YKP3089
CLINICAL STUDY PROTOCOL

RELATIVE BIOAVAILABILITY OF A SINGLE 200 MG DOSE OF CENOBAMATE (YKP3089) GIVEN AS AN ORAL TABLET OR AS AN ORAL SUSPENSION AND THE EFFECT OF FOOD ON A SINGLE 200 MG DOSE OF CENOBAMATE GIVEN AS AN ORAL SUSPENSION

SK Life Science, Inc. Study Number: YKP3089C037

IND Number: IND076809

Sponsor:	SK Life Science, Inc. 461 From Road, 5th floor Paramus NJ 07652 USA
Original Date	21 October 2020
Version Number	Amendment 1, Version 2.0
Version Date	30 November 2020
Previous Version	21 October 2020

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by SK Life Science, Inc.

Responsible Sponsor Medical Officer:

30 NOV 2020

Company/Sponsor signatory
Marc Kamin, M.D.
Chief Medical Officer
SK Life Science, Inc.
461 From Road, 5th floor
Paramus, NJ 07652
Telephone: +1 (201) 421-3830
Email: mkamin@sklsi.com

Date

Sponsor's Authorized Officer:

30 NOV 2020

Company/Sponsor signatory
Stephen Greene, Pharm.D.
Senior Manager, Clinical Pharmacology
SK Life Science, Inc.
461 From Road, 5th floor
Paramus, NJ 07652
Telephone: +1 (201) 957-0281
Email: sgreene@sklsi.com

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for cenobamate (YKP3089). I have read the YKP3089C037 Protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Ahad Sabet, MD, CPI
Principal Investigator/Research Physician, EDS
PRA Health Sciences
Medical Director − EDC SLC
Phone: (801) 904-4638, VNET: # 124.4638
Fax: (801) 261-3341
Mobile Phone: (314) 973-6949

_____

Signature of Principal Investigator

_____

Date

AMENDMENT 1 SUMMARY OF CHANGES

Section	Previous Version's text/ Content	Amended Text/ Content	Rationale/ Description
Synopsis	Healthy Male or female subjects of 18 to 50 years of age (inclusive)	Male or female subjects of 18 to 50 years of age (inclusive), at the time of screening	Deleted and added text for clarification
Synopsis	Inclusion criteria number 2 was skipped ending in number 9	Updated numbering so that number 2 was not skipped ending in number 8	Need for sequential numbering
Synopsis	Inclusion 7: Normal electrocardiogram (ECG) (12-lead), arterial blood pressure, and heart rate within the normal range of the study center or considered not clinically significant by the Investigator and in agreement with the Sponsor	Inclusion 6 (was Inclusion 7): Electrocardiogram (ECG) (12-lead), arterial blood pressure, and heart rate within the normal range of the study center or considered not clinically significant by the Investigator.	Removed redundant language and need for sponsor agreement as normal ranges are already agreed upon prior to study start
Synopsis	Inclusion 9: Females of non-childbearing potential (18 to 50 years of age (inclusive)), who have undergone a sterilization procedure at least 6 months prior to dosing with official documentation (e.g., hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy, hysterectomy, or bilateral oophorectomy), or be postmenopausal with amenorrhea for at least 1 year prior to dosing and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per Principal Investigator's judgment	Inclusion 8 (was Inclusion 9): Females of non-childbearing potential (18 to 50 years of age (inclusive)), who have undergone a sterilization procedure at least 6 months prior to dosing with official documentation (e.g., bilateral tubal ligation or bilateral salpingectomy or hysterectomy), or be postmenopausal with amenorrhea for at least 1 year prior to dosing and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per Principal Investigator's judgment	Removed procedures that may necessitate the use of HRT (HRT is not allowed in this study as a concomitant medication)

Table 4: Schedule of Assessments		Amended Table formatting to properly align visits with days they are occurring on	Formatting was off in previous protocol
Table 4: Schedule of Assessments		Added C-SSRS at Baseline (screening) And C-SSRS "Since Last Visit" to: Screening Day -28 Admit Day -1 Admit Day 41 Admit Day 62 And Follow up Visit Day 69	The C-SSRS is a commonly requested test from IRBs
Table 4: Schedule of Assessments	Inclusion/Exclusion row has a superscript a	Moved superscript a to Eligibility Confirmation assessment on Day -1	Clarification on when a review of the inclusion/exclusion is to occur in light of eligibility confirmation
Table 4: Schedule of Assessments	Randomization at Day -1	Randomization removed from Day-1 and added to Day 1	Clarification on timing of randomization
Table 4: Schedule of Assessments		Removed Tympanic Temperature from schedule of Assessments	Temperature will be taken in accordance with site SOPs as part of vitals
Table 4: Schedule of Assessments	12-Lead ECG Day1	12-Lead ECG Removed from Day 1 and added to Day-1	12-Lead ECG will only be conducted at screening and baseline
Table 4: Schedule of Assessments		Removed the duplicated word "Note:" from the footnotes	Removed redundant wording
Table 4: Schedule of Assessments	Note under table	Added "C-SSRS = Columbia Suicide Severity Rating Scale" to notes under table	Needed to add definition of C-SSRS

Table 4: Schedule of Assessments		Added Footnote b: Baseline "Baseline/Screening" version of C-SSRS will be used	Needed to add type of C-SSRS to be conducted at baseline
Table 4: Schedule of Assessments		Added Footnote c: "Since Last Visit" version of C-SSRS will be used	Needed to add type of C-SSRS to be conducted at times outside of baseline
Table 4: Schedule of Assessments		Added Footnote d: "Randomization to occur prior to dosing on Day 1"	Clarification on when randomization will occur
Table 4: Schedule of Assessments		The following footnotes were adjusted: b → e c → f d → g e → h f → i	Adjusted to make room for additional footnotes
7.1.1.1.	"Screening assessments will be comprised of relevant medical history, demographics (including the assessments of body height, weight, BMI, smoking status, and alcohol history), serum pregnancy test, serum FSH, clinical labs, serology tests (HIV and Hep B/C), urine drug screening, breath alcohol, tympanic temperature, physical examination, vital signs, 12-lead ECG, concomitant therapy, and review of inclusion/exclusion criteria"	"Screening assessments will be comprised of relevant medical history, demographics (including the assessments of body height, weight, BMI, smoking status, and alcohol history), serum pregnancy test, serum FSH, clinical labs, serology tests (HIV and Hep B/C), urine drug screening, breath alcohol, a complete physical examination, vital signs, 12-lead ECG, concomitant medications, C-SSRS and review of inclusion/exclusion criteria"	Added type of physical examination and C-SSRS to harmonize with the Schedule of Assessments
7.1.1.2.	Confirmation of eligibility (including a review of the inclusion/exclusion criteria), height/weight/BMI, urine pregnancy, clinical labs, urine drug screen, breath	Confirmation of eligibility (including a review of the inclusion/exclusion criteria), height/weight/BMI, urine pregnancy, clinical labs, urine drug screen, breath alcohol, 12-lead ECG, CSSR-S, and	Added 12-lead ECG and CSSR-S to harmonize with Schedule of Assessments

	alcohol, and concomitant medications on Day -1	concomitant medications on Day -1	
7.1.1.2.	Tympanic temperature, physical exam and vital signs on Day 1	Physical exam (symptom oriented) and vital signs on Day 1	Removed tympanic temperature and clarified physical exam type to harmonize with Schedule of Assessments
7.1.1.2.		Added: "Randomization on Day 1 prior to dosing"	Added clarifying language for randomization timing
7.1.1.2.	Clinical labs, tympanic temperature, vital signs, 12-lead ECG, and concomitant medications on Day 4	Clinical labs, vital signs, and concomitant medications on Day 4	Removed tympanic temperature and 12-lead ECG to harmonize with schedule of assessments
7.1.1.2. – 7.1.1.18.	AE Monitoring	AE Monitoring throughout	Added clarifying language about timing of assessments
7.1.1.2., 7.1.1.7, 7.1.1.12.	"… subjects will be issued a hypersensitivity card"	"… subjects will be issued a hypersensitivity safety card"	Added clarifying language to harmonize with Schedule of Assessments
7.1.1.3. – 7.1.1.6., 7.1.1.8 – 7.1.1.11., 7.1.1.13 – 7.1.1.17.	Urine drug screen, breath alcohol, Tympanic Temperature, vital signs, and concomitant medications	Urine drug screen, breath alcohol, vital signs, and concomitant medications	Removed tympanic temperature as this will be done as part of vital signs
7.1.1.7., 7.1.1.12.	Clinical labs, urine drug screen, breath alcohol, tympanic temperature, physical exam, vital signs, concomitant medications on…	Clinical labs, urine drug screen, breath alcohol, vital signs, C-SSRS, concomitant medications on…	Removed tympanic temperature, physical exam and added C-SSRS to harmonize with Schedule of Assessments

7.1.1.7.	Blood samples to determine plasma drug concentrations of cenobamate on Day 20 for end of Period 1 sampling and Day 22 to the morning of Day 25 for beginning of Period 2 sampling	Blood sample to determine plasma drug concentrations of cenobamate on Day 20 for end of Period 1 sampling And Blood sampling to determine plasma drug concentrations of cenobamate on Day 22 to the morning of Day 25 for beginning of Period 2 sampling	Split bullet up to clarify timing of events
7.1.1.7.	Tympanic temperature, physical exam and vital signs on Day 22	Physical exam (symptom oriented) and vital signs on Day 22	Removed tympanic temperature and clarified physical exam type to harmonize with schedule of assessments
7.1.1.7.	Clinical labs, tympanic temperature, vital signs, and concomitant medications on Day 25	Clinical labs, vital signs, and concomitant medications on Day 25	Removed tympanic temperature as this will be done as part of vital signs
7.1.1.12.	Blood samples to determine plasma drug concentrations of cenobamate on Day 41 for end of Period 2 sampling and Day 43 to the morning of Day 46 for beginning of Period 3 sampling	Blood sample to determine plasma drug concentrations of cenobamate on Day 41 for end of Period 2 sampling And Blood sampling to determine plasma drug concentrations of cenobamate on Day 43 to the morning of Day 46 for beginning of Period 3 sampling	Split bullet up to clarify timing of events
7.1.1.18.	Urine pregnancy, clinical labs, tympanic temperature, physical exam, vital signs, and concomitant medications	Urine pregnancy, clinical labs, physical exam (symptom oriented), vital signs C-SSRS and concomitant medications	Removed tympanic temperature, added C-SSRS and type of physical exam to harmonize with

			schedule of assessments
8.1.	Male or female subjects of 18 to 50 years of age (inclusive)	Male or female subjects of 18 to 50 years of age (inclusive), at the time of screening	Added clarifying language as to when the age will be assessed
8.1.	Normal electrocardiogram (ECG) (12-lead), arterial blood pressure, and heart rate within the normal range of the study center or considered not clinically significant by the Investigator and in agreement with the Sponsor	Electrocardiogram (ECG) (12-lead), arterial blood pressure, and heart rate within the normal range of the study center or considered not clinically significant by the Investigator.	Removed redundant language and need for sponsor agreement as normal ranges are already agreed upon prior to study start
8.1.	Females of non-childbearing potential (18 to 50 years of age (inclusive)), who have undergone a sterilization procedure at least 6 months prior to dosing with official documentation (e.g., hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy, hysterectomy, or bilateral oophorectomy), or be postmenopausal with amenorrhea for at least 1 year prior to dosing and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per Principal Investigator's judgment	Females of non-childbearing potential (18 to 50 years of age (inclusive)), who have undergone a sterilization procedure at least 6 months prior to dosing with official documentation (e.g., bilateral tubal ligation or bilateral salpingectomy orhysterectomy), or be postmenopausal with amenorrhea for at least 1 year prior to dosing and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per Principal Investigator's judgment	Removed procedures that may necessitate the use of HRT (HRT is not allowed in this study as a concomitant medication)
8.2.	Smokers (subjects who have smoked within 6 months at screening or those with positive results from smoking screening)	Smokers (subjects who have smoked within 6 months at screening)	Updated language to build in flexibility to assess this criterion
8.2.	Documented congenital QT syndrome. Corrected QT interval (QTc) using Fridericia correction	History of Familial Short QT syndrome.	Updated exlusion to be more appropriate for cenobamate

	(QTcF) at Screening or pre-dose > 450 ms		exclusion criterion
9.2.	Concomitant treatment (other than hormonal contraceptives for women of childbearing potential) is not permitted throughout the study. No medication other than the study products and hormonal contraception for women of childbearing potential is allowed during the study unless absolutely required for treatment of AEs.	The use of any investigational drug is prohibited within 30 days before the first administration of cenobamate. The use of any prescription or over-the-counter drug (other than hormonal contraceptives for women of childbearing potential) is prohibited within less than 15 days before the first administration of cenobamate, with the exception of vitamin/mineral supplements and the occasional use of acetaminophen, which is allowed up to 24 hours before dosing in any treatment period.	Updated the language to allow for the as needed administration of acetaminophen as well as the timing of when acetaminophen can be administered
10.5.	Study drug will be administered orally in either tablet or solution formulation.	Study drug will be administered orally in either tablet or suspension formulation.	Updated language to reflect proper dosage form
12.1.	Safety assessments will include physical examination, vital signs, safety laboratory tests, continuous AE monitoring, and concomitant medication recording. Additional safety measurements may be performed at the discretion of the Investigator for reasons related to subject safety.	Safety assessments will include physical examination, vital signs, safety laboratory tests, continuous AE monitoring, C-SSRS review and concomitant medication recording. Additional safety measurements may be performed at the discretion of the Investigator for reasons related to subject safety.	Added C-SSRS review to harmonize with updated schedule of assessments
12.1.	1. Vital signs; 2. PK blood sampling; 3. Blood and urine sampling for safety laboratory assays; 4. Physical examination.	1. Vital signs; 2. PK blood sampling; 3. Blood and urine sampling for safety laboratory assays; 4. Symptom oriented physical examination.	Clarified type of physical exam
12.1.3.	Blood pressure, pulse rate, and respiratory rate will be measured after being in supine position for at least 10 minutes.	Blood pressure, pulse rate, and respiratory rate will be measured after being in supine position for at least 5 minutes.	Updated supine position time requirement to allow for quicker assessment

12.1.4.		Added a "Suicidality Assessment" section to address the added C-SSRS assessment	Needed to add this section to harmonize with the updated schedule of assessments
12.1.7.	ECG will not be collected.	ECG will be collected at screening and baseline only. A subject must be in the supine position for at least 10 mins prior to any ECG reading. An ECG may be repeated if necessary	Updated language as ECG will in fact be collected at baseline and screening.
12.1.8.3.	Urine will not be collected in this study outside of pregnancy testing.	Please refer to Table 8 for urinalysis assessments to be collected throughout the study at times specified in Table 4	Updated language as urinalysis will be conducted per Table 8 and Table 4
12.1.8.8.	Intrauterine device (placement at least 3 months prior to the Screening visit) with appropriate medical documentation;	Intrauterine device (placement at least 3 months prior to the Screening visit);	Removed language to require appropriate medical documentation to add flexibility for the source of this assessment
12.5.3.	During Study Day 1, subjects will be provided a card with the following hypersensitivity information and will be instructed to carry with them at all times:	During Study Day 4 (prior to discharge from CRU), subjects will be provided a card with the following hypersensitivity information and will be instructed to carry with them at all times:	Updated timing to harmonize with schedule of assessments
19.	Cenobamate (YKP3089) Investigator's Brochure, September 27, 2019 (Version 13).	Cenobamate (YKP3089) Investigator's Brochure, October 05, 2020 (Version 14).	Updated to most recent version of the IB

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
Clinical Trial Manager	Steven Jolly	SK Life Science, Inc. 461 From Road, 5th Floor Paramus, NJ 07652 Telephone: +1 (201) 500-6024 Email: sjolly@sklsi.com
Responsible Physician	Marc Kamin, MD	SK Life Science, Inc. 461 From Road, 5th Floor Paramus, NJ 07652 Telephone: +1 (201) 421-3830 Mobile: +1 (201) 602-3235 Email: mkamin@sklsi.com
Drug Safety Physician	Marc Kamin, MD	SK Life Science, Inc. 461 From Road, 5th Floor Paramus, NJ 07652 Telephone: +1 (201) 421-3830 Mobile: +1 (201) 602-3235 Email: mkamin@sklsi.com
24-Hour Emergency Contact	Marc Kamin, MD	SK Life Science, Inc. 461 From Road, 5th Floor Paramus, NJ 07652 Telephone: +1 (201) 421-3830 Mobile: +1 (201) 602-3235 Email: mkamin@sklsi.com

2. SYNOPSIS

Name of Sponsor/Company: SK Life Science, Inc.		
Name of Investigational Product: Cenobamate (YKP3089)		
Name of Active Ingredient: [(1R)-1-(2-Chlorophenyl)-2-(tetrazol-2-yl)ethyl] carbamate		
Protocol Number: YKP3089C037	**Phase: 1**	**Country: USA**
Title of Study: Relative Bioavailability of a Single 200 mg Dose of Cenobamate Given as an Oral Tablet or as an Oral Suspension and the Effect of Food on a Single 200 mg Dose of Cenobamate Given as an Oral Suspension		
Study center(s): PRA Health Sciences, 1255 East 3900 South Salt Lake City, UT 84124		
Principal Investigator: Ahad Sabet, MD		
Studied Period (years): 2021 Estimated date first patient enrolled: 11 January 2021 Estimated date last patient completed: 21 March 2021		

Objectives:

Primary:

1. The relative bioavailability of 200 mg of cenobamate given as an oral tablet vs 200 mg of cenobamate given as an oral suspension in fasting condition and;
2. The effect of food on the bioavailability of a 200 mg oral dose of cenobamate given as a suspension

Secondary:

- The secondary objective of this study is to assess the safety and tolerability of a single 200 mg dose of cenobamate given as either an oral tablet in fasting condition or an oral suspension in fasting and fed conditions

Study Design:

- This study is an open-label, randomized, single-dose, single-center, three-period, six-sequence, balanced crossover study in healthy male and female subjects to assess the relative bioavailability of 200 mg of cenobamate given as an oral tablet or oral suspension and to evaluate the effect of food on the bioavailability of a 200 mg dose of cenobamate given as an oral suspension in fasting and fed conditions.

Endpoints:

Primary Endpoints:

Pharmacokinetic assessment for cenobamate in plasma

- C_{max}: Maximum observed plasma concentration
- t_{max}: Time to reach C_{max}
- AUC_{last}: AUC from the time of dosing to the time of the last measurable concentration
- AUC_{∞}: AUC from time 0 extrapolated to infinity

Secondary Endpoints:

Safety and Tolerability

- Adverse events (AEs)
- Safety laboratory tests (including clinical chemistry, hematology, coagulation and urinalysis)
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature)
- Physical examination

Further Endpoints:

Pharmacokinetic assessment for cenobamate in plasma

- $AUC_{\%extrap}$: Percentage of the AUC that was extrapolated
- C_{last}: Last quantifiable concentration
- $t_{½}$: Terminal half-life
- CL/F: Oral clearance
- λ_z: Terminal rate constant
- V_z/F: Apparent volume of distribution during terminal phase

Number of Subjects: 24

Subjects will be balanced amongst gender and ethnic groups to the extent possible. A subject who prematurely ends the study and who received treatment may be replaced. In case of discontinuation related to an adverse event, the replacement will be discussed between the Investigator and SKLSI.

Main Inclusion Criteria:

1. Male or female subjects of 18 to 50 years of age (inclusive), at the time of screening
2. Able to read, understand, sign, and date a written informed consent form (ICF) before study participation at screening
3. Agree to use effective methods of contraception as described in Section 12.1.7.8 and Section 12.1.7.9.
4. Body mass index (BMI) between 18.5 and 30.0 kg/m^2 (inclusive) at screening
5. Judged to be in good health on the basis of medical history, physical examination, and routine laboratory measurements (i.e., without clinically relevant pathology)
6. Electrocardiogram (ECG) (12-lead), arterial blood pressure, and heart rate within the normal range of the study center or considered not clinically significant by the Investigator.
7. Able to understand and comply with protocol requirements and instructions and likely to complete the study as planned
8. Females of non-childbearing potential (18 to 50 years of age (inclusive)), who have undergone a sterilization procedure at least 6 months prior to dosing with official documentation (e.g., bilateral tubal ligation or bilateral salpingectomy or hysterectomy), or be

postmenopausal with amenorrhea for at least 1 year prior to dosing and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per Principal Investigator's judgment

Investigational product, dosage and mode of administration:

- Active Substance: Cenobamate (YKP3089)
- Activity: Reducer of repetitive neuronal firing by enhancing the fast and slow inactivation of sodium channels and by inhibiting the persistent component of the sodium current. A positive allosteric modulator of six subtypes of the γ-aminobutyric acid (GABAA) ion channel.
- Strength: 200 mg oral tablets or 200 mg (10 mg/mL) oral suspension
- Dosage Form: Tablet or Suspension
- Manufacturer (tablets): Manufactured by Patheon, Whitby, Canada for SK Life Science, Inc.
- Manufacturer (suspension): Manufactured by CoreRx, Florida, USA for SK Life Science, Inc.

Study Treatment:

- Treatment A: Oral Dose of cenobamate administered as a single 200 mg tablet on Day 1 under fasted conditions
- Treatment B: Oral Dose of cenobamate administered as a single 200 mg/20 mL suspension on Day 1 under fasted conditions
- Treatment C: Oral Dose of cenobamate administered at a single 200 mg/20 mL suspension on Day 1 under fed conditions

Study Population: Healthy Volunteers

Study Schedule:

The study consists of a 28-day screening period, followed by single dose administration of cenobamate (tablet or suspension) on Day 1, Day 22, and Day 43, an assessment period of 62 days and a follow-up visit on Day 69. All subjects will be confined to the clinical site from Day -1 (the day before period 1 dosing) until the morning of Day 4, Day 20 (the day of the last PK sampling for period 1) until the morning of Day 25, and Day 41 (the day of the last PK sampling for period 2) until the morning of Day 46. Outpatient visits will be performed regularly until the 456-hour PK sampling for each period (See Table 4). The follow-up visit will occur on Day 69 (±1 day).

Screening:

All subjects will be screened within 28 days up to 2 days prior to the study drug administration

Admission:

Admission in the clinical unit will occur in the morning of Day -1 for Period 1, Day 20 for end of Period 1 and beginning of Period 2 and Day 41 for end of Period 2 and beginning of Period 3. All subjects will be admitted in a fasted state

Assessment Period:

The study drug will be administered in the morning of Day 1, Day 22, and Day 43 for Period 1, Period 2, and Period 3, respectively. Study drug will be administered after all pre-dose assessments have been completed. The subjects will stay at the clinical site until Day 4, Day 25, and Day 46 for Period 1, Period 2, and Period 3, respectively. The subjects will be discharged after completion of all scheduled assessments. Outpatient visits will be performed as outlined in Table 4.

Follow-up:

A follow-up visit will be performed on Day 69 (±1 day)

Refer to the Schedule of Assessments (Table 4) for further details.

Reference therapy, dosage and mode of administration:

Treatment A: Oral Dose of cenobamate administered as a single 200 mg tablet on Day 1 under fasted conditions

Treatment B: Oral Dose of cenobamate administered as a single 200 mg/20 mL suspension on Day 1 under fasted conditions

Treatment C: Oral Dose of cenobamate administered as a single 200 mg/20 mL suspension on Day 1 under fed conditions

Evaluation:

Pharmacokinetics:

Serial blood samples for PK assessments will be sampled at various time points from Day 1, Day 22, and Day 43 starting at pre-dose through 456 hours (20 days) following oral administration of cenobamate tablets or suspension (See Table 4).

The PK samples may be used for additional exploratory PK and/or metabolite analyses.

Descriptive statistics and graphs will be generated for plasma concentrations and PK parameters for each treatment.

The formulation effect will be tested for: Cenobamate oral suspension administered under fed and fasting conditions and cenobamate oral tablet administered under fasting conditions. These analyses will be conducted separately on C_{max}, AUClast and AUC∞ using a mixed model on the log transformed data with treatment, sequence and period as fixed effects and subject within sequence as random effect. Geometric mean ratios (GMRs) will be computed for:

1. Cenobamate oral suspension administered under fasted conditions versus cenobamate oral tablet administered under fasting conditions
2. Cenobamate oral suspension administered under fed conditions versus cenobamate oral suspension administered under fasting conditions

Additionally, for the above comparisons, the corresponding 90% confidence intervals (90% CIs) will be calculated. No formulation effect or food interaction will be concluded when the 90% CIs are within the reference range [0.80 – 1.25]. For each subject, the Wilcoxon signed-rank test will be used to test for differences in tmax.

Safety:

Safety data will be summarized with descriptive statistics and frequency tables. AEs will be coded using MedDRA. Prior and concomitant medications will be listed using WHO Drug Dictionary Enhanced™ (WHO DDE). Data listings and tabulations will be generated for all safety assessments.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

1. TITLE PAGE 1
SIGNATURE PAGE 2
INVESTIGATOR'S AGREEMENT 3
AMENDMENT 1 SUMMARY OF CHANGES 4
PROCEDURES IN CASE OF EMERGENCY 12
2. SYNOPSIS 13
3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 18
4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 26
5. INTRODUCTION 29
5.1. Background 29
5.1.1. Non-Clinical Experience 29
5.1.2. Clinical Human Experience 29
5.1.2.1. Clinical Pharmacokinetics 29
5.1.2.2. Clinical Safety 30
5.2. Benefit-Risk Assessment 31
5.3. Rationale for Present Study 32
5.3.1. Study Design Rationale 32
5.3.2. Anticipated Pharmacokinetic Behavior 32
5.3.2.1. Food Effect on Cenobamate Suspension 32
5.3.2.2. Relative Bioavailability Between Cenobamate Suspension and Cenobamate Tablet 32
6. TRIAL OBJECTIVES AND PURPOSE 33
6.1. Primary Objective 33
6.2. Secondary Objectives 33
6.3. Endpoints 33
6.3.1. Primary Endpoints 33
6.3.2. Secondary Endpoints 33
6.3.3. Further Endpoints 33
7. INVESTIGATIONAL PLAN 34
7.1. Overall Study Design 34

7.1.1. Visits 40
7.1.1.1. Visit 1 (Screening) 40
7.1.1.2. Visit 2 (Baseline) (Beginning Day -1) 40
7.1.1.3. Visit 3 (Morning of Day 6) 40
7.1.1.4. Visit 4 (Morning of Day 9) 41
7.1.1.5. Visit 5 (Morning of Day 12) 41
7.1.1.6. Visit 6 (Morning of Day 16) 41
7.1.1.7. Visit 7 (Beginning on the Morning of Day 20) 41
7.1.1.8. Visit 8 (Morning of Day 27) 42
7.1.1.9. Visit 9 (Morning of Day 30) 42
7.1.1.10. Visit 10 (Morning of Day 33) 42
7.1.1.11. Visit 11 (Morning of Day 37) 42
7.1.1.12. Visit 12 (Beginning on the Morning of Day 41) 43
7.1.1.13. Visit 13 (Morning of Day 48) 43
7.1.1.14. Visit 14 (Morning of Day 51) 43
7.1.1.15. Visit 15 (Morning of Day 54) 43
7.1.1.16. Visit 16 (Morning of Day 58) 44
7.1.1.17. Visit 17 (Morning of Day 62) 44
7.1.1.18. Visit 18 Follow-Up (Day 69) 44
7.2. Number of Subjects 44
7.3. Treatment Assignment 44
7.3.1. Methods for Treatment Group Assignment 45
7.3.2. Allocation of Subject Numbers 45
7.4. Dose Adjustment Criteria 45
7.4.1. Safety Criteria for Adjustment or Stopping Doses 45
7.4.2. Pharmacokinetic Criteria for Adjustment or Stopping Doses 46
7.5. Criteria for Study Termination 46
8. SELECTION AND WITHDRAWAL OF SUBJECTS 47
8.1. Subject Inclusion Criteria 47
8.2. Subject Exclusion Criteria 47
8.3. Subject Withdrawal Criteria 49
8.3.1. Withdrawn Subject Data Collection 49
8.3.2. Lost to Follow-Up 49

8.3.3. Replacement of Subjects....50
9. TREATMENT OF SUBJECTS....51
9.1. Description of Study Drug....51
9.2. Concomitant Medications....51
9.2.1. Prior Treatments....51
9.3. Treatment Compliance....52
9.3.1. Lifestyle Guidelines....52
9.3.1.1. Meals and Dietary Restrictions....52
9.3.1.2. Alcohol, Caffeine, and Tobacco....52
9.3.1.3. Physical Activity....53
9.4. Randomization and Blinding....53
10. STUDY DRUG MATERIALS AND MANAGEMENT....54
10.1. Study Drug....54
10.1.1. Cenobamate Oral Tablet....54
10.1.2. Cenobamate Oral Suspension....54
10.2. Study Drug Packaging and Labeling....54
10.3. Study Drug Storage....54
10.4. Study Drug Preparation....54
10.5. Administration....55
10.5.1. Timing of Doses in the Study....55
10.5.1.1. Timing of Doses for Treatment A and Treatment B....55
10.5.1.2. Timing of Doses for Treatment C....55
10.5.2. High-Calorie, High-Fat Meal for Treatment C....55
10.6. Study Drug Accountability....56
10.7. Study Drug Handling and Disposal....56
11. PHARMACOKINETIC ASSESSMENTS....57
11.1. Blood Sample Collection....57
11.2. Urine Sample Collection....58
11.3. Sample Analysis....58
11.3.1. Sample Processing and Handling for PK Assessment....58
11.3.2. Bioanalysis....58
11.3.3. Exploratory Pharmacogenomic Assessments....58
12. ASSESSMENT OF SAFETY....59

12.1. Safety Parameters 59
12.1.1. Adverse Events 59
12.1.2. Demographic/Medical History 60
12.1.3. Vital Signs 60
12.1.4. Suicidality Assessment 60
12.1.5. Weight and Height 60
12.1.6. Physical Examination 60
12.1.7. Electrocardiogram (ECG) 61
12.1.8. Laboratory Assessments 61
12.1.8.1. Hematology 62
12.1.8.2. Blood Chemistry 62
12.1.8.3. Urinalysis 62
12.1.8.4. Virus Serology 62
12.1.8.5. Drug Screen 63
12.1.8.6. Additional Tests 63
12.1.8.7. Pregnancy 63
12.1.8.8. Contraception for Female Subjects 63
12.1.8.9. Contraception for Male Subjects 64
12.2. Adverse and Serious Adverse Events 64
12.2.1. Definitions of Adverse Events 65
12.2.1.1. Adverse Event (AE) 65
12.2.1.2. Serious Adverse Event (SAE) 65
12.2.1.3. Severity Assessment 66
12.2.1.4. Causality Assessment 67
12.3. Relationship to Study Drug 67
12.4. Recording Adverse Events 68
12.5. Reporting Adverse Events 68
12.5.1. Routine Reporting 68
12.5.2. Serious Adverse Reporting 69
12.5.3. Rash/Hypersensitivity/DRESS Syndrome 71
13. STATISTICS 73
13.1. Statistical and Analytical Plans 73
13.1.1. Sample Size and Power 73

13.1.2. Analysis Populations 73
13.1.3. Pharmacokinetic Analysis 73
13.1.3.1. Pharmacokinetic Parameters 73
13.1.3.2. Formulation and Food Effect Analysis 74
13.1.3.3. Analysis on T_{max} 74
13.1.3.4. Summary and Presentation of PK Data and Parameters in the CSR 74
13.2. Other Statistical Analyses 75
13.2.1. Efficacy Analysis 75
13.2.2. Safety Analysis 75
13.2.3. Adverse Events 75
13.2.4. Clinical Laboratory Assessments 75
13.2.5. Vital Signs 75
13.2.6. Physical Examinations 75
13.2.7. Demographic Data 75
13.2.8. Baseline Characteristics and Other Data 76
14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS 77
14.1. Study Monitoring 77
14.2. Audits and Inspections 77
14.2.1. Electronic Data Capture (EDC) 77
14.2.2. Case Report Forms 78
14.3. Institutional Review Board (IRB) 78
15. QUALITY CONTROL AND QUALITY ASSURANCE 79
16. ETHICS 80
16.1. Ethics Review 80
16.2. Ethical Conduct of the Study 80
16.2.1. Subject Information and Informed Consent 80
16.2.2. Investigator Compliance 80
16.2.3. Access to Records 81
16.2.4. Subject Privacy 81
16.3. Written Informed Consent 81
17. DATA HANDLING AND RECORDKEEPING 82
17.1. Inspection of Records 82
17.2. Retention of Records 82

17.2.1. Screening 82
17.2.2. Data Quality Assurance 82
17.2.3. Investigator Documentation Responsibilities 83
18. PUBLICATION POLICY 84
18.1. Publication of Study Results 84
18.2. Clinical Study Report 84
19. LIST OF REFERENCES 85
20. APPENDICES 86

.

LIST OF TABLES

Table 1: Emergency Contact Information....12
Table 2: Abbreviations and Specialist Terms....26
Table 3: Randomized and Balanced Crossover Design....34
Table 4: Schedule of Assessments....37
Table 5: Investigational Product....51
Table 6: Acceptable Time Windows for PK Blood Sampling....57
Table 7: Blood Volume to be Collected per Subject for Drug Plasma Concentration Analysis After a Single Dose of Cenobamate (456 Hours)....57
Table 8: Clinical Laboratory Tests....61
Table 9: Blood Volume to be Withdrawn During the Conduct of the Study....62
Table 10: General Descriptions of Severity Scale....66
Table 11: Definitions of Causality Assessment....67
Table 12: Contact Information for IQVIA....70
Table 13: Contact Information for Sponsor Medical Monitor....70
Table 14: Contact Information for PRA Principal Investigator....70
Table 15: Serious Adverse Event Reporting Requirement....70
Table 16: Primary Pharmacokinetic Parameters....74

LIST OF FIGURES

Figure 1: Study Design.....36

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ANOVA	Analysis of Variance
AUC	Area under the concentration-time curve
AUC_{24h}	AUC from the time of dosing to the time of the last observation (24 h post-dose)
AUC_{∞}	AUC from time 0 extrapolated to infinity
AUC_{last}	AUC from the time of dosing to the time of the last measurable concentration
BMI	Body Mass Index
CI	Confidence Interval
CL/F	Oral clearance
CLcr	Renal creatinine clearance
C_{max}	Maximum observed plasma concentration
CNS	Central Nervous System
CPAP	Clinical Pharmacology Analysis Plan
CPK	Creatine Phosphokinase
CPMP	Committee for Proprietary Medicinal Products; Current name: Committee for Medicinal Products for Human Use (CHMP)
CRO	Clinical Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CV	Coefficient of Variation
CYP	Cytochrome P450
DDI	Drug-Drug Interactions

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
DNA	Deoxyribonucleic Acid
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GABA	Gamma-aminobutyric Acid
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LC-MS/MS	Liquid Chromatography with Tandem Mass Spectrometry
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
PI	Principal Investigator
PK	Pharmacokinetic(s)
POS	Partial Onset Seizures

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PT	Prothrombin Time; Preferred Term
QA	Quality Assurance
QC	Quality Control
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia correction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SD	Standard Deviation
SI	International System of units
SKLSI	SK Life Science, Inc.
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal half-life
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time at maximum concentration
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper Limit of Normal
US	United States
USCS	United States Customary System
V_z/F	Apparent volume of distribution during terminal phase
λ_z	Terminal rate constant

5. INTRODUCTION

5.1. Background

Cenobamate (YKP3089) is a small molecule approved in the United States (US) for the treatment of partial onset seizures (POS) in adult patients.

Refer to the most recent version of the Investigator's Brochure (IB)[1] of cenobamate for more details.

5.1.1. Non-Clinical Experience

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 $GABA_A$ 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, 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.

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.

5.1.2. Clinical Human Experience

To date, approximately 2500 subjects have been exposed to cenobamate in the clinical development program. For further details about the completed and ongoing clinical studies, please refer to the most recent version of the Investigator Brochure[1].

5.1.2.1. Clinical Pharmacokinetics

In humans, the pharmacokinetics (PK) of cenobamate has been studied after both single dose and multiple dosing in healthy subjects. The PK of cenobamate in plasma appears to be non-proportional after single oral doses ranging from 5 to 750 mg and multiple dosing ranging from 50 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 was increased (approximately 30 hours at 5-10 mg to approximately 76 hours at 750 mg). Steady state is generally achieved after 2 weeks of treatment with once daily dosing of cenobamate, and the accumulation of cenobamate in plasma over the 50-300 mg dose range was approximately 5-fold based on total exposure (AUC).[2]

Cenobamate is extensively metabolized and primarily eliminated in the urine (88% of the dose).[3] The disposition of cenobamate following tablet administration is not affected by food. The intra-

subject variability of cenobamate in healthy subjects is relatively low (about 14% for C_{max} and 4-5% for AUCs). No pharmacokinetic difference was observed for cenobamate between Japanese and non-Japanese healthy subjects.

Multiple drug-drug interaction (DDI) studies were performed in healthy subjects. The coadministration of carbamazepine, divalproex and oral contraceptives 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 25-35%, and increased phenobarbital and phenytoin plasma exposures (AUC) by approximately 37% and 84%, respectively. The coadministration of cenobamate with oral contraceptives did not significantly modify ethinylestradiol plasma exposure (AUC) but increased slightly the exposure to norethindrone by approximately 37% for cenobamate oral doses up to 100 mg/day.

After the administration of a CYP450 probe cocktail with cenobamate in healthy subjects, the results showed that a 200 mg daily dose of cenobamate induced the activity of CYP2B6 and inhibited the activity of CYP2C19. For CYP3A, cenobamate exhibited a limited induction at 100 mg/day whereas a more marked 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.

5.1.2.2. Clinical Safety

Cenobamate at oral doses of 100 mg and 200 mg/day was generally well tolerated with a predictable and consistent adverse event (AE) profile. Cenobamate at a dose of 400 mg/day required more frequent dose reductions because of CNS related AEs and resulted in a higher frequency of discontinuations due to AEs. The median of the modal dose in the 400 mg arm of Study YKP3089C017 was 300 mg/day. Adverse events (AEs) resolved upon discontinuation of cenobamate.

The most common adverse events (AEs) reported with cenobamate in adults 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, headache, diplopia, nausea, nystagmus, balance disorder, and gait ataxia. These adverse reactions were mild to moderate in severity and resolved spontaneously upon discontinuation of treatment. SAEs considered at least possibly related to cenobamate included drug reaction with eosinophilia and systemic reaction, dizziness, vertigo, ataxia, dysarthria, nystagmus (2 subjects), and suicidal ideation (2 subjects). A complete list of all SAEs during the cenobamate development program is available in the IB.[1] The SAEs reported with cenobamate reflect an expected pattern with therapy with multiple AEDs.

In subjects taking cenobamate, the most common serious AEs (SAEs) were CNS related such as hospitalization for seizures, ataxia and dizziness particularly at higher dosages. These serious

adverse events have been readily clinically identifiable. The general nature of these SAEs reflects an expected pattern in subjects with epilepsy.

Adverse events (AEs) of special interest that emerged during the cenobamate development program include rash and hypersensitivity reactions (including three cases of DRESS syndrome) with elevations of hepatic enzymes. Drug-induced hypersensitivity reactions with or without multi organ involvement (allergic reactions which may be fatal) including DRESS syndrome have been seen in patients taking cenobamate. DRESS which has occurred in <0.5% of clinical trial participants taking cenobamate stands for Drug Reaction (or Rash) with Eosinophilia and Systemic Symptoms. This condition occurs usually in the first 8 weeks after initiation of treatment and rarely happens afterwards. In a large open label safety trial of 1339 subjects exposed to cenobamate at an initial dose of 12.5mg/day and titrated every two weeks to a maximum dose of 400mg /day no cases of DRESS were identified.

Although two cases of highly elevated hepatic enzymes were identified, there were no cases that met the criteria for Hy's Law and review of the cenobamate safety database revealed that the incidence of 3X upper limit of normal (ULN) elevation of alanine aminotransferase (ALT) did not meet the criteria for the Rezulin Rule. One of the subjects with highly elevated hepatic enzymes died of multi-organ failure with pancreatic, cardiac and pulmonary failure approximately one year after starting cenobamate and one month after initiating eslicarbazepine. Final diagnosis was sepsis. The other case had elevated hepatic enzymes in conjunction with DRESS syndrome. Hepatic enzymes are carefully monitored in all clinical trials.

It is known that antiepileptic drugs increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Although isolated reports of suicidal thoughts and behavior have been reported in studies with cenobamate, the relationship between them and cenobamate has not been confirmed. Patients treated in cenobamate studies are monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

A complete list of all SAEs during the cenobamate development program is included in the current version of the IB[1]. The general nature of these SAEs reflects an expected pattern in subjects with epilepsy.

5.2. Benefit-Risk Assessment

This Phase 1 study in healthy volunteers has no direct benefit to the participating subjects.

The results of two adequate and well-controlled studies demonstrated that 100, 200 and 400 mg/day of cenobamate are effective for the treatment of partial onset seizures. The most common AEs were nervous system and gastrointestinal disorders. Adverse events were consistent, predictable, and dose related. The primary safety issue identified was DRESS syndrome. Using a low starting dose and titration every two weeks appears to have mitigated this issue. Additionally, DRESS has not been reported in any cenobamate single dose study to date. These safety issues are readily identifiable with a predictable course and resolved with discontinuation of cenobamate. Safety profile of cenobamate is comparable with other drugs in this class. Considering the measures taken to minimize risks to patients participating in clinical trials, the potential risks identified in association with cenobamate are justified by the anticipated benefits that may be afforded to patients with partial onset epilepsy.

Any subject who reports a rash or has a developing cutaneous reaction should be carefully evaluated for a drug hypersensitivity syndrome. The evaluation should include hematology and chemistry blood tests. If a subject reports a rash by telephone, an unscheduled visit should be performed as soon as possible. Investigators and coordinators must remind study subjects about the possibility of allergic reaction including rash.

Hepatic enzymes will be carefully monitored to detect any potential liver toxicity.

The subjects in this clinical study will receive single oral doses of 200 mg of cenobamate at 3 occasions in fasting or fed conditions administered as either a tablet or suspension formulation. Thus, the overall risk to the subjects enrolled in this study is deemed acceptable. Nevertheless, the subjects will be closely monitored using frequent clinical laboratory investigations and a continuous observation of their well-being.

5.3. Rationale for Present Study

5.3.1. Study Design Rationale

A new oral suspension formulation of cenobamate has recently been developed and will be used to support the cenobamate pediatric clinical program. Since a suspension formulation has not been used in any clinical trials to date, the pharmacokinetics (PK) of the suspension formulation will be investigated and compared to tablet formulation. The relative BA assessment between these 2 formulations will be performed using a single 200 mg dose of cenobamate. Additionally, a food effect on the PK of the suspension formulation will be evaluated in this study. These 2 assessments with the suspension formulation will provide the needed information to use appropriately the oral suspension formulation in future clinical studies conducted in pediatric populations.

5.3.2. Anticipated Pharmacokinetic Behavior

5.3.2.1. Food Effect on Cenobamate Suspension

A previous clinical study conducted in healthy volunteers assessing the relative bioavailability of an oral tablet formulation of cenobamate administered in fasting and fed conditions showed no statistically significant difference in the pharmacokinetics of cenobamate between the fed and fasted populations. As such, it is expected that the disposition of cenobamate will be comparable with the suspension formulation.

5.3.2.2. Relative Bioavailability Between Cenobamate Suspension and Cenobamate Tablet

The disposition of cenobamate has been previously studied after the administration of different oral formulations (capsule and tablet). No statistically significant differences were observed in the pharmacokinetics of cenobamate between these formulations. However, an oral suspension of cenobamate has not been tested in clinical studies to date. Therefore, the disposition of cenobamate as an oral liquid formulation is unknown.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objectives of this study are to assess (1) the relative bioavailability of 200 mg of cenobamate given as an oral tablet vs 200 mg of cenobamate given as an oral suspension in fasting condition and (2) the effect of food on the bioavailability of a 200 mg oral dose of cenobamate given as a suspension.

6.2. Secondary Objectives

The secondary objective of this study is to assess the safety and tolerability of a single 200 mg dose of cenobamate given as either an oral tablet in fasting condition or an oral suspension in fasting and fed conditions.

6.3. Endpoints

6.3.1. Primary Endpoints

The following primary cenobamate PK endpoints will be determined for each subject as the data permits:

- AUC_{∞}: The AUC from time 0 extrapolated to infinity
- AUC_{last}: AUC from time of dosing to the time of the last measurable concentration, and
- C_{max}: Maximum plasma concentration

6.3.2. Secondary Endpoints

The following secondary safety endpoints will be collected for each subject:

- Physical examination (PE)
- Adverse events (AEs)
- Vital signs
- Clinical laboratory safety tests including hematology

6.3.3. Further Endpoints

The following additional PK endpoints will be determined for each subject as the data permits:

- $t_{½}$: Terminal half-life
- t_{max}: Time to maximum cenobamate plasma concentration
- CL/F: Oral clearance
- λ_z: Terminal rate constant
- V_z/F: Apparent volume of distribution during terminal phase
- C_{last}: Last observed cenobamate plasma concentration

Additional PK parameters may be calculated as deemed appropriate. A complete list of all PK parameters will be provided in the Clinical Pharmacology Analysis Plan (CPAP).

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study is an open-label, randomized, single-dose, single-center, three-period, six-sequence, balanced crossover study in which healthy subjects, balanced amongst gender and ethnic groups to the extent possible, will receive either a single oral 200 mg dose of cenobamate given as a tablet under fasted conditions (Treatment A), a single oral 200 mg dose of cenobamate given as an oral suspension under fasted conditions (Treatment B), or a single oral 200 mg dose of cenobamate given as an oral suspension under fed conditions (Treatment C). All subjects will be screened to ensure that inclusion and exclusion criteria are met. The study will be explained to each subject prior to providing written informed consent.

The study will consist of a screening period followed by a dosing period where each subject will be randomized into one of six sequences in Table 3.

Table 3: Randomized and Balanced Crossover Design

	Treatment Sequence		
1	A	B	C
2	B	C	A
3	C	A	B
4	C	B	A
5	A	C	B
6	B	A	C

The study will be conducted in three periods each with single dose followed by a 21-day washout during which PK samples will be taken. The study periods will be conducted as follows:

Period 1

- Day -1 to Day 4 (morning) – Subject Confinement
- Day 1 – Dosing
- Day 6 (morning) – Subjects return to clinic for 120-hour PK sample and medical check
- Day 9 (morning) – Subject to return to clinic for 192-hour PK sample and medical check
- Day 12 (morning) – Subject to return to clinic for 264-hour PK sample and medical check
- Day 16 (morning) – Subject to return to clinic for 360-hour PK sample and medical check
- Day 20 (morning) – Subject to return to clinic for 456-hour PK sample and medical check and begin confinement for Period 2

Period 2

- Day 20 to Day 25 (morning) – Subject Confinement
- Day 22 – Pre-dose PK Sample and Dosing
- Day 27 (morning) – Subjects return to clinic for 120-hour PK sample and medical check
- Day 30 (morning) – Subject to return to clinic for 192-hour PK sample and medical check
- Day 33 (morning) – Subject to return to clinic for 264-hour PK sample and medical check
- Day 37 (morning) – Subject to return to clinic for 360-hour PK sample and medical check
- Day 41 (morning) – Subject to return to clinic for 456-hour PK sample and medical check and begin confinement for Period 3

Period 3

- Day 41 to Day 46 (morning) – Subject Confinement
- Day 43 – Pre-dose PK Sample and Dosing
- Day 48 (morning) – Subjects return to clinic for 120-hour PK sample and medical check
- Day 51 (morning) – Subject to return to clinic for 192-hour PK sample and medical check
- Day 54 (morning) – Subject to return to clinic for 264-hour PK sample and medical check
- Day 58 (morning) – Subject to return to clinic for 360-hour PK sample and medical check
- Day 62 (morning) – Subject to return to clinic for 456-hour PK sample and medical check

Follow-Up

- Day 69 ± 1 day (morning) – Subject to return to clinic for follow-up visit

The study design is outlined in Figure 1.

Figure 1: Study Design

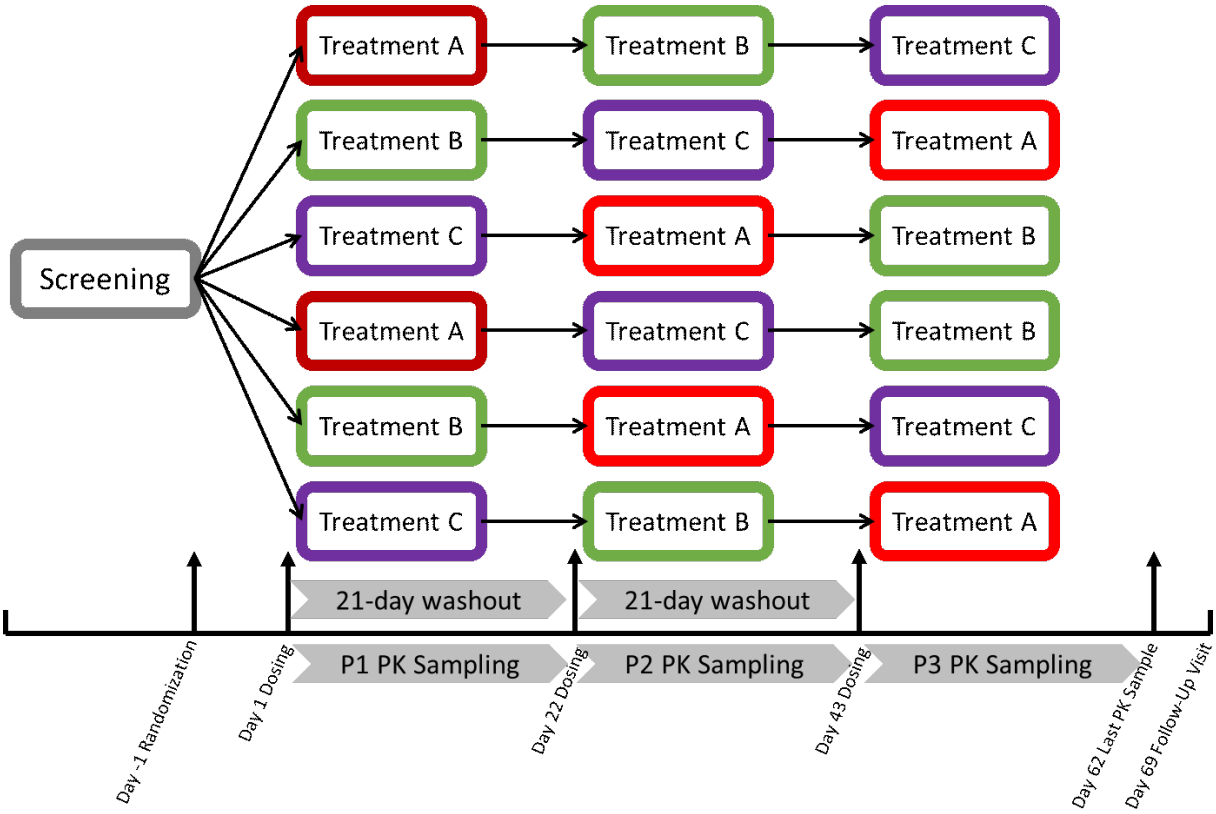

Table 4: Schedule of Assessments

Assessment	Screening	Base	Treatment Period																							FU
Visit(s)	**1**	**2,7,12[j]**																			**3,8, 13**	**4,9, 14**	**5,10, 15**	**6,11, 16**	**7,12, 17[i]**	**18**
Study Day(s)	**-28 to -2**	**-1**	**1,22,43**															**2,23, 44**	**3,24, 45**	**4,25, 46**	**6,27, 48**	**9,30, 51**	**12,33, 54**	**16,37, 58**	**20,41, 62**	**69 (±1)**
Post-Dose Time (hr)	**--**	**--**	**0**	**0.5**	**1**	**2**	**2.5**	**3**	**3.5**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**18**	**24**	**36**	**48**	**72**	**120**	**192**	**264**	**360**	**456**	**504**
Informed Consent	X																										
Inclusion/ Exclusion	X	X																									
Eligibility Confirmation		X[a]																									
C-SSRS	X[b]	X[c]																								X[c]	X[c]
Dispense Safety Card																				X							
Randomization[d]			X																								
Medical History	X																										
Demographics	X																										
Weight/ BMI	X	X																									
Height	X																										
Serum Pregnancy[e]	X																										
Urine Pregnancy[e]		X																									X
Serum FSH[e,f]	X																										

Assessment	Screening	Base	Treatment Period																							FU
Visit(s)	**1**	**2,7,12[j]**																			**3,8, 13**	**4,9, 14**	**5,10, 15**	**6,11, 16**	**7,12, 17[i]**	**18**
Study Day(s)	**-28 to -2**	**-1**	**1,22,43**															**2,23, 44**	**3,24, 45**	**4,25, 46**	**6,27, 48**	**9,30, 51**	**12,33, 54**	**16,37, 58**	**20,41, 62**	**69 (±1)**
Post-Dose Time (hr)	**--**	**--**	**0**	**0.5**	**1**	**2**	**2.5**	**3**	**3.5**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**18**	**24**	**36**	**48**	**72**	**120**	**192**	**264**	**360**	**456**	**504**
Clinical Laboratory	X	X																			X					X	X
HIV, Hep B/C	X																										
Urine Drug Screen	X	X																				X	X	X	X	X	
Breath Alcohol	X	X																				X	X	X	X	X	
Physical Exam[g]	X		X																								X
Vital Signs[h]	X		X																		X	X	X	X	X	X	X
12-lead ECG	X	X																									
Concomitant Medications		X																			X	X	X	X	X	X	X
AE Monitoring			Continuous Throughout																								
Treatment Administration			X																								
PK Blood Sampling			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacogenomic Blood Sampling		X																									
Discharge																					X						
Outpatient Visit																						X	X	X	X	X[i]	X

Note: C-SSRS= Columbia Suicide Severity Rating Scale; AE = adverse event; BMI = body mass index; ECG = electrocardiogram; FSH = follicle stimulating hormone; h = hour; PK = pharmacokinetic

[a] Review Inclusion/Exclusion on Day -1

[b] Baseline "Baseline/Screening" version of C-SSRS will be used

[c] "Since Last Visit" version of the C-SSRS will be used

[d] Randomization to occur prior to dosing on Day 1.
[e] Pregnancy testing for female subjects of childbearing potential only; postmenopausal women with last menses less than one year will have a serum pregnancy and FSH test during screening only
[f] Postmenopausal women only, including women with last menses less than one year
[g] Complete physical examination at Screening; Symptom-oriented physical examination on Day 1, Day 22, Day 43 and at follow-up
[h] Vital signs (supine systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) measurement in supine position (at least 5 minutes).
[i] Note that Visit 17 only is an outpatient visit while Visit 7 and 12 are CRU admission days to bridge between periods
[j] Visit 2 is baseline visit Visits 7 and 12 are the start of periods 2 and 3 respectively

7.1.1. Visits

See Table 4 for a detailed list of study assessments by visit

7.1.1.1. Visit 1 (Screening)

The following will be performed during Visit 1:

- Subject will be seen in the clinic for a Screening visit within 28 days prior to the first dose to assess eligibility for the study
- Informed consent will be obtained prior to the performance of any study-related assessments or procedures
- The optional pharmacogenomics informed consent should be obtained at this time for willing subjects
- Screening assessments will be comprised of relevant medical history, demographics (including the assessments of body height, weight, BMI, smoking status, and alcohol history), serum pregnancy test, serum FSH, clinical labs, serology tests (HIV and Hep B/C), urine drug screening, breath alcohol, a complete physical examination, vital signs, 12-lead ECG, concomitant medications, C-SSRS and review of inclusion/exclusion criteria

7.1.1.2. Visit 2 (Baseline) (Beginning Day -1)

The following will be performed during Visit 2

- Admission to the CRU on Day -1
- Pharmacogenomic blood sampling collected on Day -1 (only if consent was obtained)
- Confirmation of eligibility (including a review of the inclusion/exclusion criteria), weight/BMI, urine pregnancy, clinical labs, urine drug screen, breath alcohol, 12-lead ECG, CSSR-S, and concomitant medications on Day -1
- Physical exam (symptom oriented) and vital signs on Day 1
- Randomization on Day 1 prior to dosing.
- Dosing of cenobamate per randomized treatment allocation on Day 1
- Clinical labs, vital signs, and concomitant medications on Day 4
- Blood samples to determine plasma drug concentrations of cenobamate Day 1 to the morning of Day 4
- AE Monitoring throughout
- Discharge on the morning of Day 4; upon discharge, subjects will be issued a hypersensitivity safety card

7.1.1.3. Visit 3 (Morning of Day 6)

The following will be performed during Visit 3

- Outpatient visit
- Urine drug screen, breath alcohol, vital signs, and concomitant medications
- AE Monitoring throughout
- Blood sample to determine plasma drug concentrations of cenobamate

7.1.1.4. Visit 4 (Morning of Day 9)

The following will be performed during Visit 4

- Outpatient visit
- Urine drug screen, breath alcohol, vital signs, and concomitant medications
- AE Monitoring throughout
- Blood sample to determine plasma drug concentrations of cenobamate

7.1.1.5. Visit 5 (Morning of Day 12)

The following will be performed during Visit 5

- Outpatient visit
- Urine drug screen, breath alcohol, vital signs, and concomitant medications
- AE Monitoring throughout
- Blood sample to determine plasma drug concentrations of cenobamate

7.1.1.6. Visit 6 (Morning of Day 16)

The following will be performed during Visit 6

- Outpatient visit
- Urine drug screen, breath alcohol, vital signs, and concomitant medications
- AE Monitoring throughout
- Blood sample to determine plasma drug concentrations of cenobamate

7.1.1.7. Visit 7 (Beginning on the Morning of Day 20)

The following will be performed during Visit 7

- Admission to the CRU on Day 20
- Clinical labs, urine drug screen, breath alcohol, vital signs, C-SSRS, concomitant medications on Day 20
- Blood sample to determine plasma drug concentrations of cenobamate on Day 20 for end of Period 1 sampling
- Dosing of cenobamate per randomized treatment allocation on Day 22
- Physical exam (symptom oriented) and vital signs on Day 22

- Blood sampling to determine plasma drug concentrations of cenobamate on Day 22 to the morning of Day 25 for beginning of Period 2 sampling
- Clinical labs, vital signs, and concomitant medications on Day 25
- AE Monitoring throughout
- Discharge on the morning of Day 25; upon discharge, subjects will be issued a hypersensitivity safety card

7.1.1.8. Visit 8 (Morning of Day 27)

The following will be performed during Visit 8

- Outpatient visit
- Urine drug screen, breath alcohol, vital signs, and concomitant medications
- AE Monitoring throughout
- Blood sample to determine plasma drug concentrations of cenobamate

7.1.1.9. Visit 9 (Morning of Day 30)

The following will be performed during Visit 9

- Outpatient visit
- Urine drug screen, breath alcohol, vital signs, and concomitant medications
- AE Monitoring throughout
- Blood sample to determine plasma drug concentrations of cenobamate

7.1.1.10. Visit 10 (Morning of Day 33)

The following will be performed during Visit 10

- Outpatient visit
- Urine drug screen, breath alcohol, vital signs, and concomitant medications
- AE Monitoring throughout
- Blood sample to determine plasma drug concentrations of cenobamate

7.1.1.11. Visit 11 (Morning of Day 37)

The following will be performed during Visit 11

- Outpatient visit
- Urine drug screen, breath alcohol, vital signs, and concomitant medications
- AE Monitoring throughout
- Blood sample to determine plasma drug concentrations of cenobamate

7.1.1.12. Visit 12 (Beginning on the Morning of Day 41)

The following will be performed during Visit 12

- Admission to the CRU on Day 41
- Clinical labs, urine drug screen, breath alcohol, vital signs, C-SSRS, concomitant medications on Day 41
- Blood sample to determine plasma drug concentrations of cenobamate on Day 41 for end of Period 2 sampling
- Physical exam (symptom oriented) and vital signs on Day 43
- Dosing of cenobamate per randomized treatment allocation on Day 43
- Blood sampling to determine plasma drug concentrations of cenobamate on Day 43 to the morning of Day 46 for beginning of Period 3 sampling
- Clinical labs, vital signs, and concomitant medications on Day 46
- AE monitoring throughout
- Discharge on the morning of Day 46; upon discharge, subjects will be issued a hypersensitivity safety card

7.1.1.13. Visit 13 (Morning of Day 48)

The following will be performed during Visit 13

- Outpatient visit
- Urine drug screen, breath alcohol, vital signs, and concomitant medications
- AE Monitoring throughout
- Blood sample to determine plasma drug concentrations of cenobamate

7.1.1.14. Visit 14 (Morning of Day 51)

The following will be performed during Visit 14

- Outpatient visit
- Urine drug screen, breath alcohol, vital signs, and concomitant medications
- AE Monitoring throughout
- Blood sample to determine plasma drug concentrations of cenobamate

7.1.1.15. Visit 15 (Morning of Day 54)

The following will be performed during Visit 15

- Outpatient visit
- Urine drug screen, breath alcohol, vital signs, and concomitant medications
- AE Monitoring throughout

- Blood sample to determine plasma drug concentrations of cenobamate

7.1.1.16. Visit 16 (Morning of Day 58)

The following will be performed during Visit 16

- Outpatient visit
- Urine drug screen, breath alcohol, vital signs, and concomitant medications
- AE Monitoring throughout
- Blood sample to determine plasma drug concentrations of cenobamate

7.1.1.17. Visit 17 (Morning of Day 62)

The following will be performed during Visit 17

- Outpatient visit
- Urine drug screen, breath alcohol, vital signs, and concomitant medications
- AE Monitoring throughout
- Blood sample to determine plasma drug concentrations of cenobamate

7.1.1.18. Visit 18 Follow-Up (Day 69)

The following will be performed during Visit 18

- Final outpatient visit
- Urine pregnancy, clinical labs, physical exam (symptom oriented), vital signs C-SSRS and concomitant medications
- AE Monitoring throughout

7.2. Number of Subjects

A total of 24 (4 subjects per sequence) healthy female and male subjects, balanced by gender and race/ethnicity to the extent possible, will be included in the study.

If needed and agreed upon by SKLSI and investigator, replacement subjects will be assigned to the same treatment sequence as the subject they are replacing in order to have at least 20 subjects completing all three treatments.

7.3. Treatment Assignment

The study will contain the following treatment groups:

- **Treatment A:** 200 mg cenobamate oral tablet under fasting condition
- **Treatment B:** 200 mg cenobamate oral suspension under fasting condition
- **Treatment C:** 200 mg cenobamate oral suspension under fed condition

7.3.1. Methods for Treatment Group Assignment

After obtaining oral and written informed consent, subjects will be screened according to the inclusion and exclusion criteria (Section 8.1 and Section 8.2). Prior to dosing on Day 1, subjects will be randomized to receive one of three treatment schemes as outlined in Table 3. The randomization schedule will be generated by the statistician responsible for this study using SAS® software. One copy of the randomization list will be provided to the pharmacist for preparation of the appropriate treatment. Subjects withdrawn from the study retain their randomization number, if already given. New subjects must always be allotted a new randomization number. Once assigned, randomization numbers must not be reused within the study site.

Subjects who drop-out for any reason or withdraw consent prior to dosing will be considered as screen failures. Such subjects will not receive a unique subject number. The Investigator will keep a screening log of all screen failure subjects, along with the reasons for their screen failure.

7.3.2. Allocation of Subject Numbers

Once a subject has signed the ICF, that subject will be assigned an 8-digit subject identification number (subject ID) e.g. 01001001. The first two digits is for country, the next 3 digits for site, and the last 3 digits for subject. Subject numbers will be allocated sequentially in the order in which the subjects are screened. Once assigned, subject identification numbers must not be reused. The subject number will ensure identification throughout the study.

Subjects withdrawn from the study will retain their subject identification numbers. Any replacement subject will receive the subject number from the subject they are replacing + 100, e.g., replacement for 01001003 would have the subject identification number 01001103.

Subjects who fail screening will be allowed to re-screen only once. The re-screened subject will be assigned a new subject number, and the linking information for these two subject numbers will be recorded in CRF.

7.4. Dose Adjustment Criteria

The dose will not be adjusted in this study.

7.4.1. Safety Criteria for Adjustment or Stopping Doses

The dose of this study will not be adjusted. However, the Investigator may withdraw a subject at any time if it is determined that continuing the study would result in a significant safety risk to the subject.

Subjects will be discontinued from the clinical study for any of the following reasons:

- Females who are pregnant according to a positive pregnancy test,
- Positive screening of alcohol and/or drugs of abuse,
- If following the first dose, a subject develops any rash related to the study drug.

Furthermore, participation in the clinical study could be discontinued by the Investigator in charge of the study or by SKLSI for any of the following reasons:

- Clinically significant abnormality on vital signs, clinical laboratory, or physical examination assessments, as assessed by the investigator or designee,
- Rash or manifestation of hypersensitivity reaction such as lymphadenopathy, fever, or facial swelling related to the study drugs,
- Noncompliance with the protocol requirements (e.g., blood collection deviations which may impact the PK profile),
- The subject is uncooperative during the study,
- Occurrence of intolerable adverse event (AE),
- Lost to follow-up,
- Unanticipated event which could result in an inadequately characterized PK profile, such as missed blood draws, AE, or need to use concomitant medications.

If a subject prematurely discontinues, or is discontinued from the study, the primary reason for the discontinuation will be obtained and recorded on the CRF.

Replacement subjects may be added at SKLSI's discretion, in agreement with the investigator.

7.4.2. Pharmacokinetic Criteria for Adjustment or Stopping Doses

There are no pre-defined Pharmacokinetic criteria for adjusting or stopping doses. Subject termination will be governed by safety, tolerability and Investigator discretion.

7.5. Criteria for Study Termination

SK Life Science, Inc. (SKLSI) may terminate the study at any time. For reasonable cause, either the Investigator or the IRB may terminate the study as well. Conditions that may warrant termination include, but are not limited to:

- subject or investigator noncompliance,
- unsatisfactory subject enrollment,
- lack of adherence to protocol procedures,
- lack of evaluable and/or complete data,
- potentially unacceptable risk to study subjects,
- decision to modify drug development plan,
- decision by the FDA or other regulatory authority.

Written notification that includes the reason for the protocol termination is required.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

Healthy subjects who meet all the inclusion criteria and none of the exclusion criteria will be eligible for participation in this study. The study population will consist of a balanced representation of genders and ethnic groups to the extent possible.

Adherence to the study design requirements, including those specified in the schedule of assessments (Table 4), is essential and required for study conduct. Continued eligibility will be assessed upon entry into the clinic prior to the start of each visit.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The subject's selected by the clinical site will be reviewed by SKLSI for final approval. The investigator will maintain a screening log in order to record details of all screened subjects and to confirm eligibility or record reasons for screening failure, as applicable.

Subjects may be re-screened only once within an appropriate time window in case of out of range results.

8.1. Subject Inclusion Criteria

3. Male or female subjects of 18 to 50 years of age (inclusive), at the time of screening
4. Able to read, understand, sign, and date a written informed consent form (ICF) before study participation at screening
5. Agree to use effective methods of contraception as described in Section 12.1.7.8 and Section 12.1.7.9.
6. Body mass index (BMI) between 18.5 and 30.0 kg/m^2 (inclusive) at screening
7. Judged to be in good health on the basis of medical history, physical examination, and routine laboratory measurements (i.e., without clinically relevant pathology)
8. Electrocardiogram (ECG) (12-lead), arterial blood pressure, and heart rate within the normal range of the study center or considered not clinically significant by the Investigator.
9. Able to understand and comply with protocol requirements and instructions and likely to complete the study as planned
10. Females of non-childbearing potential (18 to 50 years of age (inclusive)), who have undergone a sterilization procedure at least 6 months prior to dosing with official documentation (e.g., bilateral tubal ligation or bilateral salpingectomy orhysterectomy), or be postmenopausal with amenorrhea for at least 1 year prior to dosing and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per Principal Investigator's judgment

8.2. Subject Exclusion Criteria

1. Clinically relevant abnormal medical history, abnormal findings on physical examination, vital signs, ECG, or laboratory tests at Screening that the Investigator judges as likely to interfere with the objectives of the trial or the safety of the volunteer

2. Smokers (subjects who have smoked within 6 months at screening)
3. History of any drug related hypersensitivity reactions as well as severe hypersensitivity reactions (like angioedema) or DRESS as evaluated by the Investigator
4. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with pharmacokinetics of the study drug (except appendectomy and simple hernia repair)
5. Any prescribed or over-the-counter medication taken within 2 weeks prior to start of administration of study drug (Day 1) or within 6 times the elimination half-life of the medication prior to start of study drug intake (whichever is longer). Occasional use of acetaminophen is allowed up until 24 hours before dosing
6. Consumption of herbal medications, dietary supplements and specific fruit products. Subjects should have stopped consumption of herbal medications or dietary supplements (e.g., St. John's Wort, ginkgo biloba, and garlic supplements), and grapefruit or grapefruit juice, or Seville oranges at least 2 weeks before the first dosing day of study drug. Vitamins/mineral supplements are allowed up until 24 hours before dosing
7. History of drug or alcohol abuse or addiction within 2 years before the start of study drug dosing, or a positive test results for alcohol or drugs of abuse, such as amphetamine, barbiturate, benzodiazepine, cocaine, methadone, opiates, oxycodone, phencyclidine, propoxyphene, cannabinoid (THC), MDMA (Ecstasy), methaqualone, and tricyclic antidepressant (TCA)
8. Regular consumption of more than 2 units of alcoholic beverages per day or more than 14 units per week (1 unit of alcohol equals 1 pint [473 mL] of beer or lager, 1 glass [125 mL] of wine, 25 mL shot of 40% spirit) before screening
9. Consumption of an average of more than 5 servings (8 ounces per serving) per day of coffee, cola, or other caffeinated or methyl xanthine beverages before screening
10. Consumption of any caffeine- or methyl xanthine-containing products (e.g., coffee, tea, chocolate, or soda) or alcoholic beverages within 48 hours prior to Day 1 of each period and until the end of each PK sampling period
11. Participation in a clinical study involving administration of either an investigational or a marketed drug within 2 months or 7 half-lives (whichever is longer) before screening
12. Blood donation or a significant loss of blood within 60 days of the start of study drug dosing or donation of more than 1 unit of plasma within 7 days before screening
13. Positive result at screening for any of the following infectious disease tests: hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab), human immunodeficiency virus antigen and antibody (HIV Ag, HIV Ab)
14. Illness within 5 days before the start of study drug dosing ("illness" is defined as an acute [serious or non-serious] condition [e.g., the flu or the common cold])
15. History of any known relevant allergy/hypersensitivity (including allergy to the trial medication or its excipients)
16. Subject who is judged not eligible for study participation by Investigator

17. History of Familial Short QT syndrome.

8.3. Subject Withdrawal Criteria

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.

8.3.1. Withdrawn Subject Data Collection

The principal Investigator and/or designee will document on the termination page of the CRF and in the subject's medical records the primary reason for the subject's withdrawal as follows:

- Lost to follow-up: subjects who leave the clinic during the hospitalization period or do not attend the following visit. Intensive efforts should be made to locate and recall them if possible and, at a minimum, to determine their health status;
- AE: an AE form must be completed; the type of AE should be specified;
- Deviation from protocol;
- Consent withdrawn;
- Other: if none of the above-mentioned reasons are applicable, then the reason will be specified.

All withdrawals will be reported immediately to SKLSI. For all dropouts, a Follow-up visit will be arranged for approximately 21 days after the most recent drug administration and will document the progress of their condition. In every case, the CRF must be filled in up to the last visit performed.

8.3.2. Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, 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 in which the subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record;

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to Follow-up.

8.3.3. Replacement of Subjects

Subjects who withdraw or are withdrawn during the study for reasons unrelated to safety may be replaced in order to have at least 20 evaluable subjects who completed the 3 treatment periods. In case of replacement, a subject will be assigned to the same treatment sequence as the discontinued subject.

In case of moderate or severe AE causing the subject to withdraw, a joint decision between SKLSI and the Investigator will be taken on the appropriateness of replacing the subject.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

Table 5 lists the details of the two cenobamate formulations to be used in this study.

Table 5: Investigational Product

	Investigational Product	
Product Name:	Cenobamate	Cenobamate
Activity:	Reducer of repetitive neuronal firing by enhancing the fast and slow inactivation of sodium channels and by inhibiting the persistent component of the sodium current. A positive allosteric modulator of six subtypes of the γ-aminobutyric acid (GABAA) ion channel.	
Dosage Form:	Tablet	Liquid Suspension
Strength:	200 mg	10 mg/mL
Route of Administration	Oral	Oral
Dosage Form	Film-coated oval (9.5 mm by 20 mm) light orange tablets	Suspension
Manufacturer	Patheon for SK Life Science, Inc	Manufactured by CoreRx, Florida, USA for SK Life Science, Inc

9.2. Concomitant Medications

The use of any investigational drug is prohibited within 30 days before the first administration of cenobamate. The use of any prescription or over-the-counter drug (other than hormonal contraceptives for women of childbearing potential) is prohibited within less than 15 days before the first administration of cenobamate, with the exception of vitamin/mineral supplements and the occasional use of acetaminophen, which is allowed up to 24 hours before dosing in any treatment period.

For any subject, if the use of any concomitant treatment becomes necessary (e.g., for the treatment of an AE), the treatment must be recorded in the CRF, including the reason for treatment, generic name of the drug, dosage, route, and date and time of administration. If a treatment is administered, SKLSI's medical monitor must be promptly notified in order to assess the subject's eligibility for continuing study participation.

9.2.1. Prior Treatments

Reasonable efforts will be made to determine all relevant treatments received by the subject within 3 months before the first administration of cenobamate (within 15 days before the first administration of cenobamate for over-the-counter drugs).

The use of any prescription or over-the-counter drugs (other than hormonal contraceptives for women of childbearing potential) as well as herbal medications, dietary supplements and specific

fruit products is prohibited within 2 weeks before the first administration of cenobamate, with the exception of vitamin/mineral supplements and the occasional use of acetaminophen, which are allowed up to 24 hours before dosing.

All relevant information must be recorded on the subject's CRF.

9.3. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All study drug administrations will be under the supervision of the Investigator or designee;
- A mouth and hand check for drug product will be carried out for each subject after dosing to ensure that all of the dose has been swallowed.

Subjects who are unable to adhere to the above measures may be removed from the study based on the SKLSI's decision (on a case-by-case basis) and the CRF will be documented accordingly.

9.3.1. Lifestyle Guidelines

9.3.1.1. Meals and Dietary Restrictions

Subjects will need to stop consuming grapefruit or drink grapefruit-containing products, or Seville oranges at least 2 weeks before the first dosing day of study drug. Vitamins/mineral supplements are allowed up until 24 hours before dosing, as specified in exclusion criteria (Section 8.2).

9.3.1.1.1. Treatment A and Treatment B Meals and Dietary Restrictions

On days that a subject will be confined to the CRU for Treatment A and/or Treatment B, an overnight fast will be imposed (when needed) so that no food is consumed within at least 10 hours before cenobamate administration. On days that a subject will be confined to the CRU, dinner will be served the day prior to dosing (Day -1, Day 21, or Day 42) ending at least 10 hours before dosing. The next meal will be a lunch approximately 4 hours after dosing the following day followed by a dinner approximately 10 hours after dosing. On subsequent days of confinement, a breakfast, lunch and dinner will be provided at appropriate times.

9.3.1.1.2. Treatment C Meals and Dietary Restrictions

On days that a subject will be confined to the CRU for Treatment C, dinner will be served the day prior to dosing (Day -1, Day 21, or Day 42) approximately 10 hours prior to dosing. On the day of dosing (Day 1, Day 22, or Day 43) a high-calorie, high-fat breakfast will be provided approximately 30 mins prior to dosing. The breakfast should be consumed with 30 minutes or less and Treatment C should be approximately 30 mins after the start of a meal (Section 10.5.2).

9.3.1.2. Alcohol, Caffeine, and Tobacco

Alcohol, caffeine, and tobacco restrictions are specified in exclusion criteria (Section 8.2). Subjects may undergo an alcohol test at the discretion of the Investigator.

9.3.1.3. Physical Activity

Subjects will abstain from strenuous exercise (e.g., heavy lifting, weight training or aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

9.4. Randomization and Blinding

This study is an open-label study.

Prior to dosing on Day 1, subjects will be randomized to receive one of six treatment sequences as outlined in Table 3. The randomization list will be generated by the statistician responsible for this study using SAS® software. One copy of the randomization list will be provided to the pharmacist for preparation of the appropriate treatment.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

10.1.1. Cenobamate Oral Tablet

The cenobamate oral tablet formulation is an Opadry® II light orange film coated tablet with the following inactive excipients: microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate.

10.1.2. Cenobamate Oral Suspension

The cenobamate oral suspension formulation is manufactured from commonly used inactive ingredients, suitable favor, preservative and sweetener.

10.2. Study Drug Packaging and Labeling

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 200 mg tablets are packaged in High Density Polyethylene (HDPE) bottles with Polypropylene (PP) CRC cap.

For oral suspension, contents are packed in amber glass bottle with CRC cap. A Push in Bottle Adapter (PIBA) suitable for the packaged bottle will be provided. The study site will obtain oral syringes of suitable capacity for dosing the oral suspension formulation of cenobamate.

SKLSI will ship a sufficient supply of cenobamate (either oral tablet formulation or oral suspension formulation) to the study site.

10.3. Study Drug Storage

At the study site, study drug must be kept in a secure, locked area or locked cabinet with access restricted to designated study site personnel. Study drug will be stored upright at room temperature in a dry area, protected from light, monitored for temperature.

10.4. Study Drug Preparation

The appropriate dose and formulation of cenobamate will be prepared and dispensed by a pharmacist at the clinical site.

Before beginning the dispensing process, the pharmacy staff will read and understand the study protocol and accompanying study treatment preparation, dispensing, and administration instructions (if applicable). Only eligible subjects participating in the study will receive the study drugs. Only authorized research site staff may supply or administer the study drugs. Any questions related to dispensing of the study drugs will be resolved prior to the start of the study by communication with an SKLSI representative. Additional study drug preparation will be followed as per the pharmacy manual.

10.5. Administration

Study drug will be administered orally in either tablet or suspension formulation.

10.5.1. Timing of Doses in the Study

10.5.1.1. Timing of Doses for Treatment A and Treatment B

- The study drug will be orally administered to subjects in the morning after a 10-hour overnight fast (no food or beverages allowed except for tap water).
- The study drug will be swallowed together with 240 mL tap water (room temperature). The study drug should be swallowed whole and should not be chewed.
- Administration of the study drug will be supervised by the Investigator or designee. After drug administration, a mouth and hand inspection will take place.
- Fasting will continue until approximately 4 hours post-dose when lunch will be served.
- Subjects will also be instructed not to drink fluids over a period extending from 2 hours prior to 2 hours after study drug administration, except water used for study drug administration.
- A dinner will be provided approximately 10 hours after dosing.

10.5.1.2. Timing of Doses for Treatment C

- The study drug will be orally administered to subjects in the morning approximately 30 minutes after the start of a high-calorie, high-fat meal.
- The study drug will be swallowed together with 240 mL tap water (room temperature). The study drug should be swallowed whole.
- Administration of the study drug will be supervised by the Investigator or designee. After drug administration, a mouth and hand inspection will take place.
- A lunch and dinner will be served approximately 4 hours and 10 hours post-dose, respectively.

10.5.2. High-Calorie, High-Fat Meal for Treatment C

Subjects that are taking the oral suspension formulation under fed conditions (Treatment C) will be given a high-calorie (approximately 800 – 1000 calories) and high-fat (approximately 50% of total caloric content of the meal) meal as recommended by the FDA.[4] This meal should derive approximately 150, 250, and 500 – 600 calories from protein, carbohydrate, and fat, respectively. For instance, the breakfast can contain 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk. Substitutions in this test breakfast can be made provided that the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. The final composition of the breakfast will be reported in the clinical study report.

Subjects receiving the high calorie, high-fat breakfast will need to adhere to the following schedule:

- The meal will be taken about 30 minutes prior to the administration of cenobamate,
- The meal should be eaten within 30 minutes or less,
- Cenobamate will be administered approximately 30 minutes after the start of the meal.

Water will be allowed ad libitum except for one hour before and after cenobamate administration, with the exception of the 240 mL of water taken with each dose.

10.6. Study Drug Accountability

The Investigator is responsible for confirming that all study drug supplies received by the study site are inventoried and accounted for throughout the study. A drug receipt log will be completed and signed by the person accepting the shipment. 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 study drug found in a given shipment will be documented in the study files. The Investigator must notify the SKLSI of any damaged or unusable study drug supplies.

10.7. Study Drug Handling and Disposal

Upon destruction of study drug, a Certificate of Destruction (COD) will be provided to SKLSI. See the Pharmacy Manual for drug handling and disposal. The clinical site will be responsible for cenobamate drug disposal.

11. PHARMACOKINETIC ASSESSMENTS

11.1. Blood Sample Collection

Blood samples for determination of cenobamate plasma concentrations will be collected by direct venipuncture into a labeled tube containing the appropriate anticoagulant as specified by the bioanalytical facilities. If judged necessary by the clinical staff, blood samples may be collected from an indwelling cannula (catheter).

The complete schedule for pharmacokinetic blood sampling is presented in Table 4. The time of blood sample collection will be calculated according to the treatment administration schedule. The clock time of the dose administration will be recorded (record time after all drug products have been swallowed). The exact actual time of blood draws will be recorded and reported for all subjects in the CRF. Actual blood collection times will be used for the PK analysis. Blood will be collected into tubes labeled with the nominal blood sampling times.

It is important to avoid hemolysis during blood collection. In case of hemolysis, this will be reported in the CRF. The impact of any observed hemolysis on the plasma concentrations may be discussed with SKLSI.

When a sampling time is close to a mealtime, the sample will be collected before the meal.

Blood samples for PK analysis should be collected at the requested times, but the allowed windows for sample collection are presented in Table 6.

Table 6: Acceptable Time Windows for PK Blood Sampling

Nominal Sampling Time	Acceptable Time Windows
Pre-dose	-30 mins before dose or immediately before dosing
0.25 to 1.5 hour post-dose	± 2 minutes
2 to 12 hours post-dose	± 5 minutes
14 to 96 hours post-dose	± 15 minutes
120 to 456 hours post-dose	± 2 hours
Follow-up	± 1 day

The approximate blood volume to be collected per subject following a single oral dose of cenobamate (tablet or suspension) is presented in Table 7.

Table 7: Blood Volume to be Collected per Subject for Drug Plasma Concentration Analysis After a Single Dose of Cenobamate (456 Hours)

Formulation (Fed Status)	Number of Timepoints	Volume per Timepoint (mL)	Total Volume (mL)
Cenobamate Oral Tablet (Fasted)	24	2	48
Cenobamate Oral Suspension (Fasted)	24	2	48
Cenobamate Oral Suspension (Fed)	24	2	48
Total	**72**	**6**	**144**

11.2. Urine Sample Collection

Urine will not be collected for PK assessment in this Study.

11.3. Sample Analysis

11.3.1. Sample Processing and Handling for PK Assessment

Detailed procedures for the sample collection, processing and handling for PK assessment will be provided in a separate document (i.e., Laboratory Manual). The shipment address and assay lab contact information will be provided to the investigational site prior to initiation of the trial.

11.3.2. Bioanalysis

Blood samples will be processed, split, stored, and shipped according to the sample processing manuals supplied by the bioanalytical facilities.

Plasma samples will be analyzed for cenobamate concentrations using a validated liquid chromatography/tandem mass spectrometry method (LC-MS/MS) with a lower limit of quantification of 0.05 µg/mL.

The method, data acceptance criteria, and criteria for sample re-assay will follow the bioanalytical facility's SOPs and the guidelines set by the Regulatory Agencies.

Pharmacokinetic sample analysis methods are further explained in Section 13.1.3.

PK blood samples may be used for metabolite or methodology exploratory analyses. Possible results from these exploratory analyses may be reported in standalone report(s) if deemed necessary.

11.3.3. Exploratory Pharmacogenomic Assessments

At the time point defined in the Schedule of Assessments (Table 4), an optional blood sample will be collected to explore the possible effect of genetic variation in the PK of cenobamate. A separate informed consent for genotyping will be obtained from each subject prior to sampling. DNA will be extracted from the blood sample in order to sequence genes coding for enzymatic or transporter systems that are involved in the absorption, distribution, metabolism and excretion (ADME) of drugs. The gene sequences to be determined include known and likely functional variations of key ADME genes and incorporate more than 90% of ADME-related genetic markers identified by the PharmaADME group (weblink.pharmaadme.org). It is not intended to include the pharmacogenomic data in the final CSR. However, this may be considered if deemed necessary. Possible results from these exploratory analyses may be reported in standalone report(s) if deemed necessary.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety assessments will include physical examination, vital signs, safety laboratory tests, continuous AE monitoring, C-SSRS review and concomitant medication recording. Additional safety measurements may be performed at the discretion of the Investigator for reasons related to subject safety.

Clinically significant physical examination findings prior to the first dose of the study treatment will be recorded as part of the medical history. Clinically significant findings after the first dose will be recorded as AEs.

The procedures and associated collection windows for vital signs will be as follows:

- On days that drug product is administered, within 2 hours for pre-dose assessments (Days 1, 22, and 43).
- ± 10 minutes for post-dose assessments (Days 4, 6, 9, 12, 16, 20, 25, 27, 30, 33, 37, 41, 46, 48, 51, 54, 58, 62 and 69).

Unless otherwise stated in this protocol, the clinical site's standard operating procedures (SOPs), which are available for all activities relevant to the quality of the study, will be followed during this study.

The study procedures to be conducted for each subject in the study are detailed in Table 4.

The order of the assessments when scheduled at the same theoretical time will be as follows:

1. Vital signs;
2. PK blood sampling;
3. Blood and urine sampling for safety laboratory assays;
4. Symptom oriented physical examination.

Any deviation from the protocol procedures will be captured in the protocol deviation tracker and filed in the Transfer Master File (TMF).

12.1.1. Adverse Events

All AEs which occur during the clinical study will be reported in detail in the source documents and documented in the eCRF from Screening, throughout the clinical conduct until the final follow-up visit. SAEs will be continuously monitored starting after the time of informed consent through the follow-up visit. The Investigator should follow all unresolved AEs until the events have resolved or have stabilized, the subject is lost to follow-up, or it has been determined that the AE is not related to study drug or study participation. Outcome of AEs (and resolution date, if applicable) should be documented on the appropriate eCRF page(s) and in the subject's medical record.

Detailed information about intensity, relationship to study drug, expectedness, seriousness criteria, follow-up and reporting of AEs and SAEs are provided in the further sections (Section 12.2 to Section 12.5).

Special attention must be given to findings and symptoms related to rash and/or hypersensitivity that might be linked to DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) syndrome. For details, see Section 12.5.3).

Pregnancy of female subjects and female partners of male subjects will be monitored along with follow-up, if warranted (see Section 12.1.7.7).

12.1.2. Demographic/Medical History

The medical history will include evaluation at Screening of ears, nose, and throat, and will comprise any ophthalmological, cardiovascular, respiratory, musculoskeletal, gastrointestinal, genitourinary, neurological, endocrine, psychiatric, immunological or allergic, dermatological, and hematological disease, and family history disorder. All findings on medical history will be evaluated by the Investigator for clinical significance.

12.1.3. Vital Signs

Vital sign measurements (oral body temperature, pulse rate, respiratory rate and blood pressure) are specified in Table 4.

Blood pressure, pulse rate, and respiratory rate will be measured after being in supine position for at least 5 minutes. The allowable time frame for collecting pre-dose vital signs is within 2 hours prior to dosing.

Vital signs can also be monitored at any time during the study when judged necessary by the Investigator.

12.1.4. Suicidality Assessment

The Columbia Suicide Severity Rating Scale (C-SSRS) is a brief questionnaire that provides for the identification, quantification, and standardized assessment of the occurrences and severity of suicidal ideation and behavior. The “Baseline/Screening Version” of the C-SSRS will be assessed at Screening. The C-SSRS “Since Last Visit” version will be assessed on Day -1,20, 41 and 69, as specified in Table 4 of the Schedule Of Assessments**.**

12.1.5. Weight and Height

Height will only be recorded at the Screening visit. Weight will be measured, and BMI will be calculated at time points indicated in the Schedule of Assessments (Table 4).

12.1.6. Physical Examination

A complete physical examination consisting of a review of all body systems and a symptom-directed physical examination will be performed at time points indicated in the Schedule of Assessments (Table 4). A symptom-directed physical examination may be conducted at any time per Investigator’s discretion.

Demographic data (date of birth, gender, race, and ethnicity), and alcohol and smoking habits will be recorded in the site’s source document at the Screening Visit.

12.1.7. Electrocardiogram (ECG)

ECG will be collected at screening and baseline only. A subject must be in the supine position for at least 10 mins prior to any ECG reading. An ECG may be repeated if necessary

12.1.8. Laboratory Assessments

The tests listed in Table 8 will be performed by the local laboratories at time points indicated in the Schedule of Assessments (Table 4).

Table 8: Clinical Laboratory Tests

Hematology and Coagulation	Serum Chemistry	Urinalysis	Additional Tests
Hemoglobin Hematocrit Erythrocytes Platelets Leukocytes Neutrophils Eosinophils Lymphocytes Monocytes Basophils INR aPTT PT	Sodium Potassium Chloride Calcium Inorganic phosphate Urea Creatinine Uric acid Total bilirubin Direct bilirubin ALT AST GGT AP LDH CPK Amylase Lipase Triglycerides Total cholesterol HDL cholesterol LDL cholesterol Total protein Albumin Glucose	pH Specific gravity Color Protein Glucose Ketones Hemoglobin (erythrocytes) Leukocytes Microscopic analysis, if urine is positive for protein, leukocytes or hemoglobin	Serology: anti-HIV-1/2, HBsAg, anti-HCV FSH test for postmenopausal women, including women whose last menstruation was < 1 year before screening Serum pregnancy test for women of childbearing potential, including women whose last menstruation was < 1 year before screening Urine drugs of abuse test including but not limited to cannabinoids, amphetamines, methamphetamines, opiates, methadone, cocaine, benzodiazepines, and barbiturates Alcohol breath test

INR: International Normalized Ratio; aPPT: Activated Partial Thromboplastin Time; PT: Prothrombin Time; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; GGT: Gamma-glutamyl Transferase; AP: Alkaline Phosphatase; LDH: Lactate Dehydrogenase; CPK: Creatine Phosphokinase; HDL: High Density Lipoprotein; LDL:

Low Density Lipoprotein; HIV: Human Immunodeficiency Virus; HBsAg: Hepatitis B Surface Antigen; HCV: Hepatitis C virus.

The clinical laboratory will clearly mark all laboratory test values that are outside the normal range and the Investigator will indicate the clinical significance according to the applicable clinical site's Standard Operating Procedure (SOP). Detailed information about follow-up of abnormal laboratory results is given in Section 12.5.1. The procedures for the collection, handling, and shipping of laboratory samples are specified in the laboratory manual(s) provided to the clinical site.

Table 9 lists the blood volume to be collected throughout the course of the study per subject. The projected total blood volume to be collected during this study is 397.7 mL. For comparison, a blood donation is generally about 450 mL.

Table 9: Blood Volume to be Withdrawn During the Conduct of the Study

Blood Draw Reason	N	Volume (mL)	Total (mL)
Pharmacogenomic Sampling	1	6	6
Hematology	12	2	24
Clinical Chemistry at Screening (includes FSH, pregnancy, lipid panel, serology)	1	17	17
Clinical Laboratory Tests (During Study)	12	5	60
Coagulation Lab Tests (Screening)	1	2.7	2.7
PK Blood Sampling	72	4	288
		TOTAL	397.7

12.1.8.1. Hematology

Please refer to Table 8 for hematological assessments to be collected throughout the study at times specified in Table 4.

12.1.8.2. Blood Chemistry

Please refer to Table 8 for serum chemistry assessments to be collected throughout the study at times specified in Table 4.

12.1.8.3. Urinalysis

Please refer to Table 8 for urinalysis assessments to be collected throughout the study at times specified in Table 4..

12.1.8.4. Virus Serology

Please refer to Table 8 for viral serology tests to be collected throughout the study at times specified in Table 4.

12.1.8.5. Drug Screen

Please refer to Table 8 for drugs that will be screened for at times specified in Table 4.

12.1.8.6. Additional Tests

Please refer to Table 8 for any assessments to be collected throughout the study at times specified in Table 4.

12.1.8.7. Pregnancy

Please refer to Table 8 for pregnancy tests to be collected throughout the study at times specified in Table 4.

Pregnancy in a female subject in the study shall be reported to the Medical Monitor, SK Life Science, Inc. (SKLSI), and IQVIA on the Pregnancy Reporting Form, faxing and emailing the form as per the Table of Contact (Table 12 to Table 14), within 24 hours of the knowledge of its occurrence by the Investigator or designee (for pregnancies occurring during the course of the study or immediately following the end of the study). Pregnancy in itself is not regarded as an AE, unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. The Investigator must discuss with the medical monitor/Sponsor, in conjunction with the Institutional Board (IRB), whether or not it would be appropriate for the subject to continue in the study. Because of the possibility that the fetus/embryo could have been exposed to the investigational product through the parent and for the subject's safety, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications. Pregnancy complications and elective terminations for medical reasons should not be reported as an AE or SAE. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs.

The pregnancy will be recorded on a Pregnancy Form and reported by the Investigator or designee to the Sponsor. Pregnancy follow-up will also be properly recorded to ensure quality and completeness of the data belonging to the investigational product and will include an assessment of the possible causal relation between the investigational product and any pregnancy outcome.

12.1.8.8. Contraception for Female Subjects

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

Women of childbearing/reproductive potential are defined as: Any female who has experienced menarche and does not meet the criteria for "Women Not of Childbearing Potential" (see below).

Acceptable contraception methods include:

- Hormonal contraception (for at least 3 months prior to the Screening visit) in combination with a barrier method;
- Intrauterine device (placement at least 3 months prior to the Screening visit);

- Diaphragm with spermicide;
- Cervical cap;
- Surgical sterilization (tubal ligation at least 6 months prior to the Screening visit or partner who has had vasectomy at least 6 months prior to the Screening visit) with appropriate medical documentation;
- Abstinence (however, if the subject becomes sexually active, one of the above methods must be utilized).

Women not of childbearing potential are defined as women who are postmenopausal or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy). Postmenopausal status is defined as absent menses for at least 12 months and confirmed serum follicle-stimulating hormone (FSH) levels equal to or greater than 25.8 mIU/mL at the Screening visit.

12.1.8.9. Contraception for Male Subjects

Male subjects with female partners of childbearing potential may be enrolled if they are:

- Surgically sterile (vasectomy) with appropriate medical documentation;
- Practicing true abstinence;
- Using two adequate forms of highly effective contraception including condom with spermicide gel/foam/cream and one additional barrier method for subject's female partner like hormonal contraception, occlusive cap (cervical cap or diaphragm) with spermicide or intrauterine device.

Contraception methods (including abstinence) must be used by male subjects from the first day of dosing through 90 days after the last dose of study drug. Subjects whose female partners become of child-bearing potential during the study must agree to the contraceptive requirements.

For male subjects with female partner(s) of non-childbearing potential (i.e., post-menopausal or post-surgical sterilization) for at least 6 months before the first dose of study drug, no additional contraception method is required.

12.2. Adverse and Serious Adverse Events

The site staff will record all AEs observed, queried, or spontaneously reported by the subjects. Review of concomitant medications will occur throughout the study.

Should subjects choose to withdraw early from the study, they will be advised of the safety precautions that should be taken. The subjects that withdraw early from the study will be contacted by site personnel via phone as a follow-up one-week (± 2 days) post discharge or withdrawal date.

Pregnancies identified during the study will be reported to SKLSI with 24 hours.

12.2.1. Definitions of Adverse Events

12.2.1.1. Adverse Event (AE)

An **AE** is defined as any untoward medical occurrence in a subject participating in a clinical investigation. This AE does not necessarily need to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

An AE may be:

- A new illness,
- Worsening of a concomitant illness or a baseline event,
- An effect of the study treatment; it could be an abnormal laboratory value as well as a significant shift from baseline within normal range which the Principal Investigator or medically qualified designate considers to be clinically important.

Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the treatment period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

A **suspected adverse reaction** (**SAR**) is any AE for which there is a reasonable possibility that the study treatment caused the adverse event. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the study treatment and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a study treatment.

12.2.1.2. Serious Adverse Event (SAE)

An **SAE** or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires nonscheduled (not routine or planned) subject hospitalization for ≥ 24 hours or prolongation of existing hospitalization for ≥ 24 hours,
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions),
- Is a congenital anomaly or birth defect,
- Is an important medical event defined as an event that does not fit one of the other outcomes but may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an

emergency room, serious blood dyscrasias (blood disorders), or seizure/convulsion that does not result in hospitalization. The development of drug dependence or drug abuse would be other examples of important medical events.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization for therapy of the target disease, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.
- An Emergency Room visit is not considered hospitalization.
- All AEs that do not meet any of the criteria for seriousness should be regarded as **non-serious AEs**
- **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 if the frequency, intensity, or the character of the condition worsens during the study period.
- At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an AE must also be recorded and documented as an AE.

Detailed information about intensity, relationship to study drug, expectedness, serious criteria, follow-up and reporting of AEs and SAEs are provided in Section 12.2.

Special attention must be given to findings and symptoms related to rash and/or hypersensitivity that might be linked to DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) syndrome. For details, see Section 12.5.3.

12.2.1.3. Severity Assessment

The Investigator or the designated person will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the subject's CRF. In classification of AEs, the term "severe" is not the same as "serious". Severity is a description of the intensity of a specific event. The term "serious" relates to a subject/event outcome or action criteria, usually associated with events that pose a threat to a subject's life or functioning.

All adverse events will be graded according to the severity scale below. General descriptions of each severity grade may be found in Table 10

Table 10: General Descriptions of Severity Scale

Severity Scale	General Descriptions
Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; The AE is easily tolerated and does not interfere with daily activities.

Moderate	Minimal, local or noninvasive intervention indicated; The AE interferes with daily activities, but the subject is still able to function.
Severe	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; The AE is incapacitating and requires medical intervention.

Every effort will be made to obtain an adequate evaluation of the severity.

12.2.1.4. Causality Assessment

An assessment should be made of the causal relationship of the adverse event to the study treatment, i.e., according to the following definitions in Table 11.

Table 11: Definitions of Causality Assessment

Causality Assessment	Definitions
Unrelated	The event is occurring before dosing The event is definitely produced by the subject's clinical state or by other modes of therapy administered to subject
Remote	The event does not follow a reasonable (poor) temporal relationship with drug treatment And/or the event is readily explained by the subject's clinical state or by other modes of therapy administered to subject
Possible	Reasonable temporal relationship with drug treatment But the event could have been produced by the subject's clinical state or by other modes of therapy administered to subject
Probable	Reasonable temporal relationship with drug treatment, abates upon discontinuation of drug And/or event cannot be reasonably explained by the known characteristics of the subject's clinical state.
Definite	Distinct temporal relationship with drug treatment, abates upon discontinuation of drug (de-challenge) and is confirmed by reappearance of the reaction on repeat exposure (re-challenge)

12.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

12.4. Recording Adverse Events

Adverse events spontaneously reported by the patient/subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as AEs. However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs and SAEs will be collected from the from first administration of study drug through the follow up visit. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2. An AE of severe intensity may not be considered serious.

Should a pregnancy occur in a subject or a male subject's partner, it must be reported and recorded on SKLSI's pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

12.5. Reporting Adverse Events

12.5.1. Routine Reporting

For the purposes of this study, the period of observation of adverse events for each subject extends from the signing of the informed consent form until their last visit including the follow-up visit or early termination, whichever is longer.

All events reported by the subject, observed by the clinical staff (events, such as abnormal, clinically significant findings from physical examinations, ECG tracings, laboratory assessments, and vital sign measurements), or elicited by general questioning will be recorded in the Institution's source document and reported as an adverse event and captured in the adverse events CRF. If necessary, every effort will be made to obtain an adequate follow-up of the subjects. Should any subject choose to withdraw early from the study, they will be advised of the safety precautions to be taken.

Early Termination and End of Study (EOS) visit assessments should be performed, including the following: medical history, vital signs, physical exam, safety and clinical laboratory tests, ECG, and adverse event/concomitant monitoring.

Subjects will be questioned on their health status at the beginning of each visit and before their departure from the clinical site. Open-ended questions will be asked.

Classification will be performed by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) with the version specified by sponsor in DMP.

In general, AEs occurring secondary to other events (e.g., clinical sequelae or a cascade of events) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as SAE or AE in the CRF. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF.

12.5.2. Serious Adverse Reporting

The Investigator or any other study center personnel's knowledge will notify any SAEs including fatal or life-threatening to SK Life Science, Inc. (SKLSI) and their designee IQVIA on an SAE report form, without regard to causality, within 24 hours after becoming aware of its occurrence.

If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The initial SAE report must be as complete as possible, including details of the current illness and SAE, and an assessment of the causal relationship between the event and the investigational product. Information not available at the time of the initial report (e.g., an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented and an updated SAE report form should be forwarded to the Sponsor and their designee IQVIA within 24 hours of new/updated information. All follow-up information must be reported as soon as the relevant information is available. The notification of all SAE's should be directed to the following Sponsor representatives (Table 12 and Table 13).

Table 12: Contact Information for IQVIA

Name	IQVIA
Email	QPV_SKLSI_SafetyMailbox@quintiles.com
Telephone	+1 (855) 564-2229
Fax	+1 (855) 638-1674

Table 13: Contact Information for Sponsor Medical Monitor

Name	Marc Kamin
Email	mkamin@sklsi.com
Telephone	+1 (201) 421-3830

Table 14: Contact Information for PRA Principal Investigator

Name	Ahad Sabet, MD, CPI
Email	SabetAhad@prahs.com
Telephone	+1 (801) 904-4638
Fax	+1 (801) 261-3341

In addition, reporting of serious adverse events should follow the procedures outlined in Table 15 based on the type of SAE.

Table 15: Serious Adverse Event Reporting Requirement

Type of SAE	Reporting Time Frame	Reporting Method	Contact Details
Rash with involvement of 1 other organ system or a suspected case of DRESS	Immediate	Email[a]	
Fatal or Life-threatening	Immediate	Email[a]	
All other SAEs	Within 24 hours of awareness	Email[a]	
Urgent safety concerns requiring a Medical Monitor	As needed	Telephone	

[a]The SAE report must be used for reporting
DRESS=Drug Reaction with Eosinophilia and Systemic Symptoms; SAE=serious adverse event; SKLSI=SK Life Science, Inc.;

At the time of the initial SAE report, the investigator should provide as much of the following information as possible:

- Study identifier;

- Study site;
- Subject 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's assessment of the association between the event and study drug.

Any adverse event that is considered serious will be reported to the IRB by the clinical site by telephone and/or by email within 3 working days. Any unexpected fatal or life-threatening SAE will be reported to the IRB by telephone and in writing within 24 hours.

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

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.

12.5.3. Rash/Hypersensitivity/DRESS Syndrome

Drug-induced hypersensitivity reactions with or without multi organ involvement (allergic reactions which may be fatal) including DRESS syndrome have been seen in patients taking cenobamate. DRESS which has occurred in <1% of clinical trial participants taking cenobamate stands for Drug Reaction (or Rash) with Eosinophilia and Systemic Symptoms. This condition occurs usually in the first 8 weeks after initiation of treatment and rarely happens afterwards.

Symptoms of DRESS may include:

- Rash;
- Fever;
- Inflammation of internal organs;
- Lymphadenopathy;
- Eosinophilia;
- Thrombocytopenia.

In order to ensure patient safety, and allow early identification and rapid intervention in suspected DRESS cases, the following measures must be followed:

- Any patient who reports a rash or is observed to have a rash should be carefully evaluated for a drug hypersensitivity syndrome; the evaluation should include hematology and chemistry blood tests. If a subject reports a rash by telephone, an unscheduled visit should be performed promptly.

- At the end of their study participation, all subjects must be informed to report any rash, hypersensitivity reaction or DRESS related symptoms to the investigative site as soon as they experience it.

During Study Day 4 (prior to discharge from CRU), subjects will be provided a safety card with the following hypersensitivity information and will be instructed to carry with them at all times:

- Rash may occur and may progress to Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- Rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy, and swelling) may herald a serious medical event and that the patient should report any such occurrence to the investigative site immediately.
- Instructions on whom and where to call in the event a symptom arises and information that can be provided to an emergency room in the event the subject cannot reach the investigator site.
- Reminder to check skin daily for evidence of rash for the first four months of therapy

At the end of their study participation, all subjects must be informed to report any rash, hypersensitivity reaction or DRESS related symptoms to the investigative site as soon as they experience it.

In addition, please remind all patients to call your office immediately if they experience any of the following symptoms:

- Rash;
- Fever;
- Swollen lymph nodes in your neck;
- Abdominal or chest pain;
- Puffy face or ankles;
- Yellowing of skin or eyes.

Investigators will be instructed to identify local specialists in dermatology, cardiology, nephrology and hepatology who can be call upon onto immediately to see the patient and manage their condition if DRESS syndrome is suspected.

The SK Life Science, Inc. (SKLSI) and their designee (see SAE Contact Information in Section 12.5.2) must be notified immediately of any suspected cases of DRESS syndrome as an SAE.

13. STATISTICS

13.1. Statistical and Analytical Plans

This section presents a summary of the planned clinical pharmacology and safety analyses for this study.

Safety statistical analysis details will be provided in the Statistical Analysis Plan (SAP) for this study. Clinical pharmacology analysis details (including the definition of the PK population) will be provided in the Clinical Pharmacology Data Analysis Plan (CPAP).

The Biostatistics Department of the CRO or SKLSI will generate the SAP. The SKLSI Clinical Pharmacology Department will generate the CPAP. Both the SAP and CPAP will be finalized prior to clinical database lock. Final analyses will take place after all subjects have completed the study and all data have been entered in the clinical study database.

Any deviation from the SAP and/or CPAP will be reported in the section "Changes in Planned Analysis" in the Clinical Study Report (CSR).

Statistical analyses will be performed using appropriate statistical software, such as SAS (Version 9.4 or above). PK parameters will be calculated using Phoenix WinNonlin (Version 8.1 or above).

13.1.1. Sample Size and Power

The number of subjects to be enrolled was chosen based on practical considerations and is considered sufficient for the study objectives. No formal sample size calculation was performed.

13.1.2. Analysis Populations

- **Safety Population**: All subjects who have received one dose of cenobamate
- **PK Population**: All subjects who have received one dose of cenobamate and have sufficient quantifiable PK samples to calculate primary PK parameters appropriately. The final decision to include subjects in the PK population set took into consideration possible AEs affecting the disposition of cenobamate (e.g., vomiting or diarrhea). Reasons supporting each decision will be clearly stated in the clinical study report. A sensitivity analysis may be performed if deemed necessary to support a subject's exclusion or inclusion.

13.1.3. Pharmacokinetic Analysis

This section will be further detailed in the CPAP.

13.1.3.1. Pharmacokinetic Parameters

The PK parameters that will be derived from the cenobamate concentration versus time profiles, where data permit, are listed in Table 16.

The plasma PK parameters will be estimated using a non-compartmental approach. A linear-up, log-down approach will be used to estimate the area under the plasma concentration versus time curve, and the terminal half-life will be estimated where appropriate.

Further information on the determination of PK parameters is outlined in the Clinical Pharmacology Analysis Plan (CPAP).

Table 16: Primary Pharmacokinetic Parameters

PK Parameter	Definition
C_{max}	Maximum plasma concentration
AUC_{last}	Area under the plasma concentration vs. time curve calculated from time zero to the last sampling point that is above the lower limit of quantification
AUC_{∞}	Area under the plasma concentration vs. time curve from time zero to the last sampling point that is above the lower limit of quantification and extrapolated to infinite time
$AUC_{\%extrap}$	Ratio of AUC_t to AUC_{∞} expressed as percentage
λ_z	Terminal rate constant
$t_{½}$	Terminal half-life
t_{max}	Time of maximum plasma concentration
C_{last}	Concentration measured at the last time point
CL/F	Oral clearance
V_z/F	Apparent volume of distribution

Other PK parameters will be determined if deemed appropriate. Details of the PK analysis will be provided in the CPAP.

13.1.3.2. Formulation and Food Effect Analysis

An analysis of variance (ANOVA) will be used to compare suspension vs. tablet formulations and suspension under fed vs. suspension under fasted conditions. PK parameter (C_{max}, $AUC_{last,}$ and AUC_{∞}) values will be log-transformed for all subjects included in the PK population set and the ratio and corresponding 90% CIs for the ratio of the test (suspension or fed) vs. reference (tablet or fasted) will be compared. An absence of effect will be concluded if the 90% CIs lie within the 80% - 125% predefined boundaries.

13.1.3.3. Analysis on T_{max}

For each subject, the Wilcoxon signed-rank test will be used to test for differences in t_{max}.

13.1.3.4. Summary and Presentation of PK Data and Parameters in the CSR

Individual and mean plasma concentrations at each sampling time point for cenobamate will be presented in listings and tables with descriptive summary statistics including mean, geometric mean, range, standard deviation (SD) and coefficient of variation (CV). Individual, mean and/or median concentrations per treatment group will be plotted versus time on semi-logarithmic scales.

Summary statistics of PK parameters including mean, geometric mean, median, range, SD and CV will be presented by treatment group.

13.2. Other Statistical Analyses

13.2.1. Efficacy Analysis

No formal efficacy analysis will be performed.

13.2.2. Safety Analysis

Safety and tolerability will be assessed through AEs, clinical laboratory, vital signs, and physical examination findings, and any other parameter that are relevant for safety assessment. Full details of the safety analysis to be performed will be included in the SAP.

13.2.3. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA terms will be used to summarize AEs by system organ class (SOC) and preferred term (PT).

Treatment-emergent adverse events (TEAEs) are defined as adverse events that were started or worsened on or after the date of the first dose of study medication (Day 1) to the follow-up visit (Day 69).

A listing of all individual AEs will be provided. Summary tables of TEAEs will be presented by SOC and PT, including a table containing the number of subjects experiencing AEs by treatment group, and a table containing the number of subjects experiencing SAEs by treatment group (if applicable). Details of the AE summary analyses will be described in Statistical Analysis Plan (SAP).

13.2.4. Clinical Laboratory Assessments

All lab data will be displayed as International System of units (SI) and may be converted into other systems (e.g., United States customary system [USCS or USC]) for reporting and processing purposes, as appropriate.

Clinical laboratory data will be listed and accompanied by an indication flag if the parameter is outside the reference range and a summary listing of all data assessed by the Investigator as clinically significant will be prepared. Clinical laboratory data will also be summarized descriptively.

13.2.5. Vital Signs

Vital signs will be listed, and presented descriptively, where applicable.

13.2.6. Physical Examinations

Physical examination data will be listed by subject.

13.2.7. Demographic Data

Demographic data will be listed by subject and summarized across all subjects and by treatment group.

13.2.8. Baseline Characteristics and Other Data

Baseline characteristics, medical history, prior and concomitant medications, protocol deviations, study treatment exposure, disposition, etc., will be listed and summarized across all subjects, where applicable.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Monitoring and auditing procedures developed or approved by SKLSI will be followed, in order to comply with Good Clinical Practice (GCP) guidelines. On-site checking of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by SKLSI or its designee. Monitoring will be done by personal visits from a representative of the Sponsor (site monitor) who will review the eCRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

14.2. Audits and Inspections

Authorized representatives of SKLSI, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an SKLSI audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact SKLSI immediately if contacted by a regulatory agency about an inspection.

14.2.1. Electronic Data Capture (EDC)

SKLSI or designee will ensure secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the subjects for which they are responsible.

The eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, other observations, and subject status.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected. An explanation should be provided for all missing data.

The audit trail entry will show the user's identification information, and the date and time of the correction. Investigators must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the subjects for which they are responsible.

SKLSI or designee will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a CD or other electronic media will be placed in the Investigator's study file.

14.2.2. Case Report Forms

Source documents will be used to record all study-related data. Designated staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF) using Medrio, a fully validated software that conforms to 21 CFR Part 11 requirements.

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs) will be captured in EDC.

14.3. Institutional Review Board (IRB)

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, SKLSI may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to SKLSI before he or she can enroll any patient/subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. SKLSI will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be conducted in accordance with the current International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and according to local regulations. The Institutional Review Board (IRB) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the subjects. The study will be conducted at the site where IRB approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator or the Sponsor, as allowable by local regulations.

16.2.1. Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s) and will be subject to approval by SKLSI.

16.2.2. Investigator Compliance

No modifications to the protocol will be made without the approval of SKLSI. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study will require IRB notification prior to implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. SK Life Science, Inc. (SKLSI) will submit all protocol modifications to the required regulatory authorities.

When circumstances require an immediate departure from procedures set forth in the protocol, the Investigator will contact SKLSI to discuss the planned course of action. If possible, contact should be made prior to the implementation of any changes. Any departures from protocol must be fully documented in the source documentation and in a protocol deviation log.

16.2.3. Access to Records

The Investigator must make the source documents of subjects enrolled in this study available for inspection by SKLSI or its representative at the time of each monitoring visit. The records must also be available for inspection, verification, and copying, as required by regulations, by officials of the regulatory health authorities (FDA and others). The investigator must comply with applicable privacy and security laws for use and disclosure of information related to this research set forth in this protocol.

16.2.4. Subject Privacy

To maintain subject confidentiality, all eCRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers. As required by federal regulations, the Investigator will allow SKLSI and/or its representative's access to all pertinent medical records in order to allow for the verification of data gathered in the eCRFs and for the review of the data collection process. The FDA (or other regulatory authority) may also request access to all study records, including source documentation for inspection.

As applicable, in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and associated privacy regulations, a subject authorization to use personally identifiable health information may be required from each subject prior to research activities. This authorization document must clearly specify what parties will have access to a subject's personal health information, for what purpose and for how long.

16.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

SKLSI will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

17.2. Retention of Records

The Investigator will maintain all study records according to ICH-GCP and/or applicable local regulatory requirement(s), whichever is longest. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and SKLSI must be notified.

17.2.1. Screening

After signing of the ICF/assent form, each subject will be assigned an 8-digit subject identification number (i.e. 01001001). The first two digits is for country, the next 3 digits is for site, and the last 3 digits is for subject.

The subjects who screen-fail will be allowed to re-screen only once. The re-screened subject will be assigned a new subject ID, and the 2 subject IDs will be linked in the clinical database.

17.2.2. Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the sponsor or designee electronically (e.g., laboratory data).
- The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A study monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently

approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in accordance with local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

17.2.3. Investigator Documentation Responsibilities

- All individual, subject-specific study data will also be entered into a 21 Code of Federal Regulations Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.
- All data generated from external sources (e.g., laboratory and bioanalytical data), and transmitted to the sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.
- An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.
- Terms will be coded in accordance with MedDRA and WHO Drug dictionary versions specified in Data Management Plan.
- The investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

18. PUBLICATION POLICY

18.1. Publication of Study Results

Any and all scientific, commercial, and technical information disclosed by SKLSI in this protocol or elsewhere should be considered confidential and proprietary property of SKLSI The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary, in order to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The Investigator understands that the information developed from this clinical study will be used by SKLSI in connection with the development of the study drug and therefore may be disclosed as required to other clinical Investigators, the US FDA, and to other government agencies. The Investigator also understands that, in order to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide SKLSI with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between SKLSI and the Investigator and/or the Investigator's institution.

18.2. Clinical Study Report

A clinical study report that is written in accordance with ICH Guideline E3[5] will be submitted in accordance with local regulations.

19. LIST OF REFERENCES

1. Cenobamate (YKP3089) Investigator's Brochure, October 05, 2020 (Version 14).
2. Vernillet L, Greene SA, Kamin M, Pharmacokinetics of Cenobamate: Results from Single and Multiple Ascending Dose Studies in Healthy Subjects. Clinical Pharmacology in Drug Development. 2020 Feb 22. Doi:10.1002/cpdd.769
3. Vernillet L, Greene SA, et al., Mass Balance, Metabolism, and Excretion of Cenobamate, a New Antiepileptic Drug, After a Single Oral Administration in Healthy Male Subjects. Eur J Drug Metab Pharmacokinet. 2020 Apr 16. doi:10.1007/s13318-020-00615-7 PMID: 32301064
4. Assess the Effects of Food on Drugs in INDs and NDAs - Clinical Pharmacology Considerations, Guidance for Industry, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, February 2019.
5. International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95), Nov 1995.

20. APPENDICES