CGI-I Rating	3.5	3.0	2.3
	SE	0.15	0.21	0.21
	Median	4.0	3.0	2.0
	Min, Max	1, 6	1, 6	1, 7
	Clinically Meaningful Improvement, n (%) Much Improved or Very Much Improved (Score 1, 2)	4 (10.0%)	16 (41.0%)	25 (62.5%)
	Improved, n (%) Minimally Improved, Much Improved, or Very Much Improved (Score 1, 2, 3)	16 (40.0%)	23 (59.0%)	32 (80.0%)

Table 7 Summary of efficacy for Study 1504

Title: A Multicenter, Randomized, Double-blind, Placebo-controlled Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of ZX008 (Fenfluramine Hydrochloride) Oral Solution, as Adjunctive Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome: Study ZX008-1504 Cohort 2	
Study identifier	ZX008-1504 C2 IND 125797 EudraCT No. 2016-000474-38
Design	Study 1504 Cohort 2 was a multicenter, randomized, double-blind, placebo-controlled parallel group evaluation of the efficacy, safety, and tolerability of ZX008 when added to standard-of-care treatment that included stiripentol (STP) in the treatment of seizures in children and young adults with Dravet syndrome. PK and safety data from Study 1504 Cohort 1 from 18 subjects were collected and evaluated together with data from Study ZX008-1505 (healthy volunteer drug-drug interaction study) and informed the dose of ZX008 (0.5 mg/kg/day, maximum 20 mg/day) to be used in Study 1504 Cohort 2. After obtaining informed consent/assent, subjects entered a 6-week Baseline Period. This period consisted of the establishment of initial eligibility during a screening visit followed by an observation period when subjects were assessed for baseline seizure activity based on recordings of daily seizure activity entered into an electronic diary. Upon completion of the baseline period, subjects who qualified for the study were randomized (1:1) in a double-blind manner to receive ZX008 (at a dose of 0.5 mg/kg/day; maximum dose of 20 mg/day) or placebo. Randomization was stratified by age group (< 6 years, ≥ 6 years) to ensure balance across treatment arms with at least approximately 25% of subjects in each age group.

	All subjects were titrated in a blinded fashion to their randomized dose over a 3-week Titration Period. Following titration, subjects continued treatment at their randomly assigned dose during a 12-week Maintenance Period. For subjects who completed the full Titration and Maintenance Periods (T+M) total treatment time was 15 weeks. At the end of the Maintenance Period (or early discontinuation), all subjects underwent a 2-week blinded taper or transition (Taper/Transition Period), depending on whether they exited the study or were enrolled in the subsequent long-term open-label extension study. Parents/caregivers used an electronic diary every day during study participation to record the number/type of seizures, dosing, and use of rescue medication.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		16 months First Patient Enrolled: 27 January 2017 Last Patient Last Visit: 5 June 2018 Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Placebo		Placebo throughout the 3-week Titration Period (T) and 12-week Maintenance Period (M); 44 randomized
	ZX008 0.5 mg		Subjects randomized to be titrated from 0.2 mg/kg/day up to 0.5 mg/kg/day over the 3-week Titration Period (T) and then taking 0.5 mg/kg/day (up to a maximum dose of 20 mg/day) for the 12-week Maintenance Period (M); 43 randomized
Endpoints and definitions	Primary efficacy endpoint	CSF per 28 days	Change from Baseline during T+M in the mean convulsive seizure frequency (CSF) per 28 days for the ZX008 0.5 mg/kg/day group compared with the placebo group
	Key secondary endpoint #1	Proportion of subjects who achieved a ≥50% reduction from Baseline in CSF	The proportion of subjects with a ≥50% reduction from Baseline in convulsive seizure frequency for the 0.5 mg/kg/day group compared to placebo
	Key secondary endpoint #2	Longest interval between convulsive seizures	The longest interval between convulsive seizures during the T+M Period for the 0.5 mg/kg/day group compared to placebo
Database lock	21 August 2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Convulsive Seizure Frequency Per 28 Days: Baseline and T+M Period – Parametric Analysis based on log transformation (mITT Population) All efficacy parameters were summarized by descriptive statistics. Two-sided statistical significance testing (alpha level = 0.05) comparing ZX008 to placebo were performed for the primary and secondary endpoints as described below, unless otherwise noted. A serial gatekeeping strategy was developed to control the Type I error rate for pairwise comparisons between ZX008 and placebo groups across the family of the primary and key secondary efficacy parameters. Key secondary endpoints are listed below in order of testing.		
Descriptive statistics	Treatment group	Placebo	0.5 mg/kg/d

and estimate variability	Number of subjects	N=44	N=43	
	Mean baseline CSF per 28 Days (SD)	21.62 (27.7)	27.90 (36.9)	
	Median baseline CSF per 28 Days	10.67	14.3	
	Min, Max	2.7, 162.7	2.7, 213.3	
	Mean T+M CSF per 28 Days (SD)	20.97 (27.7)	24.72 72.1)	
	Median T+M CSF per 28 Days	11.43	5.17	
	Min, Max	2.2, 170.1	0.0, 458.6	
	Median CSF at end of M period (max,min)	11.4 (0.7, 169.3)	3.9 (0.0, 518.0)	
Effect estimate per comparison	Primary endpoint (M period only)	Comparison groups	0.5 mg/kg/d vs Placebo	
		Estimate of % Difference from Baseline in CSF	54.9%	
		95% CI	35.62, 68.33	
		P-value (ANCOVA)	<0.001	
	Median percent change in CSF from baseline	Comparison groups	0.5 mg/kg/d vs Placebo	
		Placebo	-1.1% (-82.8, 435.1)	
		0.5 mg/kg/d	-63.1% (-100, 115.0)	
		P-value *(Wilcoxon rank-sum tests)*	<0.001	
	Key secondary endpoint #1 50% responder rate (M period only)_	Comparison groups	Placebo	0.5 mg/kg/d
		% achieving a ≥50% reduction from Baseline CSF	9.1%	54.8%
		Relative Risk (95% CI)	6.02 (2.27, 15.95	
		P-value	< 0.001	
	Key secondary endpoint #2 Longest interval between convulsive seizures (T+M period)	Comparison groups	Placebo	0.5 mg/kg/d
		Median longest convulsive seizure-free interval (days)	13.0	22.0
		95% CI for Treatment Difference	2.00, 15.00	
		P-value	0.004	
Notes	A total of 87 subjects in Study 1504 Cohort 2 were randomized to study treatment in a 1:1 ratio (placebo: 44 subjects; and ZX008 0.5 mg/kg/day: 43 subjects) and received study drug. Overall, 77 subjects (88.5%) completed the study. Of the 10 subjects who did not complete the study, 3 subjects were in the placebo group and 7 subjects were in the ZX008 0.5 mg/kg/day group. Reasons for premature discontinuation in the placebo group were 1 subject (2.3%) with an adverse event of seizures, 1 subject (2.3%) with worsening of seizures, and 1 subject (2.3%) with uncontrolled seizures. Reasons for premature discontinuation in the ZX008 0.5 mg/kg/day group were as follows: 2 subjects (4.7%) due to AEs, 1 subject (2.3%) in each of the following: lack of efficacy, physician decision, subject early termination due to worsening seizures, and withdrawal by subject. The seventh subject with premature discontinuation in the ZX008 0.5mg/kg/day group was Subject No.			

	0201-84 was discontinued early per Sponsor due to inappropriate study enrollment - mild mitral regurgitation present at an initial Screening ECHO, but not identified at a subsequent rescreening ECHO, which allowed the subject to be inappropriately enrolled into the study.		
Analysis description	**Secondary endpoint (pre-specified)**		
	M Period: Proportion of Subjects with ≥25%, ≥75%, and 100% Reduction from Baseline in Convulsive Seizure Frequency (mITT Population)		
Descriptive statistics and estimate variability	Treatment group	Placebo	ZX008 0.5 mg/kg/d
	Number of subjects	N=44	N=43
	≥75% %	4.5	40.5
	=100% %	0 (0.0)	4.8
	Secondary analysis (pre-specified)		
	T+M Period: Investigator Ratings of Improvement on the Clinical Global Impression – Improvement (CGI-I) at Visit 12		
Descriptive statistics and estimate variability	Treatment group	Placebo	0.5 mg/kg/d
	Number of subjects	N=40	N=42
	Mean CGI-I Rating	3.5	2.7
	SE	0.17	0.20
	Median	4.0	3.0
	Min, Max	1, 6	1, 6
	Clinically Meaningful Improvement, n (%) Much Improved or Very Much Improved (Score 1, 2)	7 (15.9)	19 (44.2)
	Improved, n (%) Minimally Improved, Much Improved, or Very Much Improved (Score 1, 2, 3)	14 (31.8)	31 (72.1)

Supportive study(ies)

Study 1503 – Open Label Extension

Additional data from Study 1503, the ongoing open-label extension study for subjects from Study 1, Study 2 and Study 1504, is provided as supportive data. Subjects who had received at least 1 month of open-label treatment at the time of the Study 1503 data cut-off on 14 October 2019 were included in the interim clinical study report. The primary objective of Study 1503 is long-term safety and tolerability of fenfluramine.

330 patients enrolled in the study with a variety in time included (304/330 patients received fenfluramine for 6 months or longer and 282/330 have received fenfluramine for 1 year or longer in the OLE Study). 228 (69.1%) of the patients are still included, 27 (8.2%) patients transitioned to Study 1900 (the continuation open-label study) and continue to receive fenfluramine, and 75 (22.7%) patients discontinued from OLE Study 1503. Of the 75 patients who discontinued, the majority discontinued because of lack of efficacy 48/75 (64%). Continuation of treatment in this OLE-study is no evidence of efficacy in the long term.

2.5.3. Discussion on clinical efficacy

Efficacy data from the 2 completed studies (Study 1 and Study 1504 Cohort 2), and an interim analysis of the long-term extension study (Study 1503) were included in the application and discussed.

Due to slow enrolment, Study 1 was a combined analysis of studies 1501 and 1502, nearly identical trials running in North America and Europe/Australia respectively. The first N=119 subjects randomised from either trial comprised Study 1.

Design and conduct of clinical studies

For both studies, the patient population studied is considered overall representative of the intended target population although inclusion of patients younger than 2 years would have been preferable and there is very limited data in the adult population. The diagnosis was based on clinical criteria and both patients with and without genetic confirmation were included.

Regarding the endpoint structure, there was some deviations from guideline requirements, but it is considered overall acceptable and in accordance with CHMP advice previously provided.

Whereas the design of the individual studies 1501, 1502 and 1504c2 appears adequate, Study 1 is the pooled analysis of studies 1501 and 1502. This was not described in a protocol. In addition, a number of study conduct breaches were identified (retrospective data collection, arbitrary selection of number of seizures for cluster seizures, problems with data transfer, queries not solved, rescreened patients etc.). A GCP inspection was therefore requested and several deviations, including some critical, were made. Sensitivity analyses regarding missing data, cluster values, and GCP violations were therefore requested during the assessment. The impact of the study conduct breaches on the results of the 0.5 and 0.8 mg/kg/day was found to be small, but the results for the 0.2 mg/kg/day were considered less robust.

Efficacy data and additional analyses

In both studies, Fintepla treatment was associated with a reduction of convulsive seizure frequency.

In Study 1, the primary endpoint was met with a convulsive seizure frequency reduction from 32.95 to 18.89 in the 0.8 mg/kg/day group as compared to a reduction from 46.07 to 40.56 in the placebo group. The clinical relevance of the reduction was supported by the 50% responder analysis where 70% of the patients on 0.8 mg/kg/day achieved a 50% reduction as compared to 7.5% of patients on placebo. However, since patients were not on stiripentol, a caveat regarding clinical relevance is whether a comparable effect could have been achieved by optimising AED treatment, including by stiripentol.

It was observed that the odds ratio for the secondary endpoint varies considerably in the sensitivity analyses, which makes this estimate not reliable. It is also of concern that there was no improvement on clinically relevant outcome measures such as risk of prolonged seizures or status epilepticus. In fact, the percentage of patients with status epilepticus was higher on active treatment (35% for patients on 0.8 mg/kg/day) than on placebo (25%). Similarly, the probability of a seizure being of more than 10 minutes duration was 4.82 in the 0.8 mg/kg/day arm as compared to 2.38 in the placebo arm.

Regarding the 0.2 mg/kg/day dose, it appears that this is a suboptimal dose, supported with less robust data. However, this is noted that it is not the intended treatment maintenance dose and in clinical practice

patients will be titrated upon response and tolerability. Therefore, the level of evidence provided for this dose and the less robust data regarding efficacy are accepted.

In Study 1504, the primary endpoint was also met. The mean CSF was 21.62 at baseline and 20.97 at the end of the T+M period for the placebo group, whereas the mean CSF decreased from 27.90 at baseline to 24.72 at the end of the T+M period for the active group (a 54.0% (95% CI: 35.6%, 67.2%) greater reduction for the active group). The clinical relevance of the reduction was supported by the 50% responder analysis where 53.5% of the patients on 0.5 mg/kg/day achieved a 50% reduction as compared to 4.5% of patients on placebo. The CHMP noted however that, similarly to study 1, there was an increased incidence of status epilepticus in the active arm (32.6%) as compared to the placebo arm (18.2%).

There was very limited data presented for the adult population. Data on a subgroup of 7 patients who were 18-19 years of age at time of first dose administration in double-blind Studies 1 and 1504 were discussed (4 patients in placebo group, 1 in 0.5mg/kg fenfluramine and 2 in 0.8mg/kg fenfluramine). In the placebo group (n=4) the % change in CSF range +18.0 to – 36%. In the fenfluramine group (n=3) the % change from baseline in CSF range from -67.4% to -96.1%. These limited data support to some degree the efficacy in in fenfluramine naïve adults. During the oral explanation, the Applicant presented data on seizure type and frequency across age groups from infants to adults with Dravet syndrome confirming a high seizure burden and overall comparable distribution of seizure types independent of age (Lagae 2018). In addition, limited data from adolescents/young adults suggest efficacy in adults. Taking together the similarity of seizure burden and seizure types in adult compared to paediatric patients with Dravet syndrome and at least some evidence from the clinical studies that fenfluramine also works in adult patients, the CHMP concluded that extrapolation of efficacy is possible.

2.5.4. Conclusions on the clinical efficacy

The efficacy of Fintepla, as add-on therapy to other AEDs, in children with Dravet Syndrome is supported by 2 randomised, double-blind studies. In both studies, Fintepla treatment was associated with a reduction of convulsive seizure frequency. The CHMP agreed that the available data support the efficacy in the use of Fintepla as add-on therapy to other AEDs, in children with Dravet Syndrome from 2 years of age and older.

2.6. Clinical safety

Patient exposure

Exposure in controlled studies:

Overall, 112 patients were exposed to ZX008 in the 2 double-blind studies (N=79 from study 1, N=43 from study 1504). The duration of these trials was 2-weeks titration, 12-weeks treatment, and 2-3 weeks tapper, so overall 16-17 weeks.

Exposure in open-label extension:

330 patients had been exposed to target doses of ZX008 in the open-label extension study, with 282 patients exposed for more than 12 months and 128 patients exposed for more than 24 months. It is however noted that data on patients from study 2 (an on-going phase 3 study still blinded) who entered the open-label study are not yet available for evaluation as this study has not been unlocked.

Demographics

The included patients had a mean age of approx. 9 years in the phase 3 studies and 11 years in the open-label extension. More males (55%) than females (45%) were included reflecting a male-to-female ratio above one in DS. Baseline characteristics such as weight, height, ratio of races, and concomitant antiepileptic treatment were balanced between placebo and treatment groups.

Adverse events

Adverse events were more common in ZX008-groups than in the placebo groups. However, taking the time on study into consideration, the number of AEs, SAEs, and discontinuations due to AEs was relatively constant.

The most frequently reported TEAEs were decreased appetite (34.4% ZX008 vs. 8.3% placebo respectively), nasopharyngitis (14.8% vs. 23.8%), echocardiogram abnormal (16.4% vs. 6.0%), lethargy (13.9% vs. 4.8%), seizure (7.4% vs. 14.3%), somnolence (10.7% vs. 7.1%), pyrexia (16.4% vs. 14.3%), fatigue (15.6% vs. 3.6%) and diarrhoea (23.8% vs. 7.1%).

Treatment-emergent adverse events during double-blind treatment period by MedDRA SOC and Preferred Term in ≥ 5% subjects in any treatment groups

MedDRA System Organ Class/ Preferred Term	Placebo (N=84)	ZX008 0.2 mg (N=39)	ZX008 0.5 mg+STP (N=43)	ZX008 0.8 mg (N=40)	Any DB ZX008 (N=122)	All Subjects (N=206)
Subjects with any TEAE	68 (81.0%)	37 (94.9%)	42 (97.7%)	38 (95.0%)	117 (95.9%)	185 (89.8%)
Gastrointestinal disorders	17 (20.2%)	20 (51.3%)	16 (37.2%)	15 (37.5%)	51 (41.8%)	68 (33.0%)
Constipation	1 (1.2%)	1 (2.6%)	4 (9.3%)	4 (10.0%)	9 (7.4%)	10 (4.9%)
Diarrhea	6 (7.1%)	12 (30.8%)	10 (23.3%)	7 (17.5%)	29 (23.8%)	35 (17.0%)
Salivary hypersecretion	0	2 (5.1%)	0	1 (2.5%)	3 (2.5%)	3 (1.5%)
Vomiting	7 (8.3%)	4 (10.3%)	2 (4.7%)	3 (7.5%)	9 (7.4%)	16 (7.8%)
General disorders and administration site conditions	19 (22.6%)	13 (33.3%)	24 (55.8%)	8 (20.0%)	45 (36.9%)	64 (31.1%)
Asthenia	2 (2.4%)	1 (2.6%)	3 (7.0%)	0	4 (3.3%)	6 (2.9%)
Chills	0	0	1 (2.3%)	2 (5.0%)	3 (2.5%)	3 (1.5%)
Decreased activity	1 (1.2%)	1 (2.6%)	0	2 (5.0%)	3 (2.5%)	4 (1.9%)
Fatigue	3 (3.6%)	4 (10.3%)	11 (25.6%)	4 (10.0%)	19 (15.6%)	22 (10.7%)
Pyrexia	12 (14.3%)	7 (17.9%)	11 (25.6%)	2 (5.0%)	20 (16.4%)	32 (15.5%)
Infections and infestations	47 (56.0%)	19 (48.7%)	25 (58.1%)	13 (32.5%)	57 (46.7%)	104 (50.5%)
Bronchitis	2 (2.4%)	1 (2.6%)	5 (11.6%)	0	6 (4.9%)	8 (3.9%)
Croup infectious	1 (1.2%)	3 (7.7%)	0	1 (2.5%)	4 (3.3%)	5 (2.4%)
Ear infection	2 (2.4%)	2 (5.1%)	4 (9.3%)	1 (2.5%)	7 (5.7%)	9 (4.4%)
Nasopharyngitis	20 (23.8%)	4 (10.3%)	7 (16.3%)	7 (17.5%)	18 (14.8%)	38 (18.4%)
Rhinitis	2 (2.4%)	3 (7.7%)	3 (7.0%)	1 (2.5%)	7 (5.7%)	9 (4.4%)
Upper respiratory tract infection	8 (9.5%)	8 (20.5%)	4 (9.3%)	0	12 (9.8%)	20 (9.7%)
Urinary tract infection	0	2 (5.1%)	2 (4.7%)	0	4 (3.3%)	4 (1.9%)
Viral upper respiratory tract infection	0	1 (2.6%)	1 (2.3%)	2 (5.0%)	4 (3.3%)	4 (1.9%)
Injury, poisoning and procedural complications	12 (14.3%)	7 (17.9%)	7 (16.3%)	1 (2.5%)	15 (12.3%)	27 (13.1%)
Contusion	0	2 (5.1%)	0	0	2 (1.6%)	2 (1.0%)
Fall	4 (4.8%)	4 (10.3%)	0	0	4 (3.3%)	8 (3.9%)

MedDRA System Organ Class/ Preferred Term	Placebo (N=84)	ZX008 0.2 mg (N=39)	ZX008 0.5 mg+STP (N=43)	ZX008 0.8 mg (N=40)	Any DB ZX008 (N=122)	All Subjects (N=206)
Investigations	19 (22.6%)	24 (61.5%)	17 (39.5%)	20 (50.0%)	61 (50.0%)	80 (38.8%)
Blood glucose decreased	2 (2.4%)	0	6 (14.0%)	0	6 (4.9%)	8 (3.9%)
Blood pressure diastolic increased	4 (4.8%)	3 (7.7%)	0	3 (7.5%)	6 (4.9%)	10 (4.9%)
Blood pressure increased	3 (3.6%)	3 (7.7%)	0	2 (5.0%)	5 (4.1%)	8 (3.9%)
Blood pressure systolic increased	0	2 (5.1%)	0	0	2 (1.6%)	2 (1.0%)
Blood prolactin increased	0	0	0	3 (7.5%)	3 (2.5%)	3 (1.5%)
Echocardiogram abnormal[a]	5 (6.0%)	7 (17.9%)	4 (9.3%)	9 (22.5%)	20 (16.4%)	25 (12.1%)
Heart rate increased	2 (2.4%)	3 (7.7%)	1 (2.3%)	1 (2.5%)	5 (4.1%)	7 (3.4%)
Weight decreased	1 (1.2%)	5 (12.8%)	4 (9.3%)	2 (5.0%)	11 (9.0%)	12 (5.8%)
Metabolism and nutrition disorders	12 (14.3%)	9 (23.1%)	21 (48.8%)	17 (42.5%)	47 (38.5%)	59 (28.6%)
Decreased appetite	7 (8.3%)	8 (20.5%)	19 (44.2%)	15 (37.5%)	42 (34.4%)	49 (23.8%)
Dehydration	0	0	0	2 (5.0%)	2 (1.6%)	2 (1.0%)
Nervous system disorders	28 (33.3%)	20 (51.3%)	24 (55.8%)	16 (40.0%)	60 (49.2%)	88 (42.7%)
Ataxia	1 (1.2%)	2 (5.1%)	2 (4.7%)	3 (7.5%)	7 (5.7%)	8 (3.9%)
Balance disorder	0	2 (5.1%)	0	1 (2.5%)	3 (2.5%)	3 (1.5%)
Drooling	0	3 (7.7%)	1 (2.3%)	2 (5.0%)	6 (4.9%)	6 (2.9%)
Febrile convulsion	1 (1.2%)	0	0	0	0	1 (0.5%)
Headache	2 (2.4%)	3 (7.7%)	0	0	3 (2.5%)	5 (2.4%)
Hypotonia	0	0	0	3 (7.5%)	3 (2.5%)	3 (1.5%)
Lethargy	4 (4.8%)	4 (10.3%)	6 (14.0%)	7 (17.5%)	17 (13.9%)	21 (10.2%)
Seizure	12 (14.3%)	4 (10.3%)	2 (4.7%)	3 (7.5%)	9 (7.4%)	21 (10.2%)
Seizure cluster	1 (1.2%)	2 (5.1%)	0	0	2 (1.6%)	3 (1.5%)
Somnolence	6 (7.1%)	6 (15.4%)	3 (7.0%)	4 (10.0%)	13 (10.7%)	19 (9.2%)
Status epilepticus	2 (2.4%)	1 (2.6%)	5 (11.6%)	2 (5.0%)	8 (6.6%)	10 (4.9%)
Tremor	1 (1.2%)	1 (2.6%)	5 (11.6%)	1 (2.5%)	7 (5.7%)	8 (3.9%)

MedDRA System Organ Class/ Preferred Term	Placebo (N=84)	ZX008 0.2 mg (N=39)	ZX008 0.5 mg+STP (N=43)	ZX008 0.8 mg (N=40)	Any DB ZX008 (N=122)	All Subjects (N=206)
Psychiatric disorders	6 (7.1%)	5 (12.8%)	15 (34.9%)	10 (25.0%)	30 (24.6%)	36 (17.5%)
Abnormal behavior	1 (1.2%)	0	4 (9.3%)	3 (7.5%)	7 (5.7%)	8 (3.9%)
Irritability	2 (2.4%)	0	4 (9.3%)	1 (2.5%)	5 (4.1%)	7 (3.4%)
Respiratory, thoracic and mediastinal disorders	11 (13.1%)	7 (17.9%)	3 (7.0%)	6 (15.0%)	16 (13.1%)	27 (13.1%)
Rhinorrhea	3 (3.6%)	2 (5.1%)	1 (2.3%)	1 (2.5%)	4 (3.3%)	7 (3.4%)
Skin and subcutaneous tissue disorders	8 (9.5%)	3 (7.7%)	6 (14.0%)	5 (12.5%)	14 (11.5%)	22 (10.7%)
Rash	2 (2.4%)	2 (5.1%)	2 (4.7%)	2 (5.0%)	6 (4.9%)	8 (3.9%)

Source: ISS End-of-Text Table SADC11
Abbreviations: TEAE = Treatment-Emergent Adverse Event.
of mild MR who had been enrolled in error with a Screening ECHO finding of mild mitral valve regurgitation.
Note: Percentages are calculated based on the number of subjects in each treatment group.
Note: AEs are classified as treatment-emergent if they started on or after the date of first dose of study treatment. AEs with partial or missing start dates are classified as treatment-emergent, unless the nonmissing components of the start date confirm otherwise.
[a]All echocardiogram abnormal were limited to a finding of trace regurgitation; 1 subject (1504-C2- 0201-84) randomized to ZX008 0.5 mg/kg/day had 1 ECHO reading

Common adverse events:

Nervous system disorders were more common in the ZX008 groups than in the placebo group; especially the incidences of lethargy (14% vs. 5%), somnolence (11% vs. 7%), and status epilepticus (7 % vs. 2%). Psychiatric disorders occurred more often in the ZX008 groups than in the placebo group (25% vs. 7%), including PTs abnormal behaviour (6% vs. 1%) and irritability 4% vs. 2%.

Adverse events related to appetite regulation were also more frequent in the ZX008 group: decreased appetite (34% vs. 8%) and weight decreased (9% vs. 1%).

ECG changes were reported more often in the ZX008 group: 16% vs. 6%, as well as increased heart rate 4% vs. 2%.

Within the ZX008 dosing regimens, the following AEs occurred with a higher frequency in patients who received the ≥0.6-<0.8 mg/kg/day at the time of onset (% in patients receiving ≥0.2-<0.4 mg/kg/day vs. ≥0.4-<0.6 mg/kg/day vs. patients receiving ≥0.6-<0.8 mg/kg/day): Diarrhoea (5% vs. 3% vs. 9%), vomiting (4% vs. 1% vs. 10%), pyrexia (9% vs. 4% vs. 19%), blood glucose decreased (1% vs. 3% vs. 6%), echocardiogram abnormal (4% vs. 4% vs. 14%), decreased appetite (8% vs. 5% vs. 12%), seizures (5% vs. 2% vs. 10%).

Adverse events of special interest (AESI)

The adverse events of special interest comprise valvular heart disease and pulmonary arterial hypertension (PAH), seizures, weight decrease, changes of blood glucose and prolactin.

Valvular heart disease

Regurgitation has been evaluated by regular echocardiogram investigation. Mainly trace regurgitation was found, trace mitral valve regurgitation was most commonly reported. For all types of regurgitation, an oscillation between absent and trace regurgitation was reported. As per protocol, no patients with trace or higher degrees of valvular heart disease were included in the studies.

Mitral valve

The results of the double-blind studies show a higher incidence of mitral valve trace regurgitation in the ZX008 groups as compared to placebo (21% in the ZX008 groups vs. 10% in the placebo group).

No subject had a reading of 'moderate' or greater mitral regurgitation, and differences between the active treatment groups and placebo were driven by 'trace regurgitation'.

In the open-label extension of the studies, the overall frequency of Trace or greater mitral regurgitation was 32%. Review of the data by original core study treatment cohort shows the incidence ranges from 12/55 (22%) in the ZX008 0.2 mg/kg/day-OLE group, to 16/36 (44%) in the 0.8 mg/kg/day-OLE group.

Aortic, tricuspid, pulmonic valves and PAH

There were 4 subjects which experienced an abnormal aortic valve regurgitation. In 2 subjects, trace mitral and trace aortic valve regurgitation was reported concomitantly, but this was absent in subsequent echocardiograms. These 2 subjects continued treatment. The 2 other subjects discontinued following mild aortic regurgitation and trace aortic regurgitation. For both these subjects, follow-up echocardiograms showed absence of regurgitation, which is reassuring.

There were no signs of regurgitation over the tricuspid and pulmonic valves. Similarly, there was no sign of increased pulmonary artery systolic pressure (PASP), which, of note, was a very rare AE to the previous use of fenfluramine in the treatment of obesity.

Dose-response and time-response:

With regard to valvular heart disease, no data to allow an investigation of a possible dose-response or time-response relationship in the full safety analyses set was provided. However, the following frequencies of 'echocardiogram abnormal' have been reported in patients who entered the open-label extension from the completed phase 3 studies. 'Echocardiogram abnormal' by dose at onset was 0% in the 0-<0.2 mg/kg/day group; 3.5% in the ≥0.2-<0.4 mg/kg/day group; 4.3% in the ≥0.4-<0.6 mg/kg/day group; and 13.6% in the ≥0.6-<0.8 mg/kg/day group.

During the assessment, the Applicant conducted a series of analyses of potential correlations of the AE 'echocardiogram abnormal' with various definitions of the dose levels associated with the occurrence of this AE. It was however difficult to assess the potential correlation of the AE 'echocardiogram abnormal' with the relevant dose levels across the entire data set.

Cardiac conduction

There were no observable changes in QTc or QRS duration and treatment with fenfluramine did not influence the repolarisation of the heart.

Fenfluramine seems to influence the heart rate. Both HR increases and decreases were noted with changes of >10->20 bpm in the treatment groups. Some patients also experienced an increase of the PR-interval; the maximally recorded increases being 20-35 msec in patients aged 2-6 years and 6-12 years, respectively.

Decreased appetite and weight loss

Decreased appetite and hypophagia are known effects of fenfluramine. Among the 45/122 (36.9%) subjects in any ZX008 treatment group, who reported decreased appetite, 26/45 (57.8%) subjects had these events ongoing at the end of the double-blind treatment period.

A comparison of the ZX008 0.2 and 0.8 mg/kg/day doses from Study 1 showed a dose response with increased frequency of reporting for decreased appetite with increased dose levels of ZX008 (0.2 mg/kg/day: 9 [21.3%] and 0.8 mg/kg/day 15 [37.5%]).

At the end of the double-blind treatment period, in the placebo, ZX008 0.2 mg/kg/day, 0.5 mg/kg/day, and 0.8 mg/kg/day groups, 2 (2.4%), 5 (12.8%), 8 (18.6%), and 10 (26.3%) subjects had lost ≥ 7% of their baseline body weight while 13 (15.7%), 1 (2.6%), 2 (4.7%), and 0 (0.0%) had gained ≥ 7% of their baseline body weight respectively.

Blood glucose decrease

Blood glucose decreased was reported in 6 (14.0%) subjects randomized to ZX008 0.5 mg/kg/day + STP and 2 (2.4%) subjects in the combined placebo group, and 11 (6.3%) subjects in open-label extension Study 1503.

Among the 174 patients, who entered the open-label extension study from the completed phase 3 studies, the following AEs of 'blood glucose decreased' were reported: 0% in the 0-<0.2 mg/kg/day group; 1% in the ≥0.2-<0.4 mg/kg/day group; 3% in the ≥0.4-<0.6 mg/kg/day group; and 6% in the ≥0.6-<0.8 mg/kg/day group.

The most recent analysis of the open-label extension study however did not show any clear dose related increase in the AEs of reduced blood glucose and hypoglycemia.

It is accepted that all the AEs of blood glucose decreased or hypoglycemia were mild, transient in nature, and all resolved without treatment.

Seizures and Seizure-Related Events

Seizures were reported as AEs in 12% of the population who were enrolled in the open-label extension study. The frequency of patients who reported an AE of seizure was highest in the ≥ 0.6 - ≤0.8 mg/kg/day group; N=10, 10%.

In same population, although only reported for the time in controlled studies, the incidence rate of status epilepticus (SE) was higher in the ZX008 groups than the placebo group as shown in the table below.

Table 8: Incidence Rate Serious Adverse Events During Double-blind Treatment Period by MedDRA system Organ Class and Preferred Term; ISS-DB-SAF Population

MedDRA System Organ Class/ Preferred Term	13. Placebo (N=84)	14. ZX008 0.2 mg (N=39)	15. ZX008 0.5 mg (N=43)	16. ZX008 0.8 mg (N=40)	17. Any DB ZX008 (N=122)
Status epilepticus	7.70	8.41	23.01	17.43	16.48

A number of additional analyses in various data sets on the incidence of seizures and SE was presented and it appears that the relationship between fenfluramine, concomitant STP and the occurrence of seizure/status epilepticus is clear.

Prolactin increase

Elevation in prolactin level has been previously associated with fenfluramine and seizures in epilepsy. There was a small dose-dependent increase of prolactin levels during treatment with ZX008. The increases were independent of recent seizure frequency as the tests were taken at least 48 hours after the last seizure.

Serious adverse event/deaths/other significant events

Deaths

Three deaths (a 2-year old male, a 8-year old female and a 5-year old male) were reported during the clinical development programme. None of them were assessed as related to study medication. The medical monitor agreed with the investigator's assessment of causality.

Serious adverse events

The incidence of serious TEAEs was similar in subjects randomized to ZX008 compared to subjects randomized to placebo. Overall, 15 (12.3%) subjects in any ZX008 treatment group compared to 11 (13.1%) subjects in the combined placebo group reported at least 1 serious TEAE.

Serious TEAEs During Double-blind Treatment Period by MedDRA System Organ Class and Preferred Term; ISS-DB-SAF Population

MedDRA System Organ Class/ Preferred Term	Placebo (N=84)	ZX008 0.2 mg (N=39)	ZX008 0.5 mg (N=43)	ZX008 0.8 mg (N=40)	Any DB ZX008 (N=122)	All Subjects (N=206)
Subjects with any Serious TEAE	11 (13.1%)	4 (10.3%)	6 (14.0%)	5 (12.5%)	15 (12.3%)	26 (12.6%)
Nervous system disorders	7 (8.3%)	2 (5.1%)	5 (11.6%)	4 (10.0%)	11 (9.0%)	18 (8.7%)
Status epilepticus	2 (2.4%)	1 (2.6%)	3 (7.0%)	2 (5.0%)	6 (4.9%)	8 (3.9%)
Seizure	5 (6.0%)	1 (2.6%)	1 (2.3%)	1 (2.5%)	3 (2.5%)	8 (3.9%)
Lethargy	0	0	1 (2.3%)	1 (2.5%)	2 (1.6%)	2 (1.0%)
Somnolence	0	0	0	1 (2.5%)	1 (0.8%)	1 (0.5%)
Febrile convulsion	1 (1.2%)	0	0	0	0	1 (0.5%)
Generalised tonic-clonic seizure	2 (2.4%)	0	0	0	0	2 (1.0%)
Seizure cluster	1 (1.2%)	0	0	0	0	1 (0.5%)
Infections and infestations	4 (4.8%)	1 (2.6%)	0	0	1 (0.8%)	5 (2.4%)
Lower respiratory tract infection	1 (1.2%)	1 (2.6%)	0	0	1 (0.8%)	2 (1.0%)
Gastroenteritis viral	1 (1.2%)	0	0	0	0	1 (0.5%)
Pneumonia	2 (2.4%)	0	0	0	0	2 (1.0%)
Gastrointestinal disorders	1 (1.2%)	0	0	1 (2.5%)	1 (0.8%)	2 (1.0%)
Diarrhea	0	0	0	1 (2.5%)	1 (0.8%)	1 (0.5%)
Abdominal pain	1 (1.2%)	0	0	0	0	1 (0.5%)
General disorders and administration site conditions	1 (1.2%)	0	0	1 (2.5%)	1 (0.8%)	2 (1.0%)
Adverse drug reaction	0	0	0	1 (2.5%)	1 (0.8%)	1 (0.5%)
Pyrexia	1 (1.2%)	0	0	0	0	1 (0.5%)
Investigations	0	0	0	1 (2.5%)	1 (0.8%)	1 (0.5%)
Weight decreased	0	0	0	1 (2.5%)	1 (0.8%)	1 (0.5%)
Metabolism and nutrition disorders	0	0	0	1 (2.5%)	1 (0.8%)	1 (0.5%)
Decreased appetite	0	0	0	1 (2.5%)	1 (0.8%)	1 (0.5%)
Musculoskeletal and connective tissue disorders	0	0	1 (2.3%)	0	1 (0.8%)	1 (0.5%)
Osteochondritis	0	0	1 (2.3%)	0	1 (0.8%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	0	1 (2.6%)	0	0	1 (0.8%)	1 (0.5%)
Hypoxia	0	1 (2.6%)	0	0	1 (0.8%)	1 (0.5%)
Injury, poisoning and procedural complications	1 (1.2%)	0	0	0	0	1 (0.5%)
Head injury	1 (1.2%)	0	0	0	0	1 (0.5%)

Source: ISS Table SSAR11.
TEAE = Treatment-Emergent Adverse Event.
Note: Percentages are calculated based on the number of subjects in each treatment group.
Note: AEs are classified as treatment-emergent if they started on or after the date of first dose of study treatment.

Laboratory findings

Platelet count

In the studies, at visit 12, the mean platelet counts (10^9/L) decreased slightly from baseline for all ZX008 treatment groups.

Chemistry

Slight decreases from baseline in mean and median liver function tests including alkaline phosphatase (ALP), alanine aminotransferase (ALT), and gamma glutamyl transferase (GGT), as well as cholesterol and creatine kinase (CK) and lactate dehydrogenase (LDH) were observed in the ZX008 treatment groups compared to the combined placebo group although mean and median values remained within the normal reference ranges.

Urinalyses

There were no clinically important changes.

Safety in special populations

Age and gender were evaluated as intrinsic factors. Renal or hepatic impairment were not evaluated.

Age

Selected AEs by age groups:

MedDRA Terms	**Age <6 N (%) ZX008**	**Age <6 N (%) Placebo**	**Age ≥ 6 N (%) ZX008**	**Age ≥6 N (%) Placebo**
Total AEs	30 (94%)	21 (92%)	87 (97%)	47 (77%)
PT Diarrhoea	13 (41%)	3 (13%)	16 (18%)	3 (5%)
PT Decreased Appetite	9 (28%)	1 (4%)	33 (37%)	6 (10%)
PT Weight decreased	2 (6%)	1 (4%)	9 (10%)	0
SOC Nervous system disorder	14 (44%)	9 (39%)	46 (51%)	19 (31%)
PT Somnolence	6 (19%)	1 (4%)	7 (8%)	5 (8%)
PT Lethargy	2 (6%)	0	15 (17%)	4 (7%)
SOC Psychiatric disorders	9 (28%)	0	21 (23%)	6 (10%)
PT Echocardiogram abnormal	3 (9%)	1 (4%)	17 (19%)	4 (7%)

Gender

Overall in male subjects, 64 (97.0%) subjects in any ZX008 treatment group compared to 40 (83.3%) subjects in the combined placebo group reported at least 1 TEAE. In female subjects, 53 (94.6%) subjects in any ZX008 treatment group compared to 28 (77.8%) subjects in the combined placebo group reported at least 1 TEAE.

Concomitant treatment with stiripentol

A greater proportion of subjects not treated with concomitant STP reported echocardiogram abnormal, although all findings were non-pathologic and mostly trace regurgitation; (13 [35.1%] in the combined placebo group and 23 [32.9%] in any ZX008 treatment group) compared to subjects treated with concomitant STP (2 [7.4%] in the combined placebo group and 4 [16.7%] in any ZX008 treatment group).

A greater proportion of subjects treated with concomitant STP reported decreased appetite (12 44.4%] in the combined placebo group and 13 [54.2%] in any ZX008 treatment group) compared to subjects not treated with concomitant STP (8 [21.6%] in the combined placebo group and 27 [38.6%] in any ZX008 treatment group). This finding is not unexpected since decreased appetite is a known AE associated with STP.

Pregnancy and lactation

There are limited literature data on the use of fenfluramine during pregnancy and lactation. There were no patients who were pregnant or breast feeding in the clinical studies.

Overdose

Over-dosing errors have been reported in 4 subjects that resulted in doses of ≥ 1.0 mg/kg/day for varied periods of time due to either caregiver error, incorrect weight used in the interactive web response system, site error in providing correct dose or dosing instructions, and availability of drug. In subjects that received more than 1.0 mg/kg/day dosing, 1 TEAE (weight loss) was deemed related to the study drug and was also temporally related with dosing error.

Only limited data have been reported concerning clinical effects and management of overdosage of fenfluramine. Agitation and drowsiness, confusion, flushing, tremor (or shivering), fever, sweating, abdominal pain, hyperventilation, and dilated nonreactive pupils seem frequent in fenfluramine overdosage. Reflexes may be either exaggerated or depressed and some subjects may have rotary nystagmus. Tachycardia may be present, but blood pressure may be normal or only slightly elevated. Convulsions, coma, and ventricular extrasystoles, culminating in ventricular fibrillation, and cardiac arrest, may occur at higher dosages. Less than 5 mg/kg fenfluramine is associated with toxicity in humans with 5 to 10 mg/kg producing coma and convulsions (von Muhlendahl 1979).

Drug Abuse

Fenfluramine does not have properties associated with abuse potential. Nonclinical studies data are consistent in showing that fenfluramine does not exhibit abuse potential and human abuse liability studies have demonstrated that fenfluramine does not possess significant abuse potential, even at high doses.

Withdrawal and Rebound

A review of TEAE with onset during the Transition/Taper period of the double-blind and Month 1 of the open-label extension study in ≥ 2% of subjects in the LTS-DB Population has been conducted. The number of subjects reporting TEAEs during the Transition/Taper period was similar for subjects randomized to ZX008 compared to subjects randomized to placebo. During this time period, increased seizures occurred in 6.3% of placebo subjects, 2.6% in the 0.2mg/kg/day ZX008 group, 0% in the ZX008 0.5mg/kg/day group, and 5.7% in the ZX008 0.8mg/kg/day group.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Compounds such as ZX008 which may cause lethargy, somnolence, and/or fatigue, should be used with caution if driving or operating machinery.

Immunological events

Experience from the previous treatment of obesity indication does not indicate a risk of immunological events for ZX008.

Safety related to drug-drug interactions and other interactions

ZX008 causes a release of serotonin and the interaction with serotonergic drugs leading to an increased risk of serotonin syndrome is possible.

Discontinuation due to adverse events

Across the treatment arms, 11 subjects (3/5%) discontinued the study due to an adverse event. The highest frequency of adverse events leading to discontinuation occurred in the 0.2 mg/kg/day group. This may be driven by subjects who received placebo previously and just started fenfluramine dosing. Abnormal behaviour appears to be the most common reason in the 0.2 mg/kg/day group (n= 3, 6.8%). Across the other dosing groups there does not appear to be a particular adverse event leading more frequently to discontinuation over others.

Post marketing experience

ZX008 has not been previously marketed for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older in any country.

Fenfluramine was previously marketed and prescribed in doses of 60 to 120 mg/day for the treatment of obesity in adults and was withdrawn from the US and European Union (EU) markets in 1997 due to the risk of development of valvular heart disease.

2.6.1. Discussion on clinical safety

The safety database comprises patients from the two completed phase 3 studies, one ongoing phase 3 study and an ongoing open-label extension study. The phase 3 studies have a duration of 16-17 weeks including up-titration and tapper-period. Therefore, the majority of the safety data derives from the open-label study. Overall, 112 patients were exposed to ZX008 in the double-blind studies and, following additional safety analyses provided during the assessment, 341 patients in the open-label extension (including 284 patients exposed for more than 12 months and 138 patients exposed for more than 24 months). Even in view of Dravet Syndrome being an orphan disease, the size of safety database is considered small as it only allows identification of adverse events with a high frequency or with an incidence markedly different from the background population.

Adverse events

Between 90 and 98% of the patients experienced at least one TEAE. The incidence of serious TEAEs was similar in subjects randomized to ZX008 compared to subjects randomized to placebo. Overall, 15 (12.3%) subjects in any ZX008 treatment group compared to 11 (13.1%) subjects in the combined placebo group reported at least 1 serious TEAE.

In the open-label extension study data, which has been presented this far, the risk of seizure-AEs was 12%, with the highest frequency of events occurring in the ≥ 0.6 - ≤0.8 mg/kg/day group.

The relationship between fenfluramine treatment, concomitant STP and the increased seizures frequency/status epilepticus was further discussed. It was recognized that the numbers reported are low. However, considering that the nature of the increased seizures frequency/status epilepticus cannot be determined and given the severity of the adverse event, the CHMP agreed that prescribers should be informed. A warning is therefore included in section 4.4 of the SmPC on possible increased seizures frequency. In addition, a subheading regarding status epilepticus, with the observed incidence, is added in section 4.8 of the SmPC.

The Applicant also provided data on AEs in the most commonly used anti-epileptic drug (AED) combinations: ZX008/clobazam/valproate, ZX008/clobazam/stiripentol and ZX008/valproate/stiripentol. Higher incidences were reported for somnolence, weight decreased and decreased appetite when the AED combinations were used comparing to when not used. This was further discussed, and the analyses showed a higher incidence of decreased appetite when the AED combinations were used. A warning regarding the higher incidence of decreased appetite and weight loss when fenfluramine is combined with other antiepileptic drugs, for example stiripentol, is therefore added in section 4.4 of the SmPC.

Cardiovascular safety

ZX008 is known to cause cardiac valvulopathy and pulmonary arterial hypertension (PAH) in patients treated for obesity, albeit by an unknown mechanism. According to the literature, the risk of valvulopathy and PAH increased with increasing exposure time. The dose-levels used to support the DS indication were between 2 and 4 times lower than the dose-levels used in adults in the treatment of obesity. It is however recognized that the treatment duration of DS patients may be longer and the short duration of the double-blind studies (overall 16-17 weeks) is an issue regarding the safety concern of cardiac valvulopathy, which is likely to occur with increasing incidence over time. The frequency of the valvulopathy events may also be below the detection limits of the current safety data.

During the development programme, the patients underwent an extensive echocardiographic evaluation and mainly trace regurgitation was observed. In the double-blind studies, trace regurgitation of the mitral valve was observed twice as often in the ZX008 groups as in the placebo group (21% vs. 10%). During the open-label extension study, mitral trace regurgitation was observed in between 20 and 27% of the population.

Additional supportive safety information from the open-label observational Belgian Cohort (ZXIIS2015-004) were provided as two publications (2012 and 2016, with treatment duration is roughly 1 up to 27 years). There were 4 subjects whose most recent echocardiogram indicated some structural changes, of which 3 did not experience any dysfunction. These patients were from the original Belgian cohort, where subjects were treated with fenfluramine with the range of 10 years up to 31 years. In these cases, the structural changes appear to remain stable. The other subject with structural changes is from the prospective cohort. These 4 subjects are currently stable on a low dose of fenfluramine. As all these subjects have been treated for a long time and even though no dysfunction is observed, the uncertainty remains that cumulative exposure to fenfluramine may lead to abnormalities on the echocardiogram rather than the dosage used.

The potential risk of VHD and PAH is recognized, and considering the remaining uncertainties regarding cardiovascular risk, it is agreed that further and more robust data regarding the long-term cardiac safety profile is key to consolidate the current safety profile of Fintepla in the DS indication. An imposed category 1 PASS registry, with a focus on characterising and quantifying the important potential risks VHD and PAH, is therefore agreed. It will collect data on the frequency of echocardiographic monitoring to contribute to the assessment of the effectiveness of the risk minimisation measures. Growth retardation, another potential important risk (see below) will also be evaluated in the agreed PASS registry.

Echocardiogram monitoring

With respect to the cardiac valvulopathy and possible development of PAH, an echocardiogram monitoring programme is proposed. Further analyses of potential correlations of the AE 'echocardiogram abnormal' with dose level were provided. Most of the analyses presented did not show any clear correlation to increasing dose. It is also acknowledged that the echocardiogram findings of trace regurgitation are common and usually non-pathological. The CHMP therefore agreed that for all patients, irrespective of the doses, echocardiogram monitoring should be performed every 6 months for the first two years and annually

thereafter if symptoms and echocardiography suggest consistently low probability of pulmonary hypertension on serial testing. Patients who discontinue fenfluramine treatment will be followed up until 6 months after treatment.

Regarding the prevention of the PAH risk, the CHMP also agreed with the proposed guidance on decision criteria for stopping the treatment if echocardiogram findings are suggestive of pulmonary arterial hypertension as described in the SmPC section 4.4, with a repeat echocardiogram as soon as possible and within 3 months to confirm the findings., and - if the echocardiogram finding is confirmed suggestive of an increased probability of PAH defined as "intermediate probability" by the 2015 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) Guidelines - it should lead to a benefit-risk evaluation of continuation of Fintepla by the prescriber, carer, and cardiologist. If the echocardiogram finding, after confirmation, suggests of a high probability of pulmonary arterial hypertension, as defined by the 2015 ESC and ERS Guidelines, it is recommended fenfluramine treatment should be stopped.

The CHMP also agreed with the Applicant that physicians' adherence to the echocardiogram monitoring plan should be assessed via a category 3 study on the effectiveness of risk minimisation measures so appropriate actions can be taken if adherence is low. In addition, the evaluation of the echocardiogram monitoring compliance is added in the category 1 imposed registry PASS as secondary objective.

In conclusion, the cardiac safety risk of Fintepla is recognised. It is appropriately addressed in the RMP and the Product Information, including the echocardiogram monitoring program. An imposed PASS registry will provide further and more robust data regarding the long-term cardiac safety of Fintepla, including the important potential risks VHD and PAH.

In addition, as the benefit-risk from potential off-label use in weight management with higher doses is known to be negative, a controlled access programme (CAP) is to be implemented in order to prevent off-label use and to ensure regular cardiac monitoring.

Adverse events of special interest (other than cardiac)

Decreased appetite, weight loss and height

Adverse events related to appetite regulation and weight loss were more frequent in the ZX008 group: Decreased appetite 34% vs. 8% and weight decreased 9% vs. 1%.

The highest number of events regarding decreased appetite and hypophagia were reported in the fenfluramine + stiripentol group. For the other fenfluramine groups, a dose-related effect could be observed. In both the double-blind and open-label extension studies, these events took an average of 40 days to resolve, and in both populations approximately half of the patients did not have the event resolved at the end of the study or interim cut-off point for the open-label extension study. Additionally, decreased glucose levels were noted more commonly in the ZX008 group as compared to the placebo group. The decreased appetite and weight loss are appropriately addressed in sections 4.4 and 4.8 of the SmPC.

It is noted that weight decrease associated with fenfluramine treatment was reported infrequently in the double-blind studies and does not appear to be related to reporting of decreased appetite. Further analysis on data available up to 24 months were provided by the Applicant. The subjects treated with fenfluramine do not experience a greater impairment of growth in terms of height. However, as data over 2 years is limited, the CHMP agreed that further data are needed to evaluate the impact of fenfluramine treatment on growth. Accordingly, growth retardation is a secondary objective of the imposed category 1 PASS registry.

Cognition

Based on analysis with the Behaviour Rating Instrument of Executive Function (BRIEF) and BRIEF2 instruments, there are apparently no negative effects on cognition following fenfluramine administration in both the double-blind and long-term extension studies.

Prolactin increase

Prolactin levels increased after fenfluramine administration were observed in the double-blind studies. However, the levels of prolactin did not deviate much from the normal range and did not appear to have any clinical impact.

Decreased platelet count

In the studies, decrease in platelet count was more frequently observed in the fenfluramine groups compared to the pooled placebo group. Concomitant use with valproate also resulted in a decreased platelet count in a few patients. The decreases were however small and most subjects remained within the reference range.

Laboratory values

Evaluation of possible changes in growth hormones, precocious puberty, thyroid function and Tanner staging revealed that these conditions are not influenced by longer-term treatment with fenfluramine.

Special populations and drug-drug interactions

Being a selective serotonin releasing agent, the risk of serotonin syndrome may be increased when used in combination with similar medicinal products. This is correctly addressed in the SmPC with a statement in section 4.4.

Supportive safety data

Withdrawals and abuse potential

There was no pattern of withdrawals or abuse potentials among the reported events.

Overdose

Based on the experience from the fenfluramine overdose when used in the treatment of obesity at the approved daily dose of 60 to 120 mg/day, the relevant information is included in section 4.9 of the SmPC.

De novo adult cohort

7 adult patients aged 18-19 years at the time of their first dose were included in the phase 3 studies. The amount of safety data in these 7 patients is too limited to draw any conclusions regarding the safety of fenfluramine in fenfluramine naïve adults**.** During the assessment, 28 patients aged >18 to ≤35 years were included in a De Novo Cohort and the safety data was presented. No difference in AE pattern from the paediatric population was observed in these limited adult data.

From the safety database, all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

In conclusion, the safety data presented is sufficient to allow a benefit-risk assessment in the paediatric population in the DS indication.

The CHMP considers the following measures necessary to address issues related to safety:

In view of the recognised important potential risk of VHD and PAH and the remaining uncertainties regarding long-term cardiovascular risk, the CHMP agrees that an imposed category 1 registry PASS, with a focus on characterising and quantifying the important potential risks VHD and PAH, is required. In addition, data regarding growth retardation will be collected in the imposed PASS.

As the benefit-risk from potential off-label use in weight management with higher doses is known to be negative, a controlled access programme (CAP) is to be implemented in order to prevent off-label use and to ensure regular cardiac monitoring.

Risk Management Plan

Safety concerns

Summary table of the 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 in Dravet syndrome patients • Off-label use (in wider paediatric epilepsies; obesity) • Use in patients with renal impairment • Use in patients with hepatic impairment

Pharmacovigilance plan

Table 9: Summary of On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
A **registry of subjects with Dravet syndrome treated with fenfluramine** Planned **Category 1**	**Primary objective**: to assess the long-term cardiac safety of fenfluramine prescribed in routine practice for subjects with Dravet syndrome, with a focus on: 1. Incidence of cardiac valvular disease (≥mild aortic regurgitation or ≥ moderate mitral regurgitation); 2. Incidence of PAH The **secondary objective** of this study is to assess the occurrence of growth retardation, if any, for subjects with Dravet syndrome prescribed	Valvular heart disease Pulmonary arterial hypertension Long-term safety in Dravet syndrome patients Growth retardation	Protocol submission Annual Progress reports Final report	Marketing approval + 2 months PBRER* October 2031

	fenfluramine in routine practice.			
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. Ongoing **Category 3**	**Primary objective**: 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	Final report	Q4 2021
ZX008-1902: a phase 1, open label, single dose, adaptive, multipart study to evaluate the effects of renal impairment on the pharmacokinetics of ZX008 (fenfluramine hydrochloride) in subjects with varying degrees of impaired and normal renal function Ongoing **Category 3**	**Primary objective**: Assess the effect of impaired renal function on the PK of ZX008 (fenfluramine hydrochloride)	Use in patients with renal impairment	Final report	Q4 2021
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 **Category 3**	**Primary objective**: Assess the effect of hepatic insufficiency on the PK of ZX008 (fenfluramine hydrochloride) oral solution	Use in patients with hepatic impairment	Final report	Q4 2021
A **drug utilisation study of fenfluramine in Europe** Planned **Category 3**	**Primary objective**: Describe fenfluramine use in routine clinical practice with a focus on its use in epilepsies other than Dravet syndrome if any **Secondary objectives**: 1. Describe the dose, frequency and duration of fenfluramine treatment 2. Describe the demographic characteristics (e.g., age, sex,	Off-label use (in wider paediatric epilepsies; obesity) Valvular heart disease Pulmonary arterial hypertension	Protocol submission Final report	Marketing approval +2 months August 2025

	weight) of patients treated with fenfluramine in routine clinical practice 3. Describe the extent and frequency of echocardiographic monitoring **Exploratory objective**: Identify and describe prescriptions of fenfluramine for weight management			
An European study of the effectiveness of risk minimisation measures for fenfluramine in Dravet syndrome Planned **Category 3**	**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 Final report	Marketing approval + 6 months October 2023

*Registry progress reports will be provided at each scheduled PBRER.

Risk minimisation measures

Table 10: Summary table of PV activities and risk minimisation activities by safety concern

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Valvular heart disease	**Routine risk minimisation measures**: • SmPC sections 4.3, 4.4 and 4.8 • PL sections 2, 4 • Contraindications to fenfluramine treatment in SmPC section 4.3 • Direction for echocardiogram assessment to confirm absence of cardiac valve disease prior to fenfluramine initiation in SmPC section 4.4.	**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

	• Direction for echocardiogram monitoring during use of fenfluramine in SmPC section 4.4. • Recommendations for actions to take with fenfluramine if regurgitation is detected on echocardiogram in SmPC section 4.4. • Guidance that fenfluramine should not be used in patients with valve disease 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	therapy in children and young adults with Dravet syndrome • A registry of subjects with Dravet syndrome treated with fenfluramine. • An European study of the effectiveness of risk minimisation measures for fenfluramine in Dravet syndrome. • A drug utilisation study of fenfluramine in Europe
Pulmonary arterial hypertension	**Routine risk minimisation measures**: • SmPC sections 4.3, 4.4 • PL sections 2, 4 • Contraindications to fenfluramine treatment in SmPC section 4.3 • Direction for echocardiogram assessment to confirm absence of pulmonary hypertension prior to fenfluramine initiation in SmPC section 4.4. • Direction for echocardiogram monitoring during use of fenfluramine in SmPC section 4.4. • Recommendations for actions to take with fenfluramine if pulmonary arterial hypertension is detected on echocardiogram in SmPC section 4.4 • Guidance that fenfluramine should not be used in patients with pulmonary arterial hypertension 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	**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 • A registry of subjects with Dravet syndrome treated with fenfluramine. • An European study of the effectiveness of risk minimisation measures for fenfluramine in Dravet syndrome. • A drug utilisation study of fenfluramine in Europe.

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
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 **Additional risk minimisation measures:** None	**Additional pharmacovigilance activities:** A registry of subjects with Dravet syndrome treated with fenfluramine
Long-term safety in Patients with Dravet syndrome	**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 • A Registry of subjects with Dravet syndrome treated with fenfluramine.
Off-label use (in wider paediatric epilepsy; obesity	**Routine risk minimisation measures**: • SmPC sections 4.1, 4.2 and 4.4 and 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 Drug utilisation study of fenfluramine in Europe.

		• An European study of the effectiveness of risk minimisation measures for fenfluramine in Dravet syndrome.
Use in patients with renal 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:** • ZX008-1902: A phase 1, open label, single-dose, adaptive, multipart study to evaluate the effects of renal impairment on the pharmacokinetics of zx008 (fenfluramine hydrochloride) in subjects with varying degrees of impaired and normal renal function
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

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 25.06.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Fintepla (fenfluramine) is included in the additional monitoring list as it has an imposed PASS registry to further characterise the long-term safety of fenfluramine regarding the important potential risks of VHD and PAH and growth retardation.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Dravet syndrome (DS) has an incidence of approximately 1:20,000 births. The prevalence estimates are uncertain, possibly around 3/100,000. DS is believed to account for approximately 7% of all severe epilepsies starting before the age of 3 years. The syndrome, also known as severe myoclonic epilepsy in infancy, is characterised by a variety of seizures (febrile and afebrile, generalized and unilateral, clonic or tonic–clonic) that occur in the first year of life. Onset usually between 4 and 8 months of age often triggered by fever. Significant developmental delay becomes apparent from the second year onwards and associated neuropsychological disturbances, such as attention deficit/hyperactivity disorder, are common. Intellectual impairment affects nearly all patients and is severe in 50% of cases. Between 70% and 80% of patients carry sodium channel α1 subunit gene (SCN1A) abnormalities.

3.1.2. Available therapies and unmet medical need

Only stiripentol (STP, Diacomit) and cannabidiol (Epidyolex), when taken in conjunction with sodium valproate (VPA) or clobazam (CLB), are currently approved in Europe for the treatment of DS. Neither VPA nor CLB are approved for DS specifically, but both are approved for use in epilepsy in the EU, and widely used. VPA is often used to prevent the initial recurrence of convulsive seizures, and benzodiazepines (e.g., diazepam, midazolam, clonazepam, or CLB) are frequently co-administered to limit the duration of long-lasting seizures. Second line and later options in DS typically include STP, topiramate, ketogenic diet, levetiracetam (LEV), bromides, and vagus nerve stimulation (VNS). Polytherapy is common. Of note, patients with DS may be prone to seizure exacerbation with sodium channel modulators such as carbamazepine, oxcarbazepine, LTG, phenytoin, and vigabatrin.

Sufficient seizure control may be difficult to achieve, and thus there is a need for new therapies with a different mode of action.

3.1.3. Main clinical studies

3.2. Favourable effects

In Study 1, the primary endpoint was met with a mean convulsive seizure frequency (CSF) reduction from 32.95 to 18.89 in the 0.8 mg/kg/day group as compared to a mean reduction from 46.07 to 40.56 in the placebo group. The median percent change in CSF from baseline was -72.4% for the 0.8 mg/kg/day group versus -17.4% for placebo. The clinical relevance of the reduction was supported by the 50% responder analysis where 72.5% of the patients on 0.8 mg/kg/day achieved a 50% reduction in the maintenance period as compared to 10.3% of patients on placebo in this period.

In Study 1504, the primary endpoint was also met. The mean CSF decreased from 27.90 at baseline to 24.72 at the end of the T+M period for the 0.5mg/kg/day group compared to 21.62 at baseline to 20.97 for the placebo. Patients randomised to Fintepla 0.5 mg/kg/day achieved a 54.9% greater reduction in monthly CSF

between the Baseline period and the M period than subjects randomised to placebo. The median percent change in CSF from baseline was -63.1% for the 0.5 mg/kg/day group versus -1.1% for placebo. The clinical relevance of the reduction was supported by the 50% responder analysis where 54.8% of the patients on 0.5 mg/kg/day achieved a 50% reduction in the maintenance period as compared to 9.1% of patients on placebo in this period.

3.3. Uncertainties and limitations about favourable effects

The design of the individual clinical studies 1501, 1502 and 1504 appears adequate, however the pooled analysis of studies 1501 and 1502 to form Study 1 was not described in a protocol and a number of study conduct breaches were identified. A GCP inspection was subsequently conducted and several violations were identified.

Sensitivity analyses indicated that the efficacy of the 0.2 mg/kg/day dose is not supported by robust clinical data.

The efficacy of fenfluramine in DS has only been investigated in children from 2-18 years old and adult data is sparse. As the pattern of seizures may change with age, the CHMP was of the opinion that efficacy data in children cannot be easily extrapolated to patients who will start treatment at adult age. However, during the oral explanation, the Applicant presented data on seizure type and frequency across age groups from infants to adults with Dravet syndrome confirming a high seizure burden and overall comparable distribution of seizure types independent of age (Lagae 2018). In addition, limited data from 7 adolescents/young adults suggest efficacy in adults. Taking together the similarity of seizure burden and seizure types in adult compared to paediatric patients with Dravet syndrome and at least some evidence from the clinical studies that fenfluramine also works in adult patients, the CHMP concluded that extrapolation of efficacy is possible.

3.4. Unfavourable effects

Nervous system disorders, such as lethargy (14% vs. 5%), somnolence (11% vs. 7%), and status epilepticus (7% vs. 2%), and psychiatric disorders, such as 'abnormal behaviour' (6% vs. 1%) and 'irritability' (4% vs. 2%) were more frequent in the ZX008 group as compared to the placebo group. These adverse reactions are also known for other AEDs.

Decreased appetite occurred in 37% of subjects in ZX008 groups as compared to 8% of subjects in the placebo group. Decreased appetite was ongoing in 60% of all subjects at the end of the double-blind treatment period. Decreased weight occurred in 9% in the ZX008 groups and 1% in the placebo group during the double-blind studies. Further, reduced blood glucose occurred in 5% in the ZX008 groups and 2% in the placebo group. Decreased appetite and weight reductions are also described for other AEDs.

3.5. Uncertainties and limitations about unfavourable effects

There is very little information regarding the exposure-safety relationship in the current dossier. The provided PK information is too limited to allow a full evaluation, in particular in terms of differential pharmacokinetics of metabolites and enantiomers.

Some analyses, conducted with various definitions of the safety variables, in different data sets and with frequencies are expressed in different ways, were difficult to assess. However, in several cases it seems acceptable to rely on the largest data set (330 patients) from the open-label extension study 1503.

Across the various data sets, the relationship between fenfluramine treatment, concomitant STP and the occurrence of seizure/status epilepticus is still unclear.

Reduced weight is a known risk with this product. Even though the data are currently not conclusive, there are also concern about reduced growth. Growth retardation is classified as an important potential risk in the RMP.

With respect to the safety database, the Applicant will perform a long-term registry PASS study to complement the rather small safety database from the current program. Focus will be on VHD and PAH, as well as growth retardation.

With respect to the safety database, the Applicant will perform a long-term registry PASS study to complement the rather small safety database from the current program. Focus will be on VHD and PAH, as well as growth retardation.

Although data in adult patients are limited, no difference in AE pattern was observed compared to paediatric patients.

Risk minimisation measures are considered adequate to mitigate the uncertainties.

The known risk of VHD and PAH from the use of fenfluramine as an appetite suppressant is considered a potential important risk in the DS indication (maximum doses 2-4 times lower than those used in weight management). This potential risk is addressed in the RMP, including the imposed PASS registry study, and in the echocardiogram monitoring program.

Considering that the potential risk for off-label use in weight management with the higher doses may not be addressed by these measures and in view of the known negative benefit-risk in such off-label use, the CHMP agreed that Fintepla should be prescribed and dispensed according to a controlled access programme.

3.6. Effects Table

Table 11: Effects Table for Fintepla in Dravet Syndrome indication

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Mean Convulsive seizure frequency reduction	0.8 mg, no stiripentol 0.5 mg, add-on to stiripentol	CSF per 28 days	-14.06 -3.18	-5.51 -0.65	p<0.001, observed values only, missing protocol p<0.001, observed values only	
Median percent change in CSF from baseline	0.8 mg, no stiripentol 0.5 mg, add-on to stiripentol	%	-72.4 -63.1	-17.4 -1.1	p-value <0.001 (Wilcoxon rank-sum test) p-value <0.001 (Wilcoxon rank-sum test)	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Proportion of patients with 50% reduction Maintenance period	0.8 mg, no stiripentol 0.5 mg, add-on to stiripentol	%	72.5 54.8	10.3 9.1	p<0.001, observed values only, missing protocol p<0.001, observed values only	
Unfavourable Effects						
Mitral valve trace regurgitation	Oscillations between absent and trace regurgitation occurred twice as often in the ZX008 groups than in the placebo group	%	21%	10%	Trace regurgitation is not clinically significant	SCS
Lethargy	PT, results from the two completed phase 3 DB-RCTs		14%	5%		SCS Table 10
Somnolence	As above		11%	7%		SCS Table 10
Status Epilepticus	As above		7%	2%		SCS Table 10
Psychiatric disorders	A mixture of different PTs		25%	7%	No single PT seemed to be markedly more common in the ZX008 group as compared to the placebo group	SCS Table 10
Heart rate increased			4%	2%		SCS Table 10
Decreased appetite			34%	8%		SCS Table 10
Weight decreased			9%	1%		SCS Table 10

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The reported reductions in seizure frequency and the number of patients achieving a 50% reduction in seizure frequency on Fintepla comparing to placebo appear to be clinically relevant. However, the frequency of prolonged seizures and status epilepticus is similar or paradoxically slightly worse on Fintepla comparing to placebo.

Data in adult fenfluramine naïve patients are limited but the continued high seizure burden emphasises the medical need. Based on published data, the frequency and types of seizures appear to be comparable across age groups and, together with evidence of efficacy in a limited number of adult patients and no specific safety concerns, it is considered acceptable to extrapolate the results from the primarily paediatric patients in the clinical studies to an adult population.

Regarding the unfavourable effects, Fintepla is associated with number of adverse events, including lethargy, somnolence, abnormal behaviour, irritability, decreased appetite and weight loss. These AEs, not uncommon for other AEDs and as such are not prohibitive for the use of Fintepla, should however be taken into consideration when evaluating the risk benefit. Previous experience with fenfluramine in the treatment of obesity in adults has demonstrated that the drug is associated with potentially serious cardiovascular toxicity, in particular VHD. While the data presented for Fintepla does not indicate similar problems in DS patients exposed to 2-4 fold lower doses, the safety database, in terms of both number of subjects exposed and duration of exposure, is too limited to provide reassurance that this concern is not relevant for the DS indication.

Therefore, a rigorous approach to the echocardiogram monitoring and strict decision criteria for stopping the treatment as described in the SmPC is pivotal. An imposed PASS is also considered necessary to address these safety uncertainties.

In addition, in order to prevent the off-label use in weight management where the benefit-risk is known to be negative, a controlled access programme should be established in each Member State prior to the launch of Fintepla.

3.7.2. Balance of benefits and risks

In paediatric subjects with DS, the effect on seizure frequency is clinically relevant and outweighs the unfavourable effect. In adults, data are limited but extrapolation is considered acceptable. The well-known risks of the product are adequately handled in SmPC, Annex II and RMP. In addition, Fintepla is to be prescribed and dispensed according to a controlled access programme.

Third party intervention during the evaluation of Fintepla

During the assessment of Fintepla, on 7 September and 12 September 2020, the CHMP received from the Dravet Syndrome European Federation a correspondence and survey analyses regarding the benefit of fenfluramine from the perspective of DS patients. On 09.09.2002, the CHMP also received a correspondence from the Spanish Fundación Síndrome de Dravet (FSD).

The correspondences and data highlighted the importance of increased treatment options for the DS patients and supported the Marketing Authorisation of Fintepla.

The CHMP noted those interventions.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Fintepla is positive.

The divergent position is appended to this report.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus 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.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority that the benefit-risk balance of Fintepla is favourable in the following indication:

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

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Fintepla in each Member State (MS), the marketing authorisation holder (MAH) must agree the content and format of the educational materials (EM) and the controlled access programme (CAP) including communication media, distribution modalities and any other aspects of the programme, with the National Competent Authorities (NCA).

The MAH shall ensure that, in each MS where Fintepla is marketed, a **CAP** is implemented to prevent off-label use for weight management in obese patients, since the benefit-risk ratio in this population is known to be negative.

In addition, the CAP shall be implemented to confirm that prescribing physicians have been informed of the need for periodic cardiac monitoring in patients taking Fintepla due to the potential risk of valvular heart disease and pulmonary arterial hypertension.

The MAH shall ensure that in each MS where Fintepla is marketed, all healthcare professionals who are expected to prescribe the product are aware of the CAP and are provided with the educational package consisting of:

- Summary of product characteristics (SmPC)
- HCP guide

The educational material for healthcare professionals (**HCP guide**) shall address the following risks:

- Valvular heart disease (VHD)
- Pulmonary arterial hypertension (PAH)
- Off-label use for weight management

The HCP guide shall contain the following key messages:

- Brief information about the historical background on fenfluramine and its market withdrawal due to the risks of VHD and PAH.
- Emphasis that the currently approved indication has to be strictly adhered to and access is therefore controlled ensuring proper information of physicians before prescribing.

- Informing physicians about the conditions of the Fintepla Controlled Access Programme (that are agreed on national level).
- Instruction on detection, monitoring, and/or proper management of VHD and PAH associated with fenfluramine.
- Advice to encourage patients/carers to enrol patients in the fenfluramine registry to collect long-term safety data.

The educational material for patients and/or caregivers should address the following risks:

- Valvular heart disease (VHD)
- Pulmonary arterial hypertension (PAH)

The **patient/carer guide** shall contain the following key messages:

- Information about the importance of periodic cardiac monitoring (ECHOs)
- Education about the detection and proper management of VHD and PAH associated with fenfluramine
- Encouragement to participate in the fenfluramine registry to collect long-term safety data.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
FINTEPLA Registry on long-term safety The MAH shall perform an observational registry to provide data on long-term safety of fenfluramine in routine practice, with a focus on characterising and quantifying the important potential risks VHD and PAH (primary objective), and growth retardation (secondary objective). In addition, data on the frequency of echocardiographic monitoring will contribute to assess the effectiveness of risk minimisation measures.	Final report: October 2031

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

The Member States should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

Prior to launch of Fintepla, the Member States should agree with the marketing authorisation holder (MAH) the content and format of the educational materials (EM) and the controlled access programme (CAP) including communication media, distribution modalities and any other aspects of the programme, with the National Competent Authorities (NCA).

The Member State where Fintepla is marketed should ensure that the MAH has implemented a **CAP** to prevent off-label use for weight management in obese patients, since the benefit-risk ratio in this population is known to be negative.

In addition, the CAP shall be implemented to confirm that prescribing physicians have been informed of the need for periodic cardiac monitoring in patients taking Fintepla due to the potential risk of valvular heart disease and pulmonary arterial hypertension.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0354/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Appendix

1. CHMP AR on similarity dated 15 October 2020
2. Divergent position to the majority recommendation

DIVERGENT POSITION DATED 15 October 2020

Fintepla EMEA/H/C/003933

The undersigned member of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the following indication for Fintepla oral solution, 2.2 mg/ml (Fenfluramine hydrochloride) for the treatment of seizures associated with Dravet syndrome as an add on therapy to other antiepileptic medicines in children aged 2 years and older. The reason for divergent opinion was the following:

In paediatric subjects with DS, the effect of Fintepla on seizure frequency is clinically relevant and could outweighs the unfavourable effects taking into account the proposed CAP measures. However, the initiation of treatment in adults is not substantiated by efficacy and safety data and cannot be extrapolated from the paediatric population to the adult population taking into account disease and patients characteristics, which evolve from children to adults, and management in adults. As a consequence, since clinical efficacy cannot be considered established for the adult population and does not outweigh the risk, the B/R is overall negative in the adult population.

CHMP Member expressing a divergent position:

Alexandre Moreau (FR)