Clinical trial results:
A Multicenter, 2-Cohort Trial to First Assess the Pharmacokinetic and Safety Profile of a Single Dose of ZX008 (Fenfluramine hydrochloride) Oral Solution When Added to Standard of Care (Cohort 1), Followed by a Randomized, Double-blind, Placebo-controlled Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of ZX008 as Adjunctive Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome (Cohort 2)

Summary

EudraCT number	2016-000474-38
Trial protocol	NL DE GB ES
Global end of trial date	05 June 2018

Results information

Result version number	v1 (current)
This version publication date	23 June 2022
First version publication date	23 June 2022

Trial information

Trial identification

Sponsor protocol code	ZX008-1504

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02926898
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zogenix International Limited
Sponsor organisation address	Siena Court, Broadway, Maidenhead, United Kingdom, SL6 1NJ
Public contact	Zogenix International Limited, Zogenix International Limited, Zogenixeu@druginfo.com
Scientific contact	Zogenix International Limited, Zogenix International Limited, Zogenixeu@druginfo.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001990-PIP01-16
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 June 2018
Global end of trial reached?	Yes
Global end of trial date	05 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that fenfluramine hydrochloride was superior to placebo for the treatment of Dravet syndrome in children and young adults stabilized on a STP regimen based on the change in convulsive seizure frequency (CSF) from Baseline to the combined Titration and Maintenance Periods (T+M period)

Protection of trial subjects:

The study procedures set out in the protocol were designed to ensure that the Sponsor and the Investigators abided by the principles of the current International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guideline on the conduct, evaluation and documentation of this study, as described in ICH Topic E6 Guideline. The study was also carried out according to all applicable international and national regulatory requirements. The Sponsor ensured that all ethical and legal requirements were met before the first subject was enrolled into the study.
The Investigator was responsible for obtaining a subject's informed consent to participate in the study. A Subject Information Sheet and study master ICFs, including a subject ICF (for adult subjects), subject assent form (for subjects under the age of consent), and an ICF for the parent/caregiver, were prepared by the Sponsor according to the provisions of ICH GCP and local legal requirements.
For pediatric subjects (<18 years of age), or young adult subjects (18 years of age) unable to provide consent due to intellectual disability, the written informed consent of a legally acceptable representative was required. Pediatric and young adult subjects who could understand the nature, scope, and possible consequences of the study must also have given their assent, orally and/or in writing via the assent document, as appropriate.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	27 January 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 3

Country: Number of subjects enrolled	United States: 22
Country: Number of subjects enrolled	Canada: 7
Worldwide total number of subjects	87
EEA total number of subjects	58

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	57
Adolescents (12-17 years)	28
Adults (18-64 years)	2
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 28 study sites in Canada, France, Germany, the Netherlands, Spain, the United Kingdom, and the United States enrolled participants for Study 1504 Cohort 2.

Pre-assignment

Screening details:

A total of 115 subjects were screened for eligibility to participate in Study 1504 Cohort 2. Of these, 87 subjects were enrolled and randomized.

Period 1

Period 1 title	Overall Study Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

Matching fenfluramine placebo was supplied as an oral solution.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 2: fenfluramine hydrochloride 0.5 mg/kg/day

Arm description:

Subjects received fenfluramine hydrochloride 0.5 mg/kg/day (maximum dose of 20 mg/day) added to a standard-of-care regimen that included at a minimum stiripentol (STP) plus clobazam (CLB) and/or valproic acid (VPA). Study medication was administered twice daily (BID) in equally divided doses with food.

Arm type	Experimental
Investigational medicinal product name	fenfluramine hydrochloride
Investigational medicinal product code	ZX008
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Upon completion of the 6-week Baseline Period, subjects received fenfluramine hydrochloride (at a dose of 0.5 mg/kg/day; maximum dose of 20 mg/day). All subjects were titrated to their randomized dose during the Titration Period. The duration of the titration period was 21 days.
Following titration, subjects continued treatment at their assigned dose of fenfluramine 0.5 mg/kg/day over a 12-week Maintenance Period. The total treatment time from the beginning of the Titration Period through the end of the maintenance period was a maximum of 15 weeks.

Arm title	Cohort 2: Placebo

Arm description:

Subjects received placebo, volume matched to the 0.5 mg/kg/day dose level, added to a standard-of-care regimen that included STP at a minimum plus CLB and/or VPA. Placebo
was administered twice daily (BID) in equally divided doses with food.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Upon completion of the 6-week Baseline Period, subjects received placebo, volume matched to the 0.4

mg/kg/day dose level. To maintain the blinded aspect of the study, subjects titrated the placebo dose over 21 days and remained at this dose for the 12-week Maintenance Period.

Number of subjects in period 1	Cohort 2: fenfluramine hydrochloride 0.5 mg/kg/day	Cohort 2: Placebo
Started	43	44
Completed	36	41
Not completed	7	3
Worsening of seizures	1	-
Uncontrolled seizures	-	1
Patient decision	1	-
Physician decision	1	-
Early transition to OLE	-	1
Adverse event, non-fatal	2	1
Protocol deviation	1	-
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 2: fenfluramine hydrochloride 0.5 mg/kg/day
Reporting group description:	
Subjects received fenfluramine hydrochloride 0.5 mg/kg/day (maximum dose of 20 mg/day) added to a standard-of-care regimen that included at a minimum stiripentol (STP) plus clobazam (CLB) and/or valproic acid (VPA). Study medication was administered twice daily (BID) in equally divided doses with food.	
Reporting group title	Cohort 2: Placebo
Reporting group description:	
Subjects received placebo, volume matched to the 0.5 mg/kg/day dose level, added to a standard-of-care regimen that included STP at a minimum plus CLB and/or VPA. Placebo was administered twice daily (BID) in equally divided doses with food.	

Reporting group values	Cohort 2: fenfluramine hydrochloride 0.5 mg/kg/day	Cohort 2: Placebo	Total
Number of subjects	43	44	87
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	31	26	57
Adolescents (12-17 years)	11	17	28
Adults (18-64 years)	1	1	2
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	8.8	9.4	
standard deviation	± 4.56	± 5.05	-
Gender categorical Units: Subjects			
Female	20	17	37
Male	23	27	50

End points

End points reporting groups

Reporting group title	Cohort 2: fenfluramine hydrochloride 0.5 mg/kg/day

Reporting group description:

Subjects received fenfluramine hydrochloride 0.5 mg/kg/day (maximum dose of 20 mg/day) added to a standard-of-care regimen that included at a minimum stiripentol (STP) plus clobazam (CLB) and/or valproic acid (VPA). Study medication was administered twice daily (BID) in equally divided doses with food.

Reporting group title	Cohort 2: Placebo

Reporting group description:

Subjects received placebo, volume matched to the 0.5 mg/kg/day dose level, added to a standard-of-care regimen that included STP at a minimum plus CLB and/or VPA. Placebo was administered twice daily (BID) in equally divided doses with food.

Primary: Change in Convulsive Seizure Frequency (CSF) From the Baseline Period (Baseline) to the Combined Titration + Maintenance (T+M) Period

End point title	Change in Convulsive Seizure Frequency (CSF) From the Baseline Period (Baseline) to the Combined Titration + Maintenance (T+M) Period

End point description:

Baseline-adjusted in CSF (mean number of convulsive seizures per 28 days) from Baseline to the T + M Period in ZX008 0.5 mg/kg/day vs placebo. Modified intent-to-treat (mITT) Population, defined as all randomized subjects who received at least 1 dose of ZX008 or placebo and for whom at least 1 week of diary data were available.

End point type	Primary

End point timeframe:

15 weeks (combined Titration + Maintenance Period)

End point values	Cohort 2: fenfluramine hydrochloride 0.5 mg/kg/day	Cohort 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: Baseline-adjusted CSF per 28 days				
least squares mean (confidence interval 95%)	7.0 (5.4 to 8.9)	15.1 (11.7 to 19.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 2: fenfluramine hydrochloride 0.5 mg/kg/day v Cohort 2: Placebo

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	ANCOVA
Parameter estimate	percent difference
Point estimate	-54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-67.2
upper limit	-35.6

Notes:

[1] - ANCOVA model with treatment group (ZX008 or placebo) and age group (< 6 years, ≥ 6 years) as factors, and with log baseline frequency as a covariate, and log CSF as the outcome variable.

Secondary: Percentage of Participants Who Achieved ≥ a 50% Reduction in Convulsive Seizure Frequency From Baseline to the Combined Titration + Maintenance Period

End point title	Percentage of Participants Who Achieved ≥ a 50% Reduction in Convulsive Seizure Frequency From Baseline to the Combined Titration + Maintenance Period

End point description:

Percentage of participants who achieved ≥ a 50% reduction in convulsive seizure frequency from Baseline compared to the combined Titration + Maintenance Periods in the ZX008 0.5 mg/kg/day vs placebo groups. Modified intent-to-treat (mITT) Population, defined as all randomized subjects who received at least 1 dose of ZX008 or placebo and for whom at least 1 week of diary data were available.

End point type	Secondary

End point timeframe:

15 weeks (combined Titration + Maintenance Period)

End point values	Cohort 2: fenfluramine hydrochloride 0.5 mg/kg/day	Cohort 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: percentage of participants				
number (not applicable)	53.5	4.5		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 2: fenfluramine hydrochloride 0.5 mg/kg/day v Cohort 2: Placebo

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Regression, Logistic

Notes:

[2] - A logistic regression model using a categorical response variable as a function of Treatment group, Baseline seizure frequency, and age group.

Secondary: Longest Convulsive Seizure-Free Interval (Days)

End point title	Longest Convulsive Seizure-Free Interval (Days)

End point description:

Comparison of the duration of the longest convulsive seizure–free interval (days) during the combined Titration + Maintenance Periods for the ZX008 0.5 mg/kg/day and placebo groups. Modified intent-to-treat (mITT) Population, defined as all randomized subjects who received at least 1 dose of ZX008 or placebo and for whom at least 1 week of diary data were available.

End point type	Secondary

End point timeframe:

15 weeks (combined Titration + Maintenance Period)

End point values	Cohort 2: fenfluramine hydrochloride 0.5 mg/kg/day	Cohort 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	44		
Units: Days				
median (full range (min-max))	22.00 (3.0 to 105.0)	13.00 (1.0 to 40.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 2: Placebo v Cohort 2: fenfluramine hydrochloride 0.5 mg/kg/day
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of observation for Adverse Events extended from the time the subject gave informed consent until the end of the Follow-up Visit (up to Day 120 [Visit 13]).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Cohort 2: fenfluramine 0.5 mg/kg/day

Reporting group description:

Subjects received fenfluramine 0.5 mg/kg/day (maximum dose of 20 mg/day) added to a standard-of-care regimen that included at a minimum STP plus CLB and/or VPA. Study medication was administered twice daily (BID) in equally divided doses with food.

Reporting group title	Cohort 2: Placebo

Reporting group description:

Subjects received placebo, volume matched to the 0.5 mg/kg/day dose level, added to standard-of-care treatment that included STP. Study medication was administered twice daily (BID) in equally divided doses with food.

Serious adverse events	Cohort 2: fenfluramine 0.5 mg/kg/day	Cohort 2: Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 43 (13.95%)	7 / 44 (15.91%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 43 (2.33%)	4 / 44 (9.09%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Seizure cluster			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	3 / 43 (6.98%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteochondritis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort 2: fenfluramine 0.5 mg/kg/day	Cohort 2: Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 43 (97.67%)	42 / 44 (95.45%)	
Investigations			
Blood glucose decreased			
subjects affected / exposed	6 / 43 (13.95%)	2 / 44 (4.55%)	
occurrences (all)	6	3	
Blood pressure diastolic increased			
subjects affected / exposed	0 / 43 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	6	
Blood pressure increased			
subjects affected / exposed	0 / 43 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	4	
Echocardiogram abnormal			
subjects affected / exposed	4 / 43 (9.30%)	0 / 44 (0.00%)	
occurrences (all)	4	0	
Weight decreased			
subjects affected / exposed	4 / 43 (9.30%)	1 / 44 (2.27%)	
occurrences (all)	4	1	
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 43 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	4	
Lethargy			
subjects affected / exposed	6 / 43 (13.95%)	2 / 44 (4.55%)	
occurrences (all)	6	2	
Seizure			
subjects affected / exposed	2 / 43 (4.65%)	7 / 44 (15.91%)	
occurrences (all)	2	14	

Somnolence			
subjects affected / exposed	3 / 43 (6.98%)	3 / 44 (6.82%)	
occurrences (all)	4	3	
Status epilepticus			
subjects affected / exposed	5 / 43 (11.63%)	0 / 44 (0.00%)	
occurrences (all)	21	0	
Tremor			
subjects affected / exposed	5 / 43 (11.63%)	0 / 44 (0.00%)	
occurrences (all)	5	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 43 (6.98%)	2 / 44 (4.55%)	
occurrences (all)	3	2	
Fatigue			
subjects affected / exposed	11 / 43 (25.58%)	2 / 44 (4.55%)	
occurrences (all)	11	2	
Pyrexia			
subjects affected / exposed	11 / 43 (25.58%)	4 / 44 (9.09%)	
occurrences (all)	21	6	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 43 (9.30%)	1 / 44 (2.27%)	
occurrences (all)	4	1	
Diarrhoea			
subjects affected / exposed	10 / 43 (23.26%)	3 / 44 (6.82%)	
occurrences (all)	12	5	
Vomiting			
subjects affected / exposed	2 / 43 (4.65%)	3 / 44 (6.82%)	
occurrences (all)	2	3	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	4 / 43 (9.30%)	1 / 44 (2.27%)	
occurrences (all)	4	1	
Irritability			
subjects affected / exposed	4 / 43 (9.30%)	2 / 44 (4.55%)	
occurrences (all)	4	2	

Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 43 (11.63%)	2 / 44 (4.55%)	
occurrences (all)	5	2	
Ear infection			
subjects affected / exposed	4 / 43 (9.30%)	2 / 44 (4.55%)	
occurrences (all)	5	2	
Nasopharyngitis			
subjects affected / exposed	7 / 43 (16.28%)	15 / 44 (34.09%)	
occurrences (all)	7	19	
Rhinitis			
subjects affected / exposed	3 / 43 (6.98%)	1 / 44 (2.27%)	
occurrences (all)	7	1	
Sinusitis			
subjects affected / exposed	1 / 43 (2.33%)	3 / 44 (6.82%)	
occurrences (all)	1	3	
Upper respiratory tract infection			
subjects affected / exposed	4 / 43 (9.30%)	3 / 44 (6.82%)	
occurrences (all)	4	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	19 / 43 (44.19%)	5 / 44 (11.36%)	
occurrences (all)	23	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2016	- Addition of chest x-ray prior to and after 13 weeks of treatment with study medication (France and The Netherlands) - Addition of 24-month cardiac safety follow-up for subjects who have completed more than 13 weeks of double-blind or open-label treatment with study medication (France, The Netherlands, and Germany) - Updated prohibited medication/food section to include the prohibition of alcohol - Added new section of transition for subjects who will enter the open-label extension study, including updates as appropriate in inclusion/exclusion criteria, study design, study visits, blood volumes to be taken, statistical methods, etc. - Increased the number of sites and countries - Clarified the use of midazolam and diazepam as rescue medication did not require Medical Monitor approval prior to use - Clarified that QOLCE was to be administered to all children - Clarified seizure type definitions -The participating countries were expanded to include Canada and Germany
30 September 2016	- The participating countries were expanded to include Belgium, Italy, Spain, and United States - The number of participating sites was updated. - The required number of seizures during the Baseline period was corrected due to a typographical error. - The Screening was extended to 21 days - Corrections were made to state that ECGs were to be read centrally - SAE reporting process was updated
13 December 2016	Clarifications and changes were made to the various sections of the protocol based on the selected dose of ZX008 0.5 mg/kg/day, maximum 20 mg/day for Cohort 2, including the Schedule of Assessments, risk-benefit rationale, and description of the primary outcome.
02 February 2018	- Sample size was updated (sample size had been expanded to include approximately 90 subjects) - Updates were made to statistical analysis and efficacy objectives to align with the SAP. - The AESI list was updated to 1) remove cardiovascular/respiratory items, including discontinuation of the reporting of ECHOs with trace mitral regurgitation as AESIs; 2) remove serotonin syndrome; 3) remove hallucinations, psychosis, euphoria, mood disorders; 4) remove galactorrhea, gynecomastia, priapism; and 5) remove fasting serum blood glucose ≥2×ULN

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported