STUDY NUMBER:	YKP3089C025
PROTOCOL TITLE:	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
SHORT TITLE	Study to Evaluate the Efficacy and Safety of Cenobamate Adjunctive Therapy in Subjects with PGTC Seizures
IND NUMBER:	IND 76,809
EUDRACT NUMBER:	2018-001337-41
EU CT Number	2023-506687-13-00
SPONSOR:	SK Life Science, Inc. 461 From Road, 5th FL Paramus, NJ 07652 USA
ORIGINAL PROTOCOL DATE:	11 April 2018
VERSION NUMBER:	Amendment 5
VERSION DATE:	11 October 2024

CLINICAL PROTOCOL APPROVAL FORM

AMENDMENT 5

Protocol Title: 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
Study No: YKP3089C025
Amendment 5 Date: 11 Oct 2024
Amendment 4 Date: 27 Oct 2022
Amendment 3 Date: 19 Aug 2019
Amendment 2 Date: 03 Jun 2019
Amendment 1 Date: 20 Jul 2018
Original Protocol Date: 11 Apr 2018

This study protocol was critically reviewed and has been approved by the Sponsor's protocol review committee. The information contained in this protocol is consistent with:

The current risk-benefit evaluation of the investigational product.

The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (US CFR), 21 CFR Sections 50, 54, 56, and 312 and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Name and Title	Signature	Date (dd-mmm-yyyy)
Sunita Misra, MD, PhD VP and Acting Chief Medical Officer SK Life Science, Inc.	(See Appended Signature Page)	

YKP3089C025

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

AMENDMENT 5

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to cenobamate are the confidential and proprietary information of SK Life Science, Inc., and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission from SK Life Science, Inc.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Code of Federal Regulations for Good Clinical Practices and International Council for Harmonisation guidelines and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by SK Life Science, Inc., or specified designees. I will discuss the material with them to ensure that they are fully informed about cenobamate and the study.

_____	_____
Principal Investigator Name (printed)	Signature

_____	_____	_____
Date (dd-mmm-yyyy)	Country	Site Number

PROTOCOL AMENDMENTS

Amendment 5

Rationale for amendment:

1. Add the language as per new EU CTR requirement
2. Update study contact information
3. Update study primary and secondary efficacy endpoints
4. Removal of manufacturer information and quantitative information of formulation

Amendment 5 Summary of Changes

Section	Old Text	Amended Text	Rationale
Title Page	N/A	EU CT Number 2023-506687-13-00 Move short title from header to cover page.	Addition of EU CT Number due to EU regulation
Version Number and Date	Amendment 4, 17OCT2022	Amendment 5, 11OCT2024	Version number and date updated throughout the entire document
Clinical Protocol Approval Form	Marc Kamin, MD Chief Medical Officer SK Life Science, INC.	Sunita Misra, MD, PhD VP and Acting Chief Medical Officer SK Life Science, Inc.	Change in SKLSI medical lead and protocol approver
Study Summary and Section 11.3	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.	Approximately 170 subjects will be randomized at approximately 100 study sites in multiple countries. At least 34 adolescent subjects to be randomized. At least Approximately, 20% of the total subject sample size will be adolescents aged 12 to < 18 years.	Update to add expected adolescent subjects.
All applicable sections	10 mg/kg	10 mg/mL	Updated to use the correct unit
All applicable sections	DRESS	DRESS syndrome	Updated to use the correct term
Synopsis: Study Drug Titration and Maintenance Plan	9, 10, 11, 12, 13	9, 10, 11, 12, 13, 14/ET[a]	Updated for clarify the study drug titration and maintenance plan
Synopsis: Study Drug Titration and Maintenance Plan	14[a] (Non-OLE) OR ET visit	15[a] (Non-OLE)	Updated for clarify the study drug titration and maintenance plan

Synopsis: Inclusion Criteria	#2. Written informed consent signed by the subject, legal guardian, or legally authorized representative (LAR) prior to entering the study, in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Age-appropriate assent will be obtained for adolescents. If the written informed consent is provided by the legal guardian because the subject is unable to do so, a written or verbal assent from the subject must also be obtained. As required by country-specific regulations, only the subject may sign the ICF in accordance with ICH guidelines. Female subjects of childbearing potential are willing to use an acceptable form of birth control, as outlined in Section 8.10.	#2. Written informed consent signed by the subject, legal guardian, or legally authorized representative (LAR) prior to entering the study, in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Age-appropriate assent will be obtained for adolescents. If the written informed consent is provided by the legal guardian because the subject is unable to do so, a written or verbal assent from the subject must also be obtained. As required by country-specific regulations, only the subject may sign the ICF in accordance with ICH guidelines.	Removed last sentence as this inclusion #3
Synopsis: Inclusion Criteria	N/A	3. Female subjects of childbearing potential are willing to use an acceptable form of birth control, as outlined in Section 8.10.	Updated to be aligned with the language in Section 5.2
Synopsis: Exclusion Criteria	17. Subject has evidence of clinically significant abnormalities or disease (e.g., psychiatric, cardiac, respiratory,	17. Subject has evidence of clinically significant abnormalities or disease (e.g., psychiatric, cardiac, respiratory, gastrointestinal, hepatic [AST or	Updated to correct the language

	gastrointestinal, hepatic [AST or ALT more than 2 times the upper limit of normal (ULN), or total or direct bilirubin not more than ULN], or renal disease) that, in the opinion of the Principal Investigator, could affect the subject's safety or conduct of the study.	ALT more than 2 times the upper limit of normal (ULN), or total or direct bilirubin more than ULN], or renal disease) that, in the opinion of the Principal Investigator, could affect the subject's safety or conduct of the study.	
Synopsis: Primary Endpoint	The primary efficacy endpoint will include: • USA and Rest of the World (RoW): median percent change from baseline in PGTC seizure frequency per 28-day interval during the Maintenance Phase.	The primary efficacy endpoint will include: • 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.	Updated to revise the period of primary efficacy endpoint
Synopsis: Secondary Endpoints	The secondary efficacy endpoints will include: • 50%, 75% and 100% responder rate for PGTC seizures during the Maintenance Phase and the Double-blind treatment period relative to baseline. • Europe, South Africa, Australia, and New Zealand only: median percent change from baseline in PGTC seizure frequency per 28-day interval during the Maintenance Phase and the Double-blind	The secondary efficacy endpoints will include: • 100 % responder rates for PGTC seizures during the Maintenance Phase relative to baseline. • 75% responder rates for PGTC seizures during the Maintenance Phase relative to baseline. • 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 secondary safety endpoints will include adverse events and concomitant medication reporting, clinical laboratory results, vital signs,	Updated to align with health authority and other anti-seizure medications

	treatment period relative to baseline. • Median percent change in all generalized seizure frequency per 28-day interval during the Maintenance Phase and the 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 Maintenance Phase and 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 and the Double-blind treatment period relative to baseline. • Median percent change in seizure frequency for other types of generalized	electrocardiograms (ECGs), physical examinations, neurologic examinations, and Columbia Suicide Severity Rating Scale (C-SSRS) results will be summarized using descriptive statistics. The secondary pharmacokinetic endpoints will include: • Summary of individual patients' plasma concentrations of cenobamate at their respective doses and visits. • 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.	

	seizures including myoclonic or absence seizures per 28-day interval during the Maintenance Phase and the Double-blind treatment period relative to baseline.		
Synopsis: Statistical Analysis	<u>Primary Efficacy Endpoint Analysis:</u> • The primary efficacy endpoint for the USA and RoW is the median percent change from baseline in PGTC seizure frequency per 28-day interval during the Maintenance Phase. • The primary efficacy analysis will be based on the modified intent-to-treat maintenance (MITT-M) population, which is defined as randomized subjects who received at least 1 dose of study drug during the Maintenance Phase and have at least 1 efficacy measurement in the Maintenance Phase. An analysis of covariance (ANCOVA) model will be fit to the ranked values of	<u>Primary Efficacy Endpoint Analysis:</u> • USA and 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 modified intent-to-treat (MITT) population, which is defined as randomized subjects who received at least 1 dose of study drug and have at least 1 efficacy measurement in the Double-blind treatment period. An analysis of covariance (ANCOVA) model will be fit to the ranked values of the primary efficacy endpoint. 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. The data will be summarized using frequencies and percentages of subjects achieving at least a 50% reduction	Updated to align with health authority and other anti-seizure medications

	the primary efficacy endpoint. The ANCOVA will have terms for ranked baseline seizure rate and randomized treatment group. • The primary efficacy endpoint for Europe, South Africa, Australia, and New Zealand is the 50% responder rate for PGTC seizures during the Maintenance Phase. The primary efficacy analysis will be based on the MITT-M population. 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.	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 significant level of 0.05. Secondary efficacy endpoints which will be adjusted for multiplicity using hierarchical as below: • 100% responder rates for PGTC seizures during the Maintenance Phase relative to baseline. • 75% responder rates for PGTC seizures during the Maintenance Phase relative to baseline. • 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.	

Synopsis: Statistical Analysis	The Population PK analysis results will be reported separately, but cenobamate plasma concentration data may be reported as part of this study report.	The Population PK analysis results will be reported separately, but cenobamate plasma concentration data will be reported as part of this study report.	Updated to clarify that Bioanalysis report will be included in appendix of Clinical Study Report
LIST OF ABBREVIATIONS	N/A	MITT – Modified Intention-to-treat EU CTR – EU Clinical Trial Regulation No. 536/2014	Updated to add abbreviations
1.1.1 Epilepsy and Primary Generalized Tonic-Clonic Seizures	The primary treatment for seizures is antiepileptic drug (AED) therapy. The majority of AEDs have been approved for focal seizures (partial epilepsy), with or without secondary generalization, whereas the number of AEDs with specific efficacy in PGTC seizures is limited. Since 1993, 15 AEDs have been approved in the United States, but only 4 AEDs (lamotrigine, levetiracetam, perampanel and topiramate) have been approved for the treatment of PGTC seizures.[10] These AEDs have been shown to be efficacious in randomized, double-blind, placebo---controlled studies of the adjunctive treatment for drug -resistant PGTC seizures, however, there remains an unmet need for additional AEDs that treat PGTC seizures.[11, 12, 13, 14, 15, 16]	The primary treatment for seizures is antiepileptic drug (AED) therapy. The majority of AEDs have been approved for focal seizures (partial epilepsy), with or without secondary generalization, whereas the number of AEDs with specific efficacy in PGTC seizures is limited. Since 1993, 15 AEDs have been approved in the United States, but only **5** AEDs (lamotrigine, levetiracetam, perampanel, **lacosamide** and topiramate) have been approved for the treatment of PGTC seizures.[10] These AEDs have been shown to be efficacious in randomized, double-blind, placebo---controlled studies of the adjunctive treatment for drug -resistant PGTC seizures, however, there remains an unmet need for additional AEDs that treat PGTC seizures.[11, 12, 13, 14, 15, 16]	Add lacosamide to approved list of AEDs.
1.1.2 Cenobamate Background	Cenobamate (also known as YKP3089) is carbamate (R)-(+)	Cenobamate (also known as YKP3089) is [(1R)-1-(2-Chlorophenyl)-2-(tetrazol-2-	Updated to clarify the chemical

	-1-(2-chloro-phenyl)-2-tetrazol-2-yl-ethyl ester, which has the chemical formula C10 H10 Cl N5	yl)ethyl] carbamate, which has the chemical formula C10 H10 Cl N5.	structure of cenobamate
1.1.2 Cenobamate Background	Cenobamate (YKP3089) is a small molecule approved in the United States (US) and Europe for the treatment of partial/focal seizures in adult subjects. It is currently in Phase 3 of development as an AED for treatment of partial onset seizures (POS) in pediatric subjects ≥2 years of age. This study (YKP3089C025) will be the first to investigate its antiepileptic activity in PGTC seizures	Cenobamate (YKP3089) is a small molecule. The oral tablet formulation of cenobamate has been authorized for marketing in the United States under the tradename XCOPRI. It has also received marketing approval under the tradename Ontozry in the European Union and member states Iceland, Norway, and Liechtenstein for adjunctive treatment of focal onset seizures with or without secondary generalization. Additionally, the cenobamate oral tablet formulation received approval in the UK and in Switzerland under the trade name Ontozry. Cenobamate was also approved under the trade name XCOPRI Tablets in Hong Kong. All marketing authorizations of the cenobamate oral tablet formulation to date have been for use in adult patients. The oral suspension of cenobamate has not been authorized for marketing in any country and is currently in clinical development.	Added as per new EU CTR requirement
1.2.3.2 Clinical Safety	Overall, 236 serious adverse events (SAEs), including 11 deaths, have been reported during the cenobamate development program. Of these, 210 SAEs occurred in subjects who were randomized to receive cenobamate. The SAEs considered at least possibly related to cenobamate and reported in more than 1 subject included drug reaction with	Overall, 724 serious adverse events (SAEs), including 23 deaths, have been reported during the cenobamate development program. Of these, 637 SAEs occurred in subjects who were randomized to receive cenobamate. The SAEs considered at least possibly related to cenobamate and reported in more than 1 subject included vertigo (4), vomiting (3), constipation (2), hyponatremia (4), ataxia (5), balance disorder	Updated to reflect current information

	eosinophilia and systemic reaction (3 subjects), dizziness (5 subjects), vertigo (5 subjects), ataxia (2 subjects), dysarthria (2 subjects), nystagmus (2 subjects), and suicidal ideation (2 subjects).	(3), dizziness (11), dysarthria (2), nystagmus (2), somnolence (4), drug reaction with eosinophilia and systemic symptoms (3), and rash papular (2).	
3 STUDY ENDPOINTS	3.1 Primary 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 Maintenance Phase.	3.1 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.	Updated to revise the period of primary efficacy endpoint
3. STUDY ENDPOINTS	3.2 Secondary The secondary efficacy endpoints will include: • 50%, 75% and 100% responder rate for PGTC seizures during the Maintenance Phase and the Double-blind treatment period relative to baseline. • Europe, South Africa, Australia, and New Zealand only: median percent change from baseline in PGTC seizure frequency per 28-day interval during the Maintenance Phase and the Double-blind	3.2 Secondary Efficacy Endpoints The secondary efficacy endpoints which will be adjusted for multiplicity using hierarchical method are listed below: • 100% responder rates for PGTC seizures during the Maintenance Phase relative to baseline • 75% responder rates for PGTC seizures during the Maintenance Phase relative to baseline Percentage of subjects who achieved a 50% reduction in all generalized seizures frequency per 28-day period during the Maintenance Phase relative to baseline.	Updated to align with health authority and other anti-seizure medications

	treatment period relative to baseline. • Median percent change in all generalized seizure frequency per 28-day interval during the Maintenance Phase and the Double-blind treatment period relative to baseline relative to baseline. • The percentage of subjects who have a 50% reduction in all generalized seizure frequency per 28-day interval during the Maintenance Phase and the Double-blind treatment period relative to baseline 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 and the Double-blind treatment period relative to baseline relative to baseline. • Median percent change in seizure frequency for other	Safety analyses will be performed by treatment group on the Safety Population. The secondary pharmacokinetic endpoints will include: • Summary of individual patients' plasma concentrations of cenobamate at their respective doses and visits. • 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.	

	types of generalized seizures including myoclonic or absence seizures per 28-day interval during the Maintenance Phase and the Double-blind treatment period relative to baseline relative to baseline.		
5.3 Exclusion Criteria	17. Subject has evidence of clinically significant abnormalities or disease (e.g., psychiatric, cardiac, respiratory, gastrointestinal, hepatic [AST or ALT more than 2 times the upper limit of normal (ULN), or total or direct bilirubin not more than ULN], or renal disease) that, in the opinion of the Principal Investigator, could affect the subject's safety or conduct of the study.	17. Subject has evidence of clinically significant abnormalities or disease (e.g., psychiatric, cardiac, respiratory, gastrointestinal, hepatic [AST or ALT more than 2 times the upper limit of normal (ULN), or total or direct bilirubin more than ULN], or renal disease) that, in the opinion of the Principal Investigator, could affect the subject's safety or conduct of the study.	Updated to correct the language
6.3 Withdrawal and Premature Discontinuation	N/A	Any subject may be withdrawn from the study at the discretion of the Investigator. The subject is also free to terminate his/her participation at any time. However, if the subject has been dosed with study medication, it is recommended to ask the subject to remain in contact with the center, and the investigational site should make every effort to convince the subject to return for a safety follow-up visit. The Investigator will also undertake to obtain more detailed information about any subject lost to follow-up. Subjects withdrawn from the study must not be re-included	Added as per new EU CTR requirement

6.4 End of Study	N/A	End of the study is defined as the last patient last visit.	Added as per new EU CTR requirement
7.3.2 Pregnancy	To ensure subject safety, each pregnancy in randomized subjects must be reported to SK Life Science, Inc. (SKLSI) within 2 weeks of learning of its occurrence, and to the IRB/IEC within the time period as per their reporting requirements.	To ensure subject safety, each pregnancy in randomized subjects must be reported to SK Life Science, Inc. (SKLSI) within 24 hours of learning of its occurrence, and to the IRB/IEC within the time period as per their reporting requirements.	Updated to revise the reporting timeline of pregnancy
7.4 Pharmacokinetics	N/A	Detailed procedures for the bioanalytical sample collection, processing and shipping to the central lab are included in the Medpace Laboratory Manual. The Bioanalytical lab shipment address and assay lab contact information is provided in the Laboratory service agreement. These will be provided as separate documents	Added as per new EU CTR requirement
8.2 Formulation	The tablet is Manufactured by Patheon located in Whitby, Ontario, Canada for SK Life Science, Inc. The oral suspension is Manufactured by CoreRx located in Clearwater, Florida, USA for SK Life Science, Inc. The qualitative and quantitative composition of tablets, cenobamate oral suspension and placebo for cenobamate oral suspension is provided in the table below.	The qualitative composition of tablets, cenobamate oral suspension and placebo for cenobamate oral suspension is provided in the table below.	Updated to delete manufacturer information and quantitative information
8.2 Formulation	Table 8.2-1: Quantitative and Qualitative Composition of Cenobamate Tablets	Table 8.2-1: Qualitative Composition of Cenobamate Tablets	Updated to delete quantitative information

		(Quantitative information in table 8.2-1, 8.2-2, and 8.2-3 has been deleted) Placebo tablets have same qualitative composition as active except that they do not contain Cenobamate (Active)	
8.6 Dose and Administration	In addition, the Principal Investigator or designee will record in the source documents the medication number printed on each card from which study drug was dispensed.	In addition, the Principal Investigator or designee will record in the source documents the medication number printed on each card or bottle from which study drug was dispensed.	This change is for clarity for oral suspension.
Table 8-1: Study Drug Titration and Maintenance Plan	9, 10, 11, 12, 13	9, 10, 11, 12, 13, 14/ET[a]	Updated for clarify the study drug titration and maintenance plan
Table 8-1: Study Drug Titration and Maintenance Plan	14[a] (Non-OLE) OR ET visit	15[a] (Non-OLE)	Updated for clarify the study drug titration and maintenance plan
10.1 Definition of Serious Adverse Event	Blood dyscrasias or convulsions that do not result in inpatient hospitalization.	Blood dyscrasias that do not result in inpatient hospitalization.	Updated to clarify the language as convulsions is the part of the indication being studied
10.2.1 Study Sponsor Notification by Investigator	N/A	SKLSI will be responsible for evaluating the events for expedited reporting, and for reporting them to the applicable regulatory agencies. The Sponsor pharmacovigilance vendor for YKP3089C025, IQVIA, will report suspected unexpected serious adverse reactions to the Eudravigilance database as part of regular pharmacovigilance reporting activities. If reports of any new and unexpected AEs become available	Added as per new EU CTR requirement

		to SKLSI during the clinical portion of this study (related or not to the present study), SKLSI must advise the clinical site, through its Principal Investigator, of those events.	
11.2 Analysis Sets	NA	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.	Added to define the analysis population
11.5 Statistical Methods	11.5.1 **Primary** Endpoint(s) The primary efficacy endpoint for the USA and RoW is the median percent change from baseline in PGTC seizure frequency per 28-day interval during the Maintenance Phase. The primary efficacy analysis for the USA and RoW will be based on the MITT-M population (as defined in Section 11.2). An analysis of covariance (ANCOVA) model will be fit to the ranked values of the primary efficacy endpoint. The ANCOVA will have terms for ranked baseline seizure rate and randomized treatment group.	11.5.1 Primary Endpoint(s) • <u>USA and Rest of the World (RoW)</u> 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. 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. • <u>Europe, South Africa, Australia, and New Zealand:</u> 50% responder rate for PGTC seizures during the Maintenance Phase. The primary efficacy analysis will be based on the MITT-M population. A responder is defined as a subject who achieves at least a 50% reduction in PGTC	Updated to align with health authority and other anti-seizure medications

		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. The primary analysis for this study will be conducted on MITT population for endpoint defined in USA and Rest of the World, and MITT-M population 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 11-1). Table 11-1 is added to describe the list of estimands for primary efficacy endpoints	
11.5 Statistical Methods	11.5.2 **Secondary Endpoint(s)** Endpoints with a continuous variable, such as median percent change, will be analyzed using the same ANCOVA method as used for the primary analysis. Categorical efficacy endpoints will be	11.5.2 **Secondary Endpoints** Secondary efficacy endpoints which will be adjusted for multiplicity using hierarchical method are listed below: • 100% responder rates for PGTC seizures during the Maintenance Phase relative to baseline. • 75% responder rates for PGTC seizures during the	Updated to align with health authority and other anti-seizure medications

	analyzed using a Chi-square test.	Maintenance Phase relative to baseline. • 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.	
12.3 Institutional Review Board/ Independent Ethics Committee		Added "in compliance with (EU) No 536/2014"	Added EU CTR compliant language
12.7 Study Files and Record Retention		Added "and in compliance with local regulations" **At a minimum**, essential documents **should must be retained for at least 25 years post study completion or**…	Added EU CTR compliant language
17.1 Data Handling	N/A	Section updated regarding data security breaches	Added EU CTR compliant language regarding data security data breaches added

19.1 Appendix I – Names of Study Personnel	Marc Kamin, MD Chief Medical Officer SK Life Science, Inc. 461 From Road, 5th FL Paramus, NJ 07652 USA Telephone: +1 201-421-3830 Email: mkamin@sk.com	Sunita Misra, MD, PhD VP, Clinical Development & Acting Chief Medical Officer SK Life Science, Inc. 461 From Road, 5th FL Paramus, NJ 07652, USA Telephone: +1 832-257-1975 Email: smisra@sklsi.com Marc Kamin, MD Safety Physician SK Life Science, Inc. 461 From Road, 5th FL Paramus, NJ 07652 USA Telephone: +1 201-421-3830 Email:mkamin@sklsi.com	Change in study contacts at SKLSI requiring updating in protocol
19.1 Appendix I – Names of Study Personnel	PRA US Medical Monitor: Wendy Martin, MD Medical Director, Medical Affairs PRA Health Sciences 4130 ParkLake Avenue, Suite 400 Raleigh, NC 27612 USA Telephone: 1 866-326-5053 Email : SKL025@prahs.com PRA Ex-US/EAPA Medical Monitor: Ali Ghabeli Juibary, MD Medical Director, Neuroscience & Pain 500 South Oak Way, Green Park Reading RG2 6AD, United Kingdom Phone: +44 (0) 118 918 1000; +44 (0) 118 918 1001 Email: SKL025@prahs.com	ICON US Medical Monitor: Wendy Martin, MD Senior Medical Director, Medical Affairs ICON Plc 4131 Park Lake Avenue Suite 600 Raleigh, NC 27612 USA Tel: +1 866-326-5053 Email: SKL025@iconplc.com ICON Ex-US/EAPA Medical Monitor: Ali Ghabeli Juibary Medical Director, Medical Affairs ICON Plc 200 Brook drive, Green Park Reading, UK, RG2 6UB Phone: +49 621 878 2850 Email: SKL025@iconplc.com ICON APAC Medical Monitor Li-Chin Ko Medical Director, Medical Affairs ICON Plc 5F, No. 2, Sec. 5, Xinyi Road, Xinyi District, Taipei 11049, Taiwan Phone: +65 63 304 014	Updated to apply latest study personnel information

		Email: SKL025@iconplc.com	
19.1 Appendix I – Names of Study Personnel	PRA Health Sciences 4130 ParkLake Avenue, Suite 400 Raleigh, NC 27612 USA	ICON Plc 4131 Park Lake Avenue, Suite 600 Raleigh, NC 27612 USA	Updated to reflect CRO name change
19.1 Appendix I – Names of Study Personnel	NA	Hungaro Medical Monitor: Tamara Babic, MD Medical Advisor 11000 Belgrade, Serbia Phone: +381 11 407 3825 Email: YKP3089C025_medical@hungarotrial.com GCT Medical Monitor: Daria Podgorska, MD, Ph.D. Managing Director, Safety Officer (Physician), Medical Monitor Mlądzka 10, 04-136 Warsaw Poland Phone: +48 22 617 0042 Email: skl025@gctrials.com Clinical Research Organization: HUNGAROTRIAL Zrt. Fehérvári út 89-95, 1119 Budapest, Hungary Clinical Research Organization: Global Clinical Trials, LLC 256 Bunn Drive, Suite 6 Princeton, NJ 08540 USA	Updated to add study contacts of newly added CROs

PROTOCOL AMENDMENTS

Amendment 4

Rationale for amendment:

1. Update inclusion criteria to allow for the addition of subjects ages 12 to <18years
2. Clarify the number of subjects to be enrolled in adolescent subject population
3. Include weight-based dosing using oral suspension for adolescent subjects
4. Update study contact information
5. Include clarification of exclusion criteria of illicit drugs

Amendment 4 Summary of Changes

Section	Old Text	Amended Text	Rationale
Version number and date updated	Amendment 3, 19 August 2019	Amendment 4 dated	Version number and date updated throughout the entire document
Study Summary	Investigational Product: Cenobamate	Investigational Product: Cenobamate (tablets or oral suspension)	Included the different methods of drug delivery throughout the entire document
Study Summary: Number of Subjects	Approximately 152 subjects will be enrolled at approximately 100 study sites in multiple countries	Approximately 170 subjects will be enrolled at approximately 100 study sites in multiple countries and approximately 20% of the subjects randomized will be adolescents ages 12 to <18y.	Updated number of subjects to account for adolescent population
Section 5.2 Inclusion criteria 1	Subject is male or female and aged ≥18 years.	Subject is male or female and aged ≥12 years.	Updated inclusion criteria to allow for adolescent subjects
Section 5.2 Inclusion criteria 2	Written informed consent signed by the subject or legal guardian prior to entering the study, in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.	Written informed consent signed by the subject, legal guardian, or legally authorized representative (LAR) prior to entering the study, in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Age-appropriate assent will be obtained for adolescents.	Included LAR and mention of age-appropriate assent for adolescents
Section 5.3 Exclusion Criteria 13	Subject tests positive, via urine drug screen at Visit 1 (Screening/Baseline), for illicit drugs (e.g., tetrahydrocannabinol, amphetamines), or for a drug that has not been prescribed (e.g., certain opiates).	Subject tests positive, via urine drug screen at Visit 1 (Screening/Baseline), for illicit drugs not legalized in your state or for a drug that has not been prescribed (e.g., certain opiates).	Incorporate language that doesn't exclude drugs that are legalized in the site's state
Section 5.3 Exclusion Criteria 27	N/A	Previous exposure to cenobamate or sensitivity/allergy to components of the oral suspension.	Include exclusion as cenobamate is approved

Section 8 Study Drug Management	N/A	Included information regarding Oral Suspension	
Section 9.2 Reporting Adverse Events	The latest version of Medical Dictionary for Regulatory Activities (MedDRA).	Medical Dictionary for Regulatory Activities (MedDRA), with the version specified by sponsor in the Data Management Plan	Clarification on AE coding
11.3 Sample Size Calculation	A sample size of 68 subjects per treatment group in the MITT-M population will provide 82% power to detect a 30% difference… …a sample size of 68 subjects in each treatment group in the MITT-M population will have > 82% power…	A sample size of 80 subjects per treatment group in the MITT-M population will provide 862% power to detect a 30% difference… …a sample size of 80 subjects in each treatment group in the MITT-M population will have > 86% power…	Sample size updated to reflect increase to total enrolled number
11.3 Sample Size Calculation	N/A	Approximately, 20% of the total subject sample size will be adolescents aged 12 to < 18 years old.	Define the portion of the population that will be adolescents
11.5.3 Analysis of Safety	Adverse events will be coded using the latest version of MedDRA.	Adverse events will be coded using MedDRA, with the version specified by sponsor in the Data Management Plan	Clarification on AE coding
Section 18 References	18. SK Life Science, Inc. YKP3089 for Epilepsy, Neuropathic Pain and Anxiety. Investigator's Brochure, Version 10.0. Fair lawn (NJ); September 29, 2017.	18. SK Life Science, Inc. YKP3089 for Epilepsy, Neuropathic Pain and Anxiety. Investigator's Brochure, Version 14.0. Paramus (NJ); October 05, 2020.	Updated to account for most current version of IB.
Section 19.1 Appendix I – Names of Study Personnel	Tommaso Fadini, MD Medical Director Neurology – Medical Affairs PURIS Building Potsdamer Platz 10 4th Floor Berlin 10785, Germany Telephone: +44 179-252-5608	Ali Ghabeli Juibary, MD Medical Director, Neuroscience & Pain 500 South Oak Way, Green Park Reading RG2 6AD, United Kingdom Phone: +44 (0) 118 918 1000; +44 (0) 118 918 1001 Email: SKL025@prahs.com	Updated PRA Ex-US/EAPA Medical Monitor and contact details from Tommaso Fadini, MD to Ali Ghabeli Juibary, MD

PROTOCOL AMENDMENTS

Amendment 3

Rationale for amendment:

1. Modify the seizure frequency inclusion criterion for PGTC modified from 3 seizures in 12 weeks to 5 seizures in 12 weeks.
2. To more precisely define what should be considered an overdose.
3. Removal of Screening visit window for Visit 1.
4. Provide clarification on schedule of assessment.
5. Update storage temperature conditions.
6. Clarify structure of DMC.
7. Clarify pregnancy reporting requirement

Amendment 3 Summary of Changes

Section	Old Text	Amended Text	Rationale
Version number and date updated		Amendment 3	Version number and date updated throughout the entire document
Study Summary: Inclusion Criterion	Subject experiences at least 3 PGTC seizures in 12 weeks during the Pre-Randomization Period	Subject experiences at least 5 PGTC seizures in 12 weeks during the Pre-Randomization Period	Enable better interpretation of results because of higher baseline seizure frequency
Section 1.2.6		The initial inclusion criteria indicated that subjects were to have 3 PGTC seizures in 12 weeks prior to randomization. This would be an average of 1 seizure per 28 days. Previous studies of new AEDs for PGTC have used 1.5 seizures per 28 days as the inclusion criteria. Analysis of the first 22 subjects randomized indicated that the median 28-day baseline PGTC frequency was 2.0. This is lower than all previous placebo-controlled studies of AEDs for PGTC seizures. [11, 12, 13, 14, 15, 16, 19, 20] In order to ensure the best possible interpretation of the results of this study, the baseline PGTC seizure requirement will be increased to 5 in 12 weeks or an average of 1.67 per 28 days	
Section 4.2	Randomization Number At Visit 4, after confirmation of a subject's eligibility, a randomization number will be assigned to each subject using the IRT and will be the next available randomization number in the randomization code list.		Removed as subjects are not assigned a randomization number and maintain their 8-digit screening number throughout the study.

Table 4-1: Schedule of Assessment	84 ±2 56 ±2	-84 -56 ±2	Removal of screening window from the first visit and clarify Pre-Randomization Period days
Table 4-1: Schedule of Assessment	Pre-Randomization Period (8 weeks)	Pre-Randomization Period (12 weeks)	Correct the number of weeks of the Pre-Randomization Period
Table 4-1: Schedule of Assessment	Physical examination[g]	Full physical examination[g] Symptom-directed physical examination[g]	Clarify when a full physical exam vs. a symptom-directed physical exam should be performed
Table 4-1: Schedule of Assessment		Retrospective Diary Review form[m] Pre-randomization Diary information form[n]	Clarify when sites should submit forms required for confirming inclusion #5.
Table 4-1: Schedule of Assessment	Urine drug screen[l]	Urine drug screen[l] Onsite urine drug screen[l]	Clarify when the urine drug screen is to be performed centrally, vs on-site.
Table 4-1: Schedule of Assessment	g. A symptom-directed physical examination for hypersensitivity may be performed, if necessary, at Visits 5 through 14. A full physical examination will be performed at Visit 1, Visit 4, ET visit, if applicable, and at Follow-up visit.	g. A symptom-directed physical examination for hypersensitivity may be performed, if necessary, at Visits 5 through 13. See section 7.3.3 for further details. A full physical examination will be performed at Visit 1, Visit 4, Visit 14, ET visit (if applicable), and at Follow-up visit. See section 7.3.7 for further details.	Modified footnote to correct inconsistency between the Schedule of Assessments and sections 7.3.3 & 7.3.7 of the protocol.

Table 4-1: Schedule of Assessment		l. The urine drug screen will be performed via the central lab at Visit 1. The urine drug screen will be performed at the site at Visit 4,Visit 14, and ET Visit (if applicable). M. The retrospective diary review form is only required to be submitted when a subject maintains a personal seizure diary and a reduced prospective pre-randomization period is being requested. n. The Review of Pre-randomization Diary Information form must be submitted and medical monitor approval received, prior to randomizing the subject.	Added footnotes to provide further guidance on visit procedures.
Section 5.2: Inclusion criterion	Subject experiences 3 PGTC seizures in 12 weeks during the Pre-Randomization period.	Subject experiences 5 PGTC seizures in 12 weeks during the Pre-Randomization period.	Enable better interpretation of results because of higher baseline seizure frequency
Section 7.3.2	Any pregnancy that occurs during study participation must be reported using a pregnancy reporting form. To ensure subject safety, each pregnancy must be reported to SK Life Science, Inc. (SKLSI) within 2 weeks of learning of its occurrence, and to the IRB/IEC within the time period as per their reporting requirements.	Any pregnancy that occurs during the screening period will result in the subject being screen-failed. Any pregnancy that occurs after the subject is randomized must be reported using a pregnancy reporting form. To ensure subject safety, each pregnancy in randomized subjects must be reported to SK Life Science, Inc. (SKLSI) within 2 weeks of learning of its occurrence, and to the IRB/IEC within the time period as per their reporting requirements.	Clarify the requirements on reporting pregnancies for subjects in screening vs. subjects that have been randomized.
Section 8.4: Storage	Study drug must be stored at 20°C – 23 °C temperature in a dry area.	Study drug must be stored at controlled room temperature of 20°C – 25 °C (68°F – 77°F), with excursions allowed between 15°C – 30°C (59°F – 86°F).	Update storage temperature conditions

Section 8.9.2		All concomitant AEDs are permitted so long as they are stable for 30 days, unless otherwise specified.	Added detail for clarity.
Section 9.1.1	In this study, AEs will be elicited beginning at the Screening ….	In this study, AEs will be recorded beginning at the Screening ….	Fixed minor grammatical error
Section 9.6	An exposure to the study drug higher than the subject's randomized treatment assignment will be considered an overdose.	An exposure to the study drug > 120% of the subject's randomized treatment assignment will be considered an overdose.	More precisely defined definition of overdose
Section 12.2	The DMC will be composed of an unblinded biostatistician and 4 physicians.	The DMC will consist of at least two experts physicians (at least one epileptologist and one physician with expertise in AED safety issues) and one unblinded biostatistician	Added flexibility to the compliment of physicians on the DMC
Section 12.2	The physicians in the DMC shall not be participating in the clinical study as Investigators	The DMC members shall not be involved in subject recruitment or conduct this clinical study (e.g. physician members may not be Investigators).	Added detail for greater clarity
Section 19.1	Herbert Achtereekte, MD Medical Director Neurology – Medical Affairs Gottlieb-Daimler-Str 10 Mannheim, 68116 Germany Telephone: +44 179-252-5608 Email: SKL025@prahs.com	Tommaso Fadini, MD Medical Director Neurology – Medical Affairs PURIS Building Potsdamer Platz 10 4th Floor Berlin 10785, Germany Telephone: +44 179-252-5608 Email: SKL025@prahs.com	

Amendment 2

Rationale for Update

SKLSI Life Science Inc Address Change

Amendment 2 Summary of Changes

Section	Old Text	Amended Text	Rationale
Page 1	SK Life Science, Inc., 22-10 Route 208 South Fair Lawn, NJ 07410 USA	SK Life Science, Inc., 461 From Road, 5th FL, Paramus, NJ 07652 USA	SKLSI Life Science Inc Address Change

Amendment 1

Amendment 1 Summary of Changes

Change	Page(s) Affected	Summary
Designation of study periods and phases	Not applicable	Terminology updated to Pre-Randomization Period, Double-blind Treatment Period, Titration Phase, Maintenance Phase, and Follow-up Period.
References to Principal Investigator	Not applicable	"Principal Investigator" was updated to "Principal Investigator or designee" where appropriate.
Addition of new visit (Visit 2) in Pre-randomization Period and update in the subsequent visit numbers	Not applicable	A new visit (Visit 2) was added in Pre-randomization Period and subsequent visits were re-numbered to increase by 1.
Study Schematic (Figure 1, Figure 4-1)	14, 35	The row for treatment weeks was deleted to simplify. Visit 8 (now Visit 9) moved from Titration Phase to Maintenance Phase. Day of randomization visit updated to -1.
Section 1.2.2 Clinical Pharmacokinetics	23-24	The pharmacokinetic (PK) profile of cenobamate was updated based on latest information available for subjects with hepatic impairment and results of drug-drug interaction study.
Section 1.2.3 Clinical Safety and Efficacy	24	The number of subjects treated with cenobamate in clinical trials was updated from 1900 to 2500.
Section 1.2.4 Rash and Hypersensitivity Reactions and Drug Reaction with Eosinophilia and Systemic Symptoms	25	The number of subjects in the large open-label safety study was updated from 1300 to 1400.
Section 4.1.1 Pre-Randomization Period (Visit 1 to Visit 3)	30-31	The duration of Pre-randomization Period was increased from 8 weeks to 12 weeks. The retrospective diary data, if considered acceptable by Medical Monitor, to be allowed for 4 weeks or 8 weeks.
Section 4.1.2 Randomization (Day -1)	31	The text of this section was moved under Section 4.1.3.1, now Section 4.1.2.1 (Titration Phase). The initial randomized dose for cenobamate was clarified to be 12.5 mg. Day of Visit updated to -1.
Section 4.1.3.1 Titration Phase (now Section 4.1.2.1)	31	Text updated for clarification.

Section 4.1.3.2 Maintenance Phase (now Section 4.1.2.2)	32	Text updated for clarification.
Section 4.1.4 Follow-up Period (now Section 4.1.3)	32	The process for enrolling subjects in the open-label extension study, the timing of down-titration, and the Follow-up Period were clarified.
Section 4.1.5.1 Discontinuation During the Titration Period (now Section 4.1.4.1)	33	The process for down-titration and the timing of the Follow-up Visit were clarified.
Table 4-1 Schedule of Assessments	36-38	The treatment weeks were deleted. Additional information was added to footnote (k) describing PK blood draws at Visit 10 (now Visit 11) and Visit 12 (now Visit 13). Day of randomization visit updated to -1.
Section 5.2 Inclusion Criterion # 5	39	The duration of requirement of 5 Primary Generalized Tonic-Clonic (PGTC) seizures increased from 8 weeks to 12 weeks.
Section 5.3 Exclusion Criterion #7	40-41	Intermittent rescue diazepam was excluded from the exclusion criterion.
Section 5.3 Exclusion Criterion #10	41	Revised to increase the limit on intermittent benzodiazepine rescue medication from 2 or more to 4 or more times within the 30 days prior to Visit 1 (Screening/Baseline).
Section 5.3 Exclusion Criterion #18	41	Added new exclusion criterion, “Presence of congenital short QT syndrome or relevant replicated change in QT/QTc interval less than 340 msec on ECG.
Section 5.4 Subject Screening	42	The text clarified for subjects who are unable to sign informed consent form (ICF) and their legal guardians will sign the ICF.
Section 6.1 General Information	43	The process of getting informed consent when a subject is unable to give informed consent was clarified.
Section 6.3 Withdrawal and Premature Discontinuation	44	Text describing the process for down-titration revised to improve clarity.
Section 7.1.5 Baseline Imaging	46	Added text regarding when repeated imaging tests are needed.
Section 7.1.6 Additional Screening Assessments	46	Specific clinical laboratory tests added as examples.
Section 7.3 Safety Assessments	47	A statement was added that there is no prescribed order for performing the safety assessments.

Section 7.3.1 Adverse Events	47	The text was revised to clarify how long serious adverse events should be elicited and monitored.
Section 7.3.2 Pregnancy	48	The statement about determining the status of mother and child was revised to indicate that both mother and child should be monitored until the child reaches at least 1 month of age.
Section 7.3.7 Physical and Neurological Examinations	51	References to Physical and Neurological Examination were revised to include references to appendices, that list the assessments to be performed. Forms added as Appendices 19.4, 19.5, and 19.6, for Full Physical Examination, Full Neurological Examination, and Brief Neurological Examination, respectively.
Section 7.3.8 Columbia Suicide Severity Rating Scale	51	Added a stipulation that site personnel will be trained in the administration of the Columbia Suicide Severity Rating Scale. Also added a requirement for sites to have an escalation and management care plan to address subjects who answer YES to Question 4 and/or Question 5 regarding suicidality.
Section 7.4 Pharmacokinetics	52-53	Details added regarding the process for timing the collection of PK blood samples according to when a subject has taken the last dose of study drug before the sampling.
Section 8.5 Packaging and Shipment	54-55	Deleted references to 150 mg and 200 mg tablets. Text revised for clarity.
Table 8-1 Study Drug Titration and Maintenance Plan	56	Visit 8 (now Visit 9) was moved from Titration Phase to the Maintenance Phase.
Section 8.9.2 Permitted Prior and Concomitant Medications	58	Conditions for the use of intermittent benzodiazepines as rescue medication were updated.
Section 8.9.3 Prohibited Prior and Concomitant Medications	58-59	Conditions for the prohibition of intermittent benzodiazepines as rescue medication were updated.
Section 8.11 Treatment Compliance	60	The upper limit of treatment compliance updated from 100 % to 120%.
Section 10.1 Definition of Serious Adverse Event	65	Definition of persistent or significant disability revised to match ICH GCP Glossary.

Section 11.5.1 Primary Endpoints	69	Cross-reference to the definition of the modified intent-to-treat maintenance population added.
Section 12.6 Source Documentation	73	The term “medical foods” was changed to “ketogenic diet” to improve comprehension.
Section 15 Study Report and Publications	77	Text was added to describe conditions for publication of study findings.
Section 17 Confidentiality	79	Text was added to include requirements based on General Data Protection Regulation for clinical sites in countries of European Union.
Section 19.1 Names of Study Personnel	82	Street and e-mail addresses and telephone numbers updated.
Study Summary	4-13	Corresponding updates listed above were made to the Study Summary.

STUDY SUMMARY

Title: 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

Rationale: The purpose of this Phase 3 study is to evaluate the safety, efficacy, and pharmacokinetics of cenobamate adjunctive therapy in subjects with primary generalized tonic-clonic seizures

Investigational Product: Cenobamate (tablets or oral suspension)

Target Population: Subjects with primary generalized tonic-clonic (PGTC) seizures

Phase of Development Phase 3

Number of Subjects: Approximately 170 subjects will be randomized at approximately 100 study sites in multiple countries. 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.

Objectives:

1.1 Primary

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

1.2 Secondary

- 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 PK of cenobamate in subjects with PGTC seizures

Study Duration: **For subjects who participate in the open-label extension (OLE) study (Study YKP3089C033) after completing YKP3089C025:** 34 weeks, as follows:

- Pre-Randomization Period: 12 weeks
- Double-blind Treatment Period: 22 weeks

For subjects who do not participate in the OLE study: 37 weeks, as follows:

- Pre-Randomization Period: 12 weeks
- Double-blind Treatment Period: 22 weeks
- Follow-up Period: 3 weeks

Study Design:

This is a multicenter, randomized, double-blind, placebo controlled-, parallel-group, adjunctive therapy study in subjects with PGTC seizures. The study schematic is provided in Figure 4-1. 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 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. 55 for seizure frequency.

Soon after Visit 1, the Principal Investigator or the designee will complete and submit the Diagnostic Review Form to the independent consulting physician group (e.g., Epilepsy Study Consortium). See Section 7.1.1 for details on the Diagnostic Review Form.

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

Double-blind Treatment Period (Visit 4 to Visit 13)

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 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 volumes based on weight that will provide the adolescent equivalent dose of cenobamate at each titration and maintenance step. The study drug will be dispensed at each visit starting at Visit 4. Subjects will be instructed to start taking the first dose of 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.

Study Drug Titration and Maintenance Plan

Study Phase	Dispense Visit	Double-blind Treatment	
		Adult Tablets – Total Daily Dose	**Adolescents** Oral Suspension – Total Daily Dose
Titration	4	12.5 mg cenobamate tablet, or matching placebo	Volume to deliver 0.2 mg/kg, or matching placebo not to exceed 12.5 mg
	5	25 mg cenobamate tablet, or matching placebo	Volume to deliver 0.4 mg/kg, or matching placebo not to exceed 25 mg

	6	50 mg cenobamate, or matching placebo	Volume to deliver 0.8 mg/kg, or matching placebo not to exceed 50 mg
	7	100 mg cenobamate tablet, or matching placebo	Volume to deliver 1.5 mg/kg, or matching placebo not to exceed 100 mg
	8	150 mg (100 mg + 50 mg) cenobamate tablet, or matching placebo	Volume to deliver 2.0 mg/kg, or matching placebo not to exceed 150 mg
Maintenance	9, 10, 11, 12, 13, 14/ET[a]	200 mg (100 mg + 100 mg) cenobamate tablet, or matching placebo	Volume to deliver 3.0 mg/kg, or matching placebo not to exceed 200 mg
Follow-up (Optional down-titration)	15[a] (Non-OLE)	100 mg cenobamate tablet, or matching placebo	Volume to deliver 1.5 mg/kg, or matching placebo not to exceed 100 mg

Abbreviation: ET= early termination, OLE=open-label extension

a. For subjects not enrolling into the OLE or prematurely discontinuing the study during the Maintenance Phase. Down titration after premature discontinuation is at the discretion of the Investigator depending on reason for discontinuation (e.g., rash).

During the 10-week Titration Phase, the study drug will be titrated as shown in the table above starting at cenobamate 12.5 mg tablet or matching placebo in adults and in adolescents (12 to <18 years old) 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 dose, in adolescents as an oral suspension equivalent based on weight or matching placebo volume dose 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 (Section 8.6.2).

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

Maintenance Phase (Visit 9 to Visit 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, in adolescents as an oral suspension equivalent based on weight or matching placebo volume by the Principal Investigator or designee. 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 (Section 8.6.2).

At each study visit, subjects will undergo study procedures, as provided in the Schedule of Assessments in 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 in the OLE study. Subjects willing to enroll in the OLE study 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 in Table 4-1.

Early Termination and 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

(Table 4-1) 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 should 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 adolescent as an oral suspension equivalent based on weight or matching placebo volume may receive a down-titrated dose of cenobamate 100 mg, in adolescent 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, 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 should 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 in Table 4-1.

Inclusion Criteria:

Each subject must meet the following inclusion criteria to be enrolled in the study:

1. Subject is male or female and aged ≥12 years.
2. Written informed consent signed by the subject, legal guardian, or legally authorized representative (LAR) prior to entering the study, in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Age-appropriate assent will be obtained for adolescents. If the written informed consent is provided by the legal guardian because the subject is unable to do so, a written or verbal assent from the subject must also be obtained. As required by country-specific regulations, only the subject may sign the ICF in accordance with ICH guidelines.

3. Female subjects of childbearing potential are willing to use an acceptable form of birth control, as outlined in Section 8.10.
4. Subject has a clinical diagnosis of PGTC seizures (with or without other subtypes of generalized seizures) in the setting of idiopathic generalized epilepsy. Refer to Section 7.1.1 for information regarding confirmation of PGTC seizure diagnosis.
5. Subject experiences at least 5 PGTC seizures in 12 weeks during the Pre--Randomization Period. Refer to Section 7.1.2 for information regarding confirmation of PGTC seizure frequency.
6. Subject has had a routine electroencephalogram (EEG) within 5 years prior to Visit 1 (Screening/Baseline) or during the Pre-Randomization Period with electroencephalographic features consistent with idiopathic generalized epilepsy; other concomitant anomalies must be explained by adequate past medical history.
7. Subject has undergone computed tomography (CT) or magnetic resonance imaging (MRI) within 10 years prior to Visit 1 (Screening/Baseline) or during the Pre-Randomization Period that ruled out a progressive cause of epilepsy.
8. Subject is currently receiving 1 to a maximum of 3 concomitant antiepileptic drugs (AEDs) with fixed dosing regimens for a minimum of 30 days prior to Visit 1 (Screening/Baseline).
    a) Benzodiazepines (except diazepam, see Exclusion Criterion No. 7) taken at least once per week during the 30 days prior to Visit 1 (Screening/Baseline) for epilepsy, anxiety, or sleep disorder will be counted as 1 AED and the dosage must be continued unchanged throughout the study. Therefore, only a maximum of 2 additional approved AEDs will be allowed. (See Exclusion Criterion No. 10 for intermittent benzodiazepine rescue parameters.)
    b) Subjects receiving felbamate as a concomitant AED must meet the following criteria:
        i. Have a 2-year history of felbamate use and a history of a fixed dosing regimen for a minimum of 60 days prior to Visit 1 (Screening/Baseline).
        ii. No prior or known history of hepatotoxicity or hematologic disorder due to felbamate.
9. Subject with an implanted vagal nerve or deep brain stimulator will be allowed if the stimulator was implanted at least 5 months prior to Visit 1 (Screening/Baseline) and the stimulator parameters are not changed for 30 days prior to Visit 1 and for the duration of the study.

10. Subject taking a ketogenic diet will be allowed as long as the diet has been stable for at least 3 months prior to Visit 1 (Screening/Baseline) and will remain stable for the duration of the study.

Exclusion Criteria:

Subjects meeting any of the following criteria will be excluded from the study:

1. Female subjects who are pregnant (or planning to become pregnant during the study), lactating, or breast-feeding.
2. Subject has a history of status epilepticus that required hospitalization within 12 months prior to Visit 1 (Screening/Baseline).
3. Subject has PGTC seizure clusters where individual seizures cannot be counted or classified.
4. Subject has a history of non-epileptic psychogenic seizures.
5. Subject has a concomitant diagnosis of partial onset seizure (POS).
6. Subject has a clinical diagnosis of Lennox-Gastaut syndrome.
7. Subject is currently taking (within the 30 days prior to Visit 1 [Screening/Baseline]) any of the following medications: diazepam (for any reason other than as intermittent benzodiazepine rescue medication), phenytoin, mephenytoin, fosphenytoin, phenobarbital, primidone, ethotoin, clopidogrel, fluvoxamine, amitriptyline, clomipramine, bupropion, methadone, ifosfamide, cyclophosphamide, or efavirenz.
8. Subject has participated in previous cenobamate clinical studies.
9. Subject has a history of vigabatrin use within 5 months prior to Visit 1 (Screening/Baseline), or the subject plans to begin treatment with vigabatrin during the study.
    a) A subject with a history of vigabatrin use that ended more than 5 months prior to Visit 1 may be enrolled after documented evidence of no vigabatrin associated clinically significant abnormality in an automated visual perimetry test.
10. Subject has a history of intermittent use of rescue benzodiazepines (i.e., 1 to 2 doses over a 24-hour period is considered a 1-time rescue) 4 or more times within the 30 days prior to Visit 1 (Screening/Baseline).
11. Subject has received an investigational drug or device within 30 days prior to Visit 1 (Screening/Baseline).
12. Subject has a history of drug or alcohol dependency or abuse within 2 years prior to Visit 1 (Screening/Baseline).

13. Subject tests positive, via urine drug screen at Visit 1 (Screening/Baseline), for illicit drugs not legalized in your region/state, or for a drug that has not been prescribed (e.g., certain opiates).
14. Subject has a history of any serious drug-induced hypersensitivity reaction (including, but not limited to, Stevens Johnson syndrome, toxic epidermal necrolysis, or Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS] syndrome) or any drug-related rash requiring hospitalization.
15. History of AED-associated rash that involved conjunctiva or mucosae.
16. History of more than one non-serious drug-related hypersensitivity reaction that required discontinuation of the medication.
17. Subject has evidence of clinically significant abnormalities or disease (e.g., psychiatric, cardiac, respiratory, gastrointestinal, hepatic [AST or ALT more than 2 times the upper limit of normal (ULN), or total or direct bilirubin more than ULN], or renal disease) that, in the opinion of the Principal Investigator, could affect the subject's safety or conduct of the study.
18. Presence of congenital short QT syndrome or relevant replicated change in QT/QTc interval less than 340 msec on ECG.
19. Subject has any significant active central nervous system (CNS) infection, demyelinating disease, degenerative neurologic disease or any CNS disease deemed to be progressive during the course of the study that may confound the interpretation of the study results.
20. Subject has a creatinine clearance less than 50 mL/min, as calculated by Cockcroft-Gault equation.
21. Subject has an absolute neutrophil count less than 1500/µL.
22. Subject has platelet count lower than 80,000/µL in subjects treated with valproate.
23. Subject has a history of positive antibody/antigen test for hepatitis A, hepatitis B, hepatitis C, or HIV.
24. Subject has any suicidal ideation (with intent with or without a plan) at Visit 1 (Screening/Baseline) or Visit 4 (Randomization) (i.e., answering YES to Questions 4 and/or Question 5 on the Suicidal Ideation section of the Columbia Suicide Severity Rating Scale [C-SSRS]).
25. Subject has more than 1 lifetime suicide attempt.
26. Subject is a staff member or immediate family member of study staff.
27. Previous exposure to cenobamate or sensitivity/allergy to components of the oral suspension.

Any potential exception to the inclusion as well as exclusion criteria allowing *de minimis* (clinically trivial and meaningless) variations must be approved by the Medical Monitor.

Primary Endpoint:

The primary efficacy endpoint will include:

- 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.

Secondary Endpoints:

The secondary efficacy endpoints will include:

- 100% responder rates for PGTC seizures during the Maintenance Phase relative to baseline.
- 75% responder rates for PGTC seizures during the Maintenance Phase relative to baseline.
- 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 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.

The secondary pharmacokinetic endpoints will include:

- Summary of individual patients' plasma concentrations of cenobamate at their respective doses and visits.
- 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.

Statistical Analysis:

Categorical variables will be summarized as frequencies and percentages. Descriptive statistics for continuous variables will include number of subjects, mean, median, standard deviation, minimum, and maximum. Analyses will be conducted using SAS® Version 9.4 or later.

Primary Efficacy Endpoint Analysis:

- USA and 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 modified intent--to--treat (MITT) population, which is defined as randomized subjects who received at least 1 dose of study drug and have at least 1 efficacy measurement in the Double-blind treatment period. An analysis of covariance (ANCOVA) model will be fit to the ranked values of the primary efficacy endpoint. 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. 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 significant level of 0.05.

Secondary efficacy endpoints which will be adjusted for multiplicity using hierarchical as below:

- 100% responder rates for PGTC seizures during the Maintenance Phase relative to baseline.
- 75% responder rates for PGTC seizures during the Maintenance Phase relative to baseline.
- 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.

Safety Analyses:

The number and percentage of subjects reporting adverse events and serious adverse events will be reported. Physical and neurologic examinations, clinical laboratory results, vital signs, concomitant medications, electrocardiograms, and C-SSRS results will be summarized using descriptive statistics.

Pharmacokinetic Analyses:

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, but cenobamate plasma concentration data will be reported as part of this study report. In addition, a population PK/pharmacodynamic analysis may be conducted as a stand-alone approach for PGTC or in combination with POS data.

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

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AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}tlast}$	AUC from time 0 to last determination
C_{max}	maximum plasma concentration
C-SSRS	Columbia Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CNS	central nervous system
CT	computed tomography
CYP	cytochrome P450
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DSMC	Data and Safety Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalogram
EMA	European Medicines Agency
ET	Early Termination
EU	European Union
EU CTR	EU Clinical Trial Regulation No. 536/2014
FDA	Food and Drug Administration
FUP	follow-up
GCP	Good Clinical Practice
ICF	informed consent form
IB	investigator's brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IRT	Interactive Response Technology
MedDRA	Medical Dictionary of Regulatory Activities
MITT	Modified Intention To Treat
MITT-M	Modified Intent To Treat Maintenance
MRI	magnetic resonance imaging

OLE	open-label extension
PGTC	Primary Generalized Tonic-Clonic
PK	pharmacokinetic
POS	partial onset seizure
RoW	rest of the world
SAE	serious adverse event
SOP	standard operating procedure
SKLSI	SK Life Science, Inc.
WHO	World Health Organization

1 INTRODUCTION AND RATIONALE

1.1 Background

1.1.1 Epilepsy and Primary Generalized Tonic-Clonic Seizures

According to the World Health Organization (WHO), epilepsy afflicts more than 50 million people worldwide. Globally, an estimated 2.4 million people are diagnosed with epilepsy each year. In high-income countries, annual new cases are between 30 and 50 per 100,000 people in the general population. In low- and middle-income countries, this figure can be up to 2 times higher.[1] Epilepsy leads to an increased risk of injury from accidents, an increased rate of mortality, and has a significant impact on quality of life.

Epilepsy is classified as idiopathic (no identifiable cause) or symptomatic/secondary (e.g., structural brain abnormality, head injury, or brain tumor). Idiopathic epilepsy is the most common type, affecting 60% of the epilepsy subjects.[1] Further differentiation can be made based on whether the seizures begin in a focal region (partial epilepsy) or diffusely (generalized epilepsy). Approximately 25% of the 82% of subjects, who could be classified to have a clinically dominant seizure type, based on the International Classification of Epileptic Seizures, were classified as having generalized seizures.[2]

Partial and generalized epilepsy are further classified, in terms of seizure subtype, by the electroencephalographic patterns and clinical characteristics observed when the seizure is occurring. Subjects with partial epilepsy may experience simple partial seizures or complex partial seizures. Subjects with idiopathic generalized epilepsy may experience one or more seizure subtypes such as Primary Generalized Tonic-Clonic (PGTC) seizures, absence seizures, and myoclonic seizures. PGTC seizure is the most common generalized seizure type and is also the most serious seizure due to the risks for seizure-related injury and sudden unexpected death in epilepsy.[3, 4, 5, 6, 7, 8, 9]

The primary treatment for seizures is antiepileptic drug (AED) therapy. The majority of AEDs have been approved for focal seizures (partial epilepsy), with or without secondary generalization, whereas the number of AEDs with specific efficacy in PGTC seizures is limited. Since 1993, 15 AEDs have been approved in the United States, but only 5 AEDs (lamotrigine, levetiracetam, perampanel, lacosamide, and topiramate) have been approved for the treatment of PGTC seizures.[10] These AEDs have been shown to be efficacious in randomized, double-blind, placebo---controlled studies of the adjunctive treatment for drug -resistant PGTC seizures, however, there remains an unmet need for additional AEDs that treat PGTC seizures.[11, 12, 13, 14, 15, 16]

1.1.2 Cenobamate Background

Cenobamate (also known as YKP3089) is [(1R)-1-(2-Chlorophenyl)-2-(tetrazol-2-yl)ethyl] carbamate, which has the chemical formula C10 H10 Cl N5.

Cenobamate (YKP3089) is a small molecule. The oral tablet formulation of cenobamate has been authorized for marketing in the United States under the tradename XCOPRI. It has also received marketing approval under the tradename Ontozry in the European Union and member states Iceland, Norway, and Liechtenstein for adjunctive treatment of focal onset seizures with or without secondary generalization. Additionally, the cenobamate oral tablet formulation received approval in the UK and in Switzerland under the trade name Ontozry. Cenobamate was also approved under the trade name XCOPRI Tablets in Hong Kong. All marketing authorizations of the cenobamate oral tablet formulation to date have been for use in adult patients. The oral suspension of cenobamate has not been authorized for marketing in any country and is currently in clinical development.

Oral cenobamate was found to be effective in standard animal models of epilepsy. Refer to the investigator's brochure (IB) for details regarding nonclinical pharmacology and toxicology of cenobamate. In *in vitro* electrophysiology assays, YKP3089 was noted to be an inhibitor of the slow inactivated state and persistent current of sodium channels and to be a positive allosteric modulator of multiple $GABA_A$ ion channel subtypes. Nonclinical testing in mouse and rat models suggests that cenobamate has a broad spectrum of antiepileptic effects.

1.2 Study Rationale

1.2.1 Nonclinical Safety

Non-clinical testing of cenobamate suggests a broad spectrum of antiepileptic effects, as well as therapeutic potential for treatment of neuropathic pain, and possible future investigations for treatment of anxiety. In in vitro electrophysiology assays, cenobamate was shown to be an inhibitor of the fast and slow inactivated state and persistent current of sodium channels and to be a positive allosteric modulator of 6 GABAA ion channel subtypes ($\alpha1\beta2\gamma2$, $\alpha2\beta3\gamma2$, $\alpha3\beta3\gamma2$, $\alpha4\beta3\gamma2$, $\alpha5\beta3\gamma2$ and $\alpha6\beta3\gamma2$).

Cenobamate has been assessed in a large number of safety pharmacology and toxicology studies including single-dose toxicity, repeat-dose toxicity, cardiotoxicity, genetic toxicity, reproductive toxicity, juvenile toxicity and carcinogenicity in animals. Safety pharmacology studies showed that the doses that produced beneficial central nervous system (CNS) effects of cenobamate in animal models do not result in obvious negative effects on the CNS. No evidence of cardiovascular effects was observed by telemetric electrocardiography in male monkeys. There was no carcinogenic potential for cenobamate in transgenic rasH2 mice or Sprague Dawley rats. Definitive juvenile rat study showed additional adverse effects including delayed sexual maturation, decreased grip strength, learning and memory deficits, decreased sperm count, decreased brain weight, and ocular histopathology; however, recovery from these effects was observed following discontinuation of dosing.

Cenobamate is extensively metabolized. The primary metabolic pathways are by glucuronidation via UGT2B7 and to a lesser extent by UGT2B4, and by oxidation via CYP2E1, CYP2A6, CYP2B6, and to a lesser extent by CYP2C19 and CYP3A4/5.

1.2.2 Clinical Pharmacokinetics

In humans, the pharmacokinetics (PK) of cenobamate has been studied following single and multiple doses in healthy subjects. The PK of cenobamate in plasma appears to be non-linear after single oral doses ranging from 5 mg to 750 mg and multiple dosing ranging from 50 mg/day to 500 mg/day. Maximum plasma concentration of cenobamate was generally observed between 1 and 4 hours post-dosing and a longer terminal half-life was observed as the cenobamate dose increased (approximately 30 hours at 5-10 mg to approximately 76 hours at 750 mg). Steady state was generally achieved after 2 weeks of treatment with cenobamate and the accumulation of cenobamate in plasma over the 50 mg to 300 mg dose range was approximately 5-fold based on the total exposure (AUC).

Cenobamate is extensively metabolized in the liver and primarily eliminated in the urine (88% of a single oral radioactive dose). The absorption of cenobamate does not appear to be affected by food. A two-fold increase in cenobamate AUC and limited effect on C_{max} were noted after a single oral dose of 200 mg cenobamate in subjects with mild or moderate hepatic impairment, indicating that these subjects would likely require lower therapeutic doses of cenobamate compared to subjects with normal hepatic function.

Multiple drug-drug interaction (DDI) studies were performed in healthy subjects. The coadministration of carbamazepine and divalproex did not significantly modify the PK of cenobamate whereas the coadministration of phenobarbital and phenytoin significantly decreased cenobamate plasma exposure (AUC) by approximately 15% and 28%, respectively. The coadministration of cenobamate significantly decreased carbamazepine plasma exposure (AUC) by approximately 25 to35%, and increased phenobarbital and phenytoin plasma exposures (AUC) by approximately 37% and 84%, respectively.

After the administration of a CYP450 probe cocktail with cenobamate in healthy subjects, the results showed that a 200 mg daily dose of cenobamate weakly induced the activity of CYP2B6 and moderately inhibited the activity of CYP2C19. For CYP3A, cenobamate exhibited a weak induction at 100 mg/day whereas moderate induction was observed at 200 mg/day. No significant effect of cenobamate was observed on CYP2C9 activity at 200 mg/day.

The effect of renal impairment on the PK of cenobamate led to an increase in plasma exposure to cenobamate by 1.4-fold and 1.5-fold in mild and moderate renal impaired subjects, respectively. The effect of hepatic impairment on the PK of cenobamate led to an increase in plasma exposure to cenobamate by 1.9-fold and 2.3-fold in mild and moderate hepatic impaired subjects, respectively. No clinical meaningful effect of sex or age is expected on the PK of cenobamate.

1.2.3 Clinical Safety and Efficacy

To date, approximately 2500 subjects have been exposed to cenobamate in the clinical development program, which comprises twenty Phase 1 studies, three Phase 2 studies, and one Phase 3 clinical study. For further details about the completed and ongoing clinical studies, please refer to the most recent version of the IB.[18]

1.2.3.1 Clinical Efficacy

The efficacy of cenobamate was demonstrated in 2 adequate well-controlled studies. The daily oral doses of cenobamate 100 mg, 200 mg, and 400 mg were found to be effective for the treatment of POS.

1.2.3.2 Clinical Safety

The most common adverse events (AEs) reported with cenobamate were mild to moderate in severity. CNS-related AEs were dose dependent, with higher incidence reported at higher doses. Adverse reactions due to cenobamate may include somnolence, dizziness, fatigue, diplopia, nausea, nystagmus, balance disorder, and gait ataxia. These adverse reactions were mild to moderate in severity and resolved spontaneously upon discontinuation of treatment.

Overall, 724 serious adverse events (SAEs), including 23 deaths, have been reported during the cenobamate development program. Of these, 637 SAEs occurred in subjects who were randomized to receive cenobamate. The SAEs considered at least possibly related to cenobamate and reported in more than 1 subject included vertigo (4), vomiting (3), constipation (2), hyponatremia (4), ataxia (5), balance disorder (3), dizziness (11), dysarthria (2), nystagmus (2), somnolence (4), drug reaction with eosinophilia and systemic symptoms (3), and rash papular (2). A complete list of all SAEs during the cenobamate development program is available in the IB. The SAEs reported with cenobamate reflect an expected pattern with AED therapy.

1.2.4 Rash and Hypersensitivity Reactions and Drug Reaction with Eosinophilia and Systemic Symptoms

During the cenobamate development program, there have been reports of rash and hypersensitivity reactions, some resulting in hospitalization and/or treatment discontinuation. To date, 3 events of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome have been reported. These subjects began taking cenobamate at doses of 50 mg to 200 mg per day and titrated at 50 mg to 100 mg weekly increments. An aggregate analysis of the rate of Rash and Hypersensitivity Reactions and DRESS syndrome in subjects exposed to multiple doses of cenobamate was performed. The results of the aggregate analysis and careful review by the external subject matter experts suggest that lower cenobamate starting dose and slower titration rate are associated with a lower risk of Rash and Hypersensitivity Reactions and DRESS syndrome. Preliminary results of a large open-label safety study, with over 1400 subjects, using

12.5 mg per day as the initial dose and the same dose titration scheme used in this protocol, demonstrate that there were no cases of DRESS syndrome.

1.2.5 Potential Risk-Benefit Assessment

The potential risks related to cenobamate exposure include the following:

- Rash and hypersensitivity reactions
- DRESS syndrome
- Other cenobamate dose-related toxicities

The early signs and symptoms associated with hypersensitivity reaction that may progress to DRESS syndrome are easily identifiable by subjects and clinicians. When detected early and managed adequately, the progression to DRESS syndrome can be prevented or even reversed (see Section 7.3.3 for protocol-specified detection and management procedures for suspected DRESS syndrome). This study incorporates a Titration Phase to decrease the risk of rash and hypersensitivity reactions. Subjects will be counseled regarding hypersensitivity reactions, including DRESS syndrome, and any early signs or symptoms will be monitored closely.

Adverse events will be recorded at each visit. Additionally, the effects on liver will be closely monitored with testing of hepatic enzymes conducted at each visit. Isolated reports of suicidal thoughts and behavior have been reported in subjects who received cenobamate. Even though a relationship between suicide and cenobamate has not been established, the Columbia Suicide Severity Rating Scale (C-SSRS) will be completed at each visit.

The potential benefits of cenobamate have been identified in subjects with multidrug -resistant POS, who previously continued to suffer seizures despite a history of treatment with multiple AEDs. These benefits include significant reduction in the frequency of partial seizures and substantial seizure-free rates relative to placebo (in approximately 18% of subjects).

This study will be the first to investigate potential benefits of cenobamate in subjects with PGTC seizures. Uncontrolled generalized epilepsy is a life-threatening disease with significant morbidity and high mortality rates. The study design includes close monitoring of safety and efficacy, with the goal of minimizing risk while characterizing the efficacy profile of cenobamate as a potential AED for PGTC seizures.

1.2.6 Study Design Rationale

The study will be a randomized, double-blind, placebo-controlled, adjunctive therapy study, followed by an opportunity to enroll in an open-label extension (OLE) study.

- Subjects will be randomized using appropriate statistical methods to either cenobamate or placebo treatment groups, in order to decrease bias in treatment assignment, to

increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

- The double-blind nature of the study will reduce potential bias during data collection.
- Addition of the placebo arm will allow for assessment of the added benefit of adjunctive therapy with cenobamate to be distinguished from the effect of the subject's baseline AED regimen.
- This is the first clinical study of cenobamate in subjects with PGTC seizures. Seizures are potentially life-threatening, and the use of placebo alone as a control treatment is not justified. This study follows the generally acceptable initial approach of investigating AED effects as adjunctive therapy.

  The study incorporates study design and efficacy endpoints utilized for the studies of previously approved AEDs in PGTC seizures (levetiracetam, lamotrigine, topiramate, and perampanel) according to applicable regulatory guidance documents. [11, 12, 13, 14, 15, 16, 19, 20]

The initial inclusion criteria indicated that subjects were to have 3 PGTC seizures in 12 weeks prior to randomization. This would be an average of 1 seizure per 28 days. Previous studies of new AEDs for PGTC have used 1.5 seizures per 28 days as the inclusion criteria. Analysis of the first 22 subjects randomized indicated that the median 28-day baseline PGTC frequency was 2.0. This is lower than all previous placebo-controlled studies of AEDs for PGTC seizures. [11, 12, 13, 14, 15, 16, 19, 20] In order to ensure the best possible interpretation of the results of this study, the baseline PGTC seizure requirement will be increased to 5 in 12 weeks or an average of 1.67 per 28 days.

1.2.7 Dosing Regimen

The Double-blind Treatment Period comprises 2 phases: the Titration Phase and the Maintenance Phase.

Dose titration is a well-known and well-established strategy for mitigating risk with the use of AEDs. Lower initial dose and slow titration rate are known to reduce various AEs, including events reported in nervous and gastrointestinal systems. Additionally, a low starting dose and slow titration rate have been reported to mitigate the occurrence of rash and possibly progression to more serious and potentially life-threatening adverse cutaneous reactions.[20] As reported in Section 1.2.4, lower incidences of rash, hypersensitivity reactions, and DRESS syndrome were reported with the use of lower doses and slower dose titration in a large safety study in which over 1300 subjects received cenobamate.

The titration regimen to be used in the present study is the same as that used in the large safety studies conducted in adults. The initial dose is 12.5 mg cenobamate increased to 150 mg over a 10-week period.

During the 12-week Maintenance Phase, the target dose of 200 mg per day is planned based on the efficacy, safety, and tolerability of cenobamate in recently completed and ongoing clinical studies. The 200 mg daily dose, when administered over 12 weeks, has been demonstrated to be safe and efficacious in subjects with POS. Though the 400 mg dose demonstrated efficacy in subjects with POS, data from the completed study showed that lower doses of AEDs were efficacious in generalized tonic-clonic seizures. In addition, there was little additional effect of 400 mg over 200 mg in the response of secondarily generalized tonic-clonic seizures in a prior efficacy study of cenobamate (Study YKP3089C017). Since the primary objective of this study is to demonstrate efficacy, dose reduction below 150 mg will not be permitted during the Maintenance Phase.

However, in a pediatric pharmacokinetic study, YKP3089C039, it was determined that the appropriate dose regimen for cenobamate in adolescent subjects (12 to <18 years of age) is based on weight. The dosing regimen for titration and maintenance in adult and adolescent subjects is as follows:

Study Phase	**Dispense Visit**	**Double-blind Treatment**	
		Adult Tablets – Total Daily Dose	**Adolescents** Oral Suspension – Total Daily Dose
Titration	4	12.5 mg cenobamate tablet, or matching placebo	Volume to deliver 0.2 mg/kg, or matching placebo not to exceed 12.5 mg
	5	25 mg cenobamate tablet, or matching placebo	Volume to deliver 0.4 mg/kg, or matching placebo not to exceed 25 mg
	6	50 mg cenobamate, or matching placebo	Volume to deliver 0.8 mg/kg, or matching placebo not to exceed 50 mg
	7	100 mg cenobamate tablet, or matching placebo	Volume to deliver 1.5 mg/kg, or matching placebo not to exceed 100 mg
	8	150 mg (100 mg + 50 mg) cenobamate tablet, or matching placebo	Volume to deliver 2.0 mg/kg, or matching placebo not to exceed 150 mg
Maintenance	9, 10, 11, 12, 13, 14/ET [a]	200 mg (100 mg + 100 mg) cenobamate tablet, or matching placebo	Volume to deliver 3.0 mg/kg, or matching placebo not to exceed 200 mg
Follow-up (Optional down-titration)	15[a] (Non-OLE) Or ET visit	100 mg cenobamate tablet, or matching placebo	Volume to deliver 1.5 mg/kg, or matching placebo not to exceed 100 mg

Abbreviation: ET= early termination, OLE=open-label extension

a. For subjects not enrolling into the OLE, or prematurely discontinuing the study during the Maintenance Phase. Down titration after premature discontinuation is at the discretion of the Investigator depending on reason for discontinuation (e.g., rash).

2 STUDY OBJECTIVES

2.1 Primary

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

2.2 Secondary

- 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 PK of cenobamate in subjects with PGTC seizures

3 STUDY ENDPOINTS

3.1 Primary Efficacy Endpoints

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.

3.2 Secondary Endpoints

3.2.1 Efficacy

The secondary efficacy endpoints which will be adjusted for multiplicity using hierarchical method are listed below:

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

3.2.2 Safety

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.

3.2.3 Pharmacokinetic

The secondary pharmacokinetic endpoints will include:

- Summary of individual patients' plasma concentrations of cenobamate at their respective doses and visits.
- 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.

4 STUDY PLAN

4.1 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled-, parallel-group, adjunctive therapy study in subjects with PGTC seizures. The study schematic is provided in Figure 4-1. 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 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.

4.1.1 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 this 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 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.

Soon after Visit 1, the Principal Investigator or the designee will complete and submit the Diagnostic Review Form to the independent consulting physician group (e.g., Epilepsy Study Consortium). See Section 7.1.1 for details on the Diagnostic Review Form.

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

4.1.2 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).

4.1.2.1 Titration Phase (Visit 5 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 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 an 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 as shown in Table 8–1 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 dose, in adolescents as an oral suspension equivalent based on weight or matching placebo volume 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 (Section 8.6.2).

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

4.1.2.2 Maintenance Phase (Visit 9 to Visit 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 of study drug may be decreased in adults to 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 the 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 (Section 8.6.2).

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

4.1.3 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 in the OLE study. For eligible 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 the 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 in Table 4-1.

4.1.4 Early Termination 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 (Table 4-1) 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.

4.1.4.1 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 should 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.

4.1.4.2 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 should 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 3 weeks after the ET visit.

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

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Randomization Procedure

At Visit 4, eligible subjects will be randomly assigned in a 1:1 ratio to cenobamate 12.5 mg tablet, in adolescents as an 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.

4.2.2 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.

4.3 Study Schematic

Figure 4-1: 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

4.4 Schedule of Assessments

Table 4–1: Schedule of Assessments

Assessments	Pre-Randomization Period (12 weeks)			Double-blind Treatment Period (22 weeks)											Follow-up Period [d] (3 weeks)
	Screening/ Baseline[a]	Baseline [b]		Titration Phase (10 weeks)					Maintenance Phase (12 weeks)						
Visit	**1**	**2**	**3**	**Randomization 4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 /ET [c]**	**15/FUP**
Day	**-84**	**-56 ±2**	**-28 ±2**	**-1**	**14 ±2**	**28 ±2**	**42 ±2**	**56 ±2**	**70 ±2**	**84 ±2**	**98 ±2**	**112 ±2**	**126 ±2**	**154 ±2**	**175 ±2**
Informed consent	X														
Inclusion/exclusion criteria	X	X	X	X											
Demographics	X														
Medical history including seizure history	X	X	X	X											
Documented history of MRI or CT, and EEG	X														
MRI, CT, or EEG[e]	X														
Diagnostic review form	X														
Retrospective Diary Review form[m]	X[m]														
Pre-randomization Diary information form[n]				X[n]											
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X														
Weight[l]	X			X		X			X					X	X
Full physical examination[g]	X			X										X	X
Symptom-directed physical examination[g]					X	X	X	X	X	X	X	X	X		
Full neurologic examination	X													X	
Brief neurologic examination				X	X	X	X	X	X	X	X	X	X		X
C-SSRS[h]	X			X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X			X										X	
Clinical laboratory tests[i]	X			X	X	X	X	X	X	X	X	X	X	X	X

Assessments	Pre-Randomization Period (12 weeks)			Double-blind Treatment Period (22 weeks)											Follow-up Period [d] (3 weeks)
	Screening/ Baseline[a]	Baseline [b]		Titration Phase (10 weeks)					Maintenance Phase (12 weeks)						
Visit	**1**	**2**	**3**	**Randomization 4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 /ET [c]**	**15/FUP**
Day	**-84**	**-56 ±2**	**-28 ±2**	**-1**	**14 ±2**	**28 ±2**	**42 ±2**	**56 ±2**	**70 ±2**	**84 ±2**	**98 ±2**	**112 ±2**	**126 ±2**	**154 ±2**	**175 ±2**
Urinalysis	X			X										X	X
Urine drug screen[l]	X														
Onsite urine drug screen[l]				X										X	
Urine pregnancy test in FOCBP				X		X		X		X		X			X
Serum pregnancy test in FOCBP	X													X	
Prior and concomitant medications including AEDs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization				X											
Dispense/review/collect seizure diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug				X	X	X	X	X	X	X	X	X	X	X[j]	
Study drug accountability					X	X	X	X	X	X	X	X	X	X	X
Dispense safety card				X											
Blood sample for pharmacokinetics											X[k]		X[k]		

Abbreviations: AED = antiepileptic drug, C-SSRS = Columbia Suicide Severity Rating Scale, CT = computed tomography, EC = Epilepsy consortium, ECG = electrocardiogram, EEG = electroencephalogram, ET = early termination, FOCBP = females of childbearing potential, FUP = follow-up, MRI = magnetic resonance imaging, OLE = open-label extension, UDS = urine drug screen.

a. If a subject meets Exclusion Criterion No. 17, at screening, then unscheduled clinical laboratory, ECG, or vital sign assessment(s) may be repeated for confirmation.
b. Visit 3 is omitted for subjects who have Medical Monitor approved retrospective diary data for 4 weeks prior to Visit 1. Visits 2 and 3 are omitted for subjects who have Medical Monitor approved retrospective diary data for 8 weeks prior to Visit 1
c. For subjects who have an ET visit, all Visit 14 procedures will be performed for ET procedures. See Section 4.1.4 for further details.
d. The Follow-up visit is for those subjects who do not participate in the OLE study or prematurely discontinue from the study.
e. Subject may undergo an EEG (per Inclusion Criterion No. 6), MRI or CT scan (per Inclusion Criterion No.7) during the Pre-Randomization Period if the subject does not have a documented history within the required time frame at Visit 1.
f. Vital signs include orthostatic blood pressure and pulse rate, respiratory rate, and oral body temperature.

g. A symptom-directed physical examination for hypersensitivity may be performed, if necessary, at Visits 5 through 13. See section 7.3.3 for further details. A full physical examination will be performed at Visit 1, Visit 4, Visit 14, ET visit (if applicable), and at Follow-up visit. See section 7.3.7 for further details.
h. Administer the 'Baseline/Screening' version of the C-SSRS at Visit 1. Administer the 'Since Last Visit' version of the C-SSRS at Visits 5 through 14 and during follow-up, if applicable.
i. Blood samples will be collected for serum chemistry and hematology laboratory parameter testing. See Section 7.3.4 for further details.
j. Study drug will be dispensed for this study only if subject will receive down-titrated dose of cenobamate 100 mg tablet, in adolescents as an oral suspension equivalent based on weight or matching placebo volume. The subjects enrolled in the OLE will receive study drug for that study.
k. The site personnel should call all subjects 1 day before the scheduled Visits 11 and 13 to remind them of the applicable instructions for these visits, including recording of exact timing of the dosing on the day prior to the scheduled visit. See Section 7.4 for further details.
l. The urine drug screen will be performed via the central lab at Visit 1. The urine drug screen will be performed at the site at Visit 4, Visit 14, and ET Visit (if applicable).
m. The retrospective diary review form is only required to be submitted when a subject maintains a personal seizure diary and a reduced prospective pre-randomization period is being requested.
n. The Review of Pre-randomization Diary Information form must be submitted and medical monitor approval received, prior to randomizing the subject.

5 POPULATION

5.1 Number of Subjects

Approximately 170 subjects will be enrolled at approximately 100 study sites in multiple countries. Subjects will be randomized to study drug only if they meet all the inclusion criteria and none of the exclusion criteria.

5.2 Inclusion Criteria

Each subject must meet the following inclusion criteria to be enrolled in the study:

1. Subject is male or female and aged ≥12 years.
2. Written informed consent signed by the subject, legal guardian or legally authorized representative (LAR) prior to entering the study, in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Age-appropriate assent will be obtained for adolescents. If the written informed consent is provided by the legal guardian because the subject is unable to do so, a written or verbal assent from the subject must also be obtained. As required by country-specific regulations, only the subject may sign the ICF in accordance with ICH guidelines.
3. Female subjects of childbearing potential are willing to use an acceptable form of birth control, as outlined in Section 8.10.
4. Subject has a clinical diagnosis of PGTC seizures (with or without other subtypes of generalized seizures) in the setting of idiopathic generalized epilepsy. Refer to Section 7.1.1 for information regarding confirmation of PGTC seizure diagnosis.
5. Subject experiences at least 5 PGTC seizures in 12 weeks during the Pre--Randomization Period. Refer to Section 7.1.2 for information regarding confirmation of PGTC seizure frequency.
6. Subject has had a routine electroencephalogram (EEG) within 5 years prior to Visit 1 (Screening/Baseline) or during the Pre-Randomization Period with electroencephalographic features consistent with idiopathic generalized epilepsy; other concomitant anomalies must be explained by adequate past medical history.
7. Subject has undergone computed tomography (CT) or magnetic resonance imaging (MRI) within 10 years prior to Visit 1 (Screening/Baseline) or during the Pre--Randomization Period that ruled out a progressive cause of epilepsy.
8. Subject is currently receiving 1 to a maximum of 3 concomitant AEDs with fixed dosing regimens for a minimum of 30 days prior to Visit 1 (Screening/Baseline).
    a) Benzodiazepines (except diazepam, see Exclusion Criterion No. 7) taken at least once per week during the 30 days prior to Visit 1 (Screening/Baseline) for epilepsy, anxiety, or sleep disorder will be counted as 1 AED and the dosage must be continued unchanged throughout the study. Therefore, only a maximum

of 2 additional approved AEDs will be allowed. (See Exclusion Criterion No. 10 for intermittent benzodiazepine rescue parameters.)

b) Subjects receiving felbamate as a concomitant AED must meet the following criteria:

ii. Have a 2 year history of felbamate use and a history of a fixed dosing regimen for a minimum of 60 days prior to Visit 1 (Screening/Baseline).

iii. No prior or known history of hepatotoxicity or hematologic disorder due to felbamate.

9. Subject with an implanted vagal nerve or deep brain stimulator will be allowed if the stimulator was implanted at least 5 months prior to Visit 1 (Screening/Baseline) and the stimulator parameters are not changed for 30 days prior to Visit 1 and for the duration of the study.

10. Subject taking a ketogenic diet will be allowed as long as the diet has been stable for at least 3 months prior to Visit 1 (Screening/Baseline) and will remain stable for the duration of the study.

5.3 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Female subjects who are pregnant (or planning to become pregnant during the study), lactating, or breast-feeding.

2. Subject has a history of status epilepticus that required hospitalization within 12 months prior to Visit 1 (Screening/Baseline).

3. Subject has PGTC seizure clusters where individual seizures cannot be counted or classified.

4. Subject has a history of non-epileptic psychogenic seizures.

5. Subject has a concomitant diagnosis of POS.

6. Subject has a clinical diagnosis of Lennox-Gastaut syndrome.

7. Subject is currently taking (within the 30 days prior to Visit 1 [Screening/Baseline]) any of the following medications: diazepam (for any reason other than as intermittent benzodiazepine rescue medication), phenytoin, mephenytoin, fosphenytoin, phenobarbital, primidone, ethotoin, clopidogrel, fluvoxamine, amitriptyline, clomipramine, bupropion, methadone, ifosfamide, cyclophosphamide, or efavirenz.

8. Subject has participated in previous cenobamate clinical studies.

9. Subject has a history of vigabatrin use within 5 months prior to Visit 1 (Screening/Baseline), or the subject plans to begin treatment with vigabatrin during the study.

    a) A subject with a history of vigabatrin use that ended more than 5 months prior to Visit 1 may be enrolled after documented evidence of no vigabatrin associated clinically significant abnormality in an automated visual perimetry test.

10. Subject has a history of intermittent use of rescue benzodiazepines (i.e., 1 to 2 doses over a 24-hour period is considered a 1-time rescue) 4 or more times within the 30 days prior to Visit 1 (Screening/Baseline).

11. Subject has received an investigational drug or device within 30 days prior to Visit 1 (Screening/Baseline).

12. Subject has a history of drug or alcohol dependency or abuse within 2 years prior to Visit 1 (Screening/Baseline).

13. Subject tests positive, via urine drug screen at Visit 1 (Screening/Baseline), for illicit drugs not legalized in your state, or for a drug that has not been prescribed (e.g., certain opiates).

14. Subject has a history of any serious drug-induced hypersensitivity reaction (including, but not limited to, Stevens Johnson syndrome, toxic epidermal necrolysis, or DRESS syndrome) or any drug-related rash requiring hospitalization.

15. History of AED-associated rash that involved conjunctiva or mucosae.

16. History of more than one non-serious drug-related hypersensitivity reaction that required discontinuation of the medication.

17. Subject has evidence of clinically significant abnormalities or disease (e.g., psychiatric, cardiac, respiratory, gastrointestinal, hepatic [AST or ALT more than 2 times the upper limit of normal (ULN), or total or direct bilirubin more than ULN], or renal disease) that, in the opinion of the Principal Investigator, could affect the subject's safety or conduct of the study.

18. Presence of congenital short QT syndrome or relevant replicated change in QT/QTc interval less than 340 msec on ECG.

19. Subject has any significant active CNS infection, demyelinating disease, degenerative neurologic disease or any CNS disease deemed to be progressive during the course of the study that may confound the interpretation of the study results.

20. Subject has a creatinine clearance less than 50 mL/min, as calculated by Cockcroft--Gault equation.

21. Subject has an absolute neutrophil count less than 1500/µL.

22. Subject has platelet count lower than 80,000/µL in subjects treated with valproate.

23. Subject has a history of positive antibody/antigen test for hepatitis A, hepatitis B, hepatitis C, or HIV.

24. Subject has any suicidal ideation (with intent with or without a plan) at Visit 1 (Screening/Baseline) or Visit 4 (Randomization) (i.e., answering YES to Question 4 and/or Question 5 on the Suicidal Ideation section of the C-SSRS).

25. Subject has more than 1 lifetime suicide attempt.

26. Subject is a staff member or immediate family member of study staff.

27. Previous exposure to cenobamate or sensitivity/allergy to components of theoral suspension.

Any potential exception to the inclusion as well as exclusion criteria allowing *de minimis* (clinically trivial and meaningless) variations must be approved by the Medical Monitor.

5.4 Subject Screening

Before undergoing any study procedures, all potential subjects or their legal guardians (if subject is unable to sign) will sign an ICF. An age-appropriate assent will be obtained for adolescents. Subjects will have the opportunity to have any questions answered before signing, and the Principal Investigator or designee must address all questions raised by the subject or their legal guardians (if subject is unable to sign). If the written informed consent is provided by the legal guardian because the subject is unable to do so, a written or verbal assent from the subject must also be obtained.

The Principal Investigator or designee will also sign the ICF, and a copy of the signed document will be provided to the subject or their legal guardian.

5.5 Deviation from Inclusion/Exclusion Criteria

Deviations from the inclusion and exclusion criteria are not allowed, except for the potential exception to the inclusion as well as exclusion criteria allowing *de minimis* (clinically trivial and meaningless) variations, when approved by the Medical Monitor. Adherence to the criteria, as specified in the protocol, is essential.

6 STUDY CONDUCT

6.1 General Information

All subjects must sign the ICF at the Screening visit, prior to conduct of any study-related procedures. Only the institutional review board/independent ethics committee (IRB/IEC) approved ICF can be used. An age-appropriate assent will be obtained for adolescents.

If the written informed consent is provided by the legal guardian because the subject is unable to do so, a written or verbal assent from the subject must also be obtained. As required by country-specific regulations, only the subject may sign the ICF in accordance with ICH guidelines.

Subjects are allowed to receive routinely used concomitant medications or treatments for non-excluded indications that are judged by the Principal Investigator or designee as not affecting the efficacy or safety assessments of the study, provided the medications do not fall under the list of prohibited concomitant medications provided in Section 8.9.3.

Study procedures are presented by visit in the Schedule of Assessments in Section 4.4.

6.2 Study Procedures by Time Point

The Schedule of Assessments is provided in Section 4.4. The detailed description of study procedures is provided in Section 7.

6.3 Withdrawal and Premature Discontinuation

Subjects may withdraw or be discontinued from the study at any time and for any reason without prejudice to their future medical care.

The reasons for subjects not completing the study will be recorded as follows:

- Subject withdraws consent.
- Subject fails to adhere to the protocol requirements (noncompliance).
- Subject experiences an intolerable AE.
- Subject is lost to follow-up.
- Subject becomes pregnant and it is decided to discontinue the study drug. See Section 7.3.2 for additional details.
- Study is terminated by the Sponsor.
- Principal Investigator decision.
- Other reason (e.g., subject develops contraindications for use of study drug or subject requires changes to existing AED therapy).

Whenever possible, a subject who discontinues from the study prematurely will undergo the ET procedures as described in Section 4.1.4. Subjects who discontinue during the Maintenance Phase may receive study drug (cenobamate 100 mg tablet, in adolescents as an oral suspension equivalent based on weight or matching placebo volume daily) for 1 week prior to study drug discontinuation at the discretion of the Principal Investigator or designee. Subjects who discontinue during the Titration Phase and are receiving study drug at doses equal to or less than cenobamate 100 mg tablet, in adolescents as an oral suspension equivalent based on weight or matching placebo volume will not be required to

receive down-titrated study drug. On the other hand, subjects receiving cenobamate 150 mg tablet, in adolescents as an oral suspension equivalent based on weight or matching placebo volume may receive study medication (cenobamate 100 mg tablet, in adolescents as an oral suspension equivalent based on weight or matching placebo volume daily) for 1 week prior to study drug discontinuation at the discretion of the Principal Investigator or designee. All subjects will have their last study visit (Follow-up visit) 3 weeks after the ET visit.

At the ET and Follow-up visits, subjects will undergo study procedures as outlined in the Schedule of Assessments in Section 4.4.

- Additional follow-up may be required for subjects with ongoing AEs at the discretion of the Principal Investigator or designee. See Section 9.5 for details.
- Additional follow-up is required for subjects who withdraw due to pregnancy. See Section 7.3.2 for details.

For a subject who fails to attend the study site for a required study visit, the following actions must be taken before considering the subject as lost to follow-up.

- The study site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The study site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed lost to follow-up, the Principal Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter, or equivalent process, to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical records/study files.

Should the subject continue to be unreachable, only then will he/she be considered as lost to follow-up.

Subjects who withdraw from the study will not be replaced.

Any subject may be withdrawn from the study at the discretion of the Investigator. The subject is also free to terminate his/her participation at any time. However, if the subject has been dosed with study medication, it is recommended to ask the subject to remain in contact with the center, and the investigational site should make every effort to convince the subject to return for a safety follow-up visit. The Investigator will also undertake to obtain more detailed information about any subject lost to follow-up. Subjects withdrawn from the study must not be re-included.

6.4 End of Study

End of the study is defined as the last patient last visit.

7 DESCRIPTION OF STUDY PROCEDURES

7.1 Screening and Critical Baseline Assessments

7.1.1 Diagnostic Review Form

The Diagnostic Review Form will be used to document and confirm the diagnosis of the seizure type and the agreement between the independent consulting physician group (e.g., Epilepsy Study Consortium) and the Principal Investigator regarding seizure type and subject diagnosis. Soon after Visit 1 (Screening/Baseline), the Principal Investigator or designee will submit the completed Diagnostic Review Form and supporting documentation to an independent consulting physician group (e.g., Epilepsy Study Consortium). An agreement regarding diagnosis must be reached between the Principal Investigator and the independent consulting physician group prior to randomization (i.e., prior to Visit 4). If an agreement is not reached, the subject will be screen-failed.

The completed and approved Diagnostic Review Form will be stored in the subject's source documents.

7.1.2 Seizure Diary

Details of the seizure diary are provided in Section 7.2. Screened subjects will be assessed for seizure frequency during the 12-week Pre-Randomization Period. The seizure information for the first 4 weeks or 8 weeks can be obtained from the subject's personal seizure diary, if available and acceptable. Either 4 weeks or 8 weeks of retrospective seizure diary data is allowed if, after review by the Medical Monitor, it meets criteria for PGTC seizures. See Section 4.1.1.

The Principal Investigator and Medical Monitor will review the seizure diaries to review seizure type and ensure that the seizure frequency eligibility criterion is met (Section 5.2, Inclusion Criterion No. 5).

7.1.3 Demographics

During Visit 1 (Screening/Baseline), demographic parameters (date of birth, sex, race, and ethnicity) will be recorded. The applicable demographic parameters will not be collected if prohibited by the country-specific regulations.

7.1.4 Medical History

The medical history, including seizure history, will be reviewed at Visits 1, 2 (if applicable), 3 (if applicable), and 4. After Visit 4, any change in subject's pre-existing condition may be recorded as an AE, as outlined in Section 9.1.3.

7.1.5 Baseline Imaging

The imaging procedures (EEG, MRI, or CT), conducted as part of the subject's routine clinical management and obtained prior to signing the ICF, may be utilized for screening purposes provided the procedure meets the protocol-defined criteria and has been performed within the time frame defined in Section 5.2 (Inclusion Criteria Nos. 6 and 7). An EEG, MRI, or CT scan may be performed during the Pre-Randomization Period for subjects who have not undergone the imaging procedure within the defined time frame, as specified in the inclusion criteria, or need to have the procedure repeated based on the judgment of the Principal Investigator or designee.

7.1.6 Additional Screening Assessments

As displayed in the Schedule of Assessments (Section 4.4), the following procedures will also be performed during Visit 1 (Screening/Baseline): clinical laboratory evaluations (including urinalysis, urine drug screen, and serum pregnancy test), vital sign measurements (including height and weight), 12-lead electrocardiograms (ECGs), full physical and neurologic examinations, and C-SSRS. Additionally, prior and concomitant medications (taken after randomization) will be assessed and recorded.

If a subject meets Exclusion Criterion No.17, then unscheduled clinical laboratory, ECG, or vital sign assessment(s) may be repeated for confirmation.

7.2 Efficacy Assessment

The efficacy assessment entails the recording of seizures (seizure type and frequency) in the subject's seizure diary. The seizure diary will be dispensed/collected at all visits. For subjects who do not enter the OLE, their last seizure diary for this study will be collected at Visit 14.

The seizure diary, completed daily either by the subject or their caregiver, will contain the requested information for all seizures. Twelve weeks of consecutive seizure diary data collected during the Pre-Randomization Period are required for evaluating subject eligibility prior to randomization. Either 4 or 8 of these 12 weeks of data can be obtained from the subject's personal retrospective seizure diary if collected within the 4 weeks or 8 weeks, respectively, prior to Visit 1. These seizure diaries will be reviewed by Medical Monitor for acceptability if they contain all the information, as required in the study seizure diary. The Medical Monitor will also review subject seizure diaries for the Pre--Randomization Period and must approve each subject for randomization.

Seizure diary completion compliance will be enforced as follows:

- At each visit, study site personnel will instruct the subject about diary completion and remind each subject to return the diary at their next scheduled clinic visit or at the ET visit (if applicable).

- To ensure correct seizure classification/frequency prior to randomization, the Principal Investigator or designee will review the seizure diary with the subject and Medical Monitor at Visits 1, 2 (if applicable), 3 (if applicable), and Visit 4.
- Study site personnel must counsel subjects whose diary compliance is not satisfactory (i.e., missed 3 or more consecutive daily diary entries). If a subject remains non-compliant with dairy entries, the Principal Investigator or designee must discuss with the Medical Monitor/Sponsor whether the subject should continue in the study.

7.3 Safety Assessments

Safety will be assessed by AE assessments, hypersensitivity assessments, concomitant medication reporting, clinical laboratory evaluations, vital sign measurements, 12-lead ECGs, physical and neurologic examinations, and the C-SSRS. The safety assessments do not need to be performed in any specific order.

7.3.1 Adverse Events

The definitions of an AE or SAE can be found in Sections 9.1and 10.1, respectively.

Adverse events will be elicited beginning at Screening (date of signed informed consent) and up to 14 days after the last dose of study drug. Serious AEs will be elicited beginning at Screening (date of signed informed consent) until the end of the subject's participation in the study. SAEs should be monitored until resolution or for 30 days after the end of the subject's participation in the study.

At each study visit, subjects will be asked a standard non-leading question to elicit any changes in their health. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to subject observations, AEs identified from any study data (e.g., laboratory values, physical examination findings, ECG findings, or vital sign findings) or identified from the review of other documents (e.g., subject diaries) that are relevant to subject safety will be documented on the AE page in the electronic case report form (eCRF).

7.3.2 Pregnancy

Pregnancy is not considered an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during the screening period will result in the subject being screen-failed. Any pregnancy that occurs after the subject is randomized must be reported using a pregnancy reporting form. To ensure subject safety, each pregnancy in randomized subjects must be reported to SK Life Science, Inc. (SKLSI) within 24 hours of learning of its occurrence, and to the IRB/IEC within the time period as per their reporting requirements. The Principal

Investigator or designee must discuss with the Medical Monitor/Sponsor, in conjunction with the IRB/IEC, whether it would be appropriate for the subject to continue in the study. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and the status of mother and child, even if the subject was discontinued from the study. The mother and child should be monitored until the child reaches at least the age of 1 month. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the Principal Investigator's or study site personnel's attention after the subject has completed the study and considered by the Principal Investigator or designee as at least possibly related to the study drug must be promptly reported to SKLSI.

7.3.3 Hypersensitivity Assessments

During Visit 4 (Randomization), subjects will be provided a card with the following hypersensitivity information and will be instructed to carry with them at all times:

- Rash may occur and may progress to DRESS syndrome.
- Rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy, and swelling) may herald a serious medical event, and the subject should report occurrence of such signs or symptoms to the study site immediately.
- Instructions on whom and where to call in case a symptom arises (in the event that the subject is unable to reach the study site), so that the information that can be provided to an emergency room.

If a subject reports rash by telephone, an unscheduled visit should be performed promptly. Any subject with a rash or manifestation of a hypersensitivity reaction (lymphadenopathy, fever, or facial swelling) will be instructed to seek immediate medical attention. If it is definitely determined that the rash or other symptoms are unrelated to study drug, then the subject can continue the study drug administration. If the cause of the rash or other symptoms cannot be determined immediately, then study drug administration must be discontinued immediately.

The initial physical/rash assessment for a hypersensitivity reaction at the study site will include the following:

- Measure body temperature
- Characterize lymphadenopathy, if present
- Perform hematology with manual differential and chemistry tests, including amylase, lipase, and creatine phosphokinase

- Measure and describe the extent and area of the rash

Evaluate for other causes of multi-organ dysfunction, including anti-nuclear antibody, blood culture, and serology for human immunodeficiency virus, human papilloma virus, chlamydia and mycoplasma, Epstein Barr virus, human herpesvirus 6, or cytomegalovirus, if indicated.

If the skin and physical/rash assessment results indicate a rash with involvement of one other organ system or a suspected case of DRESS syndrome, the subject will be referred immediately to a pre-identified local expert and the Principal Investigator or designee will send notifications immediately, as provided in Table 10–1.

Prior to screening subjects for this study, as a part of site-qualification, the Principal Investigator or designee must identify local medical specialists or practicing physicians, who will be able to diagnose and treat subjects with suspected DRESS syndrome. The locally identified specialists will be informed by the Principal Investigator or designee that their services may be needed during the course of the study. Specialists could include, but are not limited to: dermatologists, hepatologists, and/or cardiologists.

7.3.4 Clinical Laboratory Analyses

Blood samples for hematology and serum chemistry testing will be collected during Visit 1 (Screening/Baseline), Visit 4 (Randomization), during the Double-blind Treatment Period, Visit 15 (Follow-up), and the ET and ET Follow-up visits, if applicable.

- Hematology: hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, platelet count, and calculated indices.
- Serum chemistry: blood urea nitrogen, calcium, chloride, creatinine, glucose, total bilirubin, direct bilirubin, alkaline phosphatase, aspartate transaminase, alanine aminotransferase, total protein, albumin, globulin, sodium, potassium, phosphorus, and glucose.
- 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: [(140-age in years) × (weight in kg) / (72 × serum creatinine in mg/dL)] × 0.85 (if female). [22]

A urine sample for urine drug screen and urinalysis testing will be collected during Visit 1 (Screening/Baseline), Visit 4 (Randomization), Visit 14 (Maintenance Phase), and during the ET visit, if applicable. At the Follow-up visit, Visit 15, only urinalysis will be conducted for urine specimen.

- Urinalysis: pH, specific gravity, protein, glucose, ketone, bilirubin, blood, nitrite, urobilinogen, and microscopic examination

An abnormal laboratory finding may be recorded as an AE as described in Section 9.1.1.

Additional laboratory tests conducted during the study include:

- Pregnancy testing: During Visit 1 (Screening/Baseline) and Visit 14 (Maintenance Phase), all female subjects of childbearing potential will undergo a serum pregnancy test, for beta-human chorionic gonadotropin. Female subjects of childbearing potential will undergo a urine pregnancy test during Visit 4 (Randomization), the Double-blind Treatment Period (Visits 6 and 8 [Titration Phase] and Visits 10 and 12 [Maintenance Phase]), Visit 15 (Follow-up visit), and ET and ET Follow-up visits, if applicable.

7.3.5 Vital Signs

Vital signs (orthostatic blood pressure and pulse rate, respiratory rate, and body temperature) will be collected at all study visits, and at ET and ET Follow-up visits, if applicable.

- Orthostatic measurements: blood pressure and pulse rate will be measured after the subject has rested supine for a minimum of 5 minutes. After completion of supine measurements, blood pressure and pulse rate will be measured twice after the subject has been standing for approximately 1 and 3 minutes.

Weight will be recorded at Visit 1 (Screening/Baseline), Visit 4 (Randomization), during the Titration Phase (Visits 6 and 9), during the Maintenance Phase (Visit 14), Follow-up visit (Visit 15), and at the ET and ET Follow-up visits, if applicable.

Height will be recorded only once at Visit 1 (Screening/Baseline).

7.3.6 Twelve-lead Electrocardiogram

Routine 12-lead ECGs (after the subject has rested supine for a minimum of 5 minutes) will be performed during Visit 1 (Screening/Baseline), Visit 4 (Randomization), Visit 14 (Maintenance Phase), and during the ET visit, if applicable. Parameters including heart rate, PR interval, QRS interval, RR interval, QT interval, and QTc will be recorded. All ECGs will be read at the clinical site.

7.3.7 Physical and Neurologic Examinations

A full physical examination will be conducted at Visit 1 (Screening/Baseline), Visit 4 (Randomization), Visit 14 (Maintenance Phase), Visit 15 (Follow-up visit) and the ET and ET Follow-up visits, if applicable. The required assessments of the full physical examination are listed in Section 19.4, Appendix IV.

As described in Section 7.3.3, a symptom-directed physical examination for hypersensitivity will be performed, as necessary, during the Double-blind Treatment Period.

A full neurologic examination will be conducted at Visit 1 (Screening/Baseline), Visit 14 (Maintenance Phase), and at the ET visit, if applicable. The required assessments of the full neurological examination are listed in Section 19.5, Appendix V.

A brief neurologic examination will be conducted at Visit 4 (Randomization), during the Double-blind Treatment Period, Visit 15 (Follow-up visit), and ET Follow-up visit, if applicable. The required assessments of the brief neurologic examination are listed in Section 19.6, Appendix VI.

7.3.8 Columbia Suicide Severity Rating Scale

The C-SSRS (Baseline/Screening version [Section 19.2, Appendix II]) will be completed at Visit 1 (Screening/Baseline).

The C-SSRS (Since Last Visit version [Section 19.3, Appendix III]) will be completed at Visit 4 (Randomization), during the Double-blind Treatment Period, at Visit 15 (Follow-up visit), and during the ET and ET Follow-up visits (if applicable).

At each site, personnel will be trained and certified before administering the C-SSRS.

Each site should have as part of the study file, an escalation and care management plan, including contact information, in the event subjects respond YES to Question 4 and/or Question 5.

7.4 Pharmacokinetics

Detailed procedures for the bioanalytical sample collection, processing and shipping to the central lab; the bioanalytical lab shipment address and assay lab contact information is also provided in the Medpace Laboratory Manual.

A PK assessment of cenobamate will be conducted using the sparse sampling approach. Blood samples will be collected during Visits 11 and 13 of the Maintenance Phase. The site personnel should call all subjects 1 day before their scheduled Visits 11 and 13 to remind them of the applicable instructions for these visits, including recording of the exact timing of the dosing.

- Subjects who take their daily dose of study drug in the morning and who have their visit scheduled in the morning will be instructed at Visit 10 or Visit 12 and at the telephone reminder to not take the morning dose on the day of the next visit (Visit 11 or Visit 13) until the predose PK sample is collected at the study site. The study drug will be administered at the study site and a second PK sample will be collected any time before the end of the visit, but not earlier than 15 minutes post dose. The date/time of dose administration for the day before the visit and during the visit day will be accurately recorded.

- Subjects who take their daily dose of study drug in the morning and who have their visit scheduled in the afternoon/evening, will be instructed at the telephone reminder one day prior to Visit 11 or Visit 13 to take the morning dose and record accurately the date/time of the morning dosing on the day of Visit 11 or Visit 13. During the visit, only one PK sample, at any time during their afternoon/evening visit, will be collected. The time of PK sampling will also be accurately recorded.
- Subjects who take their daily dose of study drug in the evening and who have their visit scheduled in the afternoon/evening will be instructed at Visit 10 or Visit 12 to not take the evening dose on the day of Visit 11 or Visit 13 until the predose PK sample is collected at the study site. The study drug will then be administered at the study site and a second PK sample will be collected any time before the end of the visit but not earlier than 15 minutes post dose. The date/time of dose administration for the day before the visit and during the visit day will be accurately recorded.
- Subjects who take their daily dose of study drug in the evening and who have their visit scheduled in the morning will be instructed at the telephone reminder one day prior to Visit 11 or Visit 13 to take the evening dose and accurately record the date/time of the evening dose. During the visit, only one PK sample, at any time during the morning visit, will be collected. The timing of the PK sampling will also be accurately recorded.

PK samples collected in this study will be used to evaluate the population pharmacokinetics and/or PK/ pharmacodynamic of cenobamate in subjects with PGTC seizures.

7.5 Protocol Deviations

The Principal Investigator or designee must document and explain in the subject's source documentation any deviation from the procedures defined in the approved protocol. The Principal Investigator or designee may implement a deviation from or a change to the protocol to eliminate an immediate hazard to subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change and the reasons for it should be submitted to the IRB/IEC for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB/IEC and agreed to by the Principal Investigator. Protocol deviations will be reviewed by the site monitor throughout the course of monitoring visits. Principal Investigators will be notified regarding the deviations in writing by the site monitor. The IRB/IEC should be notified of protocol deviations in a timely manner, per local reporting requirements.

8 STUDY DRUG MANAGEMENT

8.1 Study Drug Description

Double-blind study drug includes the following tablets and oral suspension:

- 12.5 mg cenobamate tablet and matching placebo tablet
- 25 mg cenobamate tablet and matching placebo tablet
- 50 mg cenobamate tablet and matching placebo tablet
- 100 mg cenobamate tablet and matching placebo tablet
- 10 mg/mL cenobamate oral suspension unit strength and matching placebo oral suspension

8.2 Formulation

The qualitative composition of tablets, cenobamate oral suspension and placebo for cenobamate oral suspension is provided in the table below.

Table 8.2-1: Qualitative Composition of Cenobamate Tablets

Ingredient list	Function	Quantity/Unit Dose (mg/Tablet)			
		12.5	25	50	100
Cenobamate	Active substance				
Microcrystalline Cellulose	Filler/ Binder				
Lactose Monohydrate[a] PH 302	Filler				
Sodium Starch Glycolate	Disintegrant				
Colloidal Silicon Dioxide	Glidant				
Magnesium Stearate[b]	Lubricant				
Opadry™ II Brown 85F96555	Nonfunctional cosmetic coating				
Purified Water[c]	Coating Solvent				

a Lactose 316, 100 mesh and Modified Spray Dried
b Vegetable base
c Removed during processing

Placebo tablets have same qualitative composition as active except that they do not contain Cenobamate (Active).

Table 8.2-2: Cenobamate oral suspension 10 mg/mL formulation

Ingredient List	(mg/kg)
Cenobamate	10.00
Microcrystalline cellulose/carboxymethylcellulose sodium	
Magnesium Aluminium Silicate	
Poloxamer 188	
Citric Acid Monohydrate	
Sodium Citrate Dihydrate	
Sodium Benzoate	
Methylparaben Sodium	
Sucralose	
Sorbitol	
Grape Flavor	
Bitter Masker flavor	
Hydrochloric acid 1N	
Sodium hydroxide 1N	
QS Water	

Table 8.2-3: Placebo for Cenobamate oral suspension 10 mg/mL formulation

Ingredient List	(mg/kg)
Microcrystalline cellulose/carboxymethylcellulose sodium	
Magnesium Aluminium Silicate	
Poloxamer 188	
Citric Acid Monohydrate	
Sodium Citrate Dihydrate	
Sodium Benzoate	
Methylparaben Sodium	
Sucralose	
Sorbitol	
Grape Flavor	
Bitter Flavor	
Hydrochloric acid 1N	
Sodium hydroxide 1N	
QS Water	

Additional details of drug product formulation are provided in the latest version of the IB.[18]

8.3 Study Drug Supply and Disposition

The Sponsor will ship a sufficient supply of study drug to each study site from a local depot. The Principal Investigator or designee is responsible for confirming that all study drug supplies received by the study site are inventoried and accounted for throughout the study. Study drug receipt will be documented appropriately. It is important that the designated study site personnel count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment will be documented in the study files and reported in the IRT.

8.4 Storage

At the study site, study drug must be kept in a secure, locked area or locked cabinet with restricted access by only designated study site personnel. Study drug must be stored at controlled room temperature of 20°C – 25 °C (68°F – 77°F), with excursions allowed between 15°C – 30°C (59°F – 86°F).

8.5 Packaging and Shipment

Packaging and labelling will be done in accordance with the Rules Governing Medicinal Products in the European Union, Volume 4: Good Manufacturing Practice (GMP). The Study drug (investigational medicinal product) labels will include all the information required by Annex 13 to GMP.

The study drug tablets will be supplied in 2-panel blister card (1 panel for the label and 1 panel for study drug).

The oral suspension study drug will be supplied in amber glass bottle(s) with CRC cap. Each bottle will contain 250 mL of study drug. Push in Bottle Adapter (PIBA) suitable for the packaged bottle will be provided. The study site will be provided with oral syringes of suitable capacity for dosing the oral suspension formulation of cenobamate.

For the Double-blind Treatment Period, there will be 10 blister card types: 12.5 mg cenobamate tablet, in adolescents as an oral suspension equivalent based on weight and matching placebo; 25 mg cenobamate tablet, in adolescents as an oral suspension equivalent based on weight and matching placebo; 50 mg and 100 mg cenobamate tablet, in adolescents as an oral suspension equivalent based on weight and matching placebo. Each medication panel of the blister card will contain 9 rows of tablets for 7 days of treatment plus 2 extra days for a total of 9 days. Some blister cards will contain 2 columns of tablets, depending on the dose (e.g., 100 mg column and 50 mg column for the 150 mg dose), and each row will contain the total daily dose (i.e., the subject will take 1 tablet from each column in a single row).

Both active and placebo oral suspension use exactly same type of primary packaging and the formulations are designed to result in similar appearance which satisfies the requirement for double blind.

8.6 Dose and Administration

Beginning at Visit 4, the Principal Investigator or designee will access the IRT system, enter his/her username and personal identification number, and provide requested subject details (e.g., subject initials and subject's date of birth). The IRT system will assign each eligible subject a randomization number and identify the unique medication number on each blister card or bottle(s) to be dispensed to the subject. For subjects requiring 1-week down -titration, 1 blister card or bottle(s) will be dispensed for a 1-week double-blind down-titration during the Follow--up period, prior to study drug discontinuation. See Section 6.3 for subjects who prematurely discontinue from the study.

Prior to dispensing, the Principal Investigator or designee will complete the required fields on each blister card or bottle(s) label. In addition, the Principal Investigator or designee will record in the source documents the medication number printed on each card or bottle from which study drug was dispensed.

8.6.1 Dosing Instructions

Study drug will be administered orally. Subjects will be instructed to take study drug once daily starting the morning after randomization. Study drug can be taken with or without food. As described in Section 4.1.2, subjects may be instructed to take study drug in the evening if tolerability issues arise.

Study drug may be administered at the study site, during Visit 11 or Visit 13 only, as described in Section 7.4. Otherwise, subjects will take their study drug every morning/evening and prior to visiting the study site.

For Adolescent subjects, the dosing for oral suspension for the study will be based on the weight taken at Visit 4. The investigator or designee will reference the instructions in the Pharmacy Manual to determine the correct volume for each assigned dose.

The study drug titration and maintenance regimen are provided in Table 8–1.

Table 8–1: Study Drug Titration and Maintenance Plan

Study Phase	Dispense Visit	Double-blind Treatment	
		Adult Tablets – Total Daily Dose	**Adolescents** Oral Suspension – Total Daily Dose
Titration	4	12.5 mg cenobamate tablet, or matching placebo	Volume to deliver 0.2 mg/kg, or matching placebo not to exceed 12.5 mg
	5	25 mg cenobamate tablet, or matching placebo	Volume to deliver 0.4 mg/kg, or matching placebo not to exceed 25 mg
	6	50 mg cenobamate, or matching placebo	Volume to deliver 0.8 mg/kg, or matching placebo not to exceed 50 mg
	7	100 mg cenobamate tablet, or matching placebo	Volume to deliver 1.5 mg/kg, or matching placebo not to exceed 100 mg
	8	150 mg (100 mg + 50 mg) cenobamate tablet, or matching placebo	Volume to deliver 2.0 mg/kg, or matching placebo not to exceed 150 mg
Maintenance	9, 10, 11, 12, 13, 14/ET [a]	200 mg (100 mg + 100 mg) cenobamate tablet, or matching placebo	Volume to deliver 3.0 mg/kg, or matching placebo not to exceed 200 mg
Follow-up (Optional down-titration)	15[a] (Non-OLE)	100 mg cenobamate tablet, or matching placebo	Volume to deliver 1.5 mg/kg, or matching placebo not to exceed 100 mg

Abbreviation: ET= early termination, OLE=open-label extension

a. For subjects not enrolling into the OLE, or prematurely discontinuing the study during the Maintenance Phase. Down titration after premature discontinuation is at the discretion of the Investigator depending on reason for discontinuation (e.g., rash).

8.6.2 Dosing Adjustments

At the discretion of the Principal Investigator or designee, the dosing regimen may be adjusted due to tolerability issues with the study drug. The dose adjustments will be performed at a scheduled visit or at an unscheduled visit. At the visit, the subject will receive a new supply of study drug, as determined by the IRT.

If a subject experiences tolerability issues, the subject may be instructed by the Principal Investigator or designee to start taking the dose of study drug in the evening. Additional dosing adjustments that may be allowed, at discretion of the Principal Investigator or designee, are as follows:

- The goal of the 10-week Titration Phase is for all subjects to achieve the cenobamate 150 mg tablet, in adolescent as an oral suspension equivalent based on weight or matching placebo volume. Therefore, if a subject experiences tolerability issues during the Titration Phase and evening dosing does not improve tolerability, no dose adjustments other than changing the timing of dosing will be permitted, and the subject will be withdrawn from the study, based on the discretion of the Principal Investigator or designee.
- The goal of the Maintenance Phase is for all subjects to be maintained at the 200 mg dose from Visit 9 through Visit 14. If a subject experiences tolerability issues (at 200 mg cenobamate tablet, in adolescents as an oral suspension equivalent based on weight or matching placebo volume) and evening dosing does not improve tolerability, then the subject may have one 50 mg dose reduction to cenobamate 150 mg tablet, in adolescents as an oral suspension equivalent based on weight or matching placebo volume. If the 150 mg tablet dose, in adolescents as an oral suspension equivalent based on weight is not tolerable, then the subject will be withdrawn from the study, based on the discretion of the Principal Investigator or designee.

8.7 Accountability

Subjects or their legal representatives will be instructed to keep study drugs in their original containers. Subjects will be instructed to bring any unused study drug and containers to each visit. Study site personnel will keep accurate records of the study drug dispensed to, used by, and returned from each subject, and these records will be available for verification by the site monitor during monitoring visits.

For oral suspension, each bottle will be weighed at the time it is dispensed and returned and results will be entered in the EDC system. Please reference the Pharmacy Manual for more details.

Periodically, a verification of inventory will be performed by the site monitor. Any discrepancies will be investigated, resolved, and documented prior to return of study drug to the Sponsor for destruction. The final reconciliation of the study drug will be performed at the end of the study.

8.8 Blinding

Study drug packaging and labeling will maintain the double-blind design of the study. The cenobamate tablet, in adolescents as an oral suspension equivalent based on weight and

placebo volume will be identical in appearance. Therefore, the subject's treatment assignment will not be known to the subject or the study site personnel. Selected individuals from the Sponsor and/or designee (for bioanalytical analysis, select Worldwide Clinical Trials personnel) may be unblinded to the treatment assignment on a need-to-know basis, as described in standard operating procedures (SOPs) on blinding and unblinding. The study drug assignment will be unblinded following database lock according to the SOPs.

8.8.1 Breaking the Blind

During the Double-blind Treatment Period or 1-week dose titration, neither the Principal Investigator nor the study site personnel will be aware of the contents of the tablets or liquid administered; however, this information will be readily available in the event of an emergency. Principal Investigators or designee may perform emergency unblinding using the IRT system immediately, without having to first contact the Medical Monitor, if it is determined to be medically necessary and that knowledge of the treatment assignment is essential for the subject's care. If such an emergency unblinding is necessary, the Principal Investigator or designee should promptly document and explain to the Medical Monitor any premature unblinding of the study drug. Reasons for treatment unblinding must be clearly explained and documented in subject's study documents. The date of unblinding and the identity of the site personnel who were unblinded must also be documented.

8.9 Prior or Concomitant Therapy

All medications taken from 30 days prior to Visit 1 (Screening/Baseline) until the Follow--up visit will be recorded in the eCRF.

8.9.1 Required Concomitant AED Therapy

The following concomitant medication use is required during the study:

- A stable regimen of 1 to 3 AEDs for a minimum of 30 days prior to Visit 1 (Screening/Baseline) and throughout the Double-blind Treatment Period (Section 5.2, Inclusion Criterion No. 8).
    - To improve tolerability, the Principal Investigator or designee may alter the timing or amount of an individual dose of a concomitant AED, but the total daily dose and dosing frequency of the concomitant AED must remain unchanged during the Double-blind Treatment Period.

8.9.2 Permitted Prior or Concomitant Therapy

The following concomitant medications or non-pharmacologic therapies are permitted during the study:

- Felbamate use is permitted if the subject has a 2-year history with no changes over the 60 days prior to Visit 1 (Screening/Baseline) (Section 5.2, Inclusion Criterion No. 8).
- Implanted vagal nerve or deep brain stimulators are permitted if the subject has a 5-month history with no changes over the 30 days prior to Visit 1 (Screening/Baseline) and during the study (Section 5.2, Inclusion Criterion No. 9).
- A ketogenic diet is permitted if the subject has a 3-month history with no changes throughout the study (Section 5.2, Inclusion Criterion No. 10).
- Intermittent benzodiazepines (including diazepam) may be taken as rescue medication up to 3 times during any 28-day period after the signing of informed consent (2 doses in a 24-hour period will be considered 1-time rescue).
- Other concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study (with the exception of the prohibited medications outlined in Section 8.9.3).
- All concomitant AEDs are permitted so long as they are stable for 30 days, unless otherwise specified.

8.9.3 Prohibited Prior or Concomitant Therapy

The following concomitant medications are prohibited during the study:

- The use of the following medications is prohibited within the 30 days prior to Visit 1 (Screening/Baseline) and throughout the study: diazepam (except if used as an intermittent benzodiazepine rescue medication, Section 8.9.2), phenytoin, mephenytoin, fosphenytoin, phenobarbital, primidone, ethotoin, clopidogrel, fluvoxamine, amitriptyline, clomipramine, bupropion, methadone, ifosfamide, cyclophosphamide, or efavirenz. Diazepam as benzodiazepine rescue medication for more than 3 times in any 28-day period after signing of informed consent or more than 3 times in the 30 days prior to Visit 1 (Screening/Baseline) is prohibited. Two doses in a 24-hour period will be considered 1-time rescue. (Section 5.3, Exclusion Criterion No. 7).
- The use of vigabatrin is prohibited within 5 months prior to Visit 1 (Screening/Baseline) and throughout the study (Section 5.3, Exclusion Criterion No. 9).
- Investigational drugs and devices are prohibited within 30 days prior to Visit 1 (Screening/Baseline) and throughout the study (Section 5.3, Exclusion Criterion No. 11).

8.10 Birth Control Methods Allowable for Enrollment of Subjects

A woman of childbearing/reproductive potential is defined as any female who has experienced menarche and does not meet the criteria for "Women Not of Childbearing Potential". A woman not of childbearing potential is defined as any female who is postmenopausal or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy).

Sexually active female subjects of reproductive potential must practice an approved method of contraception during the entire study and for 30 days after the last dose of study drug. Hormonal contraceptives alone will not be considered an adequate method of contraception. Acceptable methods of contraception include:

- Hormonal contraception (for at least 3 months prior to Visit 1) in combination with a barrier method
- Intrauterine device (placement at least 3 months prior to Screening visit)
- Diaphragm with spermicide
- Cervical cap with spermicide
- Condoms with contraceptive gel/foam or cream
- Surgical sterilization (tubal ligation at least 6 months prior to screening or partner who has had vasectomy at least 6 months prior to screening)
- Postmenopausal (as defined by absent menses for at least 12 months)
- Abstinence; however, if the subject becomes sexually active, one of the above methods must be utilized.

8.11 Compliance

Compliance with study drug administration will be enforced as follows:

- Subjects will receive dosing instructions at the time of randomization, and the instructions will be reinforced at each visit. This will include information regarding the storage and handling as well as the proper technique for withdrawing the oral suspension from the bottle.
- Subjects will be instructed to keep study drugs in their original packaging or containers and to not combine the contents.
- Subjects receiving tablets will be instructed to take all tablets in each row, for blister cards containing 2 columns. Subjects receiving oral suspension will be instructed that each bottle is dose specific and if any dose adjustments are necessary, a new bottle(s) must be used for that new dose.
- Subjects will be instructed to return all original packaging or containers (empty or containing study drug) at each visit.

- Study site personnel will conduct study drug accountability based on the amount of drug dispensed or weighed and the amount of drug returned at each visit. Treatment compliance is defined as taking 80% to 120% of study drug.

9 ADVERSE EVENTS

9.1 Definitions of Adverse Events

9.1.1 Adverse Events

An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

In this study, AEs will be recorded beginning at Screening (date of signed informed consent) and up to 14 days after the last dose of study drug. Seizures in this subject population are anticipated. Therefore, seizures, in and of themselves, will not be considered AEs. Seizures can be considered AEs if there is clinically significant worsening compared to subject's baseline seizure frequency or duration based on Principal Investigator's discretion.

9.1.2 Suspected Adverse Reaction

Suspected adverse reaction means any AE for which there is a reasonable possibility that the study drug caused the AE. For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the study drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

9.1.3 Pre-existing Condition

A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an AE only if the frequency, intensity, or the character of the condition worsens and is considered to be a clinically significant change by the Principal Investigator or designee.

9.2 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE eCRF. Medical Dictionary for Regulatory Activities (MedDRA), with the version specified by sponsor in the Data Management Plan, will be used to code all AEs.

The information for each AE will be reported in the AE eCRF. This information may include: AE term, date/time of AE onset, Principal Investigator-specified assessment of severity and causality, date/time of AE resolution, seriousness, action taken, and outcome.

9.3 Assessment of Intensity

The severity or intensity of an AE refers to the extent to which an AE affects the subject's daily activities. The severity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild: The AE is easily tolerated and does not interfere with daily activity.

Moderate: The AE interferes with daily activity, but the subject is still able to function.

Severe: The AE is incapacitating and requires medical intervention.

Clinically significant changes in the severity of an AE may be documented as a new AE at discretion of the Principal Investigator or designee.

9.4 Assessment of Causality

All AEs occurring during this clinical study will be recorded regardless of causality. The Principal Investigator or designee will review each event and assess its relationship to study drug. The relationship of each AE to study drug will be assessed using the following definitions:

Unrelated: Event occurring before dosing
Event or intercurrent illness due wholly to factors other than study drug treatment

Remote: Poor temporal relationship with study drug treatment
Event easily explained by subject's clinical state or other factors

Possible: Reasonable temporal relationship with study drug treatment
Event could be explained by subject's clinical state or other factors

Probable: Reasonable temporal relationship with study drug treatment
Likely to be known reaction to agent or chemical group, or predicted by known pharmacology
Event cannot easily be explained by subject's clinical state or other factors

Definite: Distinct temporal relationship with study drug treatment
Known reaction to agent or chemical group, or predicted by known pharmacology
Event cannot be explained by subject's clinical state or other factors

9.5 Adverse Event Follow-up

The clinical course of each event should be followed until resolution, stabilization, the subject is lost to follow-up, or the AE is otherwise explained.

Serious AEs that are still ongoing at the end of the study must be followed up to determine the final outcome. Any SAE that occurs after study completion and is considered to be at least possibly related to the study drug or study participation should be recorded and reported immediately (no later than 24 hours) after awareness of the event.

The Sponsor should also be notified if the Principal Investigator or designee becomes aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a female subject who has participated in this study.

9.6 Overdose

An exposure to the study drug > 120% of the subject's randomized treatment assignment will be considered an overdose. There is no specific antidote for overdose with cenobamate. In the event of a suspected overdose, the Principal Investigator or designee should do the following:

- Promptly report the overdose to the Sponsor's Medical Monitor.
- The overdose should be reported as an AE/SAE in the eCRF.
- Closely monitor any signs or symptoms associated with the overdose.
- Document details of the overdose, such as the quantity of the excess dose consumption and duration of the overdose.

10 SERIOUS ADVERSE EVENT

10.1 Definition of Serious Adverse Event

A SAE is any event that meets any of the following criteria:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received cenobamate
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm
  - Blood dyscrasias that do not result in inpatient hospitalization
  - Development of drug dependency or drug abuse
  - DRESS syndrome

Definition of Terms

Life-threatening: An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Persistent or significant disability: An AE that is incapacitating or disabling and results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

10.2 Reporting Serious Adverse Events

10.2.1 Study Sponsor Notification by Investigator

The SAE Reporting Requirements and contact information are outlined in Table 10–1.

Any AE that meets SAE criteria (Section 10.1) must be reported to the SKLSI or designee.

- In the event of any fatal or life-threatening SAE, the Principal Investigator or designee must inform SKLSI or designee, immediately.
- In the event of an SAE of DRESS syndrome, the Principal Investigator or designee must inform SKLSI or designee, immediately by email (preferred) or telephone or fax.
- Any non-fatal or non-life-threatening SAE, regardless of expectedness or causality, must be reported on the SAE Report Form, scanned, and emailed to SKLSI or designee, within 24 hours of the Investigator’s or any other study site personnel’s knowledge of the event as described below.

A completed SAE Report Form, the AE record, pertinent medical records, and the concomitant medication record from the source documents should be scanned and emailed to SKLSI or designee within 24 hours of the Principal Investigator’s or any study site

personnel's knowledge of an SAE. An updated SAE Report Form should be forwarded to SKLSI or designee within 24 hours of receipt of new/updated information.

Table 10–1: Serious Adverse Event Reporting Requirements

Type of SAE	Reporting Time Frame	Reporting Method	Contact Details
Rash with involvement of 1 other organ system or a suspected case of DRESS syndrome	Immediate	Email[a]	QPV_SKLSI_SafetyMailbox@quintiles.com
Fatal or Life-threatening	Immediate	Email[a]	QPV_SKLSI_SafetyMailbox@quintiles.com
All other SAEs	Within 24 hours of awareness	Email[a]	QPV_SKLSI_SafetyMailbox@quintiles.com
Urgent safety concerns requiring a Medical Monitor	As needed	Telephone	PRA Contact information Dedicated email address: SKL025@prahs.com US: Toll-free number: 1-866-326-5053, FAX: 800-280-7035 Ex-USA: Support Center + 44 179 252 5608, FAX: + 49 621 878 2828

Abbreviations: DRESS = drug rash with eosinophilia and systemic symptoms, SAE = serious adverse event, SKLSI = SK Life Science, Inc., USA= Unites States of America
[a] The SAE Report Form must be used for reporting.

At the time of the initial SAE report, the Principal Investigator or designee should provide as much of the information as possible. The notification should include the following:

- Study identifier
- Study site
- Subject number
- Screening number
- A description of the event
- Date of onset
- Current status
- Whether study drug was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study drug

The Principal Investigator or designee must provide further information on the SAE in the form of follow-up. This should include a copy of the completed SAE form and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing SAEs should be provided promptly to the study Sponsor.

SKLSI will be responsible for evaluating the events for expedited reporting, and for reporting them to the applicable regulatory agencies.

The Sponsor pharmacovigilance vendor for YKP3089C025, IQVIA, will report suspected unexpected serious adverse reactions to the Eudravigilance database as part of regular pharmacovigilance reporting activities.

If reports of any new and unexpected AEs become available to SKLSI during the clinical portion of this study (related or not to the present study), SKLSI must advise the clinical site, through its Principal Investigator, of those events.

10.2.2 Independent Ethics Committee/Institutional Review Board Notification by Investigator

Reports of all SAEs (including follow-up information) must promptly be submitted to the IRB/IEC, per reporting requirements. Copies of each report and documentation of IRB/IEC notification and receipt will be kept in the clinical Investigator’s binder.

11 STATISTICS

11.1 General Procedures

Statistical considerations and planned analyses are summarized in this section. A detailed description of the statistical analyses will be documented in the statistical analysis plan.

11.2 Analysis Sets

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 one dose of study drug and have at least one 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 one efficacy measurement in the Maintenance Phase.

Safety population: All subjects in the randomized population who received at least one dose of study drug.

Pharmacokinetic population: All subjects in the safety population who have at least one evaluable PK sample.

11.3 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.

11.4 Description of Subgroups to be Analyzed

Subgroup analysis may be performed for primary and secondary efficacy endpoints as well as safety using the same methodology as described in Section 11.5. The subgroups to be analyzed may include the following:

- Sex (2 categories): female and male subjects
- Race (3 categories): white black/African American, and other
- Age (2 categories): 12-<18 and ≥18 years old
- Geographic region (4 categories): North America, Europe, Africa, and other

11.5 Statistical Methods

11.5.1 Primary Endpoint(s)

- 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. 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. 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.

The primary analysis for this study will be conducted on MITT population for endpoint defined in USA and Rest of the World, and MITT-M population 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 11-1).

Table 11-1: List of Estimands for Primary Efficacy Endpoints

Estimand	Endpoint/Variable	Intercurrent events and strategies
Primary E1	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. 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.
Primary E2	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. 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.

11.5.2 Secondary Endpoints

11.5.2.1 Efficacy

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

- 100% responder rates for PGTC seizures during the Maintenance Phase relative to baseline.

- 75% responder rates for PGTC seizures during the Maintenance Phase relative to baseline.
- 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.

11.5.2.2 Safety

Adverse events will be coded using MedDRA, with the version specified by sponsor in the Data Management Plan. The number and percentage of subjects reporting AEs and SAEs will be reported. Physical and neurologic examinations, clinical laboratory results, vital signs, concomitant medications, ECGs, and C-SSRS will be summarized using descriptive statistics.

11.5.2.3 Pharmacokinetic Analyses

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, cenobamate plasma concentrations will be reported as part of this study report In addition, a population PK/pharmacodynamic analysis will be conducted for PGTC or pooled analysis will be conducted with POS data, if deemed appropriate and reported separately.

PK blood samples may be used for exploratory metabolite analyses. Possible results from these exploratory analyses may be reported in a stand-alone report(s) if deemed necessary.

11.5.3 Other Analyses

Subject disposition, demographics, medical history, prior and concomitant medications, and study treatment exposure will be listed by subject and summarized descriptively. All demographic measurements (age, gender, race, ethnicity, height, and weight), baseline AED history, and all baseline safety measurements (medical and seizure history, MRI/CT, ECGs, vital signs, clinical laboratory values, physical and brief neurologic exam, and C-SSRS) will be summarized for randomized subjects, MITT-M, and safety populations, as appropriate.

11.6 Interim Analysis

No interim analysis is planned.

12 ETHICS AND RESPONSIBILITIES

12.1 Good Clinical Practice

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonised Tripartite Guideline E6 [R2]; FDA Code of Federal Regulations [CFR] [21 CFR Sections 50, 56, 312]), in compliance with (EU) No 536/2014, the general guidelines indicated in the Declaration of Helsinki (Fortaleza 2013), and all applicable regulatory requirements.

Details of the Sponsor and Contract Research Organization personnel involved in the conduct of the study are given in Section 19.1, Appendix I.

12.2 Data Monitoring Committee

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 ensuring subject safety.

The DMC will consist of at least two expert physicians (at least one epileptologist and one physician with expertise in AED safety issues) and one unblinded biostatistician. All members of the DMC will be experienced in the clinical trials process and in the assessment of safety data from clinical trials. The DMC members shall not be involved in subject recruitment or conduct this clinical study (e.g. physician members may not be Investigators).

The DMC will be provided access to the unblinded safety data and will perform the following review of the safety data at following time points in the study:

- First 40 subjects complete the Titration phase
- First 80 subjects complete the Titration phase
- First 80 subjects complete the study

The primary data to be reviewed should be AEs, but all safety data will be made available for review. After completing the review, the DMC Chair will prepare a brief report. The DMC can perform other reviews whenever it believes that a review would be informative regarding subject safety. The DMC will not review efficacy data.

The DMC will communicate with the Sponsor after each of the above-specified milestones. The DMC can communicate with the Sponsor whenever the DMC identifies a safety issue. The DMC will be granted the authority, after discussion with the Sponsor, of restricting dose escalation, adding safety assessments, or halting the study temporarily or permanently.

12.3 Institutional Review Board/Independent Ethics Committee

This study will be conducted in compliance with IRB/IEC and ICH GCP Guidelines, including Title 21 Part 56 of the US CFR relating to IRBs/IECs and GCP as described in

the US FDA CFR (21 CFR Sections 50, 56, 312), in compliance with (EU) No 536/2014, as well as all local regulatory regulations and requirements.

Before initiating a study, the Investigator/institution must have written and dated approval/favorable opinion from the IRBs/IECs for the study protocol/amendment(s), written ICF, any ICF updates, subject recruitment procedures (e.g., advertisements) and any written information to be provided to subjects, and a statement from the IRBs/IECs that these comply with GCP requirements. The IRB/IEC approval(s) must identify the protocol version as well as the documents reviewed.

12.4 Informed Consent

The Principal Investigator or designee will explain the benefits and risks of participation in the study to each subject and obtain written informed consent using the IRB/IEC approved ICF. An age-appropriate assent will be obtained for adolescents. Written informed consent must be obtained prior to the subject entering the study and before initiation of any study-related procedure (including screening procedures).

The Sponsor will provide an ICF that will require consent for the study. The final, version -dated form must be agreed to by the Sponsor and the IRBs/IECs and will contain all elements in the ICF, in language readily understood by the subject. Each subject's original ICF, personally signed and dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion, will be retained by the Principal Investigator or designee. The Principal Investigator or designee will supply all enrolled subjects with a copy of their signed ICF.

The ICF may need to be revised during the study should important new information become available that may be relevant to the safety of the subject. In this instance, approval should always be given by the IRBs/IECs, and existing subjects should be informed of the changes and re-consented. This is documented in the same way as previously described.

The Principal Investigator or designee may, with the consent of the subject, inform the subject's primary physician and/or treating neurologist about participation in the clinical study.

12.5 Records Management

Source documents contain the original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs, and recorded data from automated instruments.

All source documents from this study are to be maintained by the Principal Investigator or designee and made available for inspection by authorized persons. The original signed informed consent for each subject shall be filed with records kept by the Principal Investigator or designee, and a copy shall be given to the subject.

12.6 Source Documentation

An eCRF will be used to store and transmit subject information. The file structure and format for the eCRF will be provided by the Sponsor or their representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed and dated by the Principal Investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by examining personnel or the study coordinator. The eCRF must be completed as soon as possible after any subject evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

During each study visit, the Principal Investigator or designee will maintain progress notes, in ink or an acceptable electronic health record system, in the subject's medical records to document all significant observations. At a minimum, these notes are to contain:

- The date of the visit and the corresponding day or visit in the study schedule (e.g., Screening, Day 1)
- General condition and status remarks by the subject, including any significant medical findings, and the severity, frequency, duration, and resolution of any reported AE, and the Investigator's assessment as to whether the reported AE is study drug-related
- Changes (including dosages) in concomitant medications/therapies (including ketogenic diet) or procedures
- A general reference to the procedures completed
- The signature or initials of all designated study personnel making an entry in the medical record (progress notes).

In addition, any contact with the subject via telephone or other means that provides significant clinical information is to also be documented in the medical records (progress notes), as described above.

Information from the medical records (progress notes) and other source documents is to be promptly entered into the appropriate section of the eCRF.

Changes to information in the medical record (progress notes) and other source documents are to be initialed and dated on the day the change is made by the Principal Investigator or designee. If the reason for the change is not apparent, a brief explanation for the change is to be written adjacent to the change. Changes to the eCRF will be tracked electronically via an audit trail.

12.7 Study Files and Record Retention

All data derived from the study will remain the property of the Sponsor.

Records must be retained in accordance with the current ICH Guidelines on GCP and in compliance with local regulations. All essential study documents including records of subjects, source documents, eCRFs, and study drug inventory must be kept on file.

At a minimum, essential documents must be retained for at least 25 years post study completion or until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the Principal Investigator of when these documents need no longer be retained.

The Principal Investigator or designee is not to dispose of any records relevant to this study without written permission from the Sponsor and is to provide the Sponsor the opportunity to collect such records. The Principal Investigator or designee shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives and regulatory authorities.

If a Principal Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed upon by the Sponsor.

13 AUDITING AND MONITORING

13.1 Monitoring of the Study

The site monitor, as a representative of the Sponsor, has the obligation to monitor the study activities closely. The monitor will visit the study site at periodic intervals, in addition to maintaining necessary telephone and letter contact with the site personnel and Principal Investigator. The site monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Principal Investigator and site personnel.

All aspects of the study will be carefully monitored by the Sponsor or its designee, for compliance with applicable government regulations, ICH GCPs and current SOPs.

13.2 Inspection of Records

Principal Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Principal Investigator agrees to allow the Sponsor, representatives of the Sponsor, or a regulatory agency (e.g., FDA, EMA or other regulatory agencies) access to all study records.

The Principal Investigator or designee should promptly notify the Sponsor and its designee of any audits scheduled by any regulatory authorities and promptly forward copies of any available audit reports to the Sponsor.

14 PROTOCOL AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor, SKLSI. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days or in accordance with other applicable requirements.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC, and the Principal Investigator must await approval before implementing the changes. SKLSI will submit protocol amendments to the appropriate regulatory authorities for approval.

If, in the judgment of the IRB/IEC, the Principal Investigator, and/or SKLSI, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

15 STUDY REPORT AND PUBLICATIONS

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.[23]

When required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the Sponsor will provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Principal Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document as recommended by the International Committee of Medical Journal Editors (www.icmje.org).

Principal Investigators may not publish any study data without prior approval from the Sponsor.

16 STUDY DISCONTINUATION

Both SKLSI and the Principal Investigator reserve the right to terminate the study at the Investigator's site at any time. Should this be necessary, SKLSI or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Principal Investigator will inform the IRB/IEC of the same. In terminating the study, SKLSI and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

17 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from SKLSI. However, authorized regulatory officials, IRB/IEC personnel, SKLSI, and its authorized representatives are allowed full access to the records.

Identification of subjects in the eCRFs shall be done in compliance with applicable country regulations. Additionally, for the clinical sites in countries of the European Union (EU), all personal details will be treated as confidential by the Investigator and staff at PRA and handling of personal data will be in compliance with the EU General Data Protection Regulation. https://ec.europa.eu/info/law/law-topic/data-protection_en

17.1 Data Handling

Regarding data security breaches, the key to protecting the privacy of participants is the principle of data minimization. This is represented by the pseudonymization or "key coding" of clinical data related to participants. Wherever a stakeholder in a study can perform their function with access only to key-coded data, then this control is implemented. Only the principal investigator or designee has access to fully identified participants' clinical data

held in source documents, and they maintain the table that links participant identity to the allocated participant number (i.e., key code).

Other stakeholders, including monitors and contracted clinical and technology vendor personnel, may need access to participant identity to perform their specific function, including stakeholders supportive of televisits, home health, direct-to/from-participant clinical supplies, remote source data verification, electronic consent, and electronic COAs. Further to the principle of data minimization in which a stakeholder needs access to participant identity, but not information directly or indirectly indicative of a medical condition, this information is restricted. Study site, sponsor, and vendor processes and controls will regulate the unauthorized disclosure of prohibited subject identifiers (PSI), including appropriate remedial actions to delete PSI on receipt and in downstream systems, supported by reminders to stakeholders and staff training.

Systems, applications, and technologies will be 21 CFR 11 compliant as necessary. Data protection and privacy laws, including the EU General Data Protection Regulation (GDPR) and the Security Rule of US Health Insurance Portability and Accountability Act, mandate stakeholders to adopt measures designed to protect the confidentiality of regulated personal information. Such measures will include contractual obligations placed among and between stakeholders (eg, study sites and sponsors) and upon any clinical vendors. These are supported by information security assessments of systems, and quality and security audits where required. Expected measures will include technical and organizational controls to prevent unauthorized access, disclosure, dissemination, and alteration or loss of personal information.

Data protection and privacy laws describe the obligations when a security breach occurs involving the compromise of regulated personal information. Sponsor has a Data Privacy Policy and Data Breach SOP which describes Sponsor’s processes for managing a data breach including the involvement of an Incident Response team, working cooperatively with third parties, conducting an investigation, determining the root cause and remediation, and notification requirements in compliance with applicable law. Stakeholders in clinical studies, including study sites, , CROs, and vendors are required to have policies and procedures in place to respond to breaches, including the education of staff on necessary surveillance measures, immediate steps to take to control and investigate breaches, and the arrangement for any legally mandated notification to participants or regulatory authorities, particularly in circumstances where there is potential harm to data participants. In all cases, appropriate privacy and security personnel are to be involved.

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19 APPENDICES

19.1 Appendix I – Names of Study Personnel

Sponsor:	Sunita Misra, MD, PhD VP, Clinical Development & Acting Chief Medical Officer SK Life Science, Inc. 461 From Road, 5th Fl Paramus, NJ 07652, USA Telephone: +1 832-257-1975 Email: smisra@sklsi.com
	[redacted]
ICON US Medical Monitor:	[redacted]
ICON Ex-US/EAPA Medical Monitor:	[redacted]
ICON APAC Medical Monitor	[redacted]

Hungaro Medical Monitor:	[redacted]
GCT Medical Monitor:	[redacted]
Clinical Research Organization:	[redacted]
Clinical Research Organization:	[redacted]
Clinical Research Organization:	[redacted]
Central Laboratory:	[redacted]
SAE Reporting:	See Table 10–1 for specific reporting information

19.2 Appendix II - Columbia Suicide Severity Rating Scale (Baseline/Screening)

COLUMBIA-SUICIDE SEVERITY

RATING SCALE

(C-SSRS)

Baseline/Screening Version

Version 1/14/09

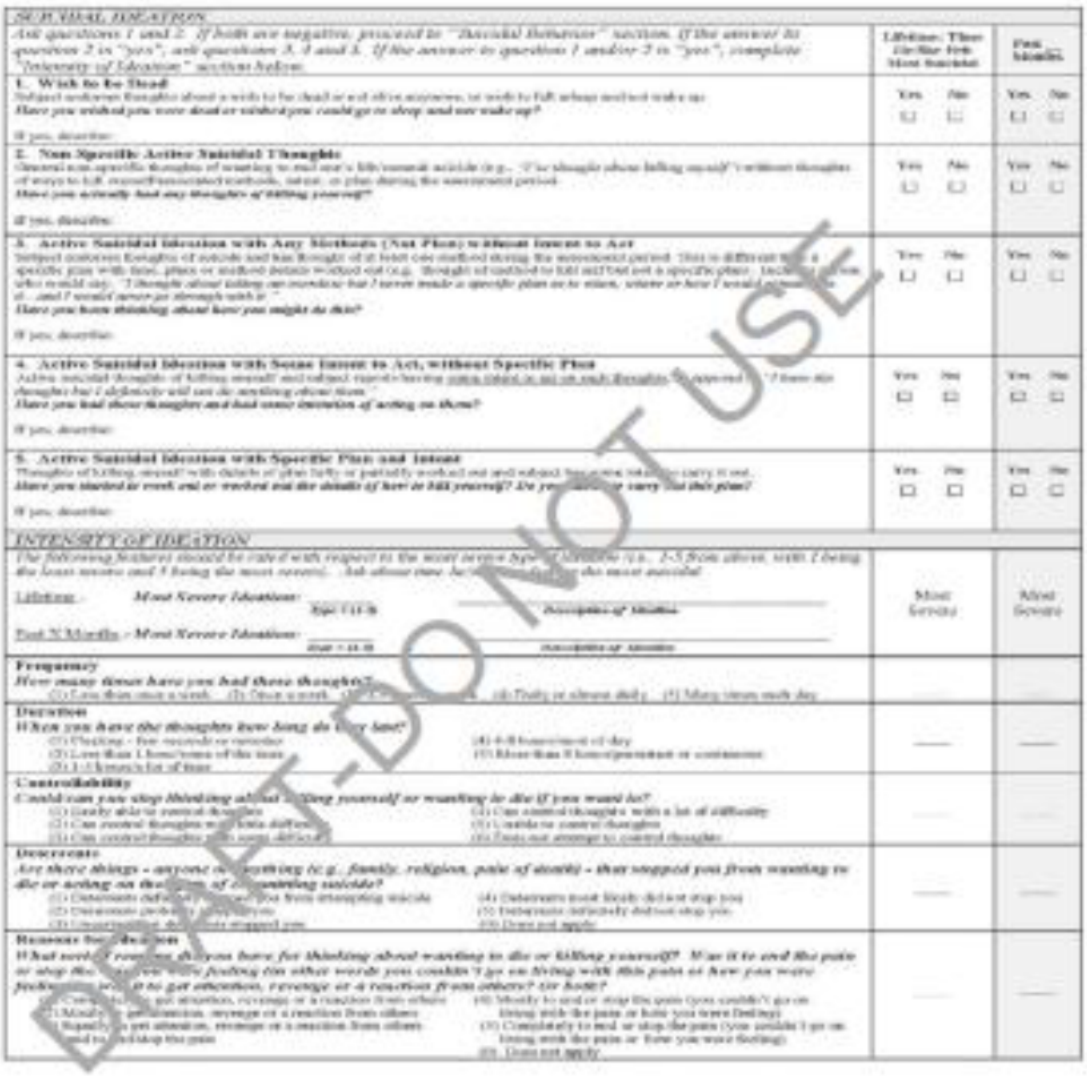
Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by: John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032. Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First (Ed.) Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu



SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section as below.

	Lifetime: Time Of/Before Feb Most Suicidal	Past Month
1. Wish to Be Dead *Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.* ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts *General non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.* ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act *Subject endorses thoughts of suicide and has thought of it/at least one method during the assessment period. (Not to differentiate from a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes client who would say: "I thought about killing my overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan *Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to "I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent *Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.* ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above), with 1 being the least severe and 5 being the most severe). Ask about time frame for the most suicidal.

Lifetime - ***Most Severe Ideation:*** Type (1-5): _____ Description of Ideation: _____

Past 1 Month - ***Most Severe Ideation:*** Type (1-5): _____ Description of Ideation: _____

	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) [illegible] (4) Daily or almost daily (5) Many times each day		
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-2 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with some difficulty (3) Can control thoughts with much difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (6) Does not attempt to control thoughts	____	____
Deterrents ***Are there things – anyone or anything (e.g., family, religion, pain of death) – that stopped you from wanting to die or acting on the thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (6) Does not apply	____	____
Reasons for Ideation ***What sorts of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? (or both)?*** (1) Mostly to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others and partly to end/stop the pain (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (6) Does not apply	____	____

SUICIDAL BEHAVIOR

Lifetime

Past __ Years

Actual Attempt:

Yes No

Total # of Attempts

Has subject engaged in Non-Suicidal Self-Injurious Behavior?

Interrupted Attempt:

Total # of interrupted

Aborted Attempt:

Total # of aborted

Preparatory Acts or Behavior:

Suicidal Behavior:

Answer for Actual Attempts Only

Enter Code

19.3 Appendix III - Columbia Suicide Severity Rating Scale (Since Last Visit)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to questions 3 and/or 4 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, "I've thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it, ...and I would never go through with it." ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to "I have the thoughts but I definitely will not do anything about them". ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry out the plan. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times a week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with much difficulty (5) Unable to control thoughts (6) Does not attempt to control thoughts	____
Deterrents ***Are there things (person, anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Definitely did/do stopped you from attempting suicide (2) Probably did stop you (3) Unsure if deterrents stopped you (4) Probably did not stop you (5) Definitely did not stop you (6) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (6) Does not apply	____

Version 1.1 (US)

SUICIDAL BEHAVIOR [illegible]	Since Last Visit
Actual Attempt: [illegible] ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you ______ as a way to end your life?*** ***Did you want to die (even a little) when you ______?*** ***Were you trying to end your life when you ______?*** ***Or did you think it was possible you could have died from ______?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** [illegible] If yes, describe:	Yes ☐ No ☐ Total # of Attempts ______
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: [illegible] ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted ______
Aborted Attempt: [illegible] ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted ______
Preparatory Acts or Behavior: [illegible] ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. [illegible] 1. [illegible] 2. [illegible] 3. [illegible] 4. [illegible] 5. Death	*Enter Code* ______
Potential Lethality: Only Answer if Actual Lethality=0 [illegible] 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* ______

19.4 Appendix IV - Full Physical Examination

BODY SYSTEM	Normal	Abnormal, NCS	Abnormal, CS	Not Done	If Abnormal, Specify Findings
General Appearance	☐	☐	☐	☐	
Head	☐	☐	☐	☐	
EENT	☐	☐	☐	☐	
Neck	☐	☐	☐	☐	
Cardiovascular	☐	☐	☐	☐	
Abdominal	☐	☐	☐	☐	
Respiratory	☐	☐	☐	☐	
Musculoskeletal	☐	☐	☐	☐	
Extremities	☐	☐	☐	☐	
Skin	☐	☐	☐	☐	

19.5 Appendix V - Full Neurologic Examination

FULL NEUROLOGIC EXAMINATION					
GENERAL	**Normal**	**Abnormal, NCS**	**Abnormal, CS**	**Not Done**	**If Abnormal,** **Specify Findings** – including laterality, as applicable
1. Level of Consciousness	☐	☐	☐	☐	
2. Mental Status	☐	☐	☐	☐	
3. Visual Fields (II)	☐	☐	☐	☐	
4. Eye Movements (III, IV, VI)	☐	☐	☐	☐	
5. Jaw Movement and Facial Sensation (V)	☐	☐	☐	☐	
6. Facial Motion (VII)	☐	☐	☐	☐	
7. Hearing (VIII)	☐	☐	☐	☐	
8. Swallowing, pharynx, larynx (IX, X)	☐	☐	☐	☐	
9. SCM, trapezius (XI)	☐	☐	☐	☐	
10. Tongue (XII)	☐	☐	☐	☐	
11. Biceps Reflexes	☐	☐	☐	☐	
12. Triceps Reflexes	☐	☐	☐	☐	
13. Patellar Reflexes	☐	☐	☐	☐	
14. Achilles Reflexes	☐	☐	☐	☐	
15. Plantar Reflexes	☐	☐	☐	☐	
16. Gait	☐	☐	☐	☐	
17. Romberg	☐	☐	☐	☐	
18. Nystagmus	☐	☐	☐	☐	
19. Tremor	☐	☐	☐	☐	
20. Finger-Nose	☐	☐	☐	☐	
21. Heel-Shin	☐	☐	☐	☐	
22. Rapid Alternating Movements	☐	☐	☐	☐	
23. Muscle Strength	☐	☐	☐	☐	
24. Pin	☐	☐	☐	☐	
25. Vibration	☐	☐	☐	☐	

19.6 Appendix VI - Brief Neurologic Examination

BRIEF NEUROLOGIC EXAMINATION					
GENERAL	**Normal**	**Abnormal, NCS**	**Abnormal, CS**	**Not Done**	**If Abnormal,** **Specify Findings** – including laterality, as applicable
1. Level of consciousness	☐	☐	☐	☐	
2. Mental status	☐	☐	☐	☐	
3. Biceps reflexes	☐	☐	☐	☐	
4. Knee reflexes	☐	☐	☐	☐	
5. General movement	☐	☐	☐	☐	
6. Gait	☐	☐	☐	☐	
7. Romberg	☐	☐	☐	☐	
8. Nystagmus	☐	☐	☐	☐	
9. Tremor	☐	☐	☐	☐	
10. Finger-nose	☐	☐	☐	☐	
11. Heel-shin	☐	☐	☐	☐	
12. Rapid alternating movements	☐	☐	☐	☐	

Signature Page for VV-CLIN-001121 v2.0

Workflow Task: Approve	Sunita Misra Medical 16-Oct-2024 16:10:27 GMT+0000

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