Clinical trial results:
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

Summary

EudraCT number	2016-002804-14
Trial protocol	GB BE DE IT DK ES FR
Global end of trial date	27 January 2023

Results information

Result version number	v1
This version publication date	12 August 2023
First version publication date	12 August 2023

Trial information

Trial identification

Sponsor protocol code	ZX008-1503

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02823145
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zogenix International Limited (a wholly owned subsidiary of Zogenix, Inc.)
Sponsor organisation address	5959 Horton Street, Emeryville, United States, CA 94608
Public contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com
Scientific contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 January 2023
Global end of trial reached?	Yes
Global end of trial date	27 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety and tolerability of ZX008

Protection of trial subjects:

During the conduct of the study all participants were closely monitored.

Background therapy:

Background therapy as permitted in the protocol.

Evidence for comparator:

Not applicable

Actual start date of recruitment	08 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	Germany: 39
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	United States: 145
Worldwide total number of subjects	375
EEA total number of subjects	161

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)	233
Adolescents (12-17 years)	100
Adults (18-64 years)	42
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll participants in Jul 2016 and concluded in Jan 2023. Participants who completed 14 weeks treatment in any of the core studies ZX008-1501/ZX008-1502 (NCT02682927), or ZX008-1504 (NCT02926898) Cohort 2, or completed ZX008-1504 Cohort 1 study, and de novo participants were eligible to participate in this study.

Pre-assignment

Screening details:

The Participant Flow refers to the Safety (SAF) Population.

Period 1

Period 1 title	Enrollment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Not Treated

Arm description:

Participant (de novo) signed the informed consent form (ICF) but never received any study medication during the study.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Any ZX008 Open Label Dose

Arm description:

Participants received ZX008 0.2 milligram per kilogram per day (mg/kg/day) as an oral solution, twice a day (bid), in equally divided doses with food for 1 month. After 1 month, investigator might have adjusted the dose of each participant based on effectiveness and tolerability. Participants who were not receiving concomitant stiripentol, dose changes should be made in increments of 0.2 mg/kg/day, to a maximum of 0.8 mg/kg/day but not to exceed total dose of 30 mg/day for 42 months of OLE Period. Participants who were receiving concomitant stiripentol, the first dose change was 0.4 mg/kg/day and the final dose change was to 0.5 mg/kg/day, but not to exceed 20 mg/day for 42 months of OLE Period.

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:

Participants received ZX008 0.2 mg/kg/day to maximum of 30 mg/kg/day as an oral solution, bid, in equally divided doses with food for up to approximately 42 months.

Number of subjects in period 1	Not Treated	Any ZX008 Open Label Dose
Started	1	374
Completed	0	374
Not completed	1	0
Unknown	1	-

Period 2

Period 2 title	Treatment
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Any ZX008 Open Label Dose

Arm description:

Participants received ZX008 0.2 milligram per kilogram per day (mg/kg/day) as an oral solution, twice a day (bid), in equally divided doses with food for 1 month. After 1 month, investigator might have adjusted the dose of each participant based on effectiveness and tolerability. Participants who were not receiving concomitant stiripentol, dose changes should be made in increments of 0.2 mg/kg/day, to a maximum of 0.8 mg/kg/day but not to exceed total dose of 30 mg/day for 42 months of OLE Period. Participants who were receiving concomitant stiripentol, the first dose change was 0.4 mg/kg/day and the final dose change was to 0.5 mg/kg/day, but not to exceed 20 mg/day for 42 months of OLE Period.

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:

Participants received ZX008 0.2 mg/kg/day to maximum of 30 mg/kg/day as an oral solution, bid, in equally divided doses with food for up to approximately 42 months.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: As pre-specified in the SAP, participant Demographics and Baseline Characteristics were summarized for the safety population. In Period 1, no participant received study medication therefore, Period 2 is considered as Baseline Period.

Number of subjects in period 2[2]	Any ZX008 Open Label Dose
Started	374
Completed	49
Not completed	325
Adverse event, serious fatal	3
Physician decision	2
Subject needed to take prohibited medication	1
Withdrawal by sponsor due to lack of compliance	1

Family Decision	1
Subject has transitioned to study 1900 OLE study	225
Transitioned to commercial supply of medication	1
Reason unknown	1
IP approved and subject moved to commercial drug	1
Non-Compliance With E-Diary	1
Withdrawal By Caregiver	1
Consent withdrawn by subject	16
Adverse event, non-fatal	11
Subject transferred to direct access programme	1
Switching to commercially available drug	11
Lack of efficacy	48

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 1 participant enrolled but discontinued the study without receiving study medication and Demographics were planned for participants who received at least one dose of ZX008 during OLE.

Baseline characteristics

Reporting groups	
Reporting group title	Any ZX008 Open Label Dose

Reporting group description:

Participants received ZX008 0.2 milligram per kilogram per day (mg/kg/day) as an oral solution, twice a day (bid), in equally divided doses with food for 1 month. After 1 month, investigator might have adjusted the dose of each participant based on effectiveness and tolerability. Participants who were not receiving concomitant stiripentol, dose changes should be made in increments of 0.2 mg/kg/day, to a maximum of 0.8 mg/kg/day but not to exceed total dose of 30 mg/day for 42 months of OLE Period. Participants who were receiving concomitant stiripentol, the first dose change was 0.4 mg/kg/day and the final dose change was to 0.5 mg/kg/day, but not to exceed 20 mg/day for 42 months of OLE Period.

Reporting group values	Any ZX008 Open Label Dose	Total	
Number of subjects	374	374	
Age Categorical Units: participants			
<6 years	92	92	
6-18 years	250	250	
>18 years	32	32	
Age Continuous Units: years			
arithmetic mean	10.3		
standard deviation	± 6.12	-	
Sex: Female, Male Units: participants			
Female	172	172	
Male	202	202	

End points

End points reporting groups

Reporting group title	Not Treated

Reporting group description:

Participant (de novo) signed the informed consent form (ICF) but never received any study medication during the study.

Reporting group title	Any ZX008 Open Label Dose

Reporting group description:

Participants received ZX008 0.2 milligram per kilogram per day (mg/kg/day) as an oral solution, twice a day (bid), in equally divided doses with food for 1 month. After 1 month, investigator might have adjusted the dose of each participant based on effectiveness and tolerability. Participants who were not receiving concomitant stiripentol, dose changes should be made in increments of 0.2 mg/kg/day, to a maximum of 0.8 mg/kg/day but not to exceed total dose of 30 mg/day for 42 months of OLE Period. Participants who were receiving concomitant stiripentol, the first dose change was 0.4 mg/kg/day and the final dose change was to 0.5 mg/kg/day, but not to exceed 20 mg/day for 42 months of OLE Period.

Reporting group title	Any ZX008 Open Label Dose

Reporting group description:

Participants received ZX008 0.2 milligram per kilogram per day (mg/kg/day) as an oral solution, twice a day (bid), in equally divided doses with food for 1 month. After 1 month, investigator might have adjusted the dose of each participant based on effectiveness and tolerability. Participants who were not receiving concomitant stiripentol, dose changes should be made in increments of 0.2 mg/kg/day, to a maximum of 0.8 mg/kg/day but not to exceed total dose of 30 mg/day for 42 months of OLE Period. Participants who were receiving concomitant stiripentol, the first dose change was 0.4 mg/kg/day and the final dose change was to 0.5 mg/kg/day, but not to exceed 20 mg/day for 42 months of OLE Period.

Primary: Percentage of participants with treatment-emergent adverse events (TEAEs) leading to withdrawal from investigational medicinal product (IMP) during the OLE Treatment Period

End point title	Percentage of participants with treatment-emergent adverse events (TEAEs) leading to withdrawal from investigational medicinal product (IMP) during the OLE Treatment Period[1]

End point description:

A TEAE was defined as any AE that based on start date information occurs after the first intake of study treatment. Percentage of participants with TEAEs leading to withdrawal from IMP during OLE Treatment Period were reported. Safety (SAF) population included all enrolled participants who received at least one dose of ZX008 during the OLE.

End point type	Primary

End point timeframe:

From Day 1 to End of OLE Treatment Period - EOS Visit (Month 42)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Any ZX008 Open Label Dose			
Subject group type	Reporting group			
Number of subjects analysed	374			
Units: percentage of participants				
number (not applicable)	3.5			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with treatment-emergent adverse events (TEAEs) during the Open-label extension (OLE) Treatment Period

End point title	Percentage of participants with treatment-emergent adverse events (TEAEs) during the Open-label extension (OLE) Treatment Period[2]

End point description:

Treatment-emergent adverse events (TEAE) were defined as any AEs that based on start date information occurs after the first intake of study treatment. Safety (SAF) population included all enrolled participants who received at least one dose of ZX008 during the OLE.

End point type	Primary

End point timeframe:

From Day 1 to End of OLE Treatment Period - End of Study (EOS) Visit (Month 42)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Any ZX008 Open Label Dose			
Subject group type	Reporting group			
Number of subjects analysed	374			
Units: percentage of participants				
number (not applicable)	98.1			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with Serious treatment-emergent adverse events (TEAEs) during the OLE Treatment Period

End point title	Percentage of participants with Serious treatment-emergent adverse events (TEAEs) during the OLE Treatment Period[3]

End point description:

Serious Adverse event (SAE) was defined as any untoward medical occurrence that at any dose: • results in death, • is life-threatening threatening, • results in initial inpatient hospitalization or prolongation of hospitalization, •results in persistent or significant disability or incapacity, • results in a congenital anomaly/birth defect, • results in any medically significant event that did not meet any of the other 5 SAE criteria, but which was judged by a physician to potentially jeopardize the participant or require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion. Safety (SAF) population included all enrolled participants who received at least one dose of ZX008 during the OLE.

End point type	Primary

End point timeframe:

From Day 1 to End of OLE Treatment Period - EOS Visit (Month 42)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Any ZX008 Open Label Dose			
Subject group type	Reporting group			
Number of subjects analysed	374			
Units: percentage of participants				
number (not applicable)	26.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Convulsive Seizure Frequency (CSF) per 28 days during the OLE Treatment Period (to Month 36)

End point title	Convulsive Seizure Frequency (CSF) per 28 days during the OLE Treatment Period (to Month 36)

End point description:

Monthly (28 day) CSF was based on electronic diary data obtained for each participant. The total number of convulsive seizures in the ith interval (CSF in OLE, where,i=1, 2, 3, … , 14) was divided by the total number of days in the ith interval with nonmissing diary data and the result was then multiplied by 28 to get a 28-day CSF of OLE. mITT population included all enrolled participants who received at least one dose of ZX008 and had at least 1 month of valid seizure data during the OLE. Here, 'n' signifies participants who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

At Month 1, Month 2, Month 3, Month 4-6, Month 7-9, Month 10-12, Month 13-15, Month 16-18, Month 19-21, Month 22-24, Month 25-27, Month 28-30, Month 31-33, and Month 34-36

End point values	Any ZX008 Open Label Dose			
Subject group type	Reporting group			
Number of subjects analysed	324			
Units: seizure frequency per 28 days				
median (full range (min-max))				
Month 1 (n=324)	6.53 (0.0 to 4876.9)			
Month 2 (n= 323)	4.67 (0.0 to 3392.7)			
Month 3 (n= 320)	4.67 (0.0 to 2593.7)			
Month 4-6 (n= 316)	4.36 (0.0 to 1725.5)			

Month 7-9 (n= 299)	3.82 (0.0 to 310.8)			
Month 10-12 (n= 284)	4.04 (0.0 to 362.4)			
Month 13-15 (n= 280)	3.11 (0.0 to 215.0)			
Month 16-18 (n= 262)	3.42 (0.0 to 243.3)			
Month 19-21 (n= 247)	3.42 (0.0 to 372.4)			
Month 22-24 (n= 234)	2.80 (0.0 to 489.5)			
Month 25-27 (n= 187)	2.80 (0.0 to 747.3)			
Month 28-30 (n= 151)	2.80 (0.0 to 242.5)			
Month 31-33 (n= 116)	3.21 (0.0 to 224.0)			
Month 34-36 (n= 73)	2.74 (0.0 to 56.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline (Core) in Convulsive Seizure Frequency per 28 days from Day 1 to End of Study (EOS) Visit (Month 42) in the OLE Treatment Period

End point title	Change From Baseline (Core) in Convulsive Seizure Frequency per 28 days from Day 1 to End of Study (EOS) Visit (Month 42) in the OLE Treatment Period

End point description:

Baseline (Core) was defined as Baseline prior to double-blind treatment in the core studies (ZX008-1501/ZX008-1502, and ZX008-1504 Cohort 2). Participants in 1504- Cohort 1 and de novo subjects (who entered 1503 without having been in any of the core studies) did not have a Baseline (Core), and were not included in the analysis of this outcome measure. The total number of convulsive seizures from Day 1 to EOS was divided by the total number of days from Day 1 to EOS with nonmissing diary data and the result was then multiplied by 28 to get a 28-day convulsive seizure frequency (CSF). The change from Baseline for any individual participant was calculated by subtracting the Baseline (Core) from the post-baseline value. Monthly (28 day) CSF was based on electronic diary data obtained for each participant. Modified Intent-to-Treat (mITT) population included all enrolled participants who received at least one dose of ZX008 and had at least 1 month of valid seizure data during the OLE.

End point type	Secondary

End point timeframe:

From Day 1 to End of OLE Treatment Period (EOS Visit - up to Month 42), compared to Baseline (Core)

End point values	Any ZX008 Open Label Dose			
Subject group type	Reporting group			
Number of subjects analysed	324			
Units: seizure frequency per 28 days				
median (full range (min-max))	-6.67 (-1757.8 to 751.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline (Core) in Convulsive Seizure Frequency per 28 days from Month 2 to EOS (Month 42) in the OLE Treatment Period

End point title	Change From Baseline (Core) in Convulsive Seizure Frequency per 28 days from Month 2 to EOS (Month 42) in the OLE Treatment Period

End point description:

Baseline (Core) was defined as Baseline prior to double-blind treatment in the core studies. Participants in 1504-Cohort 1 and de novo participants did not have a Baseline (Core), and were not included in the analysis of this outcome measure. The total number of convulsive seizures from Month 2 to EOS was divided by the total number of days from Month 2 to EOS with nonmissing diary data and the result was then multiplied by 28 to get a 28-day CSF. The change from Baseline for any individual participant was calculated by subtracting the Baseline (Core) from the post-baseline value. Monthly (28 day) CSF was based on electronic diary data obtained for each participant. mITT population included all enrolled participants who received at least one dose of ZX008 and had at least 1 month of valid seizure data during the OLE. Here, number of participants analyzed included those participants who were evaluable for the assessment.

End point type	Secondary

End point timeframe:

From Month 2 to End of OLE Treatment Period (EOS Visit - up to Month 42), compared to Baseline (Core)

End point values	Any ZX008 Open Label Dose			
Subject group type	Reporting group			
Number of subjects analysed	323			
Units: seizure frequency per 28 days				
median (full range (min-max))	-7.04 (-1986.9 to 816.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Convulsive Seizure Frequency (CSF) by Mean Daily Dose during the overall OLE Treatment Period

End point title	Convulsive Seizure Frequency (CSF) by Mean Daily Dose during the overall OLE Treatment Period

End point description:

Convulsive seizure frequency over time, reported as per 28 days was analyzed by the actual dose administered. Participants were grouped into low (0.2 to <0.4 mg/kg), medium (0.4 to <0.6 mg/kg),

and high dose (>0.6 mg/kg) groups depending on their mean daily doses of ZX008 during the OLE Treatment period. For each participant, the seizure frequency per 28 days was calculated as the number of seizures recorded during the period, divided by the number of days in the period and multiplied by 28. The convulsive seizure frequency was calculated from all available data collected. mITT population included all enrolled participants who received at least one dose of ZX008 and had at least 1 month of valid seizure data during the OLE. Here, 'n' represents the number of participants categorized by mean daily dose.

End point type	Secondary

End point timeframe:

From Day 1 to End of OLE Treatment Period - End of Study (EOS) Visit (Month 42)

End point values	Any ZX008 Open Label Dose			
Subject group type	Reporting group			
Number of subjects analysed	324			
Units: seizure frequency per 28 days				
median (full range (min-max))				
ZX008 Low Dose (0 - <0.4 mg/kg/day) (n=90)	3.94 (0.0 to 2215.3)			
ZX008 Medium Dose (0.4 - <0.6 mg/kg/day) (n=113)	4.80 (0.0 to 113.6)			
ZX008 High Dose (>=0.6 mg/kg/day) (n=121)	6.00 (0.1 to 942.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants With Changes in antiepileptic drug (AED) medications during first 6 months of OLE Treatment Period

End point title	Percentage of participants With Changes in antiepileptic drug (AED) medications during first 6 months of OLE Treatment Period

End point description:

Participants in the study were required to be on stable background therapy for the first 6 months of treatment, after which background AEDs could be reduced or withdrawn so long as one background AED remained. The percentage of participants who had changes in dose or type of concomitant AED medications during the first, second, third, fourth, fifth, and sixth months were analyzed and reported. mITT population included all enrolled participants who received at least one dose of ZX008 and had at least 1 month of valid seizure data during the OLE.

End point type	Secondary

End point timeframe:

At Month 1, 2, 3, 4 , 5, and 6 of OLE Treatment Period

End point values	Any ZX008 Open Label Dose			
Subject group type	Reporting group			
Number of subjects analysed	324			
Units: percentage of participants				
number (not applicable)				
OLE Month 1	5.2			
OLE Month 2	7.1			
OLE Month 3	7.4			
OLE Month 4	8.3			
OLE Month 5	6.8			
OLE Month 6	9.6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 up to 42 months

Adverse event reporting additional description:

A TEAE was defined as any AE that based on start date information occurs after the first intake of study treatment. The Safety (SAF) population was the set of all enrolled subjects who received at least one dose of ZX008 during the OLE. As pre-specified in the SAP, safety analyses were performed on the SAF Population.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Any ZX008 Open Label Dose

Reporting group description:

Participants received ZX008 0.2 milligram per kilogram per day (mg/kg/day) as an oral solution, twice a day (bid), in equally divided doses with food for 1 month. After 1 month, investigator might have adjusted the dose of each participant based on effectiveness and tolerability. Participants who were not receiving concomitant stiripentol, dose changes should be made in increments of 0.2 mg/kg/day, to a maximum of 0.8 mg/kg/day but not to exceed total dose of 30 mg/day for 42 months of OLE Period. Participants who were receiving concomitant stiripentol, the first dose change was 0.4 mg/kg/day and the final dose change was to 0.5 mg/kg/day, but not to exceed 20 mg/day for 42 months of OLE Period.

Serious adverse events	Any ZX008 Open Label Dose		
Total subjects affected by serious adverse events			
subjects affected / exposed	99 / 374 (26.47%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Labial frenectomy			
subjects affected / exposed	1 / 374 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Hypothermia			
subjects affected / exposed	1 / 374 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abasia			

subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sudden unexplained death in epilepsy				
subjects affected / exposed	3 / 374 (0.80%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 3			
Impaired healing				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Apnoea				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	2 / 374 (0.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Acute respiratory distress syndrome				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	2 / 374 (0.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				

Tic				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Insomnia				
subjects affected / exposed	3 / 374 (0.80%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Apathy				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Agitation				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute psychosis				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood glucose decreased				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Heart rate decreased				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Abdominal injury				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Ankle fracture				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cervical vertebral fracture				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Concussion				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Drug dose omission				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Foreign body aspiration				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hand fracture				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	2 / 374 (0.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				

subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Near drowning				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Supraventricular tachycardia				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block second degree				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Lethargy				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotonia				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperkinesia				
subjects affected / exposed	2 / 374 (0.53%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Generalised tonic-clonic seizure				
subjects affected / exposed	2 / 374 (0.53%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Febrile convulsion				

subjects affected / exposed	2 / 374 (0.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dystonia				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Change in seizure presentation				
subjects affected / exposed	5 / 374 (1.34%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Status epilepticus				
subjects affected / exposed	15 / 374 (4.01%)			
occurrences causally related to treatment / all	1 / 18			
deaths causally related to treatment / all	0 / 0			
Seizure cluster				
subjects affected / exposed	6 / 374 (1.60%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 0			
Seizure				

subjects affected / exposed	21 / 374 (5.61%)			
occurrences causally related to treatment / all	2 / 26			
deaths causally related to treatment / all	0 / 0			
Petit mal epilepsy				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Myoclonus				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Movement disorder				
subjects affected / exposed	2 / 374 (0.53%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Colitis				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	2 / 374 (0.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea haemorrhagic				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal perforation				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterovesical fistula				

subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth disorder				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	2 / 374 (0.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Erythema multiforme				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urticaria				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Foot deformity				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Aneurysmal bone cyst				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Atypical pneumonia				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	2 / 374 (0.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	2 / 374 (0.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Enterovirus infection				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epididymitis				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epstein-Barr virus infection				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				

subjects affected / exposed	3 / 374 (0.80%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Helicobacter infection				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infectious mononucleosis				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	7 / 374 (1.87%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	3 / 374 (0.80%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis media acute				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				

subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	12 / 374 (3.21%)			
occurrences causally related to treatment / all	0 / 15			
deaths causally related to treatment / all	0 / 0			
Bronchitis viral				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhinovirus infection				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 374 (0.80%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Varicella				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	5 / 374 (1.34%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Viral pharyngitis				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral upper respiratory tract infection				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyponatraemia				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperammonaemia				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Feeding intolerance				
subjects affected / exposed	1 / 374 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				

subjects affected / exposed	2 / 374 (0.53%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	1 / 374 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Any ZX008 Open Label Dose		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	342 / 374 (91.44%)		
Investigations			
Weight decreased			
subjects affected / exposed	31 / 374 (8.29%)		
occurrences (all)	33		
Echocardiogram abnormal			
subjects affected / exposed	67 / 374 (17.91%)		
occurrences (all)	82		
Blood glucose decreased			
subjects affected / exposed	88 / 374 (23.53%)		
occurrences (all)	115		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	25 / 374 (6.68%)		
occurrences (all)	26		
Nervous system disorders			
Tremor			
subjects affected / exposed	21 / 374 (5.61%)		
occurrences (all)	24		
Somnolence			
subjects affected / exposed	35 / 374 (9.36%)		
occurrences (all)	38		
Seizure			

subjects affected / exposed	46 / 374 (12.30%)		
occurrences (all)	60		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	112 / 374 (29.95%)		
occurrences (all)	229		
Fatigue			
subjects affected / exposed	34 / 374 (9.09%)		
occurrences (all)	49		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	39 / 374 (10.43%)		
occurrences (all)	50		
Diarrhoea			
subjects affected / exposed	73 / 374 (19.52%)		
occurrences (all)	102		
Constipation			
subjects affected / exposed	23 / 374 (6.15%)		
occurrences (all)	34		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	34 / 374 (9.09%)		
occurrences (all)	55		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	20 / 374 (5.35%)		
occurrences (all)	20		
Psychiatric disorders			
Irritability			
subjects affected / exposed	19 / 374 (5.08%)		
occurrences (all)	23		
Abnormal behaviour			
subjects affected / exposed	22 / 374 (5.88%)		
occurrences (all)	28		
Infections and infestations			

Ear infection subjects affected / exposed occurrences (all)	39 / 374 (10.43%) 56		
Gastroenteritis subjects affected / exposed occurrences (all)	32 / 374 (8.56%) 34		
Gastroenteritis viral subjects affected / exposed occurrences (all)	20 / 374 (5.35%) 21		
Viral infection subjects affected / exposed occurrences (all)	27 / 374 (7.22%) 40		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	65 / 374 (17.38%) 117		
Rhinitis subjects affected / exposed occurrences (all)	32 / 374 (8.56%) 62		
Nasopharyngitis subjects affected / exposed occurrences (all)	104 / 374 (27.81%) 224		
Influenza subjects affected / exposed occurrences (all)	45 / 374 (12.03%) 50		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	19 / 374 (5.08%) 36		
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	32 / 374 (8.56%) 35		
Decreased appetite subjects affected / exposed occurrences (all)	100 / 374 (26.74%) 112		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2016	Amendment 1.2-Important clarifications and changes were made to the protocol and included the following: • Addition of Study 1504 as a core study contributing subjects to this study, including updates/additions as appropriate in exploratory objectives, planned number of subjects/study centers, inclusion/exclusion criteria, study design, treatment administration, prohibited concomitant medication, study visits, assessments specific to Study 1504 subjects only, statistical methods, etc. • Clarified the use of concomitant AED treatments • Clarified the dose adjustment parameters in the first month of the study • Updated risk-benefit for the study • Updated prohibited medication/food section to include the prohibition of alcohol • Clarified how ongoing AEs from the core studies were to be handled in this study
01 November 2016	Amendment 2.0- Clarifications and changes were made to the protocol, including changes requested based on feedback received from the United States Food and Drug Administration, and included the following: • Added the criteria for dose adjustments outside the protocol-specified range for safety and/or efficacy • Clarified the criteria on inclusion for subjects who did not complete the 12-week Maintenance period of the core study • Added Pediatric Quality of Life Inventory (PedsQL) Family Impact module as an effectiveness endpoint • Reproduction requirements were updated and clarified • Clarified the transition from the core study to the OLE study • Clarified the timing of the echocardiogram (ECHO) - moved from Week 6 to Month 1 • Clarified the timing of the cardiac follow-up visits • Added guidance consistent with the Seattle Children's Research Foundation for volume of blood collected from children • Severity of valve regurgitation (tricuspid or pulmonary) was changed • Clarified the process for SAE reporting • Added the requirement for pharmacokinetic (PK) as soon as feasible after an SAE
05 May 2017	Amendment 3.0- Clarifications and changes were made to the protocol, and included the following: • Extend the study duration to 2 years (24 months) • Clarified the methodology sections regarding dosing for subjects who entered the open label extension trial from core studies and increased the study duration to 24 months • Updated the Risk Benefit Assessment with regards to ZX008 doses administered in the core studies • Increased number of subjects expected to enroll in the study • Clarified the timing for cardiac follow up visits and increased study duration to 2 years (24 months) • Updated the study drug doses for open-label Treatment period • Added visit windows for year 2 visits and clarified timing of the cardiac follow up visits in Table 6 "Time Windows for Assessments" • Clarified the timing and observation period for reporting of AEs • Clarified the process for SAE reporting

02 February 2018	Amendment 4.0- Clarifications and changes were made to the protocol, and included the following: • Updated number of enrolled subjects to 340 from the core studies and up to 50 subjects who did not participate in the core studies (de novo) • Included eligibility criteria for de novo subjects aged > 18 to 35 years of age; provided summary of eligibility, clarified language, for de novo adult subjects • Adjusted duration of study to approximately 36 months • Updated rationale to provide risk-benefit assessment that included results from Study 1. • Clarified that seizure comparisons would include the time when dose was stable • Included clinical data results from double-blind, controlled study (Study 1) • Clarified dose changes for subjects receiving and not receiving stiripentol • Corrected procedures for postdose Visit 13 • Clarified cardiac follow-up visits • Updated estimated blood volume to be collected • Clarified age range for PedsQL • Clarified how to code and report SAEs • Clarified ECHO reading severity (trace and mild) and oversight based on patient age
03 August 2020	Amendment 5.0- Clarifications and changes were made to the protocol, and included the following: • Included study conduct information for the COVID-19 pandemic • Updated background information related to existing treatments for Dravet and additional clinical and pre-clinical study data available in the updated ZX008 Investigator's Brochure (IB) • Updated language for subjects transitioning to another extension study or to commercial drug • Updated number of study centers to include Japan

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported