9. DOCUMENTATION OF STATISTICAL METHODS

The following documents are included under this Appendix:

- Statistical Analysis Plan Version 1.0 dated 21 Jul 2025

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Statistical Analysis Plan

A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Cenobamate Adjunctive Therapy in Subjects with Primary Generalized Tonic-Clonic Seizures

Sponsor:	SK Life Science, Inc. 461 From Road, 5th FL Paramus, NJ 07652 USA
Study Drug:	YKP3089
Protocol Number:	YKP3089C025
Prepared By:	NJS Associates Company

History of Changes

Version Number	Version Date	Description of Changes
1.0	21 Jul. 2025	Original document

Statistical Analysis Plan Review and Approval

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Date

Table of Contents

LIST OF ABBREVIATIONS

Abbreviations	Definition of Terms
AE	adverse event
AED	antiepileptic drug
ALT	alanine transferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BQL	below the quantifiable limit
CDER	Center for Drug Evaluation and Research
C-SSRS	Columbia Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CT	computed tomography
CV	coefficient of variation
DMC	Data Monitoring Committee
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
ECG	electrocardiogram
EEG	electroencephalogram
ET	Early Termination
FDA	Food and Drug Administration
ICF	informed consent form
IP	Investigational Product
IRT	Interactive Response Technology
LLOQ	lower limit of quantitation
MAP	modeling analysis plan
MedDRA	Medical Dictionary of Regulatory Activities
MITT	Modified Intent-to-Treat
MITT-M	Modified Intent-to-Treat Maintenance
OLE	open-label extension
PGTC	Primary Generalized Tonic-Clonic
PK	pharmacokinetic
POS	partial onset seizure
PT	preferred term
Q1	first Quartile
Q3	third Quartile
QTcB	QT interval with Bazett’s correction
QTcF	QT interval with Fridericia’s correction
RoW	rest of the world
SAP	Statistical Analysis Plan
SI	Système International
SOC	system organ class

Abbreviations	Definition of Terms
TBL	total bilirubin
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1 Introduction

This document describes the Statistical Analysis Plan for study "A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Cenobamate Adjunctive Therapy in Subjects with Primary Generalized Tonic-Clonic Seizures". The scope of SAP does not include the Open-Label Extension (OLE) study. The SAP is written based on the protocol Amendment 5 dated on 11 OCT 2024 and CRFs dated on 22 DEC 2022.

1.1 Objectives

The purpose of this randomized, double-blind, placebo-controlled, multicenter phase 3 study is to evaluate the safety, efficacy, and pharmacokinetics of cenobamate adjunctive therapy in subjects with primary generalized tonic-clonic seizures.

1.1.1 Primary Objective

To demonstrate the efficacy of adjunctive cenobamate 200 mg dose (or the adolescent equivalent) compared with placebo on Primary Generalized Tonic-Clonic (PGTC) seizures in subjects ≥ 12 years of age.

1.1.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of cenobamate in subjects with PGTC seizures
- To evaluate the seizure freedom rate for PGTC seizures during the Maintenance Phase and during the entire Double-blind treatment phase
- To evaluate the effect of cenobamate on other types of generalized seizures
- To investigate the pharmacokinetics (PK) of cenobamate in subjects with PGTC seizures

1.2 Study Endpoints

1.2.1 Primary Efficacy Endpoint

Primary endpoint, as defined for each region, is as below:

- USA and Rest of the World (RoW): median percent change from baseline in PGTC seizure frequency per 28-day interval during the Double-blind treatment period.
- Europe, South Africa, Australia, and New Zealand: 50% responder rate for PGTC seizures during the Maintenance Phase. A responder is defined as a subject who achieves at least a 50% reduction in PGTC seizure frequency per 28-day interval during the Maintenance Phase relative to baseline.

1.2.2 Secondary Efficacy Endpoints

1. 100% responder rates for PGTC seizures during the Maintenance Phase relative to baseline.
2. 75% responder rates for PGTC seizures during the Maintenance Phase relative to baseline.
3. Percentage of subjects who achieved a 50% reduction in all generalized seizures frequency per 28-day period during the Maintenance Phase relative to baseline.

1.2.3 Secondary Safety Endpoints

The secondary safety endpoints will include adverse events and concomitant medication reporting, clinical laboratory results, vital signs, electrocardiograms (ECGs), physical examinations, neurologic examinations, and Columbia Suicide Severity Rating Scale (C-SSRS) results will be summarized using descriptive

statistics.

1.2.4 Secondary Pharmacokinetic Endpoints

1. Summary of individual patients' plasma concentrations of cenobamate at their respective doses and visits.
2. Population PK analysis will be performed on data available from this study alone or integrated with data from other cenobamate studies. The population PK analysis results will be reported separately. In addition, a population PK/pharmacodynamic analysis may be conducted as a stand-alone approach for PGTC or in combination with POS data, if deemed appropriate.

1.3 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, adjunctive therapy study in subjects with PGTC seizures.

Approximately 170 subjects will be randomized at approximately 100 study sites in multiple countries. Approximately, 20% of the total subject sample

size will be adolescents aged 12 to < 18 years. Subjects will be randomized to study drug only if they meet all the inclusion criteria and none of the exclusion criteria.

The study schematic is provided below.

Figure 1: Study Schematic

Period	Pre-Randomization			Double-blind Treatment Period			Follow-up Period[a]
Phase	Screening/ Baseline	Baseline		Titration Phase		Maintenance Phase	Follow-up
Visit (s)	1	2	3	Randomization 4	5, 6, 7, 8	9, 10, 11, 12, 13, 14/ET	15/FUP
Day (s) From Randomization	-84 days	-56 days (±2 days)	-28 days (±2 days)	Day -1 [b]	Day 14 (±2 days), Day 28 (±2 days), Day 42 (±2 days), Day 56 (±2 days),	Day 70 (±2 days) Day 84 (±2 days), Day 98 (±2 days), Day 112 (±2 days, Day 126 (±2 days), Day 154 (±2 days)	Day 175 (±2 days)
	Screening & Seizure Diary	Seizure Diary	Seizure Diary	Randomize	YKP3089 → or Placebo →		3 weeks (including 1-week optional down-titration)

ET = early termination, OLE = open-label extension

a For Subjects who do not enroll in the OLE study

b First dose of study drug on Day 1

The study consists of 3 periods as follows:

- Pre-Randomization Period
- Double-blind Treatment Period
- Follow-up Period (if subject does not enroll in the open-label extension (OLE) study or prematurely discontinues from this study)

The Double-blind Treatment Period further consists of 2 phases, the Titration Phase and the Maintenance Phase. After completion of the 12-week Maintenance Phase, subjects will have the opportunity to enroll in an OLE study. A description of each study period is presented below.

Pre-Randomization Period (Visit 1 to Visit 3)

After signing the informed consent form (ICF), eligible subjects will start the study in the Pre-Randomization period. During this period, subjects will have 3 study visits at 4-week intervals, approximately 12 weeks, 8 weeks, and 4 weeks prior to randomization, during which seizure information (type and count) will be assessed using the subjects' seizure diaries.

The 12 weeks of consecutive seizure diary data will be collected during the Pre-Randomization Period and used to evaluate subject eligibility. Either 4 or 8 of the 12 weeks of this data can be obtained from the subject's personal seizure diaries if collected within the consecutive 4 weeks or 8 weeks, respectively, prior to Visit 1.

If 4-week retrospective diary information is considered acceptable by the Medical Monitor, only 8 weeks of diary information will need to be collected after Visit 1 and prior to randomization (Visit 4). Additionally, Visit 3 will be eliminated, and the subject will only have Visit 1 and Visit 2 during the Pre-Randomization Period.

If 8-week retrospective diary information is considered acceptable by the Medical Monitor, only 4 weeks of diary information will need to be collected after Visit 1 and prior to randomization (Visit 4). Additionally, Visits 2 and 3 will be eliminated, and the subject will only have Visit 1 during the Pre-Randomization Period.

Prior to randomization, the seizure diary, for a duration of 12 weeks, must be reviewed by the Medical Monitor to confirm eligibility and to ensure that the subject meets Inclusion Criterion No. 5 for seizure frequency.

Double-blind Treatment Period (Visit 4 to Visit 14)

The Double-blind Treatment Period will include 2 phases: a 10-week Titration Phase (Visits 4 to 8) and a 12-week Maintenance Phase (Visits 9 to 14).

Titration Phase (Visit 4 to Visit 8)

At the randomization visit (Visit 4), the eligibility criteria will be reviewed by the Principal Investigator or designee. Once eligibility is confirmed, eligible subjects will be randomly assigned in a 1:1 ratio to receive cenobamate or matching placebo in a blinded fashion. Adults will receive a starting dose of cenobamate 12.5 mg as a tablet or

matching placebo tablet. Adolescents (12 to <18 years old) will receive oral suspension with or without cenobamate (10 mg/ml) at a volume equivalent to 12.5 mg based on weight. The study drug will be dispensed, and subjects will be instructed to start taking study drug the next morning after Visit 4. Subjects will be advised to take the study drug orally once a day at approximately the same time of the day.

During the 10-week Titration Phase, the study drug will be titrated starting at cenobamate 12.5 mg tablet or matching placebo in adult and in adolescents as an oral suspension equivalent based on weight or matching placebo volume all administered once daily up to a dose of 150 mg. During this phase, subjects will have 5 study visits (Visit 4 to Visit 8) every 2 weeks.

Subjects who have tolerability issues during the Titration Phase, will be advised by the Principal Investigator or designee to take the study drug in the evening, instead of the morning. Subjects unable to attain the cenobamate 150 mg, in adolescents as an oral suspension equivalent based on weight or matching placebo volume level by the end of the Titration Phase due to tolerability issues will be withdrawn from the study by the Principal Investigator or designee. Dose adjustments, other than a change in timing of dose administration due to tolerability issues, will not be permitted during the Titration Phase of the study.

At each study visit, subjects will undergo study procedures, as provided in the Schedule of Assessments Protocol Table 4-1.

Maintenance Phase (Visit 9 to 14)

During the 12-week Maintenance Phase, adult subjects will receive once daily administration of Double-blind study drug, cenobamate 200 mg tablets or matching placebo and in adolescents as an oral suspension equivalent based on weight or matching placebo volume. During the Maintenance Phase, subjects will have 6 study visits, Visits 9 through 14. The first 5 visits, Visits 9 through 13, will occur at 2-week intervals. Visit 14 will occur 4 weeks after Visit 13.

Subjects who experience tolerability issues with the study drug will be advised to take study drug in the evening, instead of the morning. If the subject continues to experience tolerability issues, the dose may be decreased to cenobamate 150 mg or placebo using tablets and in adolescents as an oral suspension equivalent volume of cenobamate or placebo based on weight. If the subject continues to have tolerability issues with this lower dose, the subject will be discontinued from the study by the Principal Investigator or designee. Dose adjustments, other than a change in timing of dose administration due to tolerability issues, are permitted only once during the Maintenance Phase.

At each study visit, subjects will undergo study procedures, as provided in the Schedule of Assessments Protocol Table 4-1.

Follow-up Period (Visit 15)

After successful completion of the Double-blind Treatment Period, it is at the discretion of the Principal Investigator, to offer the opportunity to subjects to enroll into the OLE study. For subjects willing to enroll in the OLE study, they or their legal guardians (if subject is unable to sign ICF) will be asked to review and sign a separate ICF for the OLE study at their last visit (Visit 14) for this study.

Subjects who do not enroll in the OLE study will enter a 3-week Follow-up period. At Visit 14, the last visit in the Maintenance Phase, study drug will be down titrated, in a double-blind fashion to cenobamate 100 mg tablet, in adolescents as an oral suspension equivalent based on weight or matching placebo volume, which subjects will continue to take daily for 1 week. Subjects will be instructed to stop taking the study drug after 1 week and return for the Follow-up visit, Visit 15, 3 weeks after Visit 14 (i.e., 2 weeks after the last dose of study drug).

At each study visit, subjects will undergo study procedures, as provided in the Schedule of Assessments Protocol Table 4-1.

Early Termination (ET) and Early Termination Follow-up

Subjects who discontinue prematurely should be followed for 3 weeks or longer after the early termination (ET) visit, at the discretion of the Principal Investigator or designee. Once it is decided that a subject will discontinue from the study, every effort will be made to schedule an ET visit. At the ET visit, study procedures indicated for Visit 14 in the Schedule of Assessments will be performed. The follow-up duration for each phase in the Double-blind Treatment period is 3 weeks, as presented below. Depending on the reason for discontinuation, study drug may be stopped immediately or down titrated and described below.

Discontinuation during the Titration Phase

Subjects who discontinue during the Titration Phase, depending on the reason for discontinuation, will receive the last dose of study drug prior to or on the day of the ET visit. Subjects will be asked to return 3 weeks after the ET visit for the Follow-up visit. Subjects who are taking blinded study drug at the dose of cenobamate 150 mg, in adolescents as an oral suspension equivalent based on weight or matching placebo volume may receive a down-titrated dose of cenobamate 100 mg tablet, in adolescents as an oral suspension equivalent based on weight or matching placebo volume, respectively, in a Double-blind fashion for 1 week, at the discretion of the Principal Investigator or designee.

Discontinuation during the Maintenance Phase

Subjects who discontinue during the Maintenance Phase, at the discretion of Principal Investigator or designee, may receive study drug at the down-titrated dose of cenobamate 100 mg or in adolescents as an oral suspension equivalent based on weight or matching placebo volume, in double-blind fashion, for 1 week prior to discontinuation of the study drug. If the Principal Investigator or designee decides that the down-titrated dose should not be administered, subjects will be asked to return 3 weeks after the ET Visit for the

Follow-up Visit. If the Principal Investigator or designee decides that the down-titrated dose should be administered, subjects will be instructed to take the study drug for 1 week and return for the Follow-up visit 3 weeks after the ET Visit.

At each study visit, subjects will undergo study procedures, as provided in the Schedule of Assessments Protocol Table 4-1.

1.4 Method of Assigning Subjects to Treatment Groups

1.4.1 Randomization Procedure

At Visit 4, eligible subjects will be randomly assigned in a 1:1 ratio to cenobamate 12.5 mg tablet or matching placebo tablet in adults, in adolescents as cenobamate oral suspension equivalent based on weight or placebo volume treatment groups. Interactive Response Technology (IRT) will be used to determine the randomization schedule.

The biostatistician will generate a global randomization schedule using SAS® software Version 9.4 or later (SAS Institute Inc., Cary, North Carolina, USA) for the IRT. After finalization, the randomization schedule will be stored in a secure electronic location, with no access by the clinical study team. Once the database has been locked following study completion, a request for unblinding will be sent to the project biostatistician, and the treatment assignment will be disseminated to the clinical study team for statistical analysis and clinical review.

1.4.2 Screening and Subject Number

After signing of the ICF, each subject will be assigned an 8-digit screening number. The first 2 digits of the screening number will be the two-digit ID pre-assigned to each country; the next 3 digits will be the three-digit pre-assigned site ID; and the last 3 digits will be the serially assigned subject numbers assigned in the order of screening at their respective site, beginning with 001 (e.g., the third screened subject in the second site in the country assigned ID as 01, will have screening number 01002003).

Subjects who screen-fail will be allowed to re-screen only once. The re-screened subject will be assigned a new screening number, and the 2 screening numbers will be linked in the clinical database. The screening number will also be referred to as the subject number during the study.

1.5 Study Governance

The safety of subjects in the study will be monitored by an independent Data Monitoring Committee (DMC). The mandate of the DMC is to provide an independent review of the safety data during the study for the purpose of ensuring subject safety.

1.6 Sample Size Calculation

A sample size of 80 subjects per treatment group in the MITT-M population will provide 86% power to detect a 30% difference between the active and placebo groups in the percent change from baseline in PGTC seizure frequency at a 2-sided significance level of 0.05 assuming a standard deviation of the seizure frequency reduction is 60%. For the

responder rate, assuming a rate of 35% for the placebo group and 62% for the active treatment group, a sample size of 80 subjects in each treatment group in the MITT-M population will have > 86% power to detect a between-group difference in the proportion of responders based on a 2-group Chi-square test with a 2-sided significance level of 0.05.

The total sample size of both the treatment groups combined will be approximately 170 subjects to account for an estimated 6% dropout rate during the Titration Phase. At least 34 adolescent subjects to be randomized. At least 20% of the total subject sample size will be adolescents aged 12 to < 18 years old.

1.7 Timing of Analysis

The final analysis will take place when last subject rolls over to the OLE study or finishes the Follow Up visit.

2 Analysis Population

The following analysis population will be defined:

Randomized Population

All subjects who successfully meet the entry criteria, who have given informed consent to participate in this study, and who are randomized to the study treatment.

Modified Intent-To-Treat (MITT) Population

All subjects in the randomized population who received at least 1 dose of study drug and have at least 1 postbaseline efficacy measurement in Double-blind treatment period.

Modified Intent-To-Treat Maintenance (MITT-M) Population

All subjects in the randomized population who received at least 1 dose of study drug during the Maintenance Phase and have at least 1 efficacy measurement in the Maintenance Phase.

Modified Intent-To-Treat Maintenance (MITT-M) Completer Population

All subjects in the randomized population who received study drug and have efficacy measurement, at least 14 days of last 6 weeks of the Maintenance Phase.

Modified Intent-to-Treat (MITT) Population for Other Types of Generalized Seizure

All subjects in the randomized population who received at least 1 dose of study drug during the Double-Blind Treatment Period, and have >=1 baseline seizure (other types of generalized seizure) and at least 1 efficacy measurement (other types of generalized seizure) during the double-blind treatment period.

Modified Intent-to-Treat Maintenance (MITT-M) Population for Other Types of Generalized Seizure

All subjects in the randomized population who received at least 1 dose of study drug during the Maintenance Phase, and >=1 baseline seizure (other types of generalized

seizure) and at least 1 efficacy measurement (other types of generalized seizure) in the Maintenance Phase.

Safety Population

All subjects in the randomized population who received at least 1 dose of study drug.

Pharmacokinetics Population

All subjects in the Safety Population who have at least 1 evaluable PK sample.

If more than 20% of randomized subjects have major protocol deviations and their drug compliance falls outside the 80% to 120% range in either the double-blind phase or the maintenance phase, a population review meeting will be held to determine the Per-Protocol Population. The primary analyses will then be conducted based on this population in addition to the MITT or MITT-M population.

3 General Consideration

The final statistical analysis for the study will be performed by NJS Associates Company. All analyses and summaries will be produced using SAS® version 9.4 or higher.

For continuous variables, descriptive statistics (n, mean, standard deviation, Q1, Q3, median, minimum, and maximum) will be presented. Categorical variables will be summarized by frequencies and percentages.

All statistical comparisons will be two sided tests at the alpha = 0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference. All alternative hypotheses will be two-sided, unless specifically stated otherwise. No adjustment for multiple comparisons/multiplicity on efficacy analysis planned.

The durations in months or years will be calculated using the following conversion factors:

1 month = 30.4375 days, 1 year = 365.25 days.

All data listings will be provided with actual values without any imputations for missing values.

3.1 Baseline

For all safety assessments unless otherwise specified, the baseline value will be the last non-missing measurement (including unscheduled visit) taken before first dose administration date of study drug.

3.2 Study Day

Study day for safety analysis is defined as the number of days from first dose date to the event/visit date. It is calculated as follows:

- If the visit date falls on or after first dose date, Study Day = visit date − first dose date + 1

- If the visit date falls before first dose date, Study Day = visit date − first dose date

For subjects randomized but never treated, randomization date will be counted as the first date.

3.3 Analysis Window

For safety assessments, postbaseline measurements collected from unscheduled visits will not be included in the by-visit summary tables but can be selected as worst postbaseline values for shift tables. All assessments data will be included in the listings.

3.4 Handling of Missing Data

3.4.1 Handling of Missing Efficacy Data

Missing efficacy data will be imputed as described in Section 4.7.2.

3.4.2 Handling of Partial Date in Safety Data

Partial dates in adverse events and prior/concomitant medication data will be imputed based on imputation rules specified in Appendix 1.

3.5 Examination of Subgroups

Subgroup analysis may be performed for primary and secondary efficacy endpoints, as well as safety endpoints. The subgroups to be analyzed may include the following:

- Sex (2 categories): female and male
- Race group (2 categories): White, others
- Age group (≥12 to <18, ≥18)
- Geographic region (2 categories): North America, Europe
- Concomitant rescue medication use (with vs without)

4 STATISTICAL METHODOLOGY AND ANALYSES

4.1 Disposition of Subjects

Screened subjects include all subjects who signed informed consent forms. The number and percentage of screen failures will be summarized in a table with denominator being all enrolled subjects. For subjects who continued in study after rescreening, the subject will not be counted as a screen failure.

Number and percentage of subjects in each population

- Randomized population
- MITT/MITT-M population
- MITT-M completer population
- Modified Intent-to-Treat (MITT) Population for Other Types of Generalized Seizure

- Modified Intent-to-Treat Maintenance (MITT-M) Population for Other Types of Generalized Seizure
- Safety population
- Pharmacokinetic population

Treatment disposition

Randomized

- Not Treated
- Treated
    - Completed treatment of the Double-blind treatment period
    - Discontinued the treatment of the Double-blind treatment period (Titration phase/ Maintenance phase)
    - Reason for discontinuation treatment of the Double-blind treatment period
        - Adverse Event
        - Lost To Follow-up
        - Physician Decision
        - Pregnancy
        - Protocol Deviation
        - Trial Site Terminated by Sponsor
        - Study Terminated by Sponsor
        - Study Subject Withdrawal by Parent or Guardian
        - Withdrawal by Subject
        - Other
- Entered Open-Label Extension

Study Disposition

- Completed the study
- Discontinued from study
- Reason for discontinuation from study
    - Adverse Event
    - Lost To Follow-up
    - Physician Decision
    - Pregnancy
    - Protocol Deviation
    - Trial Site Terminated by Sponsor
    - Study Terminated by Sponsor
    - Study Subject Withdrawal by Parent or Guardian
    - Withdrawal by Subject
    - Other

Corresponding listing for the disposition will also be provided.

4.2 Protocol Deviations

The number of subjects with at least one major protocol deviation and the number of subjects for each protocol deviation item will be summarized by treatment group and all subjects for the Randomized Population.

Corresponding listing for protocol deviation will also be provided.

4.3 Demographic and Baseline Characteristics

The demographics and baseline characteristics data will be summarized for Randomized population, MITT-M population. Baseline and disease characteristics will be summarized for Randomized population.

Corresponding listings will also be provided.

4.3.1 Demographics

The following demographic variables will be summarized:

- Age (years) at the informed consent/assent
- Age group (≥12 to <18, ≥18 to <65, ≥65)
- Sex: Male or Female
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other
- Race group: White, Others
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown
- Geographic region: North America, Europe, Africa, and Other
- Country
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Baseline seizure frequency (PGTC)
- Baseline AED medication
- Protocol Version at the Time of Informed Consent

4.3.2 Epilepsy Seizure History

- Age at first seizure (years)
- Time Since Epilepsy Diagnosis (years: age at informed consent (years)- age at first seizure (years))
- Family history of epilepsy in any first degree relative
    - Parent
    - Sibling
    - Child
    - Other

- Seizure type of family member: Generalized Tonic-Clonic Convulsion, Absence, Myoclonus, Tonic, Atonic, Focal Aware Seizure, Focal Impaired Awareness, Focal to Bilateral Tonic Clonic, Other, Unknown

4.3.3 Inter-Ictal EEG

- Inter-Ictal EEG status: Not performed/Performed
- Inter-Ictal EEG Results: Normal EEG, Abnormal (Epileptiform), Abnormal EEG (Non-epileptiform only)
- If Abnormal (Epileptiform): Focal spikes or sharp waves, Generalized epileptiform discharges, Hypsarrhythmia, Electrographic seizures, Other
- If Abnormal EEG (Non-epileptiform only): Background slowing and/or disorganization, Focal slowing, Other

4.3.4 Ictal-EEG/Video-EEG

- Ictal-EEG/Video-EEG: Not performed/Performed.
- Ictal-EEG/Video-EEG (Captured seizures consistent with)
    - Generalized/Unclassified Seizures: Generalized tonic-clonic, Absence, Myoclonic, Atonic, Tonic, Clonic, Epileptic Spasms, Infantile Spasms
    - Focal Onset Seizures: Focal aware seizures without motor signs, Focal aware seizures with motor signs, Focal impaired awareness seizures, Focal to bilateral tonic-clonic seizures
    - Other
    - NA

4.3.5 Neuroimaging

- MRI performed: Yes, No
- MRI result (normal, abnormal, if abnormal: Focal, Diffuse, Non-specific or incidental)
- Procedure CT performed: Yes, No
- Procedure CT result (normal, abnormal, if abnormal: Focal, Diffuse, Non-specific or incidental)

4.3.6 Classification of Seizures and Etiologies

- Classification of Generalized/Unclassified seizures
    - Tonic Clonic: Current Seizure Type, Past Seizure Type, no longer present, Not Applicable
    - Absence: Current Seizure Type, Past Seizure Type, no longer present, Not Applicable
    - Myoclonic (not otherwise specified): Current Seizure Type, Past Seizure Type, no longer present, Not Applicable
    - Clonic: Current Seizure Type, Past Seizure Type, no longer present, Not Applicable

  - Tonic: Current Seizure Type, Past Seizure Type, no longer present, Not Applicable
  - Atonic: Current Seizure Type, Past Seizure Type, no longer present, Not Applicable
  - Infantile spasms (age 1 month to 36 months) or Epileptic spasms (above age 36 months): Current Seizure Type, Past Seizure Type, no longer present, Not Applicable
  - Were there any Other Seizures? : Yes, No
  - Other Seizures: Current Seizure Type, Past Seizure Type, no longer present
- Specific Etiologies
  - Viral, bacterial and parasitic infections: Definite, Possible, No
  - Traumatic brain injury: Definite, Possible, No
  - Stroke: Definite, Possible, No
  - Intraventricular hemorrhage: Definite, Possible, No
  - Hypoxic-ischemic encephalopathy: Definite, Possible, No
  - Other metabolic or toxic insults: Definite, Possible, No
  - Neurocutaneous syndromes: Definite, Possible, No
  - Inborn errors of metabolism: Definite, Possible, No
  - Genetic and chromosomal development encephalopathies: Definite, Possible, No
  - Developmental encephalopathy of unknown cause as evidenced by the presence of mental retardation, cerebral palsy, or autism with no evidence of a specific insult of disorder to which cause can be attributed preceding the onset of epilepsy: Definite, Possible, No
  - Malformations of cortical or other brain development with or without known genetic determinants: Definite, Possible, No
  - Neoplasia: Definite, Possible, No
  - Mesial temporal sclerosis: Definite, Possible, No
  - Dementia: Definite, Possible, No
  - Other degenerative neurologic diseases: Definite, Possible, No
  - Genetic or presumed genetic: Definite, Possible, No
  - Autoimmune: Definite, Possible, No
  - Epilepsy of unknown cause, without relevant abnormalities on examination, cognition, history, or imaging: Definite, Possible, No
  - Primary Etiology (subjects with only one specific etiology, or with more than one specific etiology and an etiology selected as the primary are included).
  - Secondary Etiology

By-subject listings of demographic and baseline characteristics will be produced.

4.4 Medical History

Medical history will be coded using MedDRA version 21.1 or higher.

Medical history will be summarized (number and percentage of subjects) by System Organ Class (SOC) and Preferred Term (PT) for randomized population. Subjects with two or more preferred terms in the same system organ class (or with the same preferred term) are counted only once for that system organ class (or preferred term).

The medical history data will also be presented in a by-subject listing.

4.5 Prior and Concomitant Medications

All medications will be coded using WHO-Drug Dictionary Sep 2018 or higher.

Prior medications (AED and non-AED) are defined as medications that ended before the date of first dose. Concomitant medications (AED and non-AED) are defined as medications that are used on/after the date of first dose.

For Double-blind period, concomitant medication summary tables will include medications up to last dose date for subjects who roll over to OLE; up to end of study in Double-blind treatment period for subjects who completed DB period and did not roll over to OLE or subjects who discontinued DB period early.

The number and percentage of subjects taking prior and concomitant AED medications, concomitant non-AED medications will be summarized by ATC Classification (ATC2) and preferred term (PT) in Safety Population. Subjects with two or more preferred terms in the same ATC (or with the same preferred term) are counted only once for that ATC (or preferred term).

In addition, descriptive statistics and categories (0, 1, 2, 3, >3) for the number of prior AED medications, concomitant AED medications per subject will be prepared by treatment group and for all subjects combined in Safety Population. Prior and Concomitant Medications will be listed.

4.6 Drug Exposure and Compliance

The following measurements for drug exposure will be calculated and analyses will be performed) in Safety Population.

Duration of exposure

For each subject, the duration of exposure will be calculated in days, using the following formula:

(last dose date - first dose date) + 1

Descriptive statistics will be provided to summarize duration of exposure during the Double-blind Treatment Period and separately for Titration and for Maintenance Phase.

Dosing duration will also be expressed in terms of total subject years of exposure. The calculation follows the formula below.

Total subject years of exposure = sum of all subject total exposure days / 365.25.

Total subject years of exposure will be summarized by Double-blind Treatment Period, Titration Phase, Maintenance Phase, and whole study (down-titrated dose included).

Total Dose Taken

Total dose taken will be summarized by Double-blind Treatment Period, Titration Phase, Maintenance Phase, and whole study (down-titrated dose included).

Average Daily Dose

Average daily dose will be calculated as:

[Total dose taken] / [last dose date - first dose date + 1].

Average daily dose in the Double-blind Treatment Period and Maintenance Phase will be summarized by descriptive statistics.

Maximum Dose

Maximum dose is defined as the maximum dose taken during Double-blind Treatment Period and Maintenance Phase for each subject.

Descriptive statistics will be provided to summarize maximum dose during the Double-blind Treatment Period and Maintenance Phase.

Modal Daily Dose

Modal daily dose is defined as the dose taken the most days during Double-blind Treatment Period and the Maintenance Phase, respectively; in case of ties (i.e, 2 different dose levels taken the same number of days), modal dose will be defined as the highest daily dose.

Descriptive statistics will be provided to summarize modal daily dose during the Double-blind Treatment Period and Maintenance Phase.

Compliance

Compliance rate (%) will be calculated from prescribed dose(s), dose(s) administered, and dose treatment interval data obtained from EDC for each subject directly and will be summarized by descriptive statistics for the Double-blind Treatment Period, Titration Phase, and the Maintenance Phase.

In the EDC, formulas shown below are used for the calculation of the compliances for the tablets and the oral suspension,

- **For Tablets:**

Compliance rate (%) = (actual number of tablets/planned number of tablets) x 100

- Actual number of tablets = Total number of tablets dispensed – Total number of tablets returned
- Planned number of tablets = Total number of tablets to be taken per day x Number of days study drug administered
- Number of days study drug administered = (Stop dose date (DA)-Start dose date (DA)) + 1

- Total number of tablets to be taken per day (Derived Total Daily Tablets) =
  - Per Protocol, from Visit 4 to Visit 7 / ET dose titration could go up to 100 mg. If dose is ≤100 mg then total number of tablets to be taken per day =1.
  - Per protocol, from Visit 8 to Visit 13 dose could be >100 mg. If dose is > 100 mg then total number of tablets to be taken per day =2.

- **For Oral Suspension:**

Compliance rate (%) = (Actual Amount/Planned Amount) x 100

- Actual Amount = Amount from Bottle #1 + Amount from Bottle #2 + Amount from Bottle #3, #4 etc. (if more than two bottles are dispensed)
- Amount from Bottle #1 or Bottle #2 ... = (Weight of bottle dispensed in mg – Weight of bottle returned in mg) x (1 g/1000 mg unit conversion) x (10 mg/mL cenobamate suspension strength) / (1.02 g/mL cenobamate suspension density)
- Planned Amount = Total daily dose planned (mg) x Number of days study drug administered
- Number of days study drug administered = (Stop dose date (DA)-Start dose date (DA)) + 1
- Total daily dose planned = Dose prescribed in mg

More information is in Appendix 5 (IP Compliance Calculation Specification).

4.7 Efficacy Analysis

Efficacy analysis during Double-blind treatment period will be based on MITT population. Efficacy analysis during the Maintenance Phase will be based on MITT-M population. Subjects with baseline seizure frequency per 28-day equal to 0 will be excluded from analysis, unless otherwise specified.

4.7.1 Primary Estimands

4.7.1.1 Primary Estimand

The primary analysis for this study will be conducted on MITT population (excluding subjects with PGTC baseline seizure frequency per 28-day equal to 0 from analysis) for endpoint defined in USA and Rest of the World, and MITT-M population (excluding subjects with PGTC baseline seizure frequency per 28-day equal to 0 from analysis) for endpoint defined in Europe, South Africa, Australia, and New Zealand. This estimand is defined according to the primary objective and is in alignment with the primary endpoints. The primary estimands are described in list of estimands for primary efficacy endpoints (Table 1).

Table 1 List of Estimands for Primary Efficacy Endpoints

Estimand	Population	Endpoint/Variable	Intercurrent events and strategies	Population-level summary
Primary E1	≥ 12-year-old subjects with Primary Generalized Tonic-Clonic (PGTC) seizures who satisfy the inclusion and exclusion criteria as specified in the protocol, Analysis will be based on MITT population: All subjects in the randomized population who received at least 1 dose of study drug and have at least 1 postbaseline efficacy measurement in Double-blind treatment period. Furthermore, subjects with PGTC baseline seizure frequency per 28-day equal to 0 are excluded from analysis	USA and Rest of the World (RoW): median percent change from baseline in PGTC seizure frequency per 28-day interval during the Double-blind treatment period.	Regardless of concomitant medications, efficacy data are included in the analysis. Subgroup analysis will be performed for concomitant medication groups: with concomitant rescue medication use vs. without concomitant rescue medication use (Section 4.7.6). Premature discontinuation before Visit 14: Data after the discontinuation from the study treatment due to all reasons will not be included in the primary analysis. The drop-out patterns will be summarized by treatment group to assess any imbalance using frequency counts. Sensitivity analysis using "Worst value substituted" (for Double-blind treatment period) for drop-out subjects before Visit 14 will be performed to assess the robustness of the primary analysis result (Section 4.7.6).	The difference in the primary variable median between cenobamate group and placebo.

Primary E2	≥ 12-year-old subjects with Primary Generalized Tonic-Clonic (PGTC) seizures who satisfy the inclusion and exclusion criteria as specified in the protocol, Analysis will be based on MITT-M population: All subjects in the randomized population who received at least 1 dose of study drug during the Maintenance Phase and have at least 1 efficacy measurement in the Maintenance Phase. Furthermore, subjects with PGTC baseline seizure frequency per 28-day equal to 0 are excluded from analysis	Europe, South Africa, Australia, and New Zealand: 50% responder rate for PGTC seizures during the Maintenance Phase.	Regardless of concomitant medications, efficacy data are included in the analysis. Subgroup analysis will be performed for concomitant medication groups: with concomitant rescue medication use vs without concomitant rescue medication use (Section 4.7.6). Premature discontinuation before Visit 14: Data after the discontinuation from the study treatment due to all reasons will not be included in the primary analysis. The drop-out patterns will be summarized by treatment group to assess any imbalance using frequency counts. Sensitivity analysis using "Worst value substituted" (for Maintenance Phase) for drop-out subjects before Visit 14 will be performed to assess the robustness of the primary analysis result (Section 4.7.6).	The difference in proportions between cenobamate group and placebo response rates.

4.7.2 Definitions Related to Efficacy Endpoints

Seizure frequency will be computed over non-missing diary days; missing seizure diary days will not be considered in the calculation of seizure frequency. For subjects who prematurely discontinue, or have missing diary days, the calculation of the seizure frequency over a specified period will be based on available seizure diary up to the last diary entry. This effectively imputes the unobserved seizures after discontinuation with the seizure frequency observed prior to discontinuation.

In addition, if any seizure type count is reported as unknown with seizure cluster recorded, then 2 of that unknown seizure type will be added to the total count for the day.

Baseline seizure diary:

The baseline seizure rate is calculated by counting the number of seizures over the baseline period and dividing by the number of days in the interval with non-missing seizure data and then multiplying by 28.

During study development, screening/baseline period is adjusted based on different protocol versions. Baseline period definition may be updated based on enrolment from different protocol versions.

The seizure frequency per 28-day interval during baseline phase will be calculated as the number of seizures during baseline period divided by the number of days with seizure diary entry during baseline phase multiplied by 28 days.

The seizure frequency per 28-day interval during the Double-blind Treatment Period/ Maintenance Phase will be calculated as the number of seizures during the Double-blind Treatment Period/ Maintenance Phase divided by the number of days with seizure diary entry during corresponding period/phase multiplied by 28 days.

The percent change from baseline in seizure frequency during the Double-blind Treatment Period/ Maintenance Phase will be calculated as the seizure frequency per 28-day interval during the Double-blind Treatment Period/Maintenance Phase minus the seizure frequency per 28-day interval during baseline phase and then divided by the seizure frequency per 28-day interval during baseline phase and multiplied by 100%.

The 50% (or 75% or 90% or 100%) responder during the Double-blind Treatment Period/ Maintenance Phase is defined as a subject with at least 50% (or 75% or 90% or 100%) reduction in the percent change from baseline in seizure frequency during the Double-blind Treatment Period/Maintenance Phase.

Seizure types are specified in Appendix 3.

4.7.3 Primary Efficacy Endpoint Analysis

- USA and Rest of the World (RoW):
  Median percent change from baseline in PGTC seizure frequency per 28-day interval during the Double-blind treatment period. The primary efficacy analysis

will be based on the MITT population (excluding subjects with PGTC baseline seizure frequency per 28-day equal to 0 from analysis).
An analysis of covariance (ANCOVA) model will be fit to the ranked values of the primary efficacy endpoint. Ties will be handled using TIES=MEAN. The ANCOVA will have terms for ranked baseline seizure rate as covariate and randomized treatment group as factors. The ANCOVA test will be at 2-sided with significance level of 0.05.

- Europe, South Africa, Australia, and New Zealand:
  50% responder rate for PGTC seizures during the Maintenance Phase. The primary efficacy analysis will be based on the MITT-M population (excluding subjects with PGTC baseline seizure frequency per 28-day equal to 0 from analysis). A responder is defined as a subject who achieves at least a 50% reduction in PGTC seizure frequency per 28-day interval during the Maintenance Phase relative to baseline.
  The data will be summarized using frequencies and percentages of subjects achieving at least a 50% reduction in PGTC seizure frequency during the Maintenance Phase relative to baseline (i.e., the responder rate). The responder data will be analyzed using a Chi-square test with a 2-sided significance level of 0.05.

4.7.4 Secondary Efficacy Endpoints Analysis

Secondary efficacy endpoints, which will be adjusted for multiplicity using hierarchical method, are listed below:

1. 100% responder rates for PGTC seizures during the Maintenance Phase relative to baseline.
2. 75% responder rates for PGTC seizures during the Maintenance Phase relative to baseline.
3. Percentage of subjects who achieved a 50% reduction in all generalized seizures frequency per 28-day period during the Maintenance Phase relative to baseline.

The hierarchical method will first test the primary endpoint for US and ROW (median percent change from baseline in PGTC seizure frequency during Double-blind period) and the primary endpoint for Europe, South Africa, Australia, and New Zealand (50% responder rate for PGTC seizures during the Maintenance Phase). If they meet statistical significance, the secondary efficacy endpoints will be assessed hierarchically in the numerical order listed above.

All secondary efficacy endpoints will be analyzed using a Chi-square test.

4.7.5 Exploratory Efficacy Endpoints Analysis

Exploratory efficacy endpoints are listed as below:

- 50%, 75%, and 100% responder rates for PGTC seizures during Double-blind treatment period relative to baseline.
- Median percent change from baseline in PGTC seizure frequency per 28-day interval during the Maintenance phase.
- Median percent change from baseline in all generalized seizure frequency per 28-day interval during the Maintenance Phase relative to baseline and Double-blind treatment period relative to baseline.
- The percentage of subjects who have a 50% reduction in all generalized seizure frequency per 28-day interval during the Double-blind treatment period relative to baseline.
- The percentage of subjects who have a 50%, 75%, 90%, and 100% reduction in seizure frequency for other types of generalized seizures including myoclonic or absence per 28-day interval during the Maintenance Phase relative to baseline and the Double-blind treatment period relative to baseline.
- Median percent change from baseline in seizure frequency for other types of generalized seizures including myoclonic or absence seizures per 28-day interval during the Maintenance Phase and Double-blind treatment period.

In addition, the following will be summarized both in (1) subjects who have efficacy data in that prespecified interval; and (2) subjects who completed the interval in that prespecified interval, separately:

- The median percent change from baseline in seizure frequency (seizure rate per 28-day interval) of PGTC seizure during every 2-week interval, every 4-week interval (the last interval might be 6-weeks) in the 10-week Titration Phase will be summarized descriptively.
- The percentages of subjects who have a 50%, and 100% reduction from baseline in seizure frequency of PGTC seizure per 28-day during every 2-week interval, every 4-week interval (the last interval might be 6-weeks) in the 10-week Titration Phase will be summarized descriptively.
- Bar chart for median percentage change from baseline in seizure frequency (seizure rate per 28-day interval) of PGTC seizure during every 2-week interval, every 4-week interval (the last interval might be 6-weeks) in the 10-week Titration Phase will be provided.
- Bar chart for proportion of subjects with 50%, 100% reduction of PGTC seizure during every 2-week interval, every 4-week interval (the last interval might be 6-weeks) in the 10-week Titration Phase will be provided.

4.7.6 Sensitivity Analysis

The following sensitivity analysis will be performed:

- Wilcoxon rank-sum test (exact) on primary efficacy end point percent change from baseline (in PGTC seizure frequency per 28-day interval) difference

between treatment groups

- 50% responder rate for PGTC seizures during the Maintenance Phase will be analyzed using Cochran-Mantel-Haenszel (CMH) test with a 2-sided significance level of 0.05.
- 50% responder rate for PGTC seizures
  - during the first 6 weeks of the Maintenance Phase
  - during the last 6 weeks of the Maintenance Phase
  - For subjects who have X days (<14 days) in the Maintenance Phase, the seizure frequency/type in the last (14-X) days during the Titration Phase of the Double-blind treatment period will be added for the calculation of the seizure rate per 28-day.
- The primary endpoint will be analyzed by measuring the seizure frequency, with exclusion of seizure clusters. Same method will be followed as that in section 4.7.3.
- For subjects who prematurely discontinued/withdrawn (drop-out) from study treatment based on primary estimands, "Worst value substituted" will be used to impute the seizure frequency after drop-out. Based on "Worst value substituted", primary endpoints will be analyzed. The same analysis method will be followed as that in Section 4.7.3.

  For subjects who dropout of study treatment due to all reasons, "Worst value substituted" is used to impute the frequency of seizures from the point of withdrawal/discontinuation from study treatment to the end of planned duration of Double-blinded period (Titration + Maintenance) (Europe, South Africa, Australia, and New Zealand endpoint: from the point of withdrawal/discontinuation from study treatment in Maintenance to the end of planned duration of Maintenance):

  a. If seizure frequency per 28-day interval during Double-blind treatment period (during Maintenance for Europe, South Africa, Australia, and New Zealand endpoint) is less than the seizure frequency per 28-day interval during baseline, then the baseline frequency is used to impute from the point of withdrawal to the end of planned duration.

  b. If seizure frequency per 28-day interval during Double-blind treatment period (during Maintenance for Europe, South Africa, Australia, and New Zealand endpoint) is larger than or equal seizure frequency per 28-day interval during baseline, no substitution is used.

4.7.7 Analysis Period for Efficacy

Seizures will be counted towards either the baseline or to the Double-blind treatment period (Titration and Maintenance phases) according to the table below, for the purposes of calculating seizure rates. Seizures after the defined Double-blind treatment period end

date or during the open-label extension period (OLE) will not be included in the Double-blind treatment period for prespecified statistical analyses of efficacy.

For all seizure frequency computations, seizure diary days with “No data” will be excluded from the denominator. Seizure records with “No seizure” will be included in the numerator as 0 seizures and the days will be included in the denominator. All computations using the rules listed below are based on “Visit” or “Last Dose” dates.

Table 2 Analysis period for efficacy

Analysis period	Randomized completed Double-blind Treatment Period and continued into OLE	Randomized completed Double-blind Treatment Period and did not continue into OLE	Randomized and early discontinuation in Double-blind Treatment Period
Baseline	see Section 4.7.2	see Section 4.7.2	see Section 4.7.2
Double-blind treatment period	Start date = first dose date Stop date = Visit 14 date -1	Start date = first dose date Stop date = Visit 14 date -1	Start date= first dose date Stop date = last dose date in Double-blind period
Titration phase	Start date = first dose date Stop date = Visit 9 date	Start date = first dose date Stop date = Visit 9 date	Start date= first dose date Stop date = (Visit 9 date) or last dose date in Double-blind Treatment Period whichever first.
Maintenance Phase	Start date = Visit 9 date +1 Stop date = Visit 14 date -1	Start date = Visit 9 date +1 Stop date = Visit 14 date -1	Start date= Visit 9 date +1 Stop date = last dose date in Double-blind Treatment Period (calculated only for subjects who discontinued after visit 9 before end of Double-blind period)

First 6 Weeks in Maintenance Phase	Start date = visit 9+1 date Stop date = visit 9 date+42	Start date = visit 9 +1 date Stop date = visit 9 date +42	Start date = visit 9 date +1 Stop date = visit 9 date +42 or last dose date in Double-blind Treatment Period whichever first.
Last 6 Weeks in Maintenance Phase	Start date= visit 14 date -42 Stop date = Visit 14 date -1	Start date= visit 14 date -42 Stop date = Visit 14 date -1	Start date= visit 14 date -42 Stop date = last dose date in Double-blind Treatment Period if it occurs after visit 14 date -42

4.7.8 Examination of Subgroups

Subgroup analysis may be performed for primary and secondary efficacy endpoints. The subgroups to be analyzed may include the following:

- Sex (2 categories): female and male
- Race group (2 categories): White, others
- Age (2 categories): ≥12-<18, ≥18
- Geographic region (4 categories): North America, Europe, Africa, and other
- Concomitant rescue medication use (with vs without)

4.8 Safety Analysis

All safety analyses will be performed by the treatment group on the Safety Population.

4.8.1 Adverse Events

Adverse events will be coded to system organ class (SOC) and preferred term (PT) using MedDRA version 21.1 or newer.

Treatment-emergent adverse event (TEAE) is defined as the adverse event that started or worsened after the first dose of study treatment up to 14 days after the subject's last dose (including down-titrated dose) date of study treatment for subjects who completed Double-blind treatment period and did not continue into Open-label extension study, or for subjects who discontinued early in the Double-blind treatment period; TEAEs is defined as the adverse event that started or worsened after the first dose of study treatment up to date of last dose for subjects completing Double-blind treatment period and continuing in Open-label extension study YKP3089C033. Furthermore, if an AE cannot be determined as treatment-emergent due to incomplete/missing date,

conservatively, it will be considered as treatment-emergent and included in the summary tables. Each subject will be counted only once for a preferred term or SOC.

The AEs that have a possible, probable, or definite relationship to study drug will be defined to be "related" to study drug, while others, remote and unrelated, will be defined as "not related". Any AEs, for which the relationship to study drug is missing, will be considered as related to study drug. The AEs with the closest relationship to study drug will be used in summaries.

If an adverse event changes in severity, then the adverse event will be counted only once with the worst severity. If severity is missing, the adverse event will be summarized in the most severe category.

An overview summary will be presented with the following TEAE categories:

- Any TEAEs
- Treatment Related TEAE
- Serious TEAE
- Maximum Severity TEAEs (mild, moderate, severe)
- Treatment Related Serious TEAE
- TEAEs leading to drug interrupted
- TEAEs leading to dose reduced
- TEAE leading to treatment discontinuation
- TEAE leading to study discontinuation
- TEAE leading to death

For each TEAE category, the number and percentage of subjects reporting TEAEs will be tabulated by SOC in descending frequency, and PT in descending frequency. TEAEs and treatment related TEAE will also be summarized by SOC, PT and maximum severity.

TEAEs will also be tabulated by PT in descending frequency. Nonserious TEAE will be summarized by SOC/PT as well.

TEAEs, serious TEAEs, TEAE leading to drug withdrawn, TEAE leading to drug interrupted, TEAE leading to dose reduced, TEAE leading to death will be listed.

The TEAE of DRESS Syndrome will be listed.

4.8.2 Clinical Laboratory Evaluation

Blood and urine samples will be collected for clinical laboratory evaluations (including serum chemistry, hematology, urinalysis) at the visit specified in Protocol Table 4–1: Schedule of Assessments. The data collected in different units will be converted to SI units (the International System of Units) for summary. For Double-blind period, summary tables will include results up to last dose date for subjects who completed the

Double-blind treatment period and continued in Open-label extension study; up to end of study for subjects who completed the Double-blind treatment period but did not continue in Open-label extension study or for subjects who discontinued the Double-blind treatment period early.

The following summaries will be provided for laboratory category of chemistry, hematology during Double-blind period.

- Numeric laboratory values will be summarized as descriptive statistics for both actual value and change from baseline (postbaseline minus baseline) by visit. If values that are non-missing and reported as 'below the detectable limit xx' of an assay, half the detectable limit xx will be used for summary.
- Shift table for parameters with reference range (Low, Normal, High) at baseline contrasted with postbaseline by visit including highest/lowest worst postbaseline if applicable.
- Liver function tests (AST, ALT, ALP, and Total Bilirubin) will be summarized for number of subjects (percentages) who meet following conditions:
    - AST: > 3x ULN; > 5x ULN; > 10x ULN; > 20x ULN
    - ALT: > 3x ULN; > 5x ULN; > 10x ULN; > 20x ULN
    - AST or ALT: > 3x ULN; > 5x ULN; > 10x ULN; > 20x ULN
    - TBL: > 1.5x ULN; > 2x ULN
    - ALP: > 2x ULN
    - (AST or ALT) and TBL: (AST or ALT > 3x ULN) and TBL > 1.5x ULN; (AST or ALT > 3x ULN) and TBL > 2x ULN
    - (AST or ALT) and ALP and TBL: (AST or ALT > 3x ULN) and ALP < 2x ULN and TBL > 2x ULN

The subjects with abnormal liver function tests AST > 3x ULN or ALT > 3x ULN or ALP < 2x ULN or TBL > 1.5x ULN will be listed.

All laboratory values (hematology, serum chemistry, and urinalysis) will be listed by subject and visits.

Creatinine clearance from raw data, calculated using the formula in Section 8.4 Appendix 4 for Visit 1 (Screening) and Visit 4 (Randomization), will be listed.

Pregnancy test results (both serum and urine) will be listed for female subjects.

4.8.3 Vital Sign

The actual values and changes from baseline values at each postbaseline visit for vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, and body weight) will be summarized by visits and treatment group using descriptive statistics. The vital sign baseline and change from baseline (for the corresponding position) will be derived for each assessment position: supine 5 min, standing 1 min, and standing 3 min, if the assessments are performed for multiple positions.

Systolic blood pressure, diastolic blood pressure, and pulse rate under orthostatic stress will be calculated by using the value at the supine position minus the standing position

for blood pressure, and the standing position minus the value at the supine position for pulse rate. Orthostatic values of both standing 1 min and standing 3 min will be calculated separately for each parameter. In addition, a summary of subjects who meet each orthostasis criterium or one of the criteria will be provided for both standing positions at each timepoint. The criteria for orthostasis are the following:

1) Supine systolic blood pressure – Standing systolic blood pressure ≥ 20 mmHg
2) Supine diastolic blood pressure – Standing diastolic blood pressure ≥ 10 mmHg
3) Standing pulse rate – Supine pulse rate ≥ 30 bpm

All vital signs results will be listed on a by-subject basis. In addition, the subject's orthostatic values for each standing position will be listed for each visit. Any orthostatic values meeting above criteria will be flagged in the listing.

4.8.4 Electrocardiograms (ECGs)

ECG variables including QT interval with Bazett's correction (QTcB), QT interval with Fridericia's correction (QTcF), QT, RR, PR, QRS, and Heart Rate will be summarized by visit and treatment group using descriptive statistics.

For repeated assessments at a visit, the average of these values will be taken for the summary at the visit.

For repeated assessments at a visit, the derived result will be "abnormal" if 2 or more results are "abnormal"; otherwise, the derived results will be "normal".

In addition, the QTcF interval will be summarized by the number and percentage of subjects with absolute value and/or change from baseline using the criteria identified below:

- Postbaseline QTcF (subject is counted only once with minimum category):
  - <300 msec
  - >=300 - <340 msec
  - >340 - <=400 msec
  - >400 msec
- Postbaseline QTcF (subject is counted only once with maximum category):
  - <=450 msec
  - >450 - <=500 msec
  - >500 msec
- Change from baseline (subject is counted only once with maximum category):
  - 0 to <= 30 msec
  - 30- <= 60 msec
  - >60 msec
- Change from baseline (subject is counted only once with minimum category):

- <=- 40 msec
- >-40 to <=-20 msec
- > -20 to 0 msec

All ECG results will be provided in a listing.

4.8.5 Physical Examination Findings and Neurologic Examination Results

Results from physical examination will be tabulated as number and percentage of subjects with normal, abnormal non-clinically significant, abnormal clinically significant for each body system by visit and treatment group.

All physical examination results will be provided in a listing.

A listing with only subjects having at least one abnormal result will also be prepared.

The same listings will be prepared for the neurological examination.

4.8.6 C-SSRS

C-SSRS Suicidal Ideation, Intensity of Ideation, and Behavior are collected at baseline and all postbaseline visits during the Double-blind Treatment Period. Summary (number and percentage of subjects) of response to each question will be reported by treatment group and by study visit.

All C-SSRS data will be displayed in the data listing.

4.9 Pharmacokinetic Analysis

Cenobamate sparse blood samples collected during Visits 11 and 13 of the Maintenance Phase and resultant plasma cenobamate concentration for each subject, at each visit, 11 and 13 (including pre- and post-dose depending on the subject morning or evening dosing) and total daily dose will be tabulated in a listing.

Plasma cenobamate (YKP3089) concentrations from collected sparse blood sample will be summarized in a table by treatment and age groups descriptively (n, mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, and geometric mean) for available timepoints. Descriptive statistics will not be calculated if all values are below lower limit of quantification (LLOQ), and no imputations will be done for the plasma concentration values that are below the quantifiable limit (BQL) for descriptive statistics. In cases where more than half of the individual data in a group are below LLOQ, standard deviation, and CV will not be calculated. If one or more values are below LLOQ, the geometric mean will not be calculated.

All cenobamate plasma concentration-time data will be listed in a clinical study report. A summary of the maintenance phase cenobamate concentrations in adolescents (12 to <18 years) and adults (18 years and older) will be provided in the final clinical study report.

4.10 Population PK analysis

Population PK analysis will be performed on sparse cenobamate plasma concentration-time data available from this study and integrating with data from other cenobamate studies. The population PK analysis results will be reported separately. Refer to a separate modeling analysis plan (MAP) for details.

4.11 Pharmacodynamic Analysis

PK/pharmacodynamic analysis may be conducted as a stand-alone approach for PGTC seizures or in combination with POS data, if deemed appropriate. Refer to a separate modeling analysis plan (MAP) for details.

5 INTERIM ANALYSES

No interim analysis was planned for this study.

6 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Analysis in the SAP	Analysis planned in the protocol	Reason
Race group (2 categories): White, Others	Race (3 categories): White, Black/African American, and Other	Updated based on limited sample size within certain subgroup

7 References

Statistical Review and Evaluation of Perampanel (E2007) for antiepileptic indication

CDER, FDA May 25, 2011

8 Appendix

8.1 Appendix 1: Handling Partial Date in Safety

When determining the treatment emergent adverse events, if both start date and end date are completely missing, it will be considered as treatment emergent adverse events. Partial adverse event starts and/or end dates will be handled as follows.

AE Date	Missing Part	Imputation Rule
Start Date	Day	Assign first day of month unless it is the same month and year of the first dose of study drug. Otherwise, assign date of first dose of study drug or AE end date (if not missing), whichever is earlier.
	Day, Month	Assign Jan 01 unless the year is year of first dose of study drug. Otherwise, assign date of first dose of study drug or AE end date (if not missing), whichever is earlier.
	Day, Month, Year	Assign date of first dose of study drug or AE end date (if not missing), whichever is earlier.
End Date	Day	Assign the last date of the month or death date or end of study date, whichever is earliest.
	Day, Month	Assign Dec 31 or death date or end of study date, whichever is earliest.
	Day, Month, Year	If ongoing, end date is missing. Otherwise, assign death date or end of study date, whichever is earlier.

Prior and Concomitant Medication:

When determining if a medication is a prior or concomitant medication, if both start date and end date are completely missing, it will be considered as a concomitant medication. Partial start date and/or end dates will be handled as follows.

Medication Date	Missing Part	Imputation Rule
Start Date	Day	Assign first day of month unless it is the same month and year of the first dose of study drug. Otherwise,

Medication Date	Missing Part	Imputation Rule
		assign date of first dose of study drug or medication end date (if not missing), whichever is earlier.
	Day, Month	Assign Jan 01 unless the year is year of first dose of study drug. Otherwise, assign date of first dose of study drug or medication end date (if not missing), whichever is earlier.
	Day, Month, Year	Assign date of first dose of study drug or medication end date (if not missing), whichever is earlier.
End Date	Day	Assign the last date of the month or death date or end of study date, whichever is earliest.
	Day, Month	Assign Dec 31 or death date or end of study date, whichever is earliest.
	Day, Month, Year	If ongoing, end date is missing. Otherwise, assign death date or end of study date, whichever is earlier.

8.2 Appendix 2 Analysis Phase/Period for Exposure Computation

Duration of exposure will be computed as stop date-start date+1. Start and stop dates for each analysis period accounting for subject participation in the study are included in the table below.

Analysis period	Randomized completed Double-blind Treatment Period and continued into OLE	Randomized completed Double-blind Treatment Period and did not continue into OLE	Randomized and early discontinuation in Double-blind treatment period
Double-blind treatment period	Start date= first dose date Stop date = last dose date in study	Start date= first dose date Stop date = Visit 14 date -1	Start date= first dose date Stop date = last dose date in Double-blind treatment period

	YKP3089C025		
Overall study of Double-blind treatment period (including tapering)	Start date= first dose date Stop date = last dose date in study YKP3089C025	Start date= first dose date Stop date = last dose date during study of Double-blind treatment period (including tapering period)	Start date= first dose date Stop date = last dose date during study of Double-blind treatment period (including tapering period)
Titration phase	Start date= first dose date Stop date = Visit 9 date	Start date= first dose date Stop date = Visit 9 date	Start date= first dose date Stop date = (Visit 9 date) or last dose date in Double-blind treatment period whichever first.
Maintenance Phase	Start date= Visit 9 date +1 Stop date = last dose date in study YKP3089C025	Start date= Visit 9 date +1 Stop date = Date of Visit 14 -1	Start date= Visit 9 date +1 Stop date = last dose date in in Double-blind treatment period (calculated only for subjects who discontinued after visit 9 date before end of Double-blind treatment period)

8.3 Appendix 3 Seizure Type

Seizure Type Category	**Detail***
PGTC seizure	Type A, D
All generalized seizure	Type A, B, C, D, E, F
Other types of generalized seizures including myoclonic or absence	Type B, C, E, F

*Generalized Tonic-Clonic = Type A; Absences = Type B; Myoclonic seizures = Type C; Myoclonic-tonic-clonic = Type D; Tonic = Type E; Other = Type F.

8.4 Appendix 4 Definition, derivation

Serum creatinine will be used to calculate the creatinine clearance (mL/min) during Screening/Baseline (Visit 1) and Randomization (Visit 4) according to the Cockcroft-Gault equation:

Male: [(140-age in years) × (weight in kg) / (72 × serum creatinine in mg/dL)]

Female: [(140-age in years) × (weight in kg) / (72 × serum creatinine in mg/dL)] × 0.85

8.5 Appendix 5 IP Compliance Calculation Specifications

The formulas shown below will be used for IP or Treatment compliance rate, or adherence rate.

IP taken as Tablets:

Compliance rate (%) = (Actual Number of tablets/Planned Number of tablets) x 100

Actual Number of tablets = Total number of tablets dispensed – Total number of tablets returned

Planned Number of tablets = Total number of tablets to be taken per day x Number of days study drug administered

Number of days study drug administered = (Stop dose date (DA)-Start dose date (DA)) + 1

Total number of tablets to be taken per day (Derived Total Daily Tablets) =

Per Protocol, from visit 4 to visit 7 / ET dose titration could go up to max 100 mg.

If dose is less than or equal to 100 mg then total number of tablets to be taken per day =1

Per protocol, from visit 8 to visit 13 doses could go beyond 100 mg.

If dose is greater than 100 mg then total number of tablets to be taken per day =2

Source of EDC data Compliance percentage:

- Total number of tablets dispensed.
- Total number of tablets returned.
- Number of days study drug administered.

Specified Value:

- Total number of tablets planned to be taken per day.

IP taken as Oral Suspension:

Compliance rate (%) = (Actual Amount/Planned Amount) x 100

Actual Amount = Amount from Bottle #1 + Amount from Bottle #2 + Amount from Bottle #3, #4 etc. (if more than two bottles are dispensed)

Amount from Bottle #1 or Bottle #2.... = (Weight of bottle dispensed in mg– Weight of bottle returned in mg) x (1 g/1000 mg unit conversion) x (10 mg/mL cenobamate suspension strength) / (1.02 g/mL cenobamate suspension density)

Site to weigh the bottle in grams up to 2 decimal places.

Convert the above weight in grams to milli grams by multiplying with 1000.

Planned Amount = Total daily dose planned (mg) x Number of days study drug administered

Number of days study drug administered = (Stop Dose date (DA)-Start Dose date (DA)) + 1

Total daily dose planned = Dose prescribed in mg (Study drug administration)

Source of EDC Data:

- Weight of bottle dispensed (mg)
- Weight of bottle returned (mg)
- Total daily dose planned (mg)
- Duration of study exposure in days

Specified Values:

- Concentration of oral suspension (10 mg/mL)
- Density of cenobamate suspension (1.02 g/mL)