Clinical trial results:
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

Summary

EudraCT number	2015-004167-37
Trial protocol	GB DE BE NO DK SE ES FR IT
Global end of trial date	29 July 2020

Results information

Result version number	v2 (current)
This version publication date	24 December 2022
First version publication date	10 July 2022
Version creation reason	• Correction of full data set Alignment with final posting on ClinicalTrials.gov after NIH review.

Trial information

Trial identification

Sponsor protocol code	ZX008-1502

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02826863
WHO universal trial number (UTN)	-
Other trial identifiers	Additional Sponsor Protocol Code: ZX008-1501

Notes:

Sponsors

Sponsor organisation name	Zogenix International Limited
Sponsor organisation address	5959 Horton Street, 5th Floor, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 August 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that ZX008 0.8 mg/kg/day is superior to placebo as adjunctive therapy in the treatment of Dravet syndrome in children and young adults based on change in the frequency of convulsive seizures between Baseline and the combined Titration and Maintenance Periods (T+M).

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	15 January 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	United States: 120
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Italy: 33
Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 18
Worldwide total number of subjects	262
EEA total number of subjects	92

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)	177
Adolescents (12-17 years)	76
Adults (18-64 years)	9
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study 1501 started to enroll participants in January 2016 and concluded in July 2020. The study 1502 started to enroll participants in July 2016 and concluded in July 2020. The consolidated results of Study 1 and Study 3 are included in this record. The Participant Flow refers to the Randomized Population.

Pre-assignment

Screening details:

Due to slow enrollment into both trials, the databases for the two trials were combined. The first 72 enrolled participants from ZX008-1501 and first 47 from ZX008-1502 were combined for an analysis and reported as Study 1, whereas the final 55 participants from ZX008- 1501 and the final 88 from ZX008-1502 were combined and reported as Study 3.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Study 1: Placebo

Arm description:

Participants received matching placebo as an oral solution, twice a day (bid) in equally divided doses with food for up to approximately 16 weeks. Study 1 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).

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:

Participants received matching placebo as an oral solution, bid in equally divided doses with food for up to approximately 16 weeks.

Arm title	Study 1: ZX008 0.2 mg/kg/day

Arm description:

Participants received ZX008 0.2 milligram per kilogram per day (mg/kg/day) as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 1 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).

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 as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks.

Arm title	Study 1: ZX008 0.8 mg/kg/day

Arm description:

Participants received ZX008 0.8 mg/kg/day as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 1 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).

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 0.8 mg/kg/day as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks.

Arm title	Study 3: Placebo

Arm description:

Participants received matching placebo as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 3 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).

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:

Participants received matching placebo as an oral solution, bid in equally divided doses with food for up to approximately 16 weeks.

Arm title	Study 3: ZX008 0.2 mg/kg/day

Arm description:

Participants received ZX008 0.2 mg/kg/day as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 3 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).

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 as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks.

Arm title	Study 3: ZX008 0.8 mg/kg/day

Arm description:

Participants received ZX008 0.8 mg/kg/day as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 3 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).

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 0.8 mg/kg/day as an oral solution, bid, in equally divided doses with food

for up to approximately 16 weeks.

Number of subjects in period 1	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day
Started	40	39	40
Completed	37	39	34
Not completed	3	0	6
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	2	-	1
Adverse event, non-fatal	-	-	5
Unspecified	-	-	-
Lack of efficacy	1	-	-

Number of subjects in period 1	Study 3: Placebo	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day
Started	48	46	49
Completed	43	45	46
Not completed	5	1	3
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	-	1	1
Adverse event, non-fatal	1	-	2
Unspecified	2	-	-
Lack of efficacy	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Study 1: Placebo
Reporting group description:	
Participants received matching placebo as an oral solution, twice a day (bid) in equally divided doses with food for up to approximately 16 weeks. Study 1 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).	
Reporting group title	Study 1: ZX008 0.2 mg/kg/day
Reporting group description:	
Participants received ZX008 0.2 milligram per kilogram per day (mg/kg/day) as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 1 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).	
Reporting group title	Study 1: ZX008 0.8 mg/kg/day
Reporting group description:	
Participants received ZX008 0.8 mg/kg/day as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 1 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).	
Reporting group title	Study 3: Placebo
Reporting group description:	
Participants received matching placebo as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 3 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).	
Reporting group title	Study 3: ZX008 0.2 mg/kg/day
Reporting group description:	
Participants received ZX008 0.2 mg/kg/day as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 3 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).	
Reporting group title	Study 3: ZX008 0.8 mg/kg/day
Reporting group description:	
Participants received ZX008 0.8 mg/kg/day as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 3 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).	

Reporting group values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day
Number of subjects	40	39	40
Age Categorical Units: participants			
24 Months - <12 Years	27	28	31
12 - < 18 Years	10	11	7
18 – < 65 Years	3	0	2
Age Continuous Units: years			
arithmetic mean	9.2	9.0	8.8
standard deviation	± 5.10	± 4.52	± 4.41
Sex: Female, Male Units: participants			
Female	19	17	19
Male	21	22	21

Reporting group values	Study 3: Placebo	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day
Number of subjects	48	46	49

Age Categorical Units: participants			
24 Months - <12 Years	31	30	30
12 - < 18 Years	17	15	16
18 – < 65 Years	0	1	3
Age Continuous Units: years			
arithmetic mean	9.0	9.6	9.5
standard deviation	± 4.29	± 4.42	± 5.29
Sex: Female, Male Units: participants			
Female	21	22	27
Male	27	24	22

Reporting group values	Total		
Number of subjects	262		
Age Categorical Units: participants			
24 Months - <12 Years	177		
12 - < 18 Years	76		
18 – < 65 Years	9		
Age Continuous Units: years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: participants			
Female	125		
Male	137		

End points

End points reporting groups

Reporting group title	Study 1: Placebo
Reporting group description:	
Participants received matching placebo as an oral solution, twice a day (bid) in equally divided doses with food for up to approximately 16 weeks. Study 1 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).	
Reporting group title	Study 1: ZX008 0.2 mg/kg/day
Reporting group description:	
Participants received ZX008 0.2 milligram per kilogram per day (mg/kg/day) as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 1 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).	
Reporting group title	Study 1: ZX008 0.8 mg/kg/day
Reporting group description:	
Participants received ZX008 0.8 mg/kg/day as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 1 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).	
Reporting group title	Study 3: Placebo
Reporting group description:	
Participants received matching placebo as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 3 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).	
Reporting group title	Study 3: ZX008 0.2 mg/kg/day
Reporting group description:	
Participants received ZX008 0.2 mg/kg/day as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 3 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).	
Reporting group title	Study 3: ZX008 0.8 mg/kg/day
Reporting group description:	
Participants received ZX008 0.8 mg/kg/day as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 3 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).	

Primary: Change from Baseline in the mean convulsive seizures frequency (MCSF) to the combined Titration and Maintenance Periods (T+M) in participants receiving ZX008 0.8 mg/kg/day compared to placebo

End point title	Change from Baseline in the mean convulsive seizures frequency (MCSF) to the combined Titration and Maintenance Periods (T+M) in participants receiving ZX008 0.8 mg/kg/day compared to placebo[1]
End point description:	
Monthly (28 day) convulsive seizure frequency (CSF) was based on electronic diary data obtained for each participant. Convulsive seizures included hemiclonic, focal with clear observable motor signs, generalized tonic clonic, secondarily generalized tonic clonic, tonic, clonic, and drop seizures (tonic/atonic). The number of convulsive seizures reported during the entire time interval was divided by the number of nonmissing diary days and the result was then multiplied by 28 to get a 28-day CSF. The modified intent-to-treat (mITT) population included all randomized participants 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:	
From Baseline up to 14 weeks [Titration Period (2 weeks) plus Maintenance Period (12 weeks)]	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The ZX008 0.2 mg/kg/day arm which was part of baseline period was not required for the primary endpoint assessment. Therefore, no data was reported for this arm.

End point values	Study 1: Placebo	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo	Study 3: ZX008 0.8 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	40	48	48
Units: seizure frequency per 28 days				
arithmetic mean (standard deviation)	-6.71 (± 24.263)	-13.11 (± 25.500)	1.54 (± 21.966)	-3.54 (± 124.132)

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Study 3: Placebo v Study 3: ZX008 0.8 mg/kg/day
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[2]
Parameter estimate	Percentage difference from Placebo
Point estimate	64.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	51.85
upper limit	74.19

Notes:

[2] - Estimate was obtained from the LSMeans on the log scale as follows: 100 x [1 - exp(LS mean active - LS mean placebo).

Statistical analysis title	Statistical Analysis 1
Comparison groups	Study 1: Placebo v Study 1: ZX008 0.8 mg/kg/day
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority[3]
Parameter estimate	Percentage difference from Placebo
Point estimate	62.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	47.72
upper limit	72.8

Notes:

[3] - Estimate was obtained from the LSMeans on the log scale as follows: 100 x [1 - exp(LS mean active - LS mean placebo).

Secondary: Change from Baseline in the mean convulsive seizures frequency to the combined Titration and Maintenance Period (T+M) in participants receiving ZX008 0.2 mg/kg/day compared to placebo

End point title	Change from Baseline in the mean convulsive seizures frequency to the combined Titration and Maintenance Period (T+M) in participants receiving ZX008 0.2 mg/kg/day compared to placebo[4]

End point description:

Monthly (28 day) convulsive seizure frequency (CSF) was based on electronic diary data obtained for each participant. Convulsive seizures included hemiclonic, focal with clear observable motor signs, generalized tonic clonic, secondarily generalized tonic clonic, tonic, clonic, and drop seizures (tonic/atonic). The number of convulsive seizures reported during the entire time interval was divided by the number of nonmissing diary days and the result was then multiplied by 28 to get a 28-day CSF. The mITT population included all randomized participants 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:

From Baseline up to 14 weeks [Titration Period (2 weeks) plus Maintenance Period (12 weeks)]

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The data for the ZX008 0.8 mg/kg/day arm was reported in primary endpoint therefore, this arm which was part of baseline period was not required for the secondary endpoint assessment. Hence, no data was reported for this arm.

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 3: Placebo	Study 3: ZX008 0.2 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	48	46
Units: seizure frequency per 28 days				
arithmetic mean (standard deviation)	-6.71 (± 24.263)	-18.81 (± 90.640)	1.54 (± 21.966)	-5.89 (± 84.735)

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Study 3: Placebo v Study 3: ZX008 0.2 mg/kg/day
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority[5]
Parameter estimate	Percentage difference from Placebo
Point estimate	49.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	31.31
upper limit	63.43

Notes:

[5] - Estimate was obtained from the LSMeans on the log scale as follows: 100 x [1 - exp(LS mean active - LS mean placebo).

Statistical analysis title	Statistical Analysis 1
Comparison groups	Study 1: Placebo v Study 1: ZX008 0.2 mg/kg/day

Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[6]
Parameter estimate	Percentage difference from Placebo
Point estimate	32.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.19
upper limit	51.33

Notes:

[6] - Estimate was obtained from the LSMeans on the log scale as follows: 100 x [1 - exp(LS mean active - LS mean placebo).

Secondary: Percentage of participants who achieved greater than or equal to 25% (≥25%) reduction in convulsive seizure frequency in each ZX008 treatment arm compared to placebo from Baseline during the Titration and Maintenance Period

End point title	Percentage of participants who achieved greater than or equal to 25% (≥25%) reduction in convulsive seizure frequency in each ZX008 treatment arm compared to placebo from Baseline during the Titration and Maintenance Period

End point description:

Convulsive seizures included hemiclonic, focal with clear observable motor signs, generalized tonic clonic, secondarily generalized tonic clonic, tonic, clonic, and drop seizures (tonic/atonic). A responder was a participant who experienced a 25% or greater reduction in convulsive seizure frequency per 28 days during Titration and Maintenance Period. The mITT population included all randomized participants 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:

From Baseline up to 14 weeks [Titration Period (2 weeks) plus Maintenance Period (12 weeks)]

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	48
Units: percentage of participants				
number (not applicable)	35.0	66.7	90.0	27.1

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: percentage of participants				
number (not applicable)	71.7	83.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieved a ≥50% reduction in convulsive seizure frequency in each ZX008 treatment arm compared to placebo from Baseline during the Titration and Maintenance Period

End point title	Percentage of participants who achieved a ≥50% reduction in convulsive seizure frequency in each ZX008 treatment arm compared to placebo from Baseline during the Titration and Maintenance Period

End point description:

Convulsive seizures included hemiclonic, focal with clear observable motor signs, generalized tonic clonic, secondarily generalized tonic clonic, tonic, clonic, and drop seizures (tonic/atonic). A responder was a participant who experienced a 50% or greater reduction in convulsive seizure frequency per 28 days during Titration and Maintenance Period. The mITT population included all randomized participants 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:

From Baseline up to 14 weeks [Titration Period (2 weeks) plus Maintenance Period (12 weeks)]

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	48
Units: percentage of participants				
number (not applicable)	12.5	38.5	67.5	6.3

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: percentage of participants				
number (not applicable)	45.7	72.9		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Study 1: Placebo v Study 1: ZX008 0.2 mg/kg/day

Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.773
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.475
upper limit	15.45

Statistical analysis title	Statistical Analysis 3
Comparison groups	Study 3: Placebo v Study 3: ZX008 0.2 mg/kg/day
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	13.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.6
upper limit	49.8

Statistical analysis title	Statistical Analysis 4
Comparison groups	Study 3: Placebo v Study 3: ZX008 0.8 mg/kg/day
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	53.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.9
upper limit	220.5

Statistical analysis title	Statistical Analysis 2

Comparison groups	Study 1: Placebo v Study 1: ZX008 0.8 mg/kg/day
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	14.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.484
upper limit	49.915

Secondary: Percentage of participants who achieved a ≥75% reduction in convulsive seizure frequency in each ZX008 treatment arm compared to placebo from Baseline during the Titration and Maintenance Period

End point title	Percentage of participants who achieved a ≥75% reduction in convulsive seizure frequency in each ZX008 treatment arm compared to placebo from Baseline during the Titration and Maintenance Period

End point description:

Convulsive seizures included hemiclonic, focal with clear observable motor signs, generalized tonic clonic, secondarily generalized tonic clonic, tonic, clonic, and drop seizures (tonic/atonic). A responder was a participant who experienced a 75% or greater reduction in convulsive seizure frequency per 28 days during Titration and Maintenance Period. The mITT population included all randomized participants 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:

From Baseline up to 14 weeks [Titration Period (2 weeks) plus Maintenance Period (12 weeks)]

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	48
Units: percentage of participants				
number (not applicable)	2.5	23.1	50.0	4.2

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: percentage of participants				
number (not applicable)	28.3	47.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieved a 100% reduction in convulsive seizure frequency in each ZX008 treatment arm compared to placebo from Baseline during the Titration and Maintenance Period

End point title	Percentage of participants who achieved a 100% reduction in convulsive seizure frequency in each ZX008 treatment arm compared to placebo from Baseline during the Titration and Maintenance Period

End point description:

Convulsive seizures included hemiclonic, focal with clear observable motor signs, generalized tonic clonic, secondarily generalized tonic clonic, tonic, clonic, and drop seizures (tonic/atonic). A responder was a participant who experienced a 100% reduction in convulsive seizure frequency per 28 days during Titration and Maintenance Period. The mITT population included all randomized participants 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:

From Baseline up to 14 weeks [Titration Period (2 weeks) plus Maintenance Period (12 weeks)]

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	48
Units: percentage of participants				
number (not applicable)	0	7.7	7.5	0

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: percentage of participants				
number (not applicable)	0	12.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Longest convulsive seizure-free interval in each ZX008 treatment arm compared to placebo during the Titration and Maintenance Period

End point title	Longest convulsive seizure-free interval in each ZX008 treatment arm compared to placebo during the Titration and Maintenance Period

End point description:

The longest interval between convulsive seizures was calculated over the entire Titration and Maintenance Period and was derived as the maximum of the number of days between consecutive convulsive seizures. The mITT population included all randomized participants 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:

During 14 weeks Titration (2 weeks) and Maintenance Period (12 weeks) (average of 99 days)

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	48
Units: days				
median (full range (min-max))	9.50 (2.0 to 23.0)	15.00 (3.0 to 106.0)	25.00 (2.0 to 97.0)	10 (2 to 65)

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: days				
median (full range (min-max))	18.5 (2 to 100)	30 (2 to 104)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Study 1: Placebo v Study 1: ZX008 0.2 mg/kg/day
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Wilcoxon rank sum test

Statistical analysis title	Statistical Analysis 2
Comparison groups	Study 1: Placebo v Study 1: ZX008 0.8 mg/kg/day

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon rank sum test

Statistical analysis title	Statistical Analysis 3
Comparison groups	Study 3: Placebo v Study 3: ZX008 0.2 mg/kg/day
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Wilcoxon rank sum test

Statistical analysis title	Statistical Analysis 4
Comparison groups	Study 3: Placebo v Study 3: ZX008 0.8 mg/kg/day
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon rank sum test

Secondary: Number of convulsive seizure-free days in each ZX008 treatment arm compared to placebo during the Titration and Maintenance Period

End point title	Number of convulsive seizure-free days in each ZX008 treatment arm compared to placebo during the Titration and Maintenance Period

End point description:

A convulsive seizure free day was defined as a day for which diary data are available and no convulsive seizures were reported. Convulsive seizure free days were taken from the electronic diary data. The mITT population included all randomized participants 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:

During 14 weeks Titration (2 weeks) and Maintenance Period (12 weeks) (average of 99 days)

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	48
Units: seizure free days				
median (full range (min-max))	15.14 (1.1 to	20.86 (2.2 to	24.43 (1.0 to	20.20 (1.4 to

	25.6)	28.0)	28.0)	27.1)

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: seizure free days				
median (full range (min-max))	23.36 (0.8 to 27.7)	25.33 (0.3 to 28.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in non-convulsive seizure frequency to the combined Titration and Maintenance Period in each ZX008 treatment arm compared to placebo

End point title	Change from Baseline in non-convulsive seizure frequency to the combined Titration and Maintenance Period in each ZX008 treatment arm compared to placebo

End point description:

Non-convulsive seizures included focal without clear observable motor signs, absence or atypical absence, myoclonic and atonic. The number of non-convulsive seizures reported during the entire time interval was divided by the number of nonmissing diary days and the result was then multiplied by 28 to get a 28-day non-convulsive seizure frequency. The mITT population included all randomized participants who received at least 1 dose of ZX008 or placebo and for whom at least 1 week of diary data were available. Here, number of participants analyzed included those participants who were evaluable for the assessment.

End point type	Secondary

End point timeframe:

From Baseline up to 14 weeks [Titration Period (2 weeks) plus Maintenance Period (12 weeks)]

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	23	24	26
Units: seizure frequency per 28 days				
median (full range (min-max))	-9.38 (-198.8 to 1886.1)	-4.85 (-1940.8 to 192.3)	-20.06 (-2064.8 to 9.4)	-0.68 (-160.0 to 1313.1)

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	30		
Units: seizure frequency per 28 days				
median (full range (min-max))	-0.67 (-138.7 to 111.3)	-4.35 (-1410.6 to 107.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in convulsive + non-convulsive seizure frequency to the combined Titration and Maintenance Period in each ZX008 treatment arm compared to placebo

End point title	Change from Baseline in convulsive + non-convulsive seizure frequency to the combined Titration and Maintenance Period in each ZX008 treatment arm compared to placebo

End point description:

Total seizure frequency were defined as the combination of convulsive and non-convulsive seizures. Convulsive seizures included hemiclonic, focal with clear observable motor signs, generalized tonic clonic, secondarily generalized tonic clonic, tonic, clonic, and drop seizures (tonic/atonic). Non-convulsive seizures included focal without clear observable motor signs, absence or atypical absence, myoclonic and atonic. The seizure frequency was based on electronic diary data obtained for each participant. The number of all seizures reported during the entire time interval was divided by the number of nonmissing diary days and the result was then multiplied by 28 to get a 28-day convulsive or non-convulsive seizure frequency. The mITT population included all randomized participants 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:

From Baseline up to 14 weeks [Titration Period (2 weeks) plus Maintenance Period (12 weeks)]

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	48
Units: seizure frequency per 28 days				
median (full range (min-max))	-4.45 (-198.4 to 1850.1)	-7.40 (-1955.1 to 187.1)	-22.95 (-2069.3 to 44.5)	-1.09 (-160.1 to 1310.5)

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: seizure frequency per 28 days				
median (full range (min-max))	-6.54 (-153.0 to 525.9)	-11.39 (-1504.8 to 791.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with rescue medication usage in each ZX008 treatment arm compared to placebo during the Titration and Maintenance Period

End point title	Percentage of participants with rescue medication usage in each ZX008 treatment arm compared to placebo during the Titration and Maintenance Period

End point description:

Rescue medication was administered according to each participant's usual or prescribed regimen consisting of 1 or more medications. The usage of rescue medication (number of days and number of medications used per seizure episode) was based on electronic diary data obtained for each participant. The number of days rescue medication was taken (normalized to 28 days) was calculated for each participant. Multiple medications taken on the same day were counted once for that day. The mITT population included all randomized participants 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:

From Baseline up to 14 weeks [Titration Period (2 weeks) plus Maintenance Period (12 weeks)]

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	48
Units: percentage of participants				
number (not applicable)	77.5	59.0	45.0	60.4

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: percentage of participants				
number (not applicable)	65.2	47.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with hospitalization and healthcare resource utilization to treat seizures in each ZX008 treatment arm compared to placebo during study

End point title	Percentage of participants with hospitalization and healthcare resource utilization to treat seizures in each ZX008 treatment arm compared to placebo during study

End point description:

Participants who utilized medical center care to treat a seizure during the study were reported. The mITT population included all randomized participants 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:

During 14 weeks Titration (2 weeks) and Maintenance Period (12 weeks) (average of 99 days)

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	48
Units: percentage of participants				
number (not applicable)	22.5	17.9	15.0	12.5

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: percentage of participants				
number (not applicable)	19.6	14.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with status epilepticus (SE) in each ZX008 treatment arm compared to placebo during the Titration and Maintenance Period

End point title	Percentage of participants with status epilepticus (SE) in each ZX008 treatment arm compared to placebo during the Titration and Maintenance Period

End point description:

The participants who either had SE episode recorded as an adverse event (AE) during treatment or a seizure greater than 10 minutes were reported for each treatment group. Additionally, a single participant who may had more than one episode of SE, and an episode of SE recorded as both an AE and as a seizure longer than 10 minutes was counted as a single event. The mITT population included all randomized participants 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:

During 14 weeks Titration (2 weeks) and Maintenance Period (12 weeks) (average of 99 days)

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	48
Units: percentage of participants				
number (not applicable)	27.5	28.2	35.0	16.7

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: percentage of participants				
number (not applicable)	19.6	25.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Distribution of Duration of convulsive seizures (in percentage) in each ZX008 treatment arm compared to placebo at Baseline and during the Titration and Maintenance Period

End point title	Distribution of Duration of convulsive seizures (in percentage) in each ZX008 treatment arm compared to placebo at Baseline and during the Titration and Maintenance Period

End point description:

Duration of single convulsive seizures during the Baseline and the duration over the Titration and Maintenance Period were reported by treatment group using categories as <2 minutes, 2 to 10 minutes and > 10 minutes as collected in the seizure diary. The mITT population included all randomized participants 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:

At Baseline and 14 weeks of Titration (2 weeks) and Maintenance Period (12 weeks)

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	48
Units: percentage of seizures				
number (not applicable)				
<2 min (Baseline)	69.28	64.13	71.61	64.21
2-10 min (Baseline)	26.86	34.95	24.22	34.83
>10 min (Baseline)	3.86	0.93	4.17	0.96
<2 min (Titration + Maintenance Period)	71.31	71.59	72.27	65.84
2-10 min (Titration + Maintenance Period)	26.31	25.61	22.91	33.74
>10 min (Titration + Maintenance Period)	2.38	2.79	4.82	0.43

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: percentage of seizures				
number (not applicable)				
<2 min (Baseline)	63.90	74.11		
2-10 min (Baseline)	33.66	22.78		
>10 min (Baseline)	2.45	3.10		
<2 min (Titration + Maintenance Period)	63.45	84.67		
2-10 min (Titration + Maintenance Period)	31.34	13.71		
>10 min (Titration + Maintenance Period)	5.22	1.62		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Clinical Global Impression – Improvement (CGI-I) rating score, as assessed by the Principal Investigator in each ZX008 treatment arm compared to placebo

End point title	Percentage of participants with Clinical Global Impression – Improvement (CGI-I) rating score, as assessed by the Principal Investigator in each ZX008 treatment arm compared to placebo

End point description:

CGI-I scale measures improvement in the participant's clinical status from Baseline. The severity of a participant's condition was rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse), as follows: 1-very much improved,2-much improved, 3-minimally improved, 4- no change, 5-minimally worse, 6-much worse and 7-very much worse. The Principal Investigator rated their global impression of the participant's condition during the study. The mITT population included all randomized participants 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:
At Visit 6 (Day 15), 8 (Day 43), 10 (Day 71) and 12 (Day 99)

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	48
Units: percentage of participants				
number (not applicable)				
1 = Very much improved (Visit 6)	5.0	23.1	17.5	4.2
2 = Much improved (Visit 6)	12.5	12.8	25.0	2.1
3 = Minimally improved (Visit 6)	20.0	20.5	20.0	27.1
4 = No change (Visit 6)	40.0	25.6	17.5	54.2
5 = Minimally worse (Visit 6)	5.0	7.7	5.0	4.2
6 = Much worse (Visit 6)	0	0	2.5	0
7 = Very much worse (Visit 6)	0	0	0	0
1 = Very much improved (Visit 8)	0	5.1	17.5	4.2
2 = Much improved (Visit 8)	12.5	30.8	37.5	6.3
3 = Minimally improved (Visit 8)	30.0	20.5	10.0	16.7
4 = No change (Visit 8)	30.0	17.9	10.0	50.0
5 = Minimally worse (Visit 8)	5.0	5.1	0	4.2
6 = Much worse (Visit 8)	2.5	5.1	2.5	2.1
7 = Very much worse (Visit 8)	0	0	2.5	0
1 = Very much improved (Visit 10)	2.5	17.9	20.0	4.2
2 = Much improved (Visit 10)	7.5	17.9	47.5	10.4
3 = Minimally improved (Visit 10)	30.0	25.6	5.0	12.5
4 = No change (Visit 10)	35.0	28.2	7.5	60.4
5 = Minimally worse (Visit 10)	10.0	7.7	0	0
6 = Much worse (Visit 10)	0	2.6	0	0
7 = Very much worse (Visit 10)	0	0	0	0
1 = Very much improved (Visit 12)	2.5	12.8	27.5	4.2
2 = Much improved (Visit 12)	7.5	28.2	35.0	4.2
3 = Minimally improved (Visit 12)	30.0	17.9	15.0	16.7
4 = No change (Visit 12)	47.5	28.2	12.5	58.3
5 = Minimally worse (Visit 12)	2.5	10.3	0	6.3
6 = Much worse (Visit 12)	2.5	2.6	0	0
7 = Very much worse (Visit 12)	0	0	2.5	0

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: percentage of participants				
number (not applicable)				
1 = Very much improved (Visit 6)	21.7	16.7		

2 = Much improved (Visit 6)	21.7	27.1		
3 = Minimally improved (Visit 6)	17.4	27.1		
4 = No change (Visit 6)	26.1	12.5		
5 = Minimally worse (Visit 6)	2.2	2.1		
6 = Much worse (Visit 6)	0	4.2		
7 = Very much worse (Visit 6)	0	0		
1 = Very much improved (Visit 8)	17.4	29.2		
2 = Much improved (Visit 8)	10.9	31.3		
3 = Minimally improved (Visit 8)	26.1	14.6		
4 = No change (Visit 8)	34.8	8.3		
5 = Minimally worse (Visit 8)	0	4.2		
6 = Much worse (Visit 8)	0	0		
7 = Very much worse (Visit 8)	0	0		
1 = Very much improved (Visit 10)	15.2	35.4		
2 = Much improved (Visit 10)	19.6	18.8		
3 = Minimally improved (Visit 10)	26.1	16.7		
4 = No change (Visit 10)	28.3	4.2		
5 = Minimally worse (Visit 10)	0	0		
6 = Much worse (Visit 10)	0	2.1		
7 = Very much worse (Visit 10)	0	0		
1 = Very much improved (Visit 12)	8.7	33.3		
2 = Much improved (Visit 12)	28.3	31.3		
3 = Minimally improved (Visit 12)	21.7	10.4		
4 = No change (Visit 12)	28.3	16.7		
5 = Minimally worse (Visit 12)	10.9	6.3		
6 = Much worse (Visit 12)	0	0		
7 = Very much worse (Visit 12)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Clinical Global Impression – Improvement rating score, as assessed by the Parent/Caregiver in each ZX008 treatment arm compared to placebo

End point title	Percentage of participants with Clinical Global Impression – Improvement rating score, as assessed by the Parent/Caregiver in each ZX008 treatment arm compared to placebo

End point description:

CGI-I scale measures improvement in the participant's clinical status from Baseline. The severity of a participant's condition was rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse), as follows: 1-very much improved,2-much improved, 3-minimally improved, 4- no change, 5-minimally worse, 6-much worse and 7-very much worse. The Parent/Caregiver rated their global impression of the participant's condition during the study. The mITT population included all randomized participants 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:

At Visit 6 (Day 15), 8 (Day 43), 10 (Day 71) and 12 (Day 99)

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	48
Units: percentage of participants				
number (not applicable)				
1 = Very much improved (Visit 6)	2.5	17.9	15.0	6.3
2 = Much improved (Visit 6)	22.5	20.5	27.5	2.1
3 = Minimally improved (Visit 6)	12.5	28.2	22.5	25.0
4 = No change (Visit 6)	45.0	12.8	20.0	45.8
5 = Minimally worse (Visit 6)	2.5	7.7	2.5	10.4
6 = Much worse (Visit 6)	5.0	2.6	7.5	2.1
7 = Very much worse (Visit 6)	0	0	2.5	0
1 = Very much improved (Visit 8)	0	15.4	20.0	4.2
2 = Much improved (Visit 8)	15.0	25.6	37.5	8.3
3 = Minimally improved (Visit 8)	25.0	25.6	15.0	20.8
4 = No change (Visit 8)	20.0	12.8	5.0	47.9
5 = Minimally worse (Visit 8)	15.0	10.3	2.5	6.3
6 = Much worse (Visit 8)	2.5	5.1	5.0	4.2
7 = Very much worse (Visit 8)	0	0	2.5	4.2
1 = Very much improved (Visit 10)	2.5	20.5	35.0	2.1
2 = Much improved (Visit 10)	12.5	17.9	30.0	6.3
3 = Minimally improved (Visit 10)	22.5	20.5	7.5	25.0
4 = No change (Visit 10)	32.5	25.6	10.0	45.8
5 = Minimally worse (Visit 10)	12.5	7.7	0	6.3
6 = Much worse (Visit 10)	2.5	7.7	0	0
7 = Very much worse (Visit 10)	2.5	0	2.5	0
1 = Very much improved (Visit 12)	2.5	20.5	27.5	2.1
2 = Much improved (Visit 12)	7.5	20.5	27.5	6.3
3 = Minimally improved (Visit 12)	20.0	15.4	10.0	18.8
4 = No change (Visit 12)	35.0	20.5	15.0	50.0
5 = Minimally worse (Visit 12)	17.5	15.4	5.0	10.4
6 = Much worse (Visit 12)	7.5	7.7	5.0	2.1
7 = Very much worse (Visit 12)	0	0	2.5	0

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: percentage of participants				
number (not applicable)				
1 = Very much improved (Visit 6)	13.0	16.7		
2 = Much improved (Visit 6)	23.9	31.3		
3 = Minimally improved (Visit 6)	26.1	31.3		

4 = No change (Visit 6)	19.6	2.1		
5 = Minimally worse (Visit 6)	2.2	6.3		
6 = Much worse (Visit 6)	2.2	2.1		
7 = Very much worse (Visit 6)	0	2.1		
1 = Very much improved (Visit 8)	6.5	39.6		
2 = Much improved (Visit 8)	30.4	29.2		
3 = Minimally improved (Visit 8)	28.3	14.6		
4 = No change (Visit 8)	17.4	6.3		
5 = Minimally worse (Visit 8)	6.5	0		
6 = Much worse (Visit 8)	2.2	2.1		
7 = Very much worse (Visit 8)	0	0		
1 = Very much improved (Visit 10)	8.7	41.7		
2 = Much improved (Visit 10)	28.3	22.9		
3 = Minimally improved (Visit 10)	26.1	8.3		
4 = No change (Visit 10)	26.1	6.3		
5 = Minimally worse (Visit 10)	0	4.2		
6 = Much worse (Visit 10)	4.3	0		
7 = Very much worse (Visit 10)	0	0		
1 = Very much improved (Visit 12)	6.5	33.3		
2 = Much improved (Visit 12)	28.3	29.2		
3 = Minimally improved (Visit 12)	30.4	20.8		
4 = No change (Visit 12)	13.0	4.2		
5 = Minimally worse (Visit 12)	8.7	4.2		
6 = Much worse (Visit 12)	4.3	2.1		
7 = Very much worse (Visit 12)	2.2	2.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Day 99 in the Quality of Life in Childhood Epilepsy (QOLCE) score to measure quality of life in each ZX008 treatment arm compared to placebo

End point title	Change from Baseline to Day 99 in the Quality of Life in Childhood Epilepsy (QOLCE) score to measure quality of life in each ZX008 treatment arm compared to placebo

End point description:

QOLCE is a low-burden parent/caregiver completed assessment that evaluates how epilepsy affects day-to day functioning of the participant in various life areas, including physical activities, well being, cognition, social activities, behavior, and general health. QOLCE scores items on 16 subscales with possible 5-point response for each, where scores of 5 was best possible response and 1 was worst possible response. Item scores were then transformed to a 0-100 scale as follows: 1-0, 2-25, 3-50, 4-75, 5-100. A score for each participant for each subscale was calculated by averaging that participant's responses to each item in the subscale. Subscale scores per participant were averaged to obtain an overall QoL score for each participant. Higher the subscale and overall QoL scores, better the response. The mITT population included all randomized participants 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:

From Baseline to Day 99

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	48
Units: score on a scale				
arithmetic mean (standard deviation)	1.5 (± 8.73)	0.8 (± 11.77)	5.8 (± 11.70)	1.2 (± 9.01)

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: score on a scale				
arithmetic mean (standard deviation)	6.1 (± 12.47)	5.5 (± 13.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Day 99 in the Overall Quality of Life Score from the Pediatric Quality of Life Inventory™ (PedsQL) score in each ZX008 treatment arm compared to placebo

End point title	Change from Baseline to Day 99 in the Overall Quality of Life Score from the Pediatric Quality of Life Inventory™ (PedsQL) score in each ZX008 treatment arm compared to placebo

End point description:

The Pediatric Quality of Life Inventory (PedsQL) is a pediatric modular measure of health related quality of life (QoL) completed by the parent/caregiver on behalf of the participant. It consisted of 23 items across 4 core scales that measure physical (8 items), emotional, social, and school functioning (5 items each). Each of the responses to the 23 items is initially scored on a 5-point Likert scale from 0 (Never) to 4 (Almost always). Scores are linearly transformed to a scale of 0 to 100, where 0=100, 1=75, 2=50, 3=25 and 4=0, and higher scores correspond to better health-related QoL. The Overall Quality of Life is the average of all the items over the number of items answered on all the Scales. The mITT population included all randomized participants 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:

From Baseline to Day 99

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	48
Units: score on a scale				
arithmetic mean (standard deviation)	-1.6 (± 10.43)	6.8 (± 11.25)	5.9 (± 15.11)	1.9 (± 13.26)

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: score on a scale				
arithmetic mean (standard deviation)	4.2 (± 17.65)	2.1 (± 14.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Day 99 in the Total Score from PedsQL Family Impact module score in each ZX008 treatment arm compared to placebo

End point title	Change from Baseline to Day 99 in the Total Score from PedsQL Family Impact module score in each ZX008 treatment arm compared to placebo

End point description:

PedsQL Family Impact measured impact of pediatric chronic health conditions on parents and family by measuring parent self-reported physical, emotional, social, and cognitive functioning, communication, worry, and family daily activities and relationships. A total of 36 items in scale: 6 for Physical Functioning, 5 each for Emotional Functioning, Cognitive Functioning and Worry, 4 for Social Functioning, 3 for Communication, 3 questions for Daily Activities, and 5 for Family Relationships. Each of responses are initially scored on a 5-point Likert scale from 0 (Never) to 4 (Almost always) and then linearly transformed to scale of 0 to 100,where 0=100,1=75,2=50,3=25 and 4=0, and higher scores mean better health-related QoL. mITT population included all randomized participants who received at least 1 dose of ZX008 or placebo and for whom at least 1 week of diary data were available. Here, number of participants analyzed included those participants who were evaluable for the assessment.

End point type	Secondary

End point timeframe:

From Baseline to Day 99

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	39	40	47
Units: score on a scale				
arithmetic mean (standard deviation)	-4.4 (± 13.00)	3.9 (± 9.44)	5.4 (± 15.60)	1.3 (± 14.88)

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	48		
Units: score on a scale				
arithmetic mean (standard deviation)	0.7 (± 15.78)	6.3 (± 14.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life (QoL) of the Parent/Caregiver using the EQ- 5D-5L scale in each ZX008 treatment arm compared to placebo at Baseline (BL) and Day 99 (D99)

End point title	Quality of life (QoL) of the Parent/Caregiver using the EQ- 5D-5L scale in each ZX008 treatment arm compared to placebo at Baseline (BL) and Day 99 (D99)

End point description:

The EuroQOL–5 Dimensions–5 Levels scale produced by European QOL Group (EQ-5D-5L) health questionnaire is health-related QOL instrument with 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The 5 dimensions of EQ-5D-5L health questionnaire were assessed on a Likert scale with 5 possible levels: no problems (NP), slight problems, moderate problems, severe problems, and extreme problems. The categories "slight problems", "moderate problems", "severe problems" and "extreme problems" are collapsed into one response category "problems" (Pb). The QOL of the parent/caregiver was assessed and percentage of participants was reported for each item. mITT population was used for analysis. Here, number of participants analyzed included those participants who were evaluable for the assessment and 'n' signifies participants who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

At Baseline and Day 99

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	37	39	42
Units: percentage of participants				
number (not applicable)				
Mobility- NP (BL) (n=39,34,39,40,33,35)	33.33	52.94	46.15	40.00
Mobility- Pb (BL) (n=39,34,39,40,33,35)	66.67	47.06	53.85	60.00
Mobility- NP (D99) (n=35,37,37,42,43,45)	40.00	45.95	51.35	52.38
Mobility- Pb (D99) (n=35,37,37,42,43,45)	60.00	54.05	48.65	47.62

Self-care- NP (BL) (n=39,34,39,40,33,35)	25.64	41.18	38.46	22.50
Self-care- Pb (BL) (n=39,34,39,40,33,35)	74.36	58.82	61.54	77.50
Self-care- NP (D99) n=35,37,37,42,43,45)	28.57	43.24	48.65	30.95
Self-care- Pb (D99) n=35,37,37,42,43,45)	71.43	56.76	51.35	69.05
Usual activities- NP (BL)(n=39,34,39,40,33,35)	23.08	41.18	35.90	25.00
Usual activities- Pb (BL) (n=39,34,39,40,33,35)	76.92	58.82	64.10	75.00
Usual activities- NP (D99)(n=35,37,37,42,43,45)	25.71	32.43	48.65	30.95
Usual activities- Pb (D99)(n=35,37,37,42,43,45)	74.29	67.57	51.35	69.05
Pain/discomfort- NP (BL)(n=39,34,39,40,33,35)	48.72	41.18	46.15	45.00
Pain/discomfort- Pb (BL)(n=39,34,39,40,33,35)	51.28	58.82	53.85	55.00
Pain/discomfort- NP (D99)(n=35,37,37,42,43,45)	48.57	51.35	64.86	76.19
Pain/discomfort- Pb (D99)(n=35,37,37,42,43,45)	51.43	48.65	35.14	45.24
Anxiety/depression- NP (BL)(n=39,34,39,40,33,35)	74.36	61.76	56.41	60.00
Anxiety/depression- Pb (BL)(n=39,34,39,40,33,35)	25.64	38.24	43.59	40.00
Anxiety/depression- NP (D99)(n=35,37,37,42,43,45)	65.71	67.57	67.57	69.05
Anxiety/depression- Pb (D99)(n=35,37,37,42,43,45)	34.29	32.43	32.43	30.95

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	45		
Units: percentage of participants				
number (not applicable)				
Mobility- NP (BL) (n=39,34,39,40,33,35)	54.55	28.57		
Mobility- Pb (BL) (n=39,34,39,40,33,35)	45.45	45.45		
Mobility- NP (D99) (n=35,37,37,42,43,45)	51.16	46.67		
Mobility- Pb (D99) (n=35,37,37,42,43,45)	48.84	53.33		
Self-care- NP (BL) (n=39,34,39,40,33,35)	36.36	22.86		
Self-care- Pb (BL) (n=39,34,39,40,33,35)	63.64	77.14		
Self-care- NP (D99) n=35,37,37,42,43,45)	34.88	35.56		
Self-care- Pb (D99) n=35,37,37,42,43,45)	65.12	64.44		
Usual activities- NP (BL)(n=39,34,39,40,33,35)	39.39	20.00		

Usual activities- Pb (BL) (n=39,34,39,40,33,35)	60.61	80.00		
Usual activities- NP (D99)(n=35,37,37,42,43,45)	25.58	35.56		
Usual activities- Pb (D99)(n=35,37,37,42,43,45)	74.42	64.44		
Pain/discomfort- NP (BL)(n=39,34,39,40,33,35)	51.52	51.43		
Pain/discomfort- Pb (BL)(n=39,34,39,40,33,35)	48.48	48.57		
Pain/discomfort- NP (D99)(n=35,37,37,42,43,45)	46.51	64.44		
Pain/discomfort- Pb (D99)(n=35,37,37,42,43,45)	53.49	35.56		
Anxiety/depression- NP (BL)(n=39,34,39,40,33,35)	63.64	74.29		
Anxiety/depression- Pb (BL)(n=39,34,39,40,33,35)	36.36	25.71		
Anxiety/depression- NP (D99)(n=35,37,37,42,43,45)	67.44	73.33		
Anxiety/depression- Pb (D99)(n=35,37,37,42,43,45)	32.56	26.67		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Day 99 in affective symptoms of the Parent/Caregiver using the Hospital Anxiety and Depression Scale (HADS) in each ZX008 treatment arm compared to placebo

End point title	Change from Baseline to Day 99 in affective symptoms of the Parent/Caregiver using the Hospital Anxiety and Depression Scale (HADS) in each ZX008 treatment arm compared to placebo

End point description:

The HADS is a tool that was validated to assess presence of anxiety or depression in an outpatient non-psychiatric population. The HADS a 14-item scale that generates ordinal data for 2 dimensions: 1) Anxiety (7 items), and 2) Depression (7 items). Each item has 4 possible answers rated 0 to 3, of which 0 = No distress and 3 = worst distress. All answers to the items for a dimension with their respective rating are added resulting in a range for each dimension from 0-21, out of which of 0-7 = normal; 8-10=borderline abnormal; 11-21=abnormal. Scores for the entire scale (emotional distress) range from 0 to 42, with higher scores indicating more distress. The mITT population included all randomized participants who received at least 1 dose of ZX008 or placebo and for whom at least 1 week of diary data were available. Here, number of participants analyzed included those participants who were evaluable for the assessment.

End point type	Secondary

End point timeframe:

From Baseline to Day 99

End point values	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	32	35	30
Units: score on a scale				
arithmetic mean (standard deviation)				
Anxiety	-0.4 (± 2.68)	-0.8 (± 2.84)	-0.8 (± 3.33)	-0.6 (± 3.62)
Depression	0.8 (± 4.50)	0.2 (± 4.52)	0.1 (± 4.35)	-0.7 (± 3.80)
Total emotional distress	0.4 (± 6.45)	-0.6 (± 6.60)	-0.7 (± 6.82)	-1.2 (± 6.42)

End point values	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	27		
Units: score on a scale				
arithmetic mean (standard deviation)				
Anxiety	0.2 (± 3.89)	-0.7 (± 4.00)		
Depression	2.0 (± 4.77)	-0.8 (± 4.03)		
Total emotional distress	2.2 (± 7.52)	-1.5 (± 6.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed concentration of ZX008 determined directly from the concentration time profile [Cmax] at steady state

End point title	Maximum observed concentration of ZX008 determined directly from the concentration time profile [Cmax] at steady state[7]

End point description:

Cmax is the maximum observed concentration determined directly from the concentration-time profile. PK population for each study represents participants randomized to ZX008 and provided concentrations for use in the population PK analysis.

End point type	Secondary

End point timeframe:

At Visit 8 (Day 43): pre-dose, 1, 2, and 4-6 hours postdose

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The descriptive results were planned to be reported for ZX008 arms only, as no PK parameters are collected for Placebo.

End point values	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	36	45	44
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	17.7 (± 32.5)	67.9 (± 37.4)	17.4 (± 32.3)	64.5 (± 36.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration time curve of ZX008 from time zero to time 24 hours [AUC0-24hours] at steady state

End point title	Area under the concentration time curve of ZX008 from time zero to time 24 hours [AUC0-24hours] at steady state[8]

End point description:

AUC0-24 is the area under the concentration time curve from time zero to 24 hours. PK population for each study represents participants randomized to ZX008 and provided concentrations for use in the population PK analysis. PK samples at Visit 8 (Day 43) taken pre-dose to 6 hours post-dose were used to develop a population PK model. The model was utilized to generate plasma concentration-time curve over 24 hours at steady-state in study participants. AUC0-24 was calculated by numerical integration of the individual predicted concentration-time curve.

End point type	Secondary

End point timeframe:

At Visit 8 (Day 43): pre-dose, 1, 2, and 4-6 hours postdose

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The descriptive results were planned to be reported for ZX008 arms only, as no PK parameters are collected for Placebo.

End point values	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	36	45	44
Units: nanogram*hour per milliliter (ng*h/mL)				
geometric mean (geometric coefficient of variation)	356 (± 37.0)	1390 (± 41.3)	348 (± 37.1)	1290 (± 42.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum concentration [Tmax] of ZX008 at steady state

End point title	Time to maximum concentration [Tmax] of ZX008 at steady state[9]

End point description:

Tmax is the time to maximum concentration at steady state. PK population for each study represents participants randomized to ZX008 and provided concentrations for use in the population PK analysis.

End point type	Secondary

End point timeframe:

At Visit 8 (Day 43): pre-dose, 1, 2, and 4-6 hours postdose

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The descriptive results were planned to be reported for ZX008 arms only, as no PK parameters are collected for Placebo.

End point values	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	36	45	44
Units: hours (h)				
median (full range (min-max))	2.90 (2.80 to 3.10)	3.00 (2.70 to 3.20)	2.90 (2.80 to 3.10)	2.90 (2.70 to 3.20)

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination half-life [t1/2 beta] of ZX008 at steady state

End point title	Elimination half-life [t1/2 beta] of ZX008 at steady state[10]

End point description:

t1/2 beta is the elimination half-life. PK population for each study represents participants randomized to ZX008 and provided concentrations for use in the population PK analysis.

End point type	Secondary

End point timeframe:

At Visit 8 (Day 43): pre-dose, 1, 2, and 4-6 hours postdose

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The descriptive results were planned to be reported for ZX008 arms only, as no PK parameters are collected for Placebo.

End point values	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	36	45	44
Units: hours (h)				
geometric mean (geometric coefficient of variation)	18.4 (± 32.3)	21.1 (± 51.8)	18.1 (± 32.1)	18.6 (± 42.2)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Titration Period until the Safety Follow-up Visit (up to Day 113)

Adverse event reporting additional description:

A Treatment emergent adverse event (TEAE) was defined as any AE that based on start date information occurred after the first dose of study drug. The safety population included all randomized participants who received at least 1 dose of ZX008 or placebo.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Study 1: Placebo

Reporting group description:

Participants received matching placebo as an oral solution, twice a day (bid) in equally divided doses with food for up to approximately 16 weeks. Study 1 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).

Reporting group title	Study 1: ZX008 0.2 mg/kg/day

Reporting group description:

Participants received ZX008 0.2 milligram per kilogram per day (mg/kg/day) as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 1 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).

Reporting group title	Study 1: ZX008 0.8 mg/kg/day

Reporting group description:

Participants received ZX008 0.8 mg/kg/day as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 1 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).

Reporting group title	Study 3: Placebo

Reporting group description:

Participants received matching placebo as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 3 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).

Reporting group title	Study 3: ZX008 0.2 mg/kg/day

Reporting group description:

Participants received ZX008 0.2 mg/kg/day as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 3 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).

Reporting group title	Study 3: ZX008 0.8 mg/kg/day

Reporting group description:

Participants received ZX008 0.8 mg/kg/day as an oral solution, bid, in equally divided doses with food for up to approximately 16 weeks. Study 3 is the merged analysis of 2 identical studies (ZX008-1501 and ZX008-1502).

Serious adverse events	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 40 (10.00%)	4 / 39 (10.26%)	5 / 40 (12.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			

subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 40 (2.50%)	1 / 39 (2.56%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	2 / 40 (5.00%)	1 / 39 (2.56%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden unexplained death in epilepsy			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			

subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Study 3: Placebo	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 48 (4.17%)	3 / 46 (6.52%)	3 / 48 (6.25%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	0 / 48 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			

subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 48 (2.08%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 48 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden unexplained death in epilepsy			
subjects affected / exposed	1 / 48 (2.08%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 48 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 48 (2.08%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Study 1: Placebo	Study 1: ZX008 0.2 mg/kg/day	Study 1: ZX008 0.8 mg/kg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 40 (55.00%)	35 / 39 (89.74%)	36 / 40 (90.00%)
Investigations			
Blood glucose decreased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Blood pressure diastolic increased			
subjects affected / exposed	1 / 40 (2.50%)	3 / 39 (7.69%)	3 / 40 (7.50%)
occurrences (all)	2	3	3
Echocardiogram abnormal			
subjects affected / exposed	5 / 40 (12.50%)	7 / 39 (17.95%)	9 / 40 (22.50%)
occurrences (all)	5	7	13
Blood pressure increased			
subjects affected / exposed	0 / 40 (0.00%)	3 / 39 (7.69%)	2 / 40 (5.00%)
occurrences (all)	0	4	2
Blood prolactin increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Blood pressure systolic increased			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Heart rate increased			
subjects affected / exposed	1 / 40 (2.50%)	3 / 39 (7.69%)	1 / 40 (2.50%)
occurrences (all)	1	3	1
Platelet count decreased			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Weight decreased			

subjects affected / exposed	0 / 40 (0.00%)	5 / 39 (12.82%)	1 / 40 (2.50%)
occurrences (all)	0	5	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 40 (5.00%)	4 / 39 (10.26%)	0 / 40 (0.00%)
occurrences (all)	2	5	0
Nervous system disorders			
Lethargy			
subjects affected / exposed	2 / 40 (5.00%)	4 / 39 (10.26%)	7 / 40 (17.50%)
occurrences (all)	2	6	8
Somnolence			
subjects affected / exposed	3 / 40 (7.50%)	6 / 39 (15.38%)	3 / 40 (7.50%)
occurrences (all)	4	6	3
Ataxia			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	3 / 40 (7.50%)
occurrences (all)	0	2	3
Balance disorder			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	1 / 40 (2.50%)
occurrences (all)	0	2	1
Drooling			
subjects affected / exposed	0 / 40 (0.00%)	3 / 39 (7.69%)	2 / 40 (5.00%)
occurrences (all)	0	3	2
Hypotonia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Headache			
subjects affected / exposed	1 / 40 (2.50%)	3 / 39 (7.69%)	0 / 40 (0.00%)
occurrences (all)	1	5	0
Sedation			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	4 / 40 (10.00%)	3 / 39 (7.69%)	2 / 40 (5.00%)
occurrences (all)	4	5	4
Seizure cluster			

subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Status epilepticus			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	1 / 40 (2.50%)	1 / 39 (2.56%)	1 / 40 (2.50%)
occurrences (all)	1	1	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 40 (2.50%)	4 / 39 (10.26%)	4 / 40 (10.00%)
occurrences (all)	1	4	4
Pyrexia			
subjects affected / exposed	8 / 40 (20.00%)	7 / 39 (17.95%)	2 / 40 (5.00%)
occurrences (all)	12	12	3
Asthenia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Gait disturbance			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	4 / 40 (10.00%)	4 / 39 (10.26%)	3 / 40 (7.50%)
occurrences (all)	5	5	3
Diarrhoea			
subjects affected / exposed	3 / 40 (7.50%)	12 / 39 (30.77%)	7 / 40 (17.50%)
occurrences (all)	3	14	7
Salivary hypersecretion			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	1 / 40 (2.50%)
occurrences (all)	0	2	1
Constipation			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	4 / 40 (10.00%)
occurrences (all)	0	1	4
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 40 (5.00%)	1 / 39 (2.56%)	1 / 40 (2.50%)
occurrences (all)	2	1	1
Rhinorrhoea			
subjects affected / exposed	1 / 40 (2.50%)	2 / 39 (5.13%)	1 / 40 (2.50%)
occurrences (all)	1	2	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 40 (2.50%)	2 / 39 (5.13%)	2 / 40 (5.00%)
occurrences (all)	2	2	2
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	4
Enuresis			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Irritability			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Negativism			
subjects affected / exposed	1 / 40 (2.50%)	2 / 39 (5.13%)	0 / 40 (0.00%)
occurrences (all)	1	3	0
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	1 / 40 (2.50%)
occurrences (all)	0	2	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 40 (12.50%)	4 / 39 (10.26%)	7 / 40 (17.50%)
occurrences (all)	6	4	8
Upper respiratory tract infection			
subjects affected / exposed	5 / 40 (12.50%)	8 / 39 (20.51%)	0 / 40 (0.00%)
occurrences (all)	7	13	0
Croup infectious			
subjects affected / exposed	0 / 40 (0.00%)	3 / 39 (7.69%)	1 / 40 (2.50%)
occurrences (all)	0	3	1

Ear infection			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	1 / 40 (2.50%)
occurrences (all)	0	2	1
Influenza			
subjects affected / exposed	4 / 40 (10.00%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences (all)	4	0	0
Rhinitis			
subjects affected / exposed	1 / 40 (2.50%)	3 / 39 (7.69%)	1 / 40 (2.50%)
occurrences (all)	1	3	1
Sinusitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Viral infection			
subjects affected / exposed	0 / 40 (0.00%)	0 / 39 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 40 (5.00%)	8 / 39 (20.51%)	14 / 40 (35.00%)
occurrences (all)	2	11	15
Hypoglycaemia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	1 / 40 (2.50%)
occurrences (all)	0	1	1

Non-serious adverse events	Study 3: Placebo	Study 3: ZX008 0.2 mg/kg/day	Study 3: ZX008 0.8 mg/kg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 48 (77.08%)	41 / 46 (89.13%)	41 / 48 (85.42%)
Investigations			
Blood glucose decreased			
subjects affected / exposed	6 / 48 (12.50%)	11 / 46 (23.91%)	8 / 48 (16.67%)
occurrences (all)	7	13	8
Blood pressure diastolic increased			
subjects affected / exposed	3 / 48 (6.25%)	3 / 46 (6.52%)	1 / 48 (2.08%)
occurrences (all)	3	3	1
Echocardiogram abnormal			

subjects affected / exposed	5 / 48 (10.42%)	11 / 46 (23.91%)	8 / 48 (16.67%)
occurrences (all)	5	11	8
Blood pressure increased			
subjects affected / exposed	4 / 48 (8.33%)	2 / 46 (4.35%)	2 / 48 (4.17%)
occurrences (all)	4	2	2
Blood prolactin increased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Blood pressure systolic increased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Heart rate increased			
subjects affected / exposed	3 / 48 (6.25%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences (all)	4	1	0
Platelet count decreased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	4 / 48 (8.33%)
occurrences (all)	0	0	4
Weight decreased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 46 (2.17%)	4 / 48 (8.33%)
occurrences (all)	0	1	4
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Nervous system disorders			
Lethargy			
subjects affected / exposed	2 / 48 (4.17%)	1 / 46 (2.17%)	3 / 48 (6.25%)
occurrences (all)	2	1	4
Somnolence			
subjects affected / exposed	5 / 48 (10.42%)	5 / 46 (10.87%)	10 / 48 (20.83%)
occurrences (all)	5	6	10
Ataxia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 46 (0.00%)	2 / 48 (4.17%)
occurrences (all)	1	0	2
Balance disorder			

subjects affected / exposed	1 / 48 (2.08%)	0 / 46 (0.00%)	2 / 48 (4.17%)
occurrences (all)	1	0	2
Drooling			
subjects affected / exposed	0 / 48 (0.00%)	1 / 46 (2.17%)	2 / 48 (4.17%)
occurrences (all)	0	1	2
Hypotonia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	1 / 48 (2.08%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences (all)	1	1	0
Sedation			
subjects affected / exposed	3 / 48 (6.25%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	3	0	0
Seizure			
subjects affected / exposed	1 / 48 (2.08%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	1	0	1
Seizure cluster			
subjects affected / exposed	0 / 48 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Status epilepticus			
subjects affected / exposed	0 / 48 (0.00%)	3 / 46 (6.52%)	0 / 48 (0.00%)
occurrences (all)	0	5	0
Tremor			
subjects affected / exposed	1 / 48 (2.08%)	1 / 46 (2.17%)	6 / 48 (12.50%)
occurrences (all)	1	1	6
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 48 (2.08%)	3 / 46 (6.52%)	5 / 48 (10.42%)
occurrences (all)	1	3	5
Pyrexia			
subjects affected / exposed	4 / 48 (8.33%)	5 / 46 (10.87%)	9 / 48 (18.75%)
occurrences (all)	5	7	11
Asthenia			

subjects affected / exposed	1 / 48 (2.08%)	2 / 46 (4.35%)	3 / 48 (6.25%)
occurrences (all)	1	2	3
Gait disturbance			
subjects affected / exposed	0 / 48 (0.00%)	3 / 46 (6.52%)	1 / 48 (2.08%)
occurrences (all)	0	3	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 48 (6.25%)	0 / 46 (0.00%)	3 / 48 (6.25%)
occurrences (all)	4	0	3
Diarrhoea			
subjects affected / exposed	4 / 48 (8.33%)	7 / 46 (15.22%)	7 / 48 (14.58%)
occurrences (all)	4	8	7
Salivary hypersecretion			
subjects affected / exposed	0 / 48 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 48 (0.00%)	2 / 46 (4.35%)	1 / 48 (2.08%)
occurrences (all)	0	2	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 48 (2.08%)	2 / 46 (4.35%)	3 / 48 (6.25%)
occurrences (all)	1	2	3
Rhinorrhoea			
subjects affected / exposed	0 / 48 (0.00%)	3 / 46 (6.52%)	1 / 48 (2.08%)
occurrences (all)	0	3	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 48 (2.08%)	0 / 46 (0.00%)	4 / 48 (8.33%)
occurrences (all)	1	0	4
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 48 (2.08%)	1 / 46 (2.17%)	2 / 48 (4.17%)
occurrences (all)	1	1	2
Enuresis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0

Irritability			
subjects affected / exposed	3 / 48 (6.25%)	2 / 46 (4.35%)	1 / 48 (2.08%)
occurrences (all)	3	2	1
Negativism			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	0 / 48 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 48 (10.42%)	4 / 46 (8.70%)	1 / 48 (2.08%)
occurrences (all)	8	7	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 48 (4.17%)	3 / 46 (6.52%)	4 / 48 (8.33%)
occurrences (all)	3	4	5
Croup infectious			
subjects affected / exposed	0 / 48 (0.00%)	1 / 46 (2.17%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	2 / 48 (4.17%)	3 / 46 (6.52%)	0 / 48 (0.00%)
occurrences (all)	2	3	0
Influenza			
subjects affected / exposed	2 / 48 (4.17%)	1 / 46 (2.17%)	1 / 48 (2.08%)
occurrences (all)	2	3	1
Rhinitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 46 (0.00%)	2 / 48 (4.17%)
occurrences (all)	0	0	2
Sinusitis			
subjects affected / exposed	1 / 48 (2.08%)	3 / 46 (6.52%)	1 / 48 (2.08%)
occurrences (all)	1	4	1
Urinary tract infection			
subjects affected / exposed	0 / 48 (0.00%)	2 / 46 (4.35%)	1 / 48 (2.08%)
occurrences (all)	0	3	3
Viral infection			

subjects affected / exposed	0 / 48 (0.00%)	3 / 46 (6.52%)	2 / 48 (4.17%)
occurrences (all)	0	3	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 48 (6.25%)	12 / 46 (26.09%)	18 / 48 (37.50%)
occurrences (all)	3	12	22
Hypoglycaemia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 46 (0.00%)	3 / 48 (6.25%)
occurrences (all)	1	0	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2015	Protocol 1501 Amendment 1: Clarifications and changes were made to the protocol and included the following: • Sponsor name change • Added new section of transition for subjects who would be entering the open-label extension study • Removed the following clinical laboratory tests at Visits 1 and 6: luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, testosterone, growth hormone (GH), prolactin, and insulin-like growth factor-1 (IGF-1) • Clarified the maximum dose of ZX008 is 30 mg/day • Clarified the collection duration of prior and concomitant antiepileptic drug (AEDs) • Clarified data to be collected with the use of rescue medication • Moved the BRIEF-P description from the efficacy section to the safety section • Added new section of collection of data for AEs requiring hospitalization Additional clarifications and changes were made, based on feedback received from the US Food and Drug Administration (FDA), and included the following: • Clarified randomization inclusion criteria, post-treatment cardiac follow-up, and adverse event of special interest (AESI) regarding valve regurgitation seen on echocardiogram (ECHO) • Clarified that the central cardiac reader would provide consultation to the Independent Data and Safety Monitoring Committee (IDSMC) when a subject was removed from the study due to development of signs or symptoms indicative of valvulopathy, regurgitation, or pulmonary hypertension • Clarified expedited reporting of cardiac events other than serious adverse events (SAEs) • Added section on grading of and follow-up for ECHO findings.
11 January 2016	Protocol 1502 Amendment 1: Clarifications and changes were made to the protocol and included the following: • Sponsor name change • Removed the following clinical laboratory tests at Visits 1 and 6: LH, FSH, estradiol, testosterone, GH, prolactin, and IGF-1 • Clarified the maximum dose of ZX008 is 30 mg/day • Clarified the collection duration of prior and concomitant AEDs • Clarified data to be collected with the use of rescue medication • Added new section of collection of data for AEs requiring hospitalization • Replaced CHU9D with PedsQL • Updated statistical analysis section, to be consistent with the separate statistical analysis plan • Clarified study duration for participants • Clarified Inclusion Criterion regarding the requirement for a whole blood sample for a broad epilepsy-related gene panel • Added requirement that subjects qualified for and planned to enroll into the separate open-label extension study at the end of this study should be consented prior to Visit 12 • Clarified, for all questionnaires and rating scales, when rater substitution was acceptable for the clinic staff and the arent/caregiver Clarifications and changes were made based on feedback received from the US FDA, and included the following: • Clarified randomization inclusion criteria, post-treatment cardiac follow-up, and AESI regarding valve regurgitation seen on ECHO • Clarified that the central cardiac reader would provide consultation to the IDSMC when a subject was to be removed from the study due to development of signs or symptoms indicative of valvulopathy, regurgitation, or pulmonary hypertension.

11 January 2016	Continuation of Protocol 1502 Amendment 1• Clarified expedited reporting of cardiac events other than SAEs • Added section on grading of and follow-up for ECHO findings • Added the assessment of cognition for subjects ≥5 years of age, so that all study participants were being assessed for cognition using the BRIEF. The description of the BRIEF was moved from the efficacy section to the safety section. Clarifications and changes were made based on feedback received from the European VHP Clinical Trials Group, and included the following: • Updated contraception requirements for the study • Clarified when subjects must have been discontinued from the study • Clarified that the investigator could discontinue a subject from the study in the case of a medical emergency • Added statistical information regarding sensitivity analyses for concomitant AED medication changes during the study.
18 January 2016	Protocol 1501 Amendment 2: Clarifications and changes were made to the protocol and included the following: • Replaced Child Health Utility Instrument (CHU9D) with PedsQL • Updated statistical analysis section, to be consistent with the separate statistical analysis plan • Clarified Inclusion Criterion regarding the requirement for a whole blood sample for a broad epilepsy-related gene panel A change was made based on feedback received from the US FDA, and included the following: • Added the assessment of cognition for subjects ≥5 years of age, so that all study participants were assessed for cognition using the BRIEF. The description of the BRIEF was moved from the efficacy section to the safety section. Clarifications and changes were made based on feedback received from the European Voluntary Harmonization Procedure (VHP) Clinical Trials Group, and included the following: • Updated contraception requirements for the study • Clarified when subjects must be discontinued from the study • Clarified that the investigator could discontinue a subject from the study in the case of a medical emergency • Added statistical information regarding sensitivity analyses for concomitant AED medication changes during the study.
31 October 2016	Protocol 1501 Amendment 3: Clarifications and changes were made to the protocol and included the following: • Removed atonic seizures from and added tonic-atonic to the types of convulsive seizures in Inclusion Criterion • Removal of Inclusion Criterion, to clarify that participation in the epilepsy-related genetic testing was not required at screening for participation • Updated the preclinical data information and, based on this information, revised the list of prohibited concomitant medications • Clarified that the number of convulsive seizures during the 6-week Baseline period is ≥ 6 versus > 6 as originally stated • Added PedsQL Family Impact module to the efficacy measures as intended • Clarified study days of Screening during the Baseline period and the timing of assessments in that period • Collection of blood sample for epilepsy genotype panel was mandatory but not required at screening. Added the list of countries in which Diacomit® (stiripentol) is approved • Added supporting references to existing citations of data • Clarified the safety objective • Specified that the number of study centers was approximate • Clarified the duration of use of contraception after the last dose of study drug • Removal of social media policy from the reason for removing a subject from therapy or assessment.

31 October 2016	Protocol 1502 Amendment 2: Clarifications and changes were made to the protocol and included the following: • Removed atonic seizures and added tonic-atonic from the types of convulsive seizures in Inclusion Criterion • Removal of Inclusion Criterion to clarify that participation in the epilepsy-related genetic testing was not required at screening for participation. • Updated the preclinical data information and, based on this information, revised the list of prohibited concomitant medications. • Clarified that the number of convulsive seizures during the 6-week Baseline period was ≥6 versus >6 as originally stated. • Added PedsQL Family Impact module to the efficacy measures as intended • Clarified study days of Screening during the Baseline period and the timing of assessments in that period • Collection of blood sample for epilepsy genotype panel was mandatory but not required at screening.• Added the list of countries in which Diacomit® (stiripentol) is approved • Added supporting references to existing citations of data • Clarified the safety objective • Specified that the number of study centers was approximate. • Clarified the duration of use of contraception after the last dose of study drug. • Removal of social media policy from the reason for removing a subject from therapy or assessment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This posting consists of pooled analysis (PA) 1 and 2 of ZX008-1501 and ZX008-1502. PA1 is referenced as Study 1 in SAP and CSR. PA2 is referenced as Study 2 in respective SAP and Study 3 in corresponding CSR due to timing of regulatory submissions.

Notes: