CLINICAL STUDY PROTOCOL: SKLYKP3089C037

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

Statistical Analysis Plan

Version 1.0: 26 Jul 2021

CONFIDENTIAL AND PROPRIETARY INFORMATION

Statistical Analysis Plan Signature Page

Study Title:	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
Investigational Product	SKL-YKP3089
Sponsor:	SK Life Science, Inc. 461 From Road, 5th floor Paramus, NJ 07652
Protocol Number:	SKL- YKP3089C037
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REVISION HISTORY

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LIST OF ABBREVIATIONS

AE	adverse event
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CPAP	clinical pharmacology analysis plan
CRU	clinical research unit
DB	Double-blind
ECG	electrocardiogram
ET	Early termination
HBsAG	Hepatitis B Surface Antigen
HCV (C)	Hepatitis C Virus
ICF	Informed consent form
IP	investigational product
LLN	Lower limit of normal
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
N, n	number of subjects, observations
PE	physical examination
PI	principal investigator
PK	pharmacokinetic
PT	preferred term
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia correction
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	systéme international
SOC	system organ class
SOP	standard operating procedures
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
LLN	lower limit of normal

1 INTRODUCTION

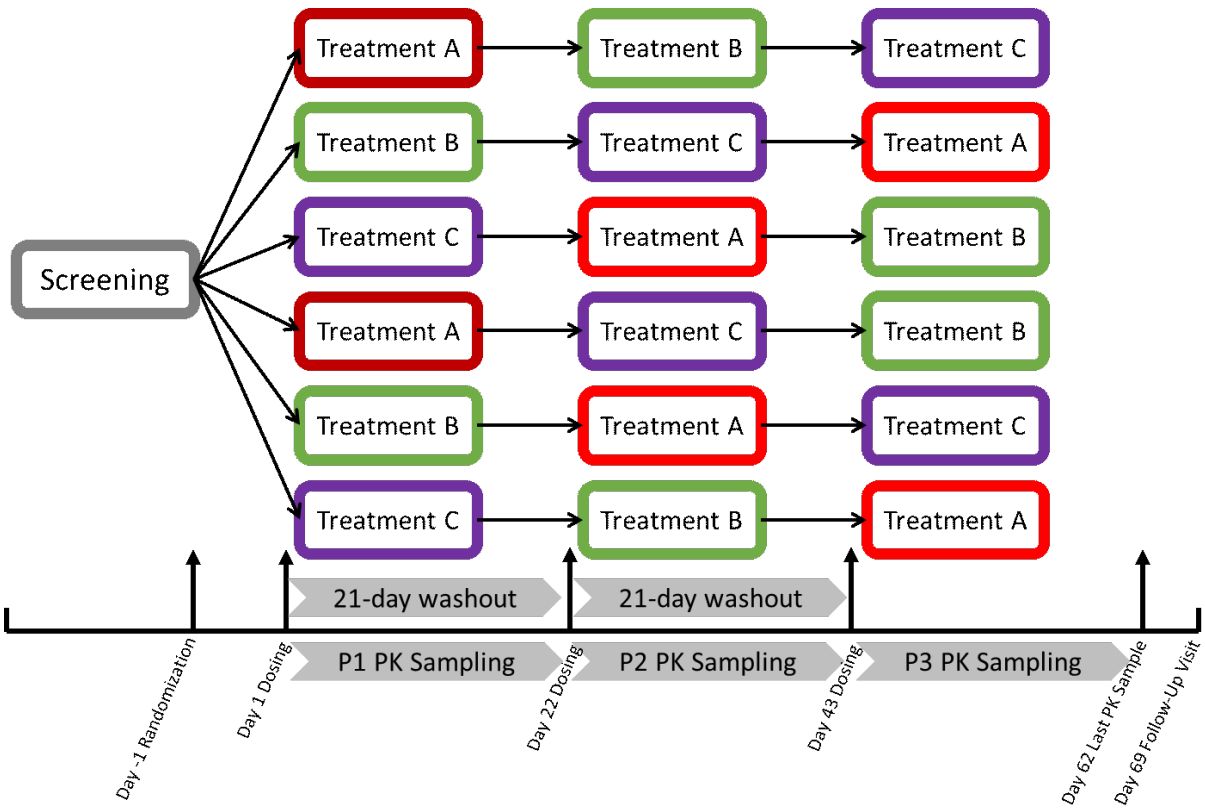
This statistical analysis plan (SAP) describes the statistical analysis methods and data presentation to be used for the analysis and summarization of the safety data from Protocol SKL-YKP3089C037. The clinical pharmacology analysis plan (CPAP) which details the planned analyses for the pharmacokinetic (PK) data for this study will be a separate document.

The SAP will be finalized before database lock. Any changes made after finalization of the SAP will be documented in the clinical study report (CSR). Related documents are the study protocol and electronic case report forms.

1.1 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). A schematic of the study design is presented below in Figure 1.

Figure 1 Schematic of Study Design



Following Screening, eligible subjects will be randomized to one of the 6 treatment sequences. Each sequence will include a single dose of the following treatments:

- **Treatment A:** single oral 200 mg dose of cenobamate tablet under fasting conditions
- **Treatment B:** single oral 200 mg dose of cenobamate suspension under fasting conditions
- **Treatment C:** single oral 200 mg dose of cenobamate suspension under fed conditions

The three-period, six-sequence Williams Design to be used in this study is displayed in Table 1 below.

Table 1: Three-period Six-sequence Williams 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 letters in the table correspond to:
A: single oral 200 mg dose of cenobamate tablet under fasting conditions
B: single oral 200 mg dose of cenobamate suspension under fasting conditions
C: single oral 200 mg dose of cenobamate suspension under fed conditions

The study will be conducted in three periods each with a 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) – Subject to 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) – Subject to 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) – Subject to 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.

Study procedures will be completed as per the Schedule of Assessments outlined in Table 2.

Table 2: 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

1.2 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, who satisfy all of the inclusion criteria (and none of the exclusion criteria), as well as all screening evaluations, before enrollment in the study, 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 15 subjects completing all three treatments,

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. Subjects who do not complete all the treatments and assessments specified in this protocol may be replaced.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

- To assess 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
- To assess the effect of food on the bioavailability of a 200 mg oral dose of cenobamate given as a suspension

The primary PK objectives are discussed in further detail in the CPAP.

2.1.2 Secondary Objectives

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 condition.

2.2 Endpoints

2.2.1 Primary Endpoints

PK parameters will be calculated for cenobamate from plasma data. PK endpoints will be defined in the CPAP.

2.2.2 Secondary Endpoints

1. Adverse events (AEs)
2. Safety laboratory tests (including clinical chemistry, hematology, coagulation and urinalysis)
3. Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature)
4. Physical examination
5. Columbia-Suicide Severity Rating Scale (C-SSRS) score.

3 ANALYSIS POPULATIONS

3.1 Safety Population

The safety population includes all subjects who are randomized and receive at least 1 dose of cenobamate.

3.2 Pharmacokinetic 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 takes 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.

4 STATISTICAL METHODOLOGY

4.1 Subject Disposition

The number and percentage of subjects in the study populations (Safety and PK) will be summarized by sequence and overall.

The number and percentage of subjects who enter, complete and prematurely discontinue from the study as recorded on the termination pages of the eCRF will be summarized (number and percentage) by sequence and overall.

Screen failure subjects (i.e.; subjects screened but not randomized) and the associated reasons for failure, inclusion (not met) and exclusion (met) criteria will be listed. A listing of subjects who prematurely discontinued will be provided. A data listing of subject disposition, study completion status, and reason for study discontinuation will also be provided. Table and listings for disposition will be provided for all randomized subjects.

4.2 Protocol Deviation

Protocol deviations for all randomized subjects will be captured in a log by the project manager, exported into a clinical dataset, and presented in a data listing.

The number and percentage of subjects with any protocol deviation will be tabulated for each type of deviation (Major/Minor and overall) by sequence and overall. A listing of all protocol deviations will also be provided for all randomized subjects.

4.3 Demographics and Other Baseline Characteristics

Demographic parameters (age; race; ethnicity; sex), baseline characteristics (weight; height; and body mass index[BMI]) will be summarized descriptively by treatment sequence and overall for the Safety population. Continuous variables will be summarized by number of subjects and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects.

A data listing will be presented for all demographic and other baseline characteristics data.

4.4 Medical History

Abnormalities collected in subjects' CRF pages of medical and surgical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0. The number and percentage of subjects with abnormalities in each system organ class (SOC) and preferred term (PT) will be summarized overall for the Safety Population.

4.5 Prior and Concomitant Medications

Prior medication is defined as any medication taken before the date of the first dose of IP. *Concomitant* medication is defined as any medication taken on or after the date of the first dose of IP.

The use of *prior* and *concomitant* medications will be summarized for the Safety Population by the number and percentage of subjects overall for prior medications, and by sequence and overall for concomitant mediations. If a subject took a specific medication multiple times or took multiple medications within a specific therapeutic class, the subject would be counted only once for the coded drug name or therapeutic class.

World Health Organization (WHO) Drug Dictionary (WHODrug Global B3 Mar2020 version), will be used to classify prior and concomitant medications by therapeutic class and drug name.

4.6 Pharmacokinetic Analysis

4.6.1 Plasma Drug Concentrations and Pharmacokinetic Parameters

The individual plasma drug concentration versus time profiles will be presented using the actual sampling times whereas the mean plasma drug concentration versus time profiles will be presented using the nominal sampling times. Descriptive statistics, N (number of datapoints available), arithmetic mean, median, arithmetic coefficient of variation (%CV), SD of the mean, geometric mean, geometric %CV, minimum value observed, and maximum value observed, will be calculated for plasma drug analyte concentrations at each individual time point for cenobamate.

PK parameters will be calculated using a non-compartmental approach. The primary PK endpoints will include AUC from 0 to infinity (AUC_{∞}), area under the concentration versus time curve (AUC) from 0 to the last time point with a concentration above the lower limit of quantitation (AUC_{last}), and maximum observed drug concentration (C_{max}) for cenobamate. These parameters will be derived for all treatments received by each subject.

Further PK endpoints for cenobamate as the data permits will include the following: terminal half-life ($t_{1/2}$), time to maximum cenobamate plasma concentration (t_{max}), oral clearance (CL/F), terminal rate constant (λ_z), apparent volume of distribution during terminal phase (Vz/F), and last observed cenobamate plasma concentration (C_{last}).

Refer to CPAP for description of summary statistics for the primary and further PK endpoints.

4.6.2 Statistical Analysis of Pharmacokinetic Data to Assess Formulation Effect

For the evaluation of the formulation effect on cenobamate PK, an analysis of variance (ANOVA) model will be used and the differences between test and reference treatments for AUC_{∞}, AUC_{last}, and C_{max} of cenobamate will be estimated (test and reference treatments are outlined below in Table 3). The PK parameters will be logarithmically transformed prior to analysis and the ANOVA models will include treatment, sequence, and period as fixed effects, and subject nested within sequence as a random effect. From this model, the difference and 90% confidence limits between the test and reference treatments on the log scale will be exponentiated to present the estimates of the geometric mean ratio and associated 90% confidence limits. The absence of a formulation effect will be concluded if the 90% CIs lie within the reference range of [0.80-1.25]. No adjustments will be made for multiplicity.

The following SAS pseudo code will be used:

```
proc mixed data=dataset;
by parameter;
class treatment sequence period subject;
model ln_aval = treatment sequence period /  ddfm=kr;
random subject (sequence);
estimate  "BioAv Trt B (Test: Suspension Fasted)  vs Trt A (Ref: Tablet Fasted)"
        treatment  -1  1  0  / cl  alpha=0.1;
run;
```

A forest plot of the geometric LS mean ratios of $AUC_{0-\infty}$, AUC_{0-last}, and C_{max} of cenobamate will be provided for a visual representation of the data. A single plot will be provided for the test versus reference formulation comparison, with all PK parameters on the plot.

In addition, Wilcoxon signed-rank tests will be used to test for the differences in t_{max}.

The following SAS pseudo code may be used for the Wilcoxon signed-rank test for each treatment comparison:

```
data data2;
set data1;
diffBA= TRTB – TRTA;
run;

ods output TestsForLocation=Tests(where=(test='Signed Rank'));
proc univariate data= data2;
var diffBA;
run;
```

4.6.3 Statistical Analysis of Pharmacokinetic Data to Assess Food Effect

The food effect will be assessed from the same ANOVA model as in section 4.6.2, with the specific contrasts as indicated in the SAS pseudo code below.

```
proc mixed data=dataset;
by parameter;
class treatment sequence period subject;
model ln_aval = treatment sequence period /  ddfm=kr;
random subject (sequence);
estimate "BioAv Trt C (Test: Suspension Fed)  vs Trt B (Ref: Suspension Fasted)"
        treatment  0  -1  1 / cl  alpha=0.1;
run;
```

A forest plot of the geometric LS mean ratios of AUC_{∞}, AUC_{last}, and C_{max} of cenobamate will be provided for a visual representation of the data. A single plot will be provided for the test versus reference food effect comparison, with all PK parameters on the plot.

In addition, Wilcoxon signed-rank tests will be used to test for the differences in t_{max} for the food effect.

The following SAS pseudo code will be used for the food effect comparison:

```
data data2;
set data1;
diffCB = TRTC – TRTB;
run;

ods output TestsForLocation=Tests(where=(test='Signed Rank'));
proc univariate data= data2;
var diffCB;
run;
```

Table 3: Test Treatment and Reference Formulation Treatment for ANOVA Analysis

Assessment	Test Treatment	Reference Treatment
Bioavailability [a]	Oral Suspension administered under fasted conditions	Oral Tablet administered under fasted conditions
Food Effect	Oral Suspension administered under fed conditions	Oral Suspension administered under fasted conditions

[a] Bioavailability is assessed for treatments administered under fasting conditions

5 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

5.1 Extent of Exposure

Study treatment exposure will be summarized by sequence, treatment period, and study day. IP administration dates and times will be provided in a data listing.

5.2 Treatment compliance

There will be no planned table or listing for treatment compliance for this study. Treatment compliance will be seen from the table above and the listing of Investigational Product Dosing Records.

5.3 Meal Record

Details of meal records, such as meal type, date/time of meal, and amount consumed will be listed.

6 SAFETY ANALYSIS

The safety analysis will be performed using the safety population. The safety parameters will include adverse events (AEs), clinical laboratory parameters, vital signs, and electrocardiographic (ECG) assessments. The last non-missing safety assessment before the date of first dose of study treatment will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by the number of subjects and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by the number and percentage of subjects.

6.1 Adverse Events

Adverse events will be coded by system organ class and preferred term using the MedDRA, Version 23.0.

Treatment-emergent AEs (TEAEs) are defined as AEs that start or worsen (increase in severity) on or after the first dose date of study medication (Day 1) to the follow-up visit (Day 69).

If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship.

Related TEAEs include all those classified by the investigator as having a possible, probable, or definite relationship to the Investigational product. Unrelated TEAEs are those events classified as unrelated or having a remote likelihood of being related to the Investigational product. If the same event occurs more than once per subject and treatment, and there is more than 1 relationship classification, the most related value will be summarized. For summaries by severity, the most severe grade will be selected.

The number and percentage of subject with TEAEs by system organ class and preferred term, and by severity, and by causal relationship to the IP, will be summarized by treatment and overall.

A listing of all AEs, along with SAEs, AEs leading to death, and AEs leading to discontinuation of IP will be provided.

The MedDRA version will be specified in a footnote in both tables and data listings.

6.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values in Table 4 (in SI units) and changes from the baseline values at each assessment time point will be presented by treatment for the following laboratory parameters, measured at Screening visit (Days -28 to -2), Day -1, post-dose Days 4 and 20 of each treatment period and Day 69 (end of study).

Table 4: Clinical Laboratory Tests

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

Smoking history and Drug of Abuse/Alcohol Screen will be measured at Screening visit and Day -1 visits.

The following clinical laboratory levels will be measured at Screening only:

- Serology: HIV-1/HIV-2 antibody, HbsAg and Anti-HCV
- FSH and Pregnancy Test for female subjects

A shift table from baseline to worst postbaseline evaluations will be presented by treatment for the following categories: low, normal, and high. The denominators for calculating the percentages will be based on the number of subjects with non-missing assessments at Baseline and at least 1 post-baseline value for each parameter.

Unscheduled assessments that are not used as Baseline will not be included in summary tables except in the shift summaries; however, all clinical laboratory values will be presented in a data listing, in chronological order, or by date for unscheduled values.

The actual values of clinical laboratory evaluations, date of collection/time, and reference range and clinical significance will be listed for each visit.

6.3 Vital Signs

Descriptive statistics for actual values and changes from Baseline for vital signs (systolic and diastolic blood pressures, heart rate, respiratory rate, and temperature in supine position) will be summarized at Screening visit (Days -28 to -2), pre-dose on Day 1, post-dose on Days 4, 6, 9, 12, 16, 20 of each treatment period and Day 69 (end of study).

The actual values of vital signs, date of collection/time, reference ranges, and clinical significance will be listed for each scheduled visit.

6.4 Safety 12-Lead Electrocardiogram

ECG parameters (heart rate (HR), RR, PR, QT, QTc intervals, and QRS duration) collected at Screening visit (Days -28 to -2), and Day -1 (prior to study drug administration) will be provided in a listing.

The actual values of ECG parameters, date of collection/time, reference ranges, and clinical significance will be listed for each scheduled time point and visit.

6.7 Columbia Suicide Severity Rating Scale

For the Columbia-Suicide Severity Rating Scale (C-SSRS), the number and percentage of subjects with suicidal ideation and suicidal behavior before the study treatment (life time history and past 6 months) and after study treatment (treatment period) will be summarized by treatment for the Safety population.

The distribution of the most severe suicidal ideation and suicidal behavior will also be presented for life history, in the past 6 months and after study treatment. Any subjects with postbaseline suicidal ideation or suicidal behavior will be included in a data listing and a separate listing will include any reported AEs. A listing of C-SSRS data for all subjects will also be provided, which will include subject number, treatment, visit, intensity of suicidal ideation, suicidal behavior type and lethality of suicidal behavior, in chronological order.

6.8 Other Safety Assessments

The physical examination findings and other safety assessments will be presented in data listings. Abnormal findings will be flagged for clinical significance based on the principal investigator's (PI) judgment.

7 INTERIM ANALYSIS

No interim analysis is planned for this study.

8 GENERAL STATISTICAL CONSIDERATION FOR DATA ANALYSIS AND HANDLING

8.1 General Statistical Procedures

The descriptive statistics for continuous variables will be the number of subjects, mean, median, standard deviations (SD), minimum, and maximum. Mean and median will be reported to 1 more decimal places than the raw data, while the SD will be reported to 2 more decimal places than the raw data. Minimum and maximum will be reported with the same decimal places as that of the original data.

Frequency distributions for all categorical variables will be presented using counts and percentages. Percentages will be reported to 1 decimal place.

Unless otherwise stated, denominators for calculating the percentages in shift analysis (to worst assessment) will be based on the number of subjects with non-missing values at both baseline and at least one post-baseline analysis visit in the Safety Population.

Unless otherwise stated, statistical analysis will be summarized for each treatment (and overall where indicated) using the Safety Population. Listings will be sorted by subject ID, sequence, and visit.

Missing data will not be imputed.

Reporting and analyses are performed using the SAS System, Version 9.4. The following CDISC version specified in Table 5 will be used.

Table 5. CDISC version

SDTM/SDTMIG Versions	ADaM/ADaMIG Version	SDTM/ADaM Controlled Terminology	SDTM/ADaM define.xml	Pinnacle 21 Validator
1.4/3.2	2.1/1.1	2019-06-28/2018-12-21	2.0/2.0	2.2.0

8.2 Study Day and Baseline

Study Day is relative to treatment start date;

If analysis date ≥ treatment start date,

Day = analysis date – treatment start date +1

Day 1= treatment start date

If analysis date ≤ treatment start date,

Day = analysis date – treatment start date +1

Day -1= day before treatment start date

There is no Day 0.

Baseline value is defined as the last available value collected before the first dose date of investigational product for all safety laboratory, safety ECG, and vital sign values, unless otherwise specified.

8.3 Data Handling Conventions

8.3.1 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the start of the first treatment, the results from the final nonmissing assessment made prior to the start of the IP will be used as baseline. If a subject has repeated postbaseline assessments for that time point, the last nonmissing postbaseline assessment within the assessment window will be used.

However, all assessments will be presented in the data listings.

8.3.2 Missing/Incomplete Date Conventions

8.3.2.1 Missing Date of the Last Dose of Study Treatment

When the date of the last dose of study treatment is missing for a subject in the Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last available dosing record date will be used as the last dose date.

8.3.2.2 Missing Date Information for Adverse Events

The following imputation rules only apply to cases in which the start date for AEs is incomplete (i.e., partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study treatment, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of study treatment, the date of the first dose of study treatment will be assigned to the missing start date

- If the stop date is before the date of the first dose of study treatment, the stop date will be assigned to the missing start date

8.3.2.3 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (i.e., partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a subject, the start date will be imputed first.

Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date. Detail rules regarding the missing date information will refer to section 8.3.2.2 Missing Date Information for Adverse Events.

Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study treatment is missing, impute it as described in Section 8.3.2.1 Missing Date of the Last Dose of Study Treatment. If the imputed stop date is before the start date (imputed or non-imputed start date), the imputed stop date will be equal to the start date. Detailed rules regarding the missing date information are outlined in section 8.3.2.2 Missing Date Information for Adverse Events.

8.3.3 Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started before the date of the first dose of study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of study treatment, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

8.3.4 Missing Causal Relationship to study drug for Adverse Events

If the causal relationship to the study treatment is missing for an AE that started on or after the date of the first dose of study treatment, a causality of yes will be assigned. The imputed values for causal relationship to study treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

8.3.5 Character Values of Clinical Laboratory Parameters

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings. Table 6 shows examples of how some possible laboratory results should be coded for the analysis.

Table 6. Examples of Coding Special Character Values for Clinical Laboratory Parameters

Laboratory Test, SI Unit	***Possible Laboratory Results***	***Coded Value for Analysis***
1 CHEMISTRY		
ALT, U/L	< 5	5
AST, U/L	< 5	5
Bilirubin, total, µmol/L	< 2	2
URINALYSIS		
Glucose, mmol/L	= OR > 55, ≥ 55, > 0	Positive
	≤ 0, negative	Negative
pH	> 8.0, ≥ 8.0	8.0
	≥ 8.5	8.5
Protein	= OR > 3.0, ≥ 3.0, > 0	Positive
	≤ 0	Negative

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SI = *Le Système International d'Unités* (International System of Units).

9 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

None

10 REFERENCES

Not applicable.