Clinical trial results:
A Phase 3 Study of Adjunctive XEN496 in Pediatric Subjects with KCNQ2 Developmental and Epileptic Encephalopathy

Summary

EudraCT number	2020-002396-35
Trial protocol	BE ES FR IT
Global end of trial date	16 May 2023

Results information

Result version number	v1 (current)
This version publication date	02 December 2023
First version publication date	02 December 2023

Trial information

Trial identification

Sponsor protocol code	XPF-009-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04639310
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Xenon Pharmaceuticals Inc.
Sponsor organisation address	200-3650 Gilmore Way, Burnaby, BC, Canada, V5G 4W8
Public contact	Medical Affairs, Xenon Pharmaceuticals Inc., +1 604-484-3300, XenonCares@xenon-pharma.com
Scientific contact	Medical Affairs, Xenon Pharmaceuticals Inc., +1 604-484-3300, XenonCares@xenon-pharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	12 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 May 2023
Global end of trial reached?	Yes
Global end of trial date	16 May 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the potential antiseizure effects of adjunctive XEN496 (ezogabine) compared with placebo in children with KCNQ2 Developmental and Epileptic Encephalopathy (KCNQ2-DEE).

Protection of trial subjects:

The study was conducted in accordance with the ethical principles of the "Declaration of Helsinki" and International Council on Harmonisation guideline on Good Clinical Practice (GCP). This clinical trial was reviewed and approved by the appropriate Regulatory Health Agency and Ethics Committee. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects/Legal guardians were required to sign the informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 March 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Belgium: 3
Worldwide total number of subjects	8
EEA total number of subjects	3

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)	3
Children (2-11 years)	5
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study enrolled pediatric subjects (aged from 1 month to less than 6 years) with documented genetic evidence consistent with a diagnosis of KCNQ2 Developmental and Epileptic Encephalopathy (KCNQ2-DEE).

Pre-assignment

Screening details:

Participants entered a 2 or 4 week baseline period based upon seizure frequency prior to enrollment. At the discretion of the investigator, the baseline period was extended by an additional 2 weeks to ensure adequate establishment of baseline seizure frequency.

Period 1

Period 1 title	Titration & Maintenance (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	Treatment

Arm description:

24-day dose titration period to a top dose of 21 mg/kg/day. Subjects continued at the top dose, or the highest tolerated dose up to the top dose, for 12-week maintenance period. If the subject did not immediately enter into the separate open-label extension (OLE) study, the maintenance period was followed by a 15-day taper period.

Arm type	Experimental
Investigational medicinal product name	XEN496
Investigational medicinal product code	
Other name	ezogabine, retigabine
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

XEN496 capsules: immediate-release, multi-particulate sprinkle capsule formulation of ezogabine administered orally 3 times a day for up to approximately 15 weeks (titration and maintenance).

Parents / caregivers were instructed to sprinkle and mix the contents of the capsules into soft foods or liquids and feed it to the child 3 times a day.

Arm title	Placebo

Arm description:

To maintain the blinded aspect of the study, subjects were titrated on placebo over the 24-day period and remain at this dose for the 12-week maintenance period. If the subject did not immediately enter into the separate OLE study, the maintenance period would be followed by a 15-day taper period.

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

Dosage and administration details:

Placebo sprinkle capsules: matching XEN496 in appearance containing only inactive ingredients.

Parents / caregivers were instructed to sprinkle and mix the contents of the capsules into soft foods or

liquids and feed it to the child three times a day.

Number of subjects in period 1	Treatment	Placebo
Started	5	3
Completed	5	2
Not completed	0	1
Subject qualified to enter OLE early per protocol	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description:	
24-day dose titration period to a top dose of 21 mg/kg/day. Subjects continued at the top dose, or the highest tolerated dose up to the top dose, for 12-week maintenance period. If the subject did not immediately enter into the separate open-label extension (OLE) study, the maintenance period was followed by a 15-day taper period.	
Reporting group title	Placebo
Reporting group description:	
To maintain the blinded aspect of the study, subjects were titrated on placebo over the 24-day period and remain at this dose for the 12-week maintenance period. If the subject did not immediately enter into the separate OLE study, the maintenance period would be followed by a 15-day taper period.	

Reporting group values	Treatment	Placebo	Total
Number of subjects	5	3	8
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	2	1	3
Children (2-11 years)	3	2	5
Gender categorical Units: Subjects			
Female	3	2	5
Male	2	1	3
Race (NIH/OMB) Units: Subjects			
Asian	1	0	1
White	3	2	5
Unknown or Not Reported	1	1	2
Region of Enrollment Units: Subjects			
Belgium	1	2	3
Australia	1	0	1
United States	3	1	4

End points

End points reporting groups

Reporting group title	Treatment

Reporting group description:

24-day dose titration period to a top dose of 21 mg/kg/day. Subjects continued at the top dose, or the highest tolerated dose up to the top dose, for 12-week maintenance period. If the subject did not immediately enter into the separate open-label extension (OLE) study, the maintenance period was followed by a 15-day taper period.

Reporting group title	Placebo

Reporting group description:

To maintain the blinded aspect of the study, subjects were titrated on placebo over the 24-day period and remain at this dose for the 12-week maintenance period. If the subject did not immediately enter into the separate OLE study, the maintenance period would be followed by a 15-day taper period.

Primary: Percent Change From Baseline in Monthly (28 Day) Countable Motor Seizure Frequency During the Blinded Treatment Period

End point title	Percent Change From Baseline in Monthly (28 Day) Countable Motor Seizure Frequency During the Blinded Treatment Period[1]

End point description:

Parent/caregiver seizure diary record will be used to assess frequency, type and duration of seizure activity

End point type	Primary

End point timeframe:

From baseline to the end of the double-blind, 12 week treatment period (maintenance)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Study terminated early with only 8 of 40 participants enrolled.

End point values	Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	3		
Units: percent				
arithmetic mean (standard deviation)	-46.0 (± 23.49)	25.6 (± 46.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With ≥50 Percent Reduction in Monthly (28 Day) Seizure Frequency

End point title	Proportion of Subjects With ≥50 Percent Reduction in Monthly (28 Day) Seizure Frequency

End point description:

Parent/caregiver seizure diary record will be used to assess frequency, type of seizure with a duration of at least 3 seconds.

End point type	Secondary

End point timeframe:

From baseline to the end of the double-blind, 12 week treatment period (maintenance)

End point values	Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	3		
Units: Count of Participants	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Caregiver Global Impression of Change (CaGI-C) Scores for the Subject's Overall Condition and for Seizures

End point title	Caregiver Global Impression of Change (CaGI-C) Scores for the Subject's Overall Condition and for Seizures

End point description:

CaGI-C scale is a caregiver-reported assessment for the subject's overall condition and for seizures. Responses to the CaGI-C questionnaire are to be rated on a 7 point Likert scale ranging from very much improved to very much worse.

Only the results for overall condition at Study Day 109 (end of treatment period; subjects with at least minimally improved overall condition [a score of <=3].) are provided.

End point type	Secondary

End point timeframe:

Study Days 24, 67, 88 and 109

End point values	Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	3		
Units: Count of Participants	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Caregiver Global Impression of Severity (CaGI-S) for the Subject's Overall Condition and for Seizures

End point title	Change From Baseline in the Caregiver Global Impression of Severity (CaGI-S) for the Subject's Overall Condition and for Seizures

End point description:

CaGI-S scale is Caregiver-reported assessment of the severity of the subject's seizures and overall

condition over the previous 7 days. Responses to the CaGI-S questionnaire are to be rated on a 5 point Likert scale ranging from none to very severe.

Only the results for overall condition at Study Day 109 (end of treatment period; responders [>= 1 level improved]) are provided.

End point type	Secondary

End point timeframe:

Study Days 1, 24, 67, 88 and 109

End point values	Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	3		
Units: Count of Participants	0	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Assess the Safety and Tolerability of XEN496 (e.g., Adverse Events) in Pediatric Subjects With KCNQ2-DEE

End point title	Assess the Safety and Tolerability of XEN496 (e.g., Adverse Events) in Pediatric Subjects With KCNQ2-DEE

End point description:

To assess adverse events as criteria for safety and tolerability

End point type	Other pre-specified

End point timeframe:

From screening through to the end of the study (maintenance phase for those continuing into the OLE) or Day 151 for those exiting the study

End point values	Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	3		
Units: Count of Participants				
No. of Subject with any AE	5	3		
No. of Subjects with any TEAE	5	3		
No. of Subjects with any Treatment Related TEAE	1	0		
Subj. with any TEAE leading to IMP discontinuation	0	0		
Subjects with TEAE leading to dose reduct/interrup	1	0		
No. of Subjects with any Severe TEAE	1	1		
No. of Subjects with any TEAE-relationship to IMP	5	3		
No. of Subjects with any Serious TEAE	1	1		

No. of Subjects with any TEAE of Special Interest	0	0		
No. of Subjects with any TEAE leading to death	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 15 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Overall - XEN496
Reporting group description: -	
Reporting group title	Overall - Placebo
Reporting group description: -	

Serious adverse events	Overall - XEN496	Overall - Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	1 / 3 (33.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Metapneumovirus pneumonia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Overall - XEN496	Overall - Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	3 / 3 (100.00%)	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Lethargy			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Conjunctival hyperemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	2 / 5 (40.00%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Hemotochemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Vomiting			

subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Teething			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary congestion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Poor quality sleep			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
COVID-19			
subjects affected / exposed	0 / 5 (0.00%)	2 / 3 (66.67%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Otitis media			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	

Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 3 (33.33%) 1	
Viral infection subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	0 / 3 (0.00%) 0	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2021	Version 1.0 of the XPF-009-301 clinical study protocol was amended to update laboratory assessments, provide clarifications
31 January 2022	Version 2.0 of the XPF-009-301 clinical study protocol was amended to incorporate requested updates from applicable Agencies.
06 May 2022	Version 3.0 of the XPF-009-301 clinical study protocol was amended confirm dose, inclusion and assessment information.
10 November 2022	Version 4.0 of the XPF-009-301 clinical study protocol was amended to clarify the inclusion criteria.

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.

In May 2023, Xenon discontinued the XEN496 program due to significant challenges encountered with enrollment. The program, including this study, was not halted due to safety reasons or for futility (inability to show efficacy).

Notes: