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Statistical Analysis Plan

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Protocol Title: AN OPEN-LABEL EXTENSION STUDY OF XEN496 IN PEDIATRIC SUBJECTS WITH KCNQ2 DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY

Protocol Number: XPF-009-302

Protocol Version, Date 3.0, 09 May 2022

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REVISION HISTORY

Version/Date	Version name	Changes implemented
Version 1.0/ 04May2023	Initial approved version	N/A

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LIST OF ABBREVIATIONS

Abbreviation or Special Term	Explanation
ABAS-3	Adaptive Behavior Assessment System, Third Edition
AEs	Adverse Events
ALT	Alanine Transaminase
ASMs	Antiseizure Medications
AST	Aspartate Transferase
ATC	Anatomic Therapeutic Classification
BSID-III	Bayley Scales of Infant Development III
CaGI-C	Caregiver Global Impression of Change
CaGI-S	Caregiver Global Impression of Severity
CGI-C	Clinician Global Impression of Change
CI	Confidence Intervals
COVID-19	Corona Virus Disease of 2019
CRA	Clinical Research Associate
CSR	Clinical Study Report
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ICF	Informed Consent Form
IRB	Institutional Review Board
KCNQ2-DEE	KCNQ2 developmental and epileptic encephalopathy
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NAMR	N-acetyl metabolite of ezogabine
OLE	Open-Label Extension
PCSA	Potentially Clinically Significant Abnormalities
PedsQL	Pediatric Quality of Life Inventory

Abbreviation or Special Term	Explanation
PedsQL-FIM	Pediatric Quality of Life Inventory, Family Impact Module
PK	Pharmacokinetics
PLT	Platelets
PT	Preferred Term
PY	Patient Year
QTcF	QT interval corrected for heart rate by Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TFL	Tables, Figures And Listings
TEAE	Treatment Emergent Adverse Event
TID	Three times a day
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHODDE	World Health Organization Drug Dictionary Enhanced

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol XPF-009-302 Version 3.0, "An open-label extension study of XEN496 in pediatric subjects with KCNQ2 developmental and epileptic encephalopathy" dated 09 May 2022 for final analysis. The table of contents and templates for the tables, figures and listings (TFLs) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Conference on Harmonization (ICH) E3 and E9 guidelines.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the long-term safety and tolerability of XEN496 in pediatric subjects with KCNQ2 developmental and epileptic encephalopathy (KCNQ2-DEE) who had participated in the primary study (XPF-009-301).	• Severity and frequency of adverse events (AEs) and serious adverse events (SAEs); clinically significant changes in laboratory tests, vital signs, electrocardiograms (ECGs), physical and neurologic examinations, CCI [redacted]
Secondary	
To evaluate the intra-subject efficacy of XEN496 in reducing seizure frequency compared to prior placebo treatment in pediatric subjects with KCNQ2-DEE who were previously randomized to receive placebo in the primary double-blind Phase 3 study (XPF-009-301).	• Change in monthly countable motor seizure frequency, comparing the first 15 weeks of XEN496 treatment in the open label extension (OLE) study to the seizure frequency reported during treatment in the preceding primary study (XPF-009-301), among only those subjects who were randomized to the placebo arm in the primary study (XPF-009-301). (key efficacy endpoint)
To assess the long-term effect of XEN496 on seizure reduction in pediatric subjects treated with XEN496.	• Change from pre-randomization baseline in the previous study over time based on response categories (<25%, 25 to <50%, 50 to <75%, 75 to <100%, 100%), based on estimated seizure frequency every 3 months during the OLE period. • Percent change from baseline in countable motor seizure frequency, relative to pre-randomization baseline of the previous study (XPF-009-301), assessed over time every 3 months during the OLE.

Objectives	Endpoints
	• Percent change from baseline in countable motor seizure frequency, relative to pre-randomization baseline of the previous study (XPF-009-301), for every 3 months based on combined data from both XPF-009-301 and the OLE, by the treatment group in the previous study.
To evaluate Caregiver Global Impression of Severity (CaGI-S) and Caregiver Global Impression of Change (CaGI-C) scores in pediatric subjects with KCNQ2-DEE.	• Change over time in CaGI-S scores for the subject's seizures and overall condition. • Change over time in CaGI-C scores for the subject in the following domains: overall condition, seizures, behavior, alertness, motor skills, visual function, and communication.
To assess neurocognitive development and behavior after dosing with XEN496 in pediatric subjects with KCNQ2-DEE.	• Change over time in neurocognitive development based on the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). • Change over time in adaptive behavior based on the Adaptive Behavior Assessment System, Third Edition (ABAS-3).
To evaluate the investigator's global impression of the change in the subject's overall condition, assessed using the Clinical Global Impression of Change (CGI-C) scale.	• Change over time in CGI-C scores for the subject's seizures and overall condition.
To evaluate the use of rescue medication and change in background antiseizure medications (ASMs).	• Use of rescue medication. • Use of concomitant medications and treatments used for seizure control.
To assess the impact of XEN496 on the	• Change in quality of life of subjects

Objectives	Endpoints
quality of life of caregivers and subjects with KCNQ2-DEE.	with KCNQ2-DEE, based on the Pediatric Quality of Life Inventory (PedsQL). • Change in quality of life of subjects with KCNQ2-DEE, based on the Pediatric Quality of Life Inventory, Family Impact Module (PedsQL-FIM).
To evaluate the plasma concentrations of ezogabine and N-acetyl metabolite of retigabine (ezogabine) (NAMR).	• Plasma concentrations of ezogabine and NAMR (for subjects treated in the OLE study only).

3 STUDY DESIGN

3.1 General study design

This is a Phase 3, open-label, long-term extension study to evaluate the safety, tolerability, and efficacy of XEN496 administered as adjunctive therapy in pediatric subjects with KCNQ2-DEE who participated in the primary study, XPF-009-301.

Approximately 40 subjects may be included in the study based on the anticipated number of subjects who could roll over from Study XPF-009-301.

Subjects will undergo the following:

- Screening/Baseline period – Subjects will undergo eligibility assessment at Visit 22 or early termination in the primary study (XPF-009-301).
- Treatment period – 36 months:
  - Blinded transition/titration period CCI
  - Open-label period – approximately 35 months.

  Subjects who received XEN496 in the primary study will continue to receive XEN496 at the same dose throughout the OLE.

  Subjects allocated to placebo in the primary study will be required to begin a titration of XEN496 CCI

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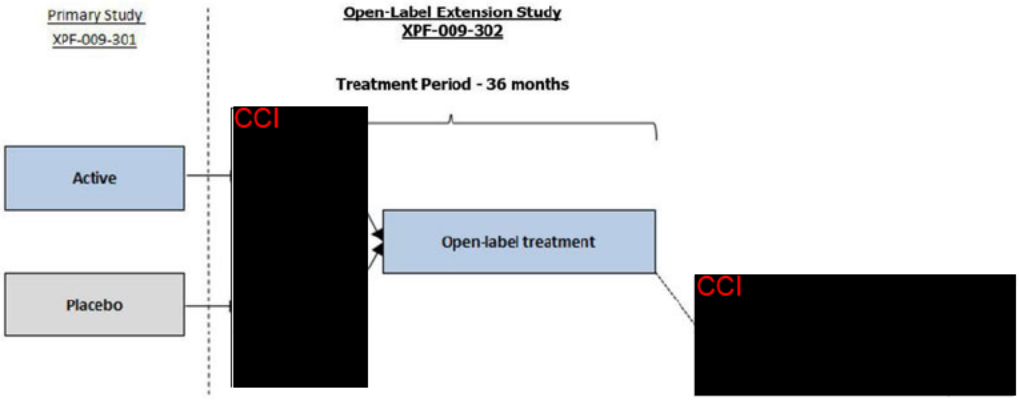
- Taper period – CCI

  Subjects who discontinue or complete the study treatment will be required to taper off study drug CCI The actual duration of the taper period will depend on the subject's dosage prior to taper.
- Follow-up – Approximately 4 weeks after subjects have tapered off of study drug.

Total study duration per subject is estimated to be 37 months.

The Study Design Schematic is presented in Figure 1.

Figure 1: Study Design Schematic



3.2 Randomization and blinding

This is an open label study and randomization is not applicable.
A double-blind transition/titration period will be used to maintain blinding to the treatment allocation in the primary study (XPF-009-301). During this period, treatment will be administered under double-blind conditions: Subjects and their caregivers, the investigators, and the outcomes assessor will be blinded to treatment assignment.

3.3 Study treatments and assessments

Total treatment duration per subject is estimated to be 36 months.

The treatment period begins with a dose transition/titration period. Subjects who received XEN496 in the preceding study will continue to receive XEN496 at the same dose, in a blinded manner, without any further titration.

Subjects allocated to placebo in the preceding study, CCI

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The dose titration scheme in Table 1 is approximate. The final dose and number of capsules, using weight-based dosing, are detailed in the pharmacy manual.

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The optimally-tolerated dose level established during the transition/titration period will be maintained throughout the duration of the open-label period unless dose adjustment is required.

A detailed description of procedures and assessments to be conducted during this study is summarized in the Scheduled of Study Assessments in Table 2 and Table 3 below.

Table 2: Schedule of Activities, Baseline and Treatment Period Up to 1 Year

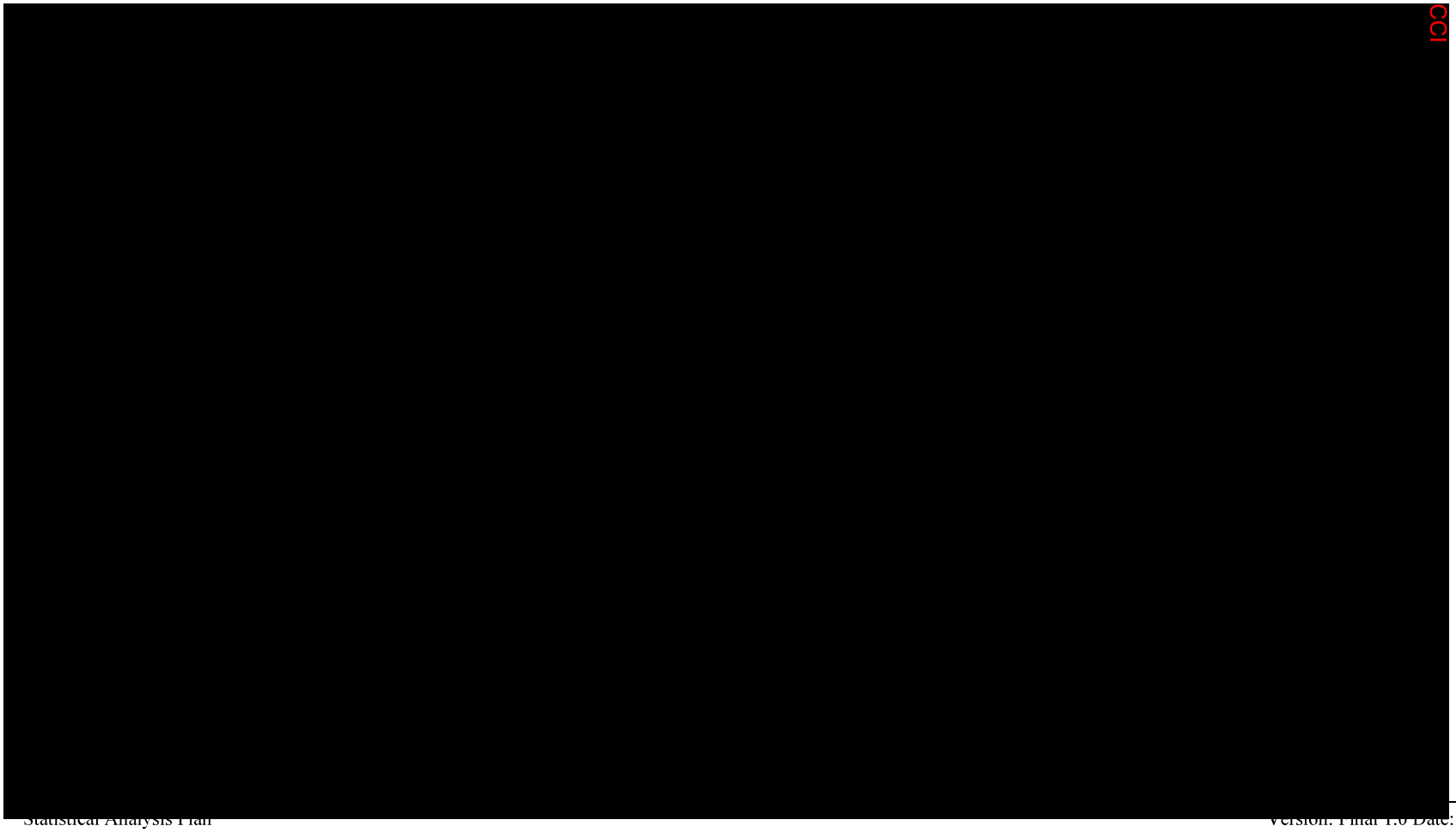

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Table 3: Schedule of Activities, Long-term Treatment Period (up to 3 Years), and Taper and Follow-up Visits

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4 SAMPLE SIZE DETERMINATION

No formal sample size calculation has been performed. Only those subjects who have completed the previous study, XPF-009-301, are eligible to be enrolled into this study. Therefore, the expected total sample size will be up to approximately 40 subjects.

5 ANALYSIS POPULATIONS

5.1 Enrolled Set

Enrolled set include all subjects who signed the informed consent form.

5.2 Safety Set

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5.3 Key Efficacy Analysis Set

The key efficacy analysis set includes those subjects who were treated with placebo in the preceding primary study (XPF-009-301) and switched to XEN496 treatment in the current study, with at least 4 weeks of evaluable seizure data in both study periods.

5.4 Secondary Efficacy Analysis Set

The secondary efficacy analysis set includes those subjects who were treated in both the preceding primary study (XPF-009-301) and the current OLE study, with at least 1 evaluable seizure data in both study periods.

6 STATISTICAL CONSIDERATIONS AND ANALYSIS

6.1 Derived Variables

The Table 4 provide the list of derived variables for demographic and baseline characteristics, various duration derivations, drug compliance, baseline derivations and other important derivations applicable for this study. Derived efficacy variables will be provided in Section 6.1.1

Table 4 Derived variables

Variables	Formula
Demographic and Baseline characteristics	
Age (in months)	integer ((Date of informed consent – Date of birth + 1)/ 30.4375)
Age (in years)	integer ((Date of informed consent – Date of birth + 1)/ 365.25)
OLE Baseline	Last non-missing value prior to start of study drug in OLE period i.e, Data collected at visit 22 or early termination (ET) visit in the primary study (XPF-009-301) will be considered. If any unscheduled non-missing value available after visit 22 or ET and before first dose in OLE, unscheduled visit value will be considered as baseline.
Double blind Baseline	Last non-missing value prior to start of study drug in XPF-009-301 study
Derivation of Duration	
Study day at any visit	Date of interest – date of first dose of study drug in OLE +1, if date of measurement is on or after the first OLE dose date, or Date of measurement – first dose date, if date of measurement is prior to the first dose date. No Study Day 0 is defined
Extent of Exposure (Days)	Date of last study medication intake in OLE – Date of first study medication intake in OLE + 1
Extent of Exposure (Weeks)	Extent of exposure (days)/7

For the computation of Bayley scores, age will need to be expressed in years, months, and days. The following algorithm can be used to derive these values:

TOTDAYS = ADT – BIRTHDT;
AGEYRS = FLOOR (TOTDAYS / 365.25); /* age in years */

REMAINDR = TOTDAYS – (365.25*AGEYRS);
AGEMTHS = FLOOR(REMAINDR / 30.4375); /* age in months */
AGEDAYS = ROUND(REMAINDR – (30.4375*AGEMTHS)); /* in days */

Visit windows for vitals, ECG, and labs are specified in the Table 5. If there is more than one observation within a visit window, the value closest to the nominal study day will be used. If two values are equidistant from the nominal study day, the later value will be used.

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6.1.1 Efficacy Variables

6.1.1.1 Seizure frequency

Caregivers will record all countable motor seizures in the daily seizure diary, which will be reviewed at selected visits as specified in Table 2 and Table 3. The following motor seizures with a duration of at least 3 seconds will be recorded in the seizure diary:

- Focal tonic.
- Focal motor.
- Focal with secondary generalization.
- Generalized tonic.
- Focal clonic.
- Generalized clonic.
- Generalized tonic-clonic.

Important exclusions to the countable seizures are:

- Single myoclonic jerks.
- Staring spells without a motor component.

If epileptic spasms are suspected or reported, the investigator must be contacted immediately to confirm the diagnosis and to initiate treatment.

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The denominator will be based on those evaluable days when an entry of yes or no is provided on occurrence of seizure of any type. Days with counts of 0 seizure will be included in the denominator; while days with missing seizure counts will be excluded from the denominator.

The average monthly seizure frequency (per 28 days) will be derived with the formula below:

$$\frac{\text{sum of daily countable seizure counts reported during the placebo (or XEN496) treatment period}}{\text{Total number of days within the time period when seizure data is reported}} \times 28$$

Percent change of average monthly seizure frequency will be derived using the below formula where $average\ monthly\ seizure\ frequency$ is defined as above and $Baseline$ refers to the comparator period appropriate for the endpoint (eg. placebo period for the key efficacy endpoint and the pre-randomization baseline period for other efficacy endpoints):

$$\frac{Average\ monthly\ seizure\ frequency\ - Baseline\ average\ monthly\ seizure\ frequency}{Baseline\ average\ monthly\ seizure\ frequency} \times 100$$

6.2 Handling of missing data and outliers

6.2.1 Missing data analysis methods

The key efficacy endpoint of seizure frequency will be derived from the days with non-missing seizure data as described in Section 6.1.1. To assess the impact of missing data due to early dropout, sensitivity analysis incorporating missing data multiple imputations with both missing at random (MAR) and missing not at random (MNAR) mechanisms. Details of the analysis will be specified in the analysis section 7.6.1..

6.2.2 Handling of missing or incomplete dates

Missing or partial AE onset dates and times will be imputed so that if the partial AE onset date/time information does not indicate that the AE started prior to treatment or after the treatment emergent adverse event (TEAE) period, the AE will be classified as treatment-emergent. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

No imputation for medication start/end dates or times will be performed. Partial dates will be used to determine whether concomitantly. If a medication date or time is missing or partially missing date cannot be determined whether it was taken concomitantly, those medications will be considered as concomitant medication.

Imputation rules for missing or partial AE start date are defined below:

1) If only Day of AE start date is missing:
   - If the AE start year and month are the same as that for the OLE first dose date, then impute the AE start day as the day of OLE first dose date, if the full (or partial) AE end date is NOT before the first dose date or AE end date is missing: otherwise, impute the AE start day as 1.
   - Otherwise, impute the AE start day as 1.

2) If Day and Month of AE start date are missing:
   - If AE start year is equal to first dose year, then impute the AE start Month and Day as the Month and Day of OLE first dose date, if the full (or partial) AE end date is NOT not before the first dose date or AE end date is missing; otherwise, impute the AE start Month as January and the Day as 1.
3) If AE start date is missing:

   - If the AE start date is completely missing, then query site with no imputation.
   - Also compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first OLE dose date, then the AE should be considered as a pre OLE treatment AE.
   - Otherwise, the AE will be considered as TEAE.

Compare the imputed AE start date with TE period to determine whether the AE is pre OLE treatment AE or TEAE.

7 STATISTICAL METHODS

7.1 General statistical conventions

All statistical procedures will be completed using SAS GRID Linux/SAS Studio version 9.4.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05. Two-sided 95% confidence intervals (CI) will be provided when relevant.

Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, geometric mean (for efficacy endpoints only), first quartile (Q1), median, third quartile (Q3), standard deviation (SD), minimum and maximum.

Categorical variables will be summarized using frequency counts and percentages in each category. The denominator for all percentages will be the number of subjects in that treatment group within the population of interest, unless otherwise noted. Percentages will be rounded to one decimal place.

For summary purposes, baseline will be defined as the last available OLE pre-dose value; all summaries will be presented by treatment group assigned in the double blind study (XPF-009-301) and overall, unless otherwise specified.

- XEN496 Only
  (Subjects who received XEN496 in the primary study and continue to receive XEN496 at the same dose throughout the OLE)
- Placebo to XEN496
  (Subjects allocated to placebo in the primary study and received XEN496 in OLE)
- Total

All subject data, will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within subject listings only. The treatment group as well as subject's sex and age will be stated on each listing. Unless otherwise stated, data listings will be based on all enrolled set.

7.2 Subject disposition

Subject disposition information will be summarized by treatment group in OLE period and overall. The disposition summary will include the number and percentage of subjects meeting the following criteria:

- Screened
- Screen failed
- Received a dose in OLE period
- Completed treatment
- Discontinued treatment

- Reasons for discontinued treatment
- Completed the study
- Completed the Taper period
- Completed Follow Up
- Discontinued from the study
- Reasons for discontinuation from study

The number of subjects who took a dose in OLE period will be used as the denominator for the percentage calculation. Subject disposition will be listed for subjects who signed informed consent form. Details of eligibility criteria for enrollment will be listed separately.

The number and percentage of subjects in each analysis set and reason for exclusion will also be tabulated separately. Population membership details will be listed, including reason for exclusion from each population

7.3 Protocol deviations

Important protocol deviations identified will be summarized based on safety set.

A listing will include all important deviations identified based on data recorded and/or protocol deviation logs. Additional listings will be provided for the details of subject's visit impact due to Corona Virus Disease of 2019 (COVID-19).

7.4 Demographics and background characteristics

7.4.1 Demographics

Demographic variables age (months), adjusted age (months), at baseline will be summarized descriptively. Age category (<2 years, ≥2 years), sex, race, ethnicity and country will be summarized using count and percentage.

7.4.2 Baseline disease characteristics

The following baseline variables from the double blind study (XPF-009-301) will be summarized using descriptive statistics or counts and percentage.

Subjects experience >= 1 seizure per day in the month prior to screening
Number of seizures per month (28 days) prior to screening
Diagnostic KCNQ2 genetic testing details
- Zygosity
- Genetic test classification

Subjects with vagus nerve stimulation therapy (Yes/No)
Pre-study seizure type (Pre-study Seizure Type and Description CRF page)

Listings will be provided for all information captured in CRF for seizure diagnosis and treatment history, diagnostic KCNQ2 genetic testing, vagus nerve stimulation therapy, pre-

study seizure type and description.

7.4.3 Concomitant medications

Medications will be coded to a preferred term and an Anatomic Therapeutic Classification (ATC) code by using the latest available version of the World Health Organization Drug Dictionary Enhanced (WHODDE).

Concomitant medications: are defined as any medications taken between first dose of study treatment (inclusive) in OLE and last dose of study treatment (including taper period). If any medication started prior to first dose in OLE and are ongoing or ended after first dose in OLE are also considered as concomitant.

Concomitant medications will be summarized descriptively using frequency tables by ATC class 2 and preferred name.

Listing will be provided for concomitant medication.

7.4.4 Concomitant procedures

Concomitant procedures (Surgical or Non-Surgical) will be presented in a listing only.

7.5 Extent of exposure

7.5.1 Treatment duration

Duration of study drug (in days) in OLE will be calculated as: last dose date – first dose date in OLE+ 1 day, regardless of study drug interruption.

Duration of study drug exposure and total dose (sum of all dose administered) administered will be summarized descriptively using safety set.

7.5.2 Treatment compliance

Study drug compliance based on the number of capsules taken will be calculated as:

$$\frac{[\text{total number of doses dispensed} - (\text{total number of doses returned, lost or damaged})]}{\text{Sum (planned doses per day} \times \text{days of the planned dose in period)}} \times 100$$

Descriptive summary for study drug compliance using safety set. They will also be summarized in categories "<80%", "80% to 100%" and ">100%" using frequency tables.

Study drug administration details will be listed.

7.6 Efficacy analyses

7.6.1 Analysis of key efficacy endpoint

Analysis of the key efficacy endpoint based on key efficacy analysis set.

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The difference between XEN496 and placebo in monthly seizure frequency among subjects who were randomized to placebo in the main study will be analyzed using a Wilcoxon signed-rank test with 2-sided significance level of 5%. The estimated pseudo-median intra-subject difference in seizure frequency will be provided with corresponding 95% CI (2-sided) based on Hodges-Lehmann method.

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Descriptive summary will be provided for average monthly (4-week) seizure frequency collected from motor seizures described above. Individual listings will also be provided.

7.6.2 Analysis of additional efficacy endpoints

Analyses of additional secondary efficacy endpoints will primarily be descriptive based on the secondary efficacy analysis set.

For the summary of data from the OLE only, a combined treatment group including those subjects treated in OLE will be included. For the summary of endpoints with a combined database from both the primary study (XPF-009-301) and the OLE study, the data will be presented by treatment group in the primary study (XPF-009-301). Data after switching from placebo to XEN496 will be clearly identified.

7.6.2.1 To assess the long-term effect of XEN496 on seizure reduction in pediatric subjects treated with XEN496

- Change from pre-randomization baseline (double blind baseline, refer Section 7.1) in the previous study over time based on response categories (<25%, 25 to <50%, 50 to <75%, 75 to <100%, 100%), based on estimated seizure frequency every 3 months during the OLE period. Proportion of subjects achieving a reduction in 3 months (90 day) seizure frequency from baseline of <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100% will be summarized using count and percentage. (refer section 6.1.1 for details).
- Descriptive summary will be given for percent change from baseline in countable motor seizure frequency, relative to pre-randomization baseline of the previous study (XPF-009-301), assessed over time every 3 months during the OLE.
- Descriptive summary will be provided for percent change from baseline in countable motor seizure frequency, relative to pre-randomization baseline of the previous study (XPF-009-301), for every 3 months based on combined data from both XPF-009-301

and the OLE, by the treatment group in the previous study.

7.6.2.2 To evaluate Caregiver Global Impression of Severity (CaGI-S) and Caregiver Global Impression of Change (CaGI-C) scores

The CaGI-S for overall condition and seizure severity will be summarized at baseline (OLE Baseline and double-blind baseline) and each of the post-baseline visit using number and percent. Change from baseline (OLE Baseline and double-blind baseline) to post baseline will also be summarized.

The CaGI-C will be summarized at each of the post-baseline visit using counts and percentage for the following domains: overall condition, seizures, behavior, alertness, motor skills, visual function, and communication.

Listings will be provided for CaGI-S and CaGI-C scores.

7.6.2.3 To assess neurocognitive development and behavior

Neurocognitive development and behavior changes will be assessed based on BSID-III and/or ABAS-3. BSID-III include 5 domains: cognition; language (expressive and receptive); motor (fine and gross motor functioning); and social, emotional, and adaptive behavior. The ABAS-3 assesses up to 11 skill areas: communication, community use, functional academics, health and safety, home or school living, leisure, motor, self-care, self-direction, social, and work (for details refer to Table 7). These raw scores and composite scores will be summarized descriptively. Use Normative and Conversion Tables in Bayley–III Administration Manual to derive scale score and composite score. Raw score, scaled score and composite scores will be presented in listing.

Table 71. Domains for BSID-III/ABAS-3

Domain Sub-skill	# of Questions	Max Value of Total Raw Score	Raw Score	Scaled Score[$]/ Range	Composite Score
1. Cognition	91	91	Y	Y/1-19	Y
2. Language	97	97	Y	Sum/2-38	Y
2.1) Expressive	49	49	Y	Y/1-19	N/A
2.2) Receptive	48	48	Y	Y/1-19	N/A
3. Motor	138	138	Y	Sum/2-38	Y
3.1) Fine	66	66	Y	Y/1-19	N/A
3.2) Gross	72	72	Y	Y/1-19	N/A
4. Social-emotional	35	175	Y	Y/1-19	Y
5. Adaptive behavior (GAC)		723	Y	Sum	Y
5.1) Conceptual		219	Y	N/A	N/A
➢ *Communication (Com)	25	75	Y	Y	N/A
➢ Functional Pre-Academics (FA)	23	69	Y	Y	N/A
➢ *Self-Direction (SD)	25	75	Y	Y	N/A
5.2) Social		138	Y	N/A	N/A

Domain Sub-skill	# of Questions	Max Value of Total Raw Score	Raw Score	Scaled Score[$]/ Range	Composite Score
➢ *Leisure (LS)	22	66	Y	Y	N/A
➢ *Social (Soc)	24	72	Y	Y	N/A
5.3) Practical		285	Y	N/A	N/A
➢ Community Use (CU)	22	66	Y	Y	N/A
➢ Home Living (HL)	25	75	Y	Y	N/A
➢ *Health and Safety (HS)	24	72	Y	Y	N/A
➢ *Self-Care (SC)	24	72	Y	Y	N/A
5.4) *Motor (MO)	27	81	Y	Y	N/A

* For children younger than one year, the GAC and composite scores are calculated using only those skill areas indicated by an asterisk (*).
[$] Sum refers to sum of scaled score of all sub-skills for the specified domain.

The observed and change from OLE baseline values in total raw score and composite score will be summarized for each domain of BSID-III and each skill areas/total scores for ABAS-3 for the scheduled visits by treatment group. Additionally, a box-plot will be given for the observed values at each scheduled visits.

7.6.2.4 To evaluate the investigator's global impression change (CGI-C)

Change over time in subject's seizures and overall condition will be assessed using an investigator-assessed CGI-C scale. Response to CGI-C scale category will be summarized at each of the scheduled visits. Individual listing will be provided for CGI-C score.

7.6.2.5 Rescue medication usage

Seizure rescue therapy details will also be summarized using frequency tables.

Listings will also be provided for seizure rescue therapy details.

7.6.2.6 To assess the impact of XEN496 on the quality of life

The PedsQL is a modular instrument designed to measure health-related quality of life in both healthy and chronically ill children. The scales include parent-reported measures of the child's physical functioning, physical symptoms, emotional functioning, social functioning, and cognitive functioning. Refer appendix 1 for domain scoring details.

The observed values and change from OLE baseline values for each domain and overall scores will be summarized descriptively for each scheduled visits by treatment groups and age group.

Listings will be provided for individual PedsQL Inventory scale score.

The PedsQL-FIM was designed to evaluate the impact of pediatric chronic health conditions on parents and the family including measures of parent self-reported physical, emotional, social and cognitive function, communication and worry, in addition to family daily activities and familfy. Refer to appendix 2 for domain scoring details.

Observed and change from OLE baseline in PedsQL-FIM for each domain and total score will be summarized descriptively for each scheduled visits.

7.7 Safety analyses

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[redacted] $\frac{Total\ number\ of\ Events}{Patient\ Year\ (PY)} \times 100$

[redacted] –

[redacted]

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7.7.2 Clinical laboratory evaluations

Observed and change from OLE baseline clinical laboratory test data will be summarized descriptively for each scheduled visit and presented based on the safety set.

Shift from baseline to post-baseline laboratory findings at each visit in normal range criteria (Low, Normal, High) will also be summarized for chemistry and hematology tests.

The incidence of potentially clinically significant abnormalities (PCSA) for liver function (Table 4) for each scheduled visit will be summarized.

Table 4: Potentially Clinically Significant Abnormality (PCSA) Liver Abnormality Criteria

Parameter	PCSA Criteria
Chemistry	Alanine transaminase (ALT) or Aspartate transferase (AST) >=3x Upper limit of normal (ULN)
	ALT or AST >=5xULN
	ALT or AST >=8xULN
	ALT or AST >=3xULN and <5xULN, with Baseline >=2xULN
	ALT or AST >=5xULN and <8xULN, with Baseline >=2xULN
	ALT or AST >=5xULN with Baseline >=2xULN
	Alkaline Phosphatase >=1.5xULN
	Total Bilirubin >=2xULN
	ALT >=3xULN and Total Bilirubin >=2xULN
	Any Chemistry Test
Hematology	White blood cells (WBC) <2.0 and >20,000 10^3 cells/uL
	Hgb:

Parameter	PCSA Criteria
	Age 30-60 days: Hgb < 7 g/dL
	Age 61 days to 6 years: Hgb <9 g/dL
	Platelets (PLT) <50 x 10^3 cells/uL
	Any Hematology Test

A listing will be provided for clinical laboratory test data. The listing will include normal ranges and clinical laboratory values that are outside the normal ranges and potentially clinically significant abnormalities will be flagged in the listing.

7.7.3 Vital signs

Observed and changes from OLE baseline for vital sign measurements will be summarized at each scheduled visit using descriptive statistics. In addition, summaries will be provided for the potentially clinicallly importance categories as presented below.

Table 5: Potentially Clinically Significant Vital Signs Abnormality Criteria

Parameter	Criterion
Systolic Blood Pressure (mmHg)	> ULN and increase of > 30
	< Lower limit of normal (LLN) and decrease of > 20
Diastolic Blood Pressure (mmHg)	> ULN and increase of > 20
	< LLN and decrease of > 15
Pulse Rate (bpm)	>= ULN
	<= LLN

Listings will be provided for vital sign data, and potentially clinically significant abnormalities will be flagged in the listing.

7.7.4 Physical examinations

All physical examination data will be listed using safety set.

7.7.5 Electrocardiograms

Observed and changes from OLE baseline of continuous ECG measurements will be summarized by treatment group and age groups (1 to 12 months and >12 to 84 months) at each scheduled visit. Additional summaries will be provided for ECG interpretation and will be summarized using frequency tables. Shift from baseline to post-baseline will also be provided for the ECG interpretation.

Potentially clinically significant abnormality categories listed below will be summarized using count and percentage.

Table 6: Potentially Clinically Significant ECG Abnormality Criteria

Variable Name	Age group	Criterion
QT interval corrected for heart rate by Fridericia's formula (QTcF) (msec)	NA	<= 300 >= 60 msec increase from baseline >= 500
QT Interval (msec)	NA	<= 300 >= 600
QRS Interval (msec)	1 to 12 months	>= 86 or >=25% increase from baseline
	>12 to 84 months	>= 95 or >=25% increase from baseline
PR Interval (msec)	1 to 12 months	>= 141 or >= 25% increase from baseline
	>12 to 84 months	>= 155 or >= 25% increase from baseline
Heart rate (bpm)	1 to 12 months	>= 194
		<= 106
Heart rate (bpm)	>12 to 84 months	>= 123
		<= 62

Listings will be provided for ECG data and potentially clinically significant abnormalities will be flagged in the listing.

7.7.6 Other safety assessments

All neurological examination data will be listed using safety population.

Average daily diaper count per month and change in daily diaper counts per month from baseline will be summarized descriptively. Listings will also be provided. monthly average count is defined as (sum of daily diaper counts reported during the period, divided by the number of days within the time period when diaper count is reported) × 28. Line plot will be provided for average daily diaper count (by monthly) by subject and treatment groups.

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CCI [redacted] results, sleep quality and palatability questionnaire values will be listed.

7.8 Interim analysis

Safety data will be reviewed periodically through an independent data and safety monitoring board (DSMB) throughout the study.

8 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

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9 REFERENCES

1. ICH Topic E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95-adopted December 1995).
2. ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).

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10 APPENDIX

Appendix 1: Pediatric Quality of Life (PedsQL) Inventory scale score

DESCRIPTION OF THE QUESTIONNAIRE (INFANTS 1-12 MONTHS):

Dimensions	Number of Items	Cluster of Items	Reversed Scoring	Direction of Dimensions
Physical Functioning	6	1-6	1-6	Higher scores indicate better HRQOL.
Physical Symptoms	10	1-10	1-10	
Emotional Functioning	12	1-12	1-12	
Social Functioning	4	1-4	1-4	
Cognitive Functioning	4	1-4	1-4	

DESCRIPTION OF THE QUESTIONNAIRE (INFANTS 13-24 MONTHS):

Dimensions	Number of Items	Cluster of Items	Reversed Scoring	Direction of Dimensions
Physical Functioning	9	1-9	1-9	Higher scores indicate better HRQOL.
Physical Symptoms	10	1-10	1-10	
Emotional Functioning	12	1-12	1-12	
Social Functioning	5	1-5	1-5	
Cognitive Functioning	9	1-9	1-9	

SCORING OF DIMENSIONS:

Item Scaling	5-point Likert scale from 0 (Never) to 4 (Almost always)
Weighting of Items	No
Extension of the Scoring Scale	Scores are transformed on a scale from 0 to 100.

Scoring Procedure	**Step 1: Transform Score** Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0. **Step 2: Calculate Scores** Score by Dimensions: • If more than 50% of the items in the scale are missing, the scale scores should not be computed. • Mean score = Sum of the items over the number of items answered. Psychosocial Health Summary Score = Sum of the items over the number of items answered in the Emotional, Social, and Cognitive Functioning Scales. Physical Health Summary Score = Sum of the items over the number of items answered in the Physical Functioning and Physical Symptoms Scales. **Total Score**: Sum of all the items over the number of items answered on all the Scales.
Interpretation and Analysis of Missing Data	If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% or more items are completed: Impute the mean of the completed items in a scale.

DESCRIPTION OF THE QUESTIONNAIRE (Ages 2-4 year)

Dimensions	Number of Items	Cluster of Items	Reversed Scoring	Direction of Dimensions
Physical Functioning	8	1-8	1-8	Higher scores indicate better HRQOL.
Emotional Functioning	5	1-5	1-5	
Social Functioning	5	1-5	1-5	
School Functioning	3	1-3	1-3	

SCORING OF DIMENSIONS:

Item Scaling	5-point Likert scale from 0 (Never) to 4 (Almost always)
Weighting of Items	No
Extension of the Scoring Scale	Scores are transformed on a scale from 0 to 100.
Scoring Procedure	**Step 1: Transform Score** Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0. **Step 2: Calculate Scores** Score by Dimensions: • If more than 50% of the items in the scale are missing, the scale scores should not be computed. • Mean score = Sum of the items over the number of items answered. Psychosocial Health Summary Score = Sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales. Physical Health Summary Score = Physical Functioning Scale Score **Total Score**: Sum of all the items over the number of items answered on all the Scales.
Interpretation and Analysis of Missing Data	If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% or more items are completed: Impute the mean of the completed items in a scale.

DESCRIPTION OF THE QUESTIONNAIRE (Ages 5-7 year)

Dimensions	Number of Items	Cluster of Items	Reversed scoring	Direction of Dimensions
Physical Functioning	8	1-8	1-8	Higher scores indicate better HRQOL.
Emotional Functioning	5	1-5	1-5	
Social Functioning	5	1-5	1-5	
School Functioning	5	1-5	1-5	

SCORING OF DIMENSIONS:

Item Scaling	5-point Likert scale from 0 (Never) to 4 (Almost always) 3-point scale: 0 (Not at all), 2 (Sometimes) and 4 (A lot) for the Young Child (ages 5-7) child report
Weighting of Items	No
Extension of the Scoring Scale	Scores are transformed on a scale from 0 to 100.
Scoring Procedure	**Step 1: Transform Score** Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0. **Step 2: Calculate Scores** Score by Dimensions: • If more than 50% of the items in the scale are missing, the scale scores should not be computed, • Mean score = Sum of the items over the number of items answered. Psychosocial Health Summary Score = Sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales. Physical Health Summary Score = Physical Functioning Scale Score **Total Score**: Sum of all the items over the number of items answered on all the Scales.
Interpretation and Analysis of Missing Data	If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% or more items are completed: Impute the mean of the completed items in a scale.

Note: Domain scores physical functioning, physical symptoms, emotional functioning, social functioning, cognitive and school functioning need to be derived according to the age group where applicable.

Appendix 2: Pediatric Quality of Life Inventory- Family Impact scale (PedsQL-FIM)

DESCRIPTION OF THE FAMILY IMPACT MODULE:

Dimensions	Number of Items	Cluster of Items	Reversed Scoring	Direction of Dimensions
Physical Functioning	6	1-6	1-6	Higher scores indicate better functioning.
Emotional Functioning	5	1-5	1-5	
Social Functioning	4	1-4	1-4	
Cognitive Functioning	5	1-5	1-5	
Communication	3	1-3	1-3	
Worry	5	1-5	1-5	
Daily Activities	3	1-3	1-3	
Family Relationships	5	1-5	1-5	

SCORING OF DIMENSIONS:

Item Scaling	5-point Likert scale from 0 (Never) to 4 (Almost always)
Weighting of Items	No
Extension of the Scoring Scale	Scores are transformed to a 0 to 100 scale.
Scoring Procedure	**Step 1: Transform Score** Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0 **Step 2: Calculate Scores by Dimensions** • If more than 50% of the items in the scale are missing, the scale scores should not be computed, • Mean score = Sum of the items over the number of items answered. **Step 3: Total Scores** • The Total Score is the sum of all 36 items divided by the number of items answered • The Parent HRQL Summary Score (20 items) is computed as the sum of the items divided by the number of items answered in the Physical, Emotional, Social, and Cognitive Functioning scales. • The Family Functioning Summary Score (8 items) is computed as the sum of the items divided by the number of items answered in the Daily Activities and family Relationships scales.

Interpretation and Analysis of Missing Data	If more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% or more items are completed: Impute the mean of the completed items in a scale.