SKL24741

CLINICAL STUDY PROTOCOL

A PHASE 1, RANDOMIZED, DOUBLE-BLINDED, SINGLE-DOSE ESCALATION STUDY FOLLOWED BY A MULTIPLE-DOSE ESCALATION STUDY OF SKL24741 IN HEALTHY SUBJECTS

SK Life Science, Inc. Study Number: SKL24741C001

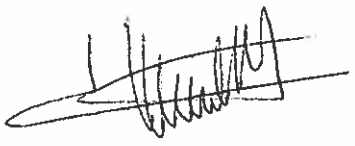
IND Number: 141225

Sponsor:	SK Life Science, Inc. 461 From Road, 5th floor Paramus NJ 07652 USA
Original Protocol Date	20 September 2019
Amendment 1	13 December 2019
Amendment 2	03 January 2020
Version Number	Amendment 3
Version Date	21 February 2020

CONFIDENTIAL

Protocol Approval Form

The protocol entitled "A Phase 1, Randomized, Double-blinded, Single-dose Escalation Study Followed By a Multiple-dose Escalation Study of SKL24741 in Healthy Subjects," (Amendment 3) dated 21 February 2020 has been approved for submission to the Institutional Review Board and regulatory authorities by:

Sponsor's Representative:  **Date:** 21 FEB 2020

Laurent Vernillet, PharmD, PhD, FCP

Principal Investigator: Carlos R. Sanabria, MD **Date:** 24 FEB 2020

Carlos Sanabria, MD

Principal Investigator's Approval

I, the undersigned, have examined this protocol and agree to conduct this trial according to this protocol, to comply with its requirements, subject to ethical and safety considerations, as set out in this protocol, the Declaration of Helsinki 1964 (latest revision Fortaleza 2013) and all other laws and regulations on the use of investigational medicinal products.

Principal Investigator: Carlos R. Sanabria, MD **Date:** 24 FEB 2020

Carlos Sanabria, MD

PROTOCOL AMENDMENTS

Amendment 1

Section	*Old text / Content*	*Amended text / Content*	*Rationale / Description*
1. Protocol Synopsis – Number of Subjects	104	98	Correction
1. Protocol Synopsis – Study Population	66 in Part A	60 in Part A	Correction
1. Protocol Synopsis – Study Population	aged 18 to 55 years (inclusive)	aged 18 to 50 years (inclusive)	Revised the age range to improve screening of healthy volunteers
1. Protocol Synopsis – Study Treatment	within 30 minutes after the end of a…breakfast	approximately 30 minutes after the start of a…breakfast	Correction per FDA guidance on the food effect assessment
4.1.1.3 Nonclinical Safety	Based on these findings, the no observed adverse effect level (NOAEL) was 30 mg/kg/day (Day 28 mean combined sex C_{max} and AUC_{24hr} values of 6.94 µg/mL and 121 µg*h/mL, respectively).	Based on FDA recommendation, a NOAEL of 15 mg/kg/day was considered for calculating the starting dose (mean combined sex C_{max} values was 3.32 µg/mL and AUC_{24hr} 61.2 µg*h/mL).	Revised the rat NOAEL doses and systemic exposure at the NOAEL dose levels per FDA recommendation
4.1.1.3 Nonclinical Safety	Based on the mild severity of findings, the NOAEL was 40 mg/kg/day (Day 28 mean combined sex C_{max} and	Based on FDA recommendation, a NOAEL of 10 mg/kg/day was considered for	Revised the dog NOAEL doses and systemic exposure at the NOAEL dose levels per

	AUC_{24hr} values of 4.18 µg/mL and 40.8 µg*h/mL, respectively).	calculating the starting dose (mean combined sex C_{max} values was 2.61 µg/mL and AUC_{24hr} 21.7 µg*h/mL).	FDA recommendation
4.2.2. Dosing Rationale	…the no observed adverse effect level (NOAEL) was established at 30 mg/kg/day in rats and 40 mg/kg/day (highest dose tested) in dogs…	…the FDA-recommended no observed adverse effect level (NOAEL) doses of 15 mg/kg/day for rats and 10 mg/kg/day for dogs were used for the human starting dose calculations…	Revised the NOAEL doses, systemic exposure, HED and MRSD values per FDA recommendation throughout the text and table presented in this section
7.1. Overview of Study Design	… a total of 72 subjects (66 male…	…a total of 66 subjects (60 male…	Correction
7.1. Overview of Study Design – Table 4	N.A.	Added a footnote of "* Refer to Section 7.1 regarding the subjects returning to the CRU for the food effect assessment."	Added a footnote for the clarification
8.1. Inclusion Criteria	…18 to 55 years of age	…18 to 50 years of age	Revised the age range to improve screening of healthy volunteers
8.1. Inclusion Criteria	Normal electrocardiogram (ECG) (12-lead), arterial blood pressure (100-140/50-90 mmHg),	Normal electrocardiogram (ECG) (12-lead), arterial blood pressure, and heart rate within the	Revised to clarify the inclusion criteria

	and heart rate (60-100 bpm)	normal range of the study center or considered not clinically significant by the investigator and in agreement with the Sponsor	
9.3. Administration	within 30 minutes after the end of a…breakfast	approximately 30 minutes after the start of a…breakfast	Correction per FDA guidance on the food effect assessment (see above)
9.3. Administration	N.A.	• The meal will be taken about 30 minutes prior to the study drug administration. • The meal will be eaten in 30 minutes or less.	Added the additional instructions on the meal intake for the food effect assessment
9.3. Administration	N.A.	Added the phrase – "with the exception of study-specific events or assessments"	Added for the clarification
9.4.1. Randomization	The randomization code will be produced by SK Life Science, Inc. designee who will review and approve the randomization list. A copy of the randomization list (in a sealed tamper-evident envelope) will be archived at SK Life Science, Inc.	The randomization list will be generated by the clinical research organization (vendor) and will be provided to the site pharmacist. The pharmacist will keep the randomization list	Removed the phrase "Study Day 1"; Revised to clarify the randomization process

	Subjects who have completed screening evaluations and are eligible for participation in the study will be randomized on Study Day 1 for study drug administration. Each randomized subject will be assigned a unique subject number from the randomization list by the investigator or designee, which will be used to identify the individual subject for the duration of the study. The unblinded authorized site personnel will prepare the appropriate study drug/placebo for each subject based on the randomization list.	in a secure location. Subjects who have completed screening evaluations and are eligible for the study participation will be randomized for study drug administration. Each randomized subject will be assigned with a unique randomization number.	
9.4.2. Allocation of Subject Numbers	Subjects fulfilling the eligibility criteria will be randomized and assigned subject numbers at dosing in the morning of Study Day 1. Subject numbers will be allocated in consecutive order and correspond to a number on the computer-generated randomization list, which determines the treatment (active drug) group. Any replacement subjects will receive the subject number from the subject that they are replacing + 100 (e.g., replacement for subject	Subjects fulfilling the eligibility criteria will be randomized to receive their treatment according to the randomization list. Randomized subjects will be assigned with a 4-digit randomization number in the order in which they are enrolled. The first digit of the randomization number will refer to the Cohort	Removed the phrase “Study Day 1”; Revised to clarify the randomization process

	number 01105 would be subject number 01205).	number. For example, subjects in Cohort 1 will have the randomization numbers 1xxx; subjects in Cohort 2 will have the randomization numbers 2xxx. In a case where a subject needs to be replaced, the last 2 digits of the randomization number for replacement participants will be identical to those of the original participant's randomization number. The second digit, however, will be replaced with a 2. For example, if the original participant's randomization number is 1101, then the randomization number for the replacement participant will be 1201. Participants who prematurely discontinue from the study may be replaced at the sponsor's discretion.	

9.10.1. Blinding	…assigned to a dosing group linked to their subject number by an unblinded pharmacist at the clinical site.	…assigned to their randomization number linked to the dosing group by an unblinded pharmacist at the clinical site.	Grammar correction; Replaced the "subject number" with "randomization number" for the clarification
9.10.1. Blinding	SK Life Science, Inc. Drug Metabolism and Pharmacokinetics [DMPK] group	SK Life Science, Inc. Toxicology group	Revised to reflect the change of department name
9.10.1. Blinding	randomization code	randomization list	Replaced the "code" with "list" throughout the protocol
9.10.2. Unblinding	…break the code…	…break the blinding…	Replaced the "code" with "blinding" for the clarification
10.3.2. Urine Sampling	N.A.	Added the time window (Table 9) for PK urine sampling	To allow a time window for PK urine sampling
10.3.3.1 Blood Sample Processing	N.A.	… on wet ice…	Added the new text to clarify the sample processing procedure
10.3.3.1 Blood Sample Processing	3000 rpm	2000 xg	Correction for the centrifuge speed
10.6.2. Clinical Laboratory Assessments - Table 10 (Urinalysis)	Occult Blood	Blood	Correction

10.6.3. Physical Examinations and Vital Signs	Vital sign evaluations include blood pressure (systolic and diastolic), temperature, heart rate, respiratory rate, and arterial oxygen saturation (SaO_2) (using pulse oximetry). These will be assessed following a 5-minute rest in the supine position.	Vital sign evaluations include blood pressure (systolic and diastolic measurements in supine and standing in the same sequence in each subject, in order to allow orthostatic measurements), temperature, heart rate, respiratory rate, and arterial oxygen saturation (SaO_2) (using pulse oximetry).	Revised and added the orthostatic measurements with vital sign assessments per FDA recommendation
10.6.4. Electrocardiograms	The device will remain connected to the subject during the collection periods.	The device will remain connected to the subject during the collection periods as appropriate.	Added a phrase "as appropriate" to clarify the procedure
10.6.4.1. Safety 12-Lead ECGs	…for 5 minutes…	…for at least 5 minutes…	Correction to keep the time of supine rest consistent throughout the ECG collection
10.6.4.2. Extensive Triplicate ECGs	at least 10 minutes before and 5 minutes during the ECG extraction window to allow for quality ECG data	for at least 5 minutes before the ECG time point in order to allow for quality ECG data	Correction to keep the time of supine rest consistent throughout the ECG collection
10.6.6. Peak Expiratory Flow Rate (PEFR) Measurement	Peak expiratory flow rate (PEFR) will be measured as specified in…	Peak expiratory flow rate (PEFR) will be measured within a 30-minute time window	Added the time window around PEFR

		around the targeted time points as outlined in the Schedule of Assessments in…	
10.6.7.1. Contraception	Subjects who can father a child must agree to use 2 highly effective method of contraception, including at least one barrier method. Subjects must use a condom…	Subjects who can father a child must agree to use 2 highly effective methods of contraception, including at least one barrier method, as follows. Male subjects must use a condom…	Grammar correction by adding the phrase, such as ", as follows" and "Male"
10.6.7.1. Contraception	…, must be in use from…	…, must be used from…	Grammar correction by replacing "in use" to "used"
10.6.7.2. Pregnancy	The investigator must notify the Medical Monitor and SK Life Science, Inc. within 24 hours of the site's knowledge of the partner's pregnancy.	The investigator must notify the Medical Monitor, SK Life Science, Inc., and IQVIA by completing the Pregnancy Report form, faxing and emailing the form as per the Table of Contact (Table 13 and Table 14), within 24 hours of the site's knowledge of the partner's pregnancy.	Correction to clarify the reporting plans for pregnancy
11. Statistical and Analytical Plans	PK analysis set	PK population	Revised the dataset names - "set" to

			"population" throughout the section per FDA guidance – E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials (2017)
11.2. Analysis Populations	Analysis Sets	Analysis Populations	Revised the section header and definition per FDA guidance (see above)
11.2. Analysis Populations	Assignment of subjects to analysis sets will be done prior to clinical database lock. The following analysis sets will be defined: Full Analysis (FA) set, Safety set, and pharmacokinetic (PK) set. • **FA set**: All randomized subjects, whether or not they received study drug. Subjects will be analyzed according to the study drug to which they were randomized. All non-safety summaries (e.g., demographics) will be prepared using the FA set, as appropriate.	N.A. (Removed the old text as shown)	Deleted the old text to revise the dataset names (see above); Replaced the phrase "FA set" with "Safety Population" throughout the section

11.2. Analysis Populations	**Safety set**: All subjects who received at least 1 dose of study drug. Subjects will be analyzed according to the study drug actually received. All summaries of safety will be referenced using the Safety set.	**Safety Population**: All subjects who were randomized and received at least 1 dose of study drug.	Revised the definition for the clarification
11.2. Analysis Populations	**PK set:** All subjects who satisfied the PK evaluation criteria and dosed with the study drug without any major protocol violations and with sufficient PK profiles	**PK population:** All subjects who received at least 1 dose of study drug and have sufficient PK data without any major protocol deviations.	Revised the definition for the clarification
11.4.2.2. Demographics and Baseline Characteristics	Demographic, background, and baseline characteristics will be summarized for the FA set and will include (but are not limited to) subject disposition, demographics, baseline characteristics, medical history, and prior medications. Continuous variables will be summarized by descriptive summary statistics and categorical variables by frequency tables.	Demographic, parameters and baseline characteristics will be summarized for the Safety Population. Continuous variables will be summarized by descriptive summary statistics and categorical variables by the number and percentage of participants.	To clarify, the following changes were made: 1. Replaced the word "background" with "parameters"; 2. Corrected the redundant phrases; 3. Replaced the "frequency tables" with "number and percentage of participants"; 4. Deleted the redundant statement as shown

11.4.2.3. Medical History	N.A.	Medical history encompassing abnormalities and surgeries reported before the Screening visit will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0 or newer.	Added a new section 11.4.2.3. in order to improve the statistical analysis plan
11.4.2.4. Prior and Concomitant Medications	…regardless of whether medication end date is missing or not. …regardless of whether medication start date is missing or not. Note that medication that started prior to initial dosing of the study drug and continued after initial dosing will be summarized as prior medication and separately as concomitant medication.	…regardless of the medication end date. …regardless of the medication start date. The prior and concomitant medications will be summarized separately.	Grammar correction and clarification
11.4.4.4. Vital Signs	systolic and diastolic blood pressure (mmHg)	systolic and diastolic blood pressure (mmHg) measurements (in supine and standing in the same sequence in each subject, in order to allow orthostatic measurements)	Added the orthostatic measurements with vital sign assessments per FDA recommendation

12.2.2. Subject Information and Informed Consent	N.A.	A subject identification number (subject ID) will be assigned to each subject at the time that informed consent is obtained; this subject ID will be used throughout the study.	Added the new text to clarify as shown

Amendment 2

Section	***Old text / Content***	***Amended text / Content***	***Rationale / Description***
9.4.2. Allocation of Subject Numbers	Randomized subjects will be assigned with a 4-digit randomization number in the order in which they are enrolled. The first digit of the randomization number will refer to the Cohort number. For example, subjects in Cohort 1 will have the randomization numbers 1xxx; subjects in Cohort 2 will have the randomization numbers 2xxx. In a case where a subject needs to be replaced, the last 2 digits of the randomization number for replacement participants will be identical to those of the original participant's randomization number. The second digit, however, will be replaced with a 2. For example, if	Randomized subjects will be assigned with a 6-digit randomization number in the order in which they are enrolled. The first digit of the randomization number will refer to the part A or B (1 or 2). The second and third digits will refer to the Cohort number. For example, subjects in Cohort 1 of part A will have the randomization numbers 101xxx; subjects in Cohort 2 of part A will have the randomization numbers 102xxx.	Changed 4-digit randomization number to 6-digit in order to accommodate part A and part B. Add one more digit to accommodate more cohorts.

	the original participant's randomization number is 1101, then the randomization number for the replacement participant will be 1201. Participants who prematurely discontinue from the study may be replaced at the sponsor's discretion.	In a case where a subject needs to be replaced, the last 2 digits of the randomization number for replacement participants will be identical to those of the original participant's randomization number. The fourth digit, however, will be replaced with a 2. For example, if the original participant's randomization number is 110101, then the randomization number for the replacement participant will be 110201. Participants who prematurely discontinue from the study may be replaced at the sponsor's discretion.	

Amendment 3

Section	***Old text / Content***	***Amended text / Content***	***Rationale / Description***
2.0. Schedule of Assessments: Table 1	N.A.	Added Pregnancy Test (Serum) at screening and admission (Day -1). Adjusted footnote letters.	Revised schedule of assessments to add pregnancy test to gender effect cohort. Added a footnote for clarification.
8.1. Inclusion Criteria	1. Male subjects of 18 to 50 years of age (inclusive).	1. Male subjects of 18 to 50 years of age (inclusive) except for the gender effect cohort.	Revised to clarify the gender effect cohort will enroll healthy female subjects of non-childbearing potential.
8.1. Inclusion Criteria	8. For Part A (gender effect cohort): Female of non-childbearing potential (18 to 50 years of age (inclusive)), who have undergone a sterilization procedure at	8. For Part A (gender effect cohort): Female 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	Added pregnancy test for screening and admission (Day -1).

	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	sterilization, bilateral tubal ligation or bilateral salpingectomy, hysterectomy, or bilateral oophorectomy), or be postmenopausal with amenorrhea for at least 1 year prior to dosing, a follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status and serum pregnancy test at screening and upon admission with a negative result as per Principal Investigator's judgment	
9.4.2 Allocation of Randomization Numbers	Allocation of Subject Numbers	Allocation of Randomization Numbers	Revised to correct wording

1. PROTOCOL SYNOPSIS

Title A Phase 1, Randomized, Double-Blinded, Single-Dose Escalation Study Followed by a Multiple-Dose Escalation Study of SKL24741 in Healthy Subjects

Clinical Phase Phase 1

Objectives

Part A (single dose administration)

Primary:

- To evaluate the safety and tolerability of single oral ascending doses of SKL24741 capsule(s) administered to healthy male subjects

Secondary:

- To evaluate the pharmacokinetics (PK) of SKL24741 (R-enantiomer), SKL24742 (S-enantiomer) (if appropriate), and its possible metabolites (if deemed necessary) following administration of single oral ascending doses of SKL24741 capsule(s) administered to healthy male subjects
- To assess the food effect on the PK of SKL24741 and SKL24742 (if appropriate) following administration of a single oral dose of SKL24741 capsule(s) administered to healthy male subjects
- To assess the gender effect on the PK of SKL24741 and SKL24742 (if appropriate) following administration of a single oral dose of SKL24741 capsule(s) administered to healthy female subjects

Part B (multiple dose administration)

Primary:

- To evaluate safety and tolerability of multiple oral ascending doses of SKL24741 capsule(s) administered for 14 days to healthy male subjects

Secondary:

- To evaluate the PK of SKL24741, SKL24742 (if appropriate), and its possible metabolites (if deemed necessary) following administration of multiple oral ascending doses of SKL24741 capsule(s) administered to healthy male subjects

Endpoints Primary:

- Safety and tolerability will be based on assessment of adverse events, clinically significant laboratory assessments, electrocardiograms (ECGs), peak expiratory flow rate (PEFR), vital signs (blood pressure, heart rate, body temperature, respiratory rate,

arterial oxygen saturation (SaO_2) (using pulse oximetry)), physical examinations, and Columbia-Suicide Severity Rating Scale (C-SSRS) (Part B only).

Secondary:

- PK parameters will be calculated for SKL24741 and SKL24742 (if appropriate) from plasma and urine PK data.

Number of Subjects

98

Study Population

Healthy male subjects (60 in Part A and 32 in Part B), aged 18 to 50 years (inclusive)

Healthy female subjects (non-childbearing potential) (6 in Part A), aged 18 to 50 years (inclusive) for gender effect cohort of Part A

Investigational Drug

Active substance: SKL24741

Activity: An inhibitor of voltage-gated sodium channels and a possible activator of Big Potassium channels

Dosage Form: Capsule

Route of Administration: Oral

Study Treatment

Part	Doses
A	A single oral dose of 10, 25, 50, 100, 200, 300, 400, 600, 800, and 1000 mg of SKL24741 or placebo will be administered to subjects in the morning of the first day, following an overnight (10-hour) fast (all doses) or approximately 30 minutes after the start of a high-calorie, high-fat breakfast (Food effect cohort).
B	Multiple oral administrations of 4 dose levels of SKL24741 or placebo administered to male subjects each day for 14 days. Dose, dosing regimen, and food status (fasting vs. fed) used in Part B will be determined based on the outcome of Part A.

Schedule of Study Visits

Subjects in **Part A** will remain in the clinic for a 4-night stay (discharged on Study Day 4). Subjects in **Part B** will remain in the clinic for a 17-night stay (discharged on Study Day 17). There will be one Follow-up visit 14 to 16 days after the last dosing occasion for all subjects.

Pharmacokinetic Evaluations

Plasma Samples for Bioanalytical (BA) Analysis

Part A

- Pre-dose, and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 18, 24, 36, 48, 60, and 72 hours post-dose following the single dose administration

Part B

- **Study Days 1 and 7:** Pre-dose, and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose. The 24-hour post-dose blood PK samples for Days 1 and 7 should be taken before dosing on Days 2 and 8, respectively
- **Study Days 3 to 6 and 9 to 13:** Pre-dose only
- **Study Day 14:** Pre-dose, and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 18, 24, 36, 48, 60, and 72 hours post-dose

Urine Samples for Bioanalytical (BA) Analysis

Part A

- Pre-dose, and 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 72 hours post-dose following the single dose administration
- No urine collection for PK analysis in the food and gender effect cohorts

Part B

- No urine collection for PK analysis in Part B

Safety Evaluations

Adverse events, clinical laboratory assessments, electrocardiograms (ECGs), peak expiratory flow rate (PEFR), vital signs (blood pressure, heart rate, body temperature, respiratory rate, arterial oxygen saturation (SaO_2) (using pulse oximetry)), physical examinations, and Columbia-Suicide Severity Rating Scale (C-SSRS) (Part B only)

2. SCHEDULE OF ASSESSMENTS

The schedule of assessments is provided in Table 1 for Part A (single dose administration) and Table 2 for Part B (multiple dose administration).

Table 1: Schedule of Assessments - Part A (Single Dose Administration)

Assessment	Screening	Admission	Confinement				Follow-up (14-16 days after dosing day)
	Study Day						
Assessment	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**15-17**
Admission[a]		X					
Randomization			X				
Confinement		X	X	X	X	X	
Discharge[b]						X	
Outpatient Visit	X						X
Informed Consent[c]	X						
Inclusion and Exclusion Criteria Check	X	X					
Demographics	X						
Medical History	X						
Smoking Screen (cotinine urine test)	X	X					
Drugs of Abuse (urine)/Alcohol Screen (urine and breath)[d]	X	X					

Assessment	**Screening**	**Admission**	**Confinement**				**Follow-up (14-16 days after dosing day)**
	Study Day						
Assessment	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**15-17**
Physical Examination[e]	X[e]	X				X	X
Prior and Concomitant Medication	Details for all medications will be taken on an ongoing basis from screening to follow-up (FU).						
Height, weight, and BMI[f]	X						X[f]
Vital Signs[g]	X	X	X[g]	X	X	X	X
Peak Expiratory Flow Rate[h]		X	X[h]	X			X
Safety Single 12-Lead ECG	X	X			X	X	X
Extensive Triplicate ECG[i]			X[i]	X			
Serology Tests (HBsAg, HCV Ab, HIVAg and Ab)	X						
Hematology, Coagulation, and Clinical Chemistry[j]	X	X		X		X	X
Urinalysis[j]	X	X					X

Assessment	Screening	Admission	Confinement				Follow-up (14-16 days after dosing day)
	Study Day						
Assessment	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**15-17**
Alpha-1-acid Glycoprotein	X						
Total, LDL, and HDL Cholesterol	X						
FSH test – Females only[k]	X						
Pregnancy Test- Females only[l]	X	X					
PK Sampling – Plasma[m]			X**Error! Reference source not found.**	X**Error! Reference source not found.**	X**Error! Reference source not found.**	X	
PK Sampling – Urine[n]			X**Error! Reference source not found.**	X**Error! Reference source not found.**	X**Error! Reference source not found.**	X	
PGX Sampling – Whole blood[o]		X					
Study Drug Dosing[p]			X				

Assessment	**Screening**	**Admission**	**Confinement**				**Follow-up (14-16 days after dosing day)**
	Study Day						
Assessment	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**15-17**
Adverse Event Assessment and Reporting	Ongoing from the time of signing the Informed Consent Form (Non-treatment and Treatment emergent adverse events)						

[a] Subjects will be admitted to the clinic the day prior to study drug administration.

[b] Subjects will be discharged on Study Day 4 after the 72-hour PK sample has been collected and the final assessment has been completed.

[c] At screening, a separate informed consent form (ICF) will be used to obtain the subject's consent for the utilization of their DNA for pharmacogenomic (PGX) testing.

[d] For drugs of abuse/alcohol screen, refer to Section 10.6.2. At the time of signing the ICF, a negative result from the breath alcohol test is required.

[e] Complete physical examination should be performed at screening only. Abbreviated physical examination should be performed at all other marked study days. See Section 10.6.3.

[f] Height and weight will be collected, and BMI calculated at screening. Only weight will be collected at FU.

[g] Highlighted time points for vital signs (Section 10.6.3) as follows: pre-dose (baseline), 1, 2, 3, 4, 6, 8, and 12 hours post-dose on Day 1. Vital signs should be assessed at all other marked study days.

[h] Peak expiratory flow rate will be assessed at admission (Day -1), pre-dose (baseline), 2 and 24 hours post-dose after the single dose, and FU.

[i] Extensive triplicate ECGs, except for the food effect cohort, will be obtained to collect continuous 12-lead ECG data from pre-dose until 24 hours post-dose as specified. Three replicates (triplicate) of ECG data will be collected as close as possible from -0.75, -0.5, and -0.25 hours pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose after single dose administration. Subjects should not eat a meal within 1 hour of digital ECG data collection. See the instruction on lunch and dinner time (Section 8.3.1) to avoid any meal intake within 1 hour of the 6-hour and 12-hour post-dose ECG time points.

[j] For clinical laboratory assessments, refer to Section 10.6.2.

[k] Postmenopausal status for females of non-childbearing potential will be further confirmed with the follicle-stimulating hormone (FSH) serum levels that are consistent with postmenopausal status. Refer to Inclusion Criteria for details (Section 8.1).

[l] Pregnancy test (serum) will be collected at screening and admission (Day -1) to confirm pregnancy status of the gender effect cohort (Section 8.1).

[m] PK blood draw will be performed at pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 18, 24, 36, 48, 60, and 72 hours post-dose following the single dose administration (Section 10.3.1). See Table 8 for PK time window.

[n] PK urine samples, except for the food and gender effect cohorts, will be collected for each specified time interval: pre-dose and between 0-4, 4-8, 8-12, 12-24, 24-48, and 48-72 hours post-dose following the single dose administration (Section 10.3.2). The urine volume at each interval should be recorded as part of PK data.

[o] PGX samples (whole blood) will only be collected from the subjects who consented for DNA testing.

[p] Details regarding study drug administration are provided in Section 9.3.

BMI: body mass index; ECG: electrocardiogram; FSH: following-stimulating hormone; FU: Follow-up; HbsAg: hepatitis B surface antigen; HCV Ab: hepatitis C antibody; HDL: high density lipoprotein; HIV Ab: human immunodeficiency virus antibody; ICF: informed consent form; LDL: low density lipoprotein; PK: pharmacokinetic(s); PGX: pharmacogenomic(s).

Table 2: Schedule of Assessments - Part B (Multiple Dose Administration)

Assessment	**Screening**	**Admission**	**Confinement**																**Follow-up (14 – 16 days after final dosing day)**
	Study Day																		
Assessment	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**28 to 30**
Admission[a]		X																		
Randomization			X																	
Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Discharge[b]																			X	
Outpatient Visit	X																			X
Informed Consent[c]	X																			
Inclusion and Exclusion Criteria Check	X	X																		
Demographics	X																			
Medical History	X																			
Smoking Screen (cotinine urine test)	X	X																		
Drugs of Abuse (urine)/Alcohol Screen (urine and breath)[d]	X	X																		

Assessment	Screening	Admission	Confinement																Follow-up (14 – 16 days after final dosing day)
	Study Day																		
Assessment	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**28 to 30**
Physical Examination[e]	X[e]	X																	X	X
Prior and Concomitant Medication	Details for all medications will be taken on an ongoing basis from screening to follow-up (FU).																			
Height, Weight, and BMI[f]	X																			X[f]
Vital Signs[g]	X	X	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X	X	X	X
Peak Expiratory Flow Rate[h]		X	X[h]	X												X[h]	X			X
Safety Single 12-lead ECG	X	X																X	X	X
Extensive Triplicate ECG[i]			X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X[i]	X			
Serology Tests (HBsAg, HCV Ab, HIVAg and Ab)	X																			
Hematology, Coagulation, and Clinical Chemistry[j]	X	X			X				X							X			X	X

Assessment	Screening	Admission	Confinement																Follow-up (14 – 16 days after final dosing day)
	Study Day																		
Assessment	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**28 to 30**
Urinalysis[j]	X	X			X				X							X			X	X
Alpha-1-acid Glycoprotein	X																			
Total, LDL, and HDL Cholesterol	X																X		X	
C-SSRS	X																X			X
PK Sampling – Plasma[k]			X[k]	X	X	X	X	X	X[k]	X	X	X	X	X	X	X[k]	X[k]	X[k]	X	
PGX Sampling – Whole blood[l]		X																		
Study Drug Dosing[m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Adverse Event Assessment and Reporting	Ongoing from the time of signing the Informed Consent Form (Non-treatment and Treatment emergent adverse events)																			

[a] Subjects will be admitted to the clinic the day prior to study drug administration.

[b] Subjects will be discharged on Study Day 17, after the 72-hour PK sample from the final dose has been collected and the final assessment has been completed.

[c] At screening, a separate informed consent form (ICF) will be used to obtain the subject's consent for the utilization of their DNA for pharmacogenomic (PGX) testing.

[d] For drugs of abuse/alcohol screen, refer to Section 10.6.2. At the time of signing the ICF, a negative result from the breath alcohol test is required.

[e] Complete physical examination should be performed at screening only. Abbreviated physical examination should be performed at all other marked study days. See Section 10.6.3.

[f] Height and weight will be collected, and BMI calculated at screening. Only weight will be collected at FU.

[g] Highlighted time points for vital signs (Section 10.6.3) as follows: pre-dose (baseline), 1, 2, 3, 4, 6, 8, and 12 hours post-dose on Day 1; pre-dose, and at 2, 6, and 8 hours post-dose on Days 2 through 14. Vital signs should be assessed at all other marked study days.

[h] Peak expiratory flow rate will be assessed at admission (Day -1), pre-dose (baseline), 2 and 24 hours post-dose after the first dose (Day 1 dosing) and the last dose (Day 14 dosing), and FU.

[i] Extensive triplicate ECGs will be obtained to collect continuous 12-lead ECG data from pre-dose until 24 hours post-dose as specified. Three replicates (triplicate) of ECG data will be collected as close as possible from -0.75, -0.5, and -0.25 hours pre-dose, and 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose on Day 1, at pre-dose only on Days 2 through 13, and -0.75, -0.5, and -0.25 hours pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose on Day 14. Subjects should not eat a meal within 1 hour of digital ECG data collection. See the instruction on lunch and dinner time (Section 8.3.1) to avoid any meal intake within 1 hour of the 6-hour and 12-hour post-dose ECG time points.

[j] Clinical laboratory specimens (Section 10.6.2) will be obtained at pre-dose, if study drug administration occurs on the marked study days.

[k] On Days 1 and 7, PK blood draw will be performed at pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose. The 24-hour post-dose PK plasma samples for Days 1 and 7 should be taken before dosing on Days 2 and 8, respectively. On Days 3 to 6 and 9 to 13, PK blood draw will be performed at pre-dose only. On Day 14, PK blood draw will be performed at pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 18, 24, 36, 48, 60, and 72 hours post-dose following the final dosing (Section 10.3.1). See Table 8 for PK time window.

[l] PGX samples (whole blood) will only be collected from the subjects who consented for DNA testing.

[m] Details regarding study drug administration are provided in Section 9.3.

BMI: body mass index; C-SSRS: Columbia-Suicide Severity Rating Scale; ECG: electrocardiogram; FU: Follow-up; HbsAg: hepatitis B surface antigen; HCV Ab: hepatitis C antibody; HDL: high density lipoprotein; HIV Ab: human immunodeficiency virus antibody; ICF: informed consent form; LDL: low density lipoprotein; PK: pharmacokinetic(s); PGX: pharmacogenomic(s).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS

Abbreviation	Term
5-HT	Serotonin 5-hydroxytryptamin
ADD	After-discharge durations
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AEDs	Antiepileptic drugs
ALT	Alkaline transaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AR	Accumulation ratio
AUC	Area under the concentration-time curve
AUC_{24hr}	Area under the concentration-time curve from time zero to 24 hours post-dose
AUC_{∞}	Area under the concentration-time curve from 0 to infinity
AUC_t	Area under the concentration-time curve from 0 to t
AUC_{τ}	Area under the concentration-time curve over the dosing interval
BA	Bioanalytical
BCRP	Breast cancer resistance protein
BK	Big Potassium
BLQ	Below the limit of quantitation
BMI	Body mass index
BSA	Body surface area
CHO	Chinese hamster ovary
CL	Total clearance
CL/F	Apparent clearance
CL_R	Renal clearance
C_{max}	Maximum concentration
CF	Cystic fibrosis
CFR	Code of Federal Regulations
CNS	Central nervous system
CPAP	Clinical pharmacology analysis plan
CRO	Contract research organization

Abbreviation	Term
CRF	Case report form
CRU	Clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Case Study Report
CV	Coefficient of Variation
CYP	Cytochrome P450
DMCM	Methyl 6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate hydrochloride
ECG	Electrocardiogram
eCRF	Electronic case report form
ED_{50}	Half-maximal effective dose
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalography
EMA	European Medicines Agency
EOS	End of Study
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FIH	First-in-human
f_e	Fraction of drug dose excreted in urine
F_{rel}	Relative bioavailability
FU	Follow-up
GABA	Gamma-aminobutyric acid
Gamma-GT	Glutamyl transpeptidase
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMS	Generalized myoclonic seizures
GTCS	Generalized tonic-clonic seizures
HBsAg	Hepatitis B surface antigen
HCN	Hyperpolarization-activated cAMP-regulated cation
HCV	Hepatitis C virus

Abbreviation	Term
HCV Ab	Hepatitis C antibody
HDL	High density lipoprotein
HED	Human equivalent dose
HEK	Human embryonic kidney
hERG	Human ether-à-go-go related gene
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV Ab	Human immunodeficiency virus antibody
HIV Ag	Human immunodeficiency virus antigen
hNav	Human voltage-gated sodium channels
hDAT	Human dopamine transporter
hNET	Human norepinephrine transporter
HR	Heart rate
IC_{50}	Half-maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IND	Investigational New Drug (application)
INR	International normalized ratio
IP	Intraperitoneal
IRB	Institutional Review Board
IV	Intravenous
K_2EDTA	Di-potassium ethylenediaminetetraacetic acid
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactic dehydrogenase
LDL	Low density lipoprotein
LMA	Locomotor activity
MAD	Multiple ascending dose(s)
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MES	Maximal electroshock seizure

Abbreviation	Term
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
Nav	Voltage-gated sodium channels
NCA	Non-compartmental analysis
NMDA	N-methyl-D-aspartate
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NTD_{50}	Median neurotoxic dose
PBR	Peripheral benzodiazepine receptor
PEFR	Peak expiratory flow rate
P-gp	P-glycoprotein
PGX	Pharmacogenomic(s)
PK	Pharmacokinetic(s)
PT	Prothrombin time; Preferred Term
PT INR	Prothrombin time (PT) international normalized ratio (INR)
PTZ	Pentylenetetrazol
QA	Quality assurance
QC	Quality control
R_{acc}	Accumulation ratio
RBC	Red blood cell
rPOS	Refractory partial-onset seizures
SAD	Single ascending dose(s)
SAE	Serious adverse event
SaO2	Arterial oxygen saturation
SAP	Statistical analysis plan
SAR	Suspected adverse reaction
SD	Standard deviation
SEM	Standard error of the mean
SI	International System of Units
SKLSI	SK Life Science, Inc.
SOC	System Organ Class

Abbreviation	**Term**
SOP	Standard operating procedure
SRS	Spontaneous recurrent seizures
τ	Dosing interval
$t_{½}$	Half-life
TCA	Tricyclic antidepressant
t_{max}	Time to maximum concentration
TK	Toxicokinetic(s)
US	United States
V_d/F	Apparent volume of distribution
WBC	White blood cell
WHO-DD	World Health Organization-Drug Dictionary

4. INTRODUCTION

4.1. Background

Epilepsy is a neurological disorder that is characterized by an enduring predisposition to generate epileptic seizures and the associated cognitive, psychological and social consequences (Fisher et al., 2014). An epileptic seizure has a transient behavioral change that might be objective signs or subjective symptoms (such as loss of awareness, stiffening, jerking, a sensation that rises from the abdomen to the chest, a smell of burnt rubber or déjà vu), caused by abnormal excessive or synchronous neuronal activity in the brain (Devinsky et al., 2018). Epilepsy is one of the most common neurologic conditions. Almost 10% of people will experience a seizure during their lifetime (Hauser and Beghi, 2008). Epilepsy is the third leading contributor to the global burden of disease for neurological disorders and affects 65 million people worldwide (Ngugi et al., 2010). About one-third of patients have refractory epilepsy (i.e., seizures not controlled by two or more antiepileptic medications or other therapies). Approximately 75% of epilepsy begins during childhood, reflecting the heightened susceptibility of the developing brain to seizures (Stafstrom and Carmant, 2015).

Although the cause of epilepsy in many patients is unknown, seizures can be the result of almost any insult that disturbs brain function. These insults include acquired causes (for example, after stroke or traumatic brain injury), infectious diseases (such as neurocysticercosis), autoimmune diseases, and genetic mutations. To date, over 500 genes associated with epilepsy have been identified (Devinsky et al., 2018).

Epilepsy is classified in terms of epilepsy syndromes and seizure types. The latter is determined by the electroencephalography (EEG) patterns observed when the seizure is occurring and by the clinical seizure characteristics. Examples of seizure types include absence seizures (previously known as petit mal), simple partial seizures (previously known as focal motor or aura), complex partial seizures (previously known as psychomotor or temporal lobe) and generalized tonic-clonic seizures (also known as grand mal) (Meinardi et al., 1985).

Once seizure types are identified, this information determines the epilepsy syndrome in conjunction with information about cause, age of onset, and interictal EEG abnormalities. Epilepsy can be basically classified as idiopathic (no apparent structural injury, probable genetic cause) or symptomatic (structural brain abnormality of known or unknown cause). Further differentiation can be made on whether the seizures begin in a focal region (partial epilepsy) or begin diffusely (generalized epilepsy). Idiopathic generalized epilepsy is the most common childhood epilepsy; absence, myoclonic, and generalized tonic-clonic seizures may also be seen. In adults, symptomatic partial epilepsy is most common and may cause simple partial, complex partial, or generalized tonic-clonic seizures (Commission on Classification and Terminology of the International League Against Epilepsy, 1981). Although the International League Against Epilepsy updated new classification of epilepsy in 2017, the previous classification method was used to avoid confusion in this summary.

SKL24741 [(1*R*)-2-(5-methyl-1,3,4-oxadiazol-2-yl)-1-[3-[4-(trifluoromethyl)phenyl]phenyl] ethanol] is a novel small molecule that is being developed by SK Life Science, Inc. for the

treatment of epilepsy. SKL24741 is intended for oral administration and is a potent inhibitor of voltage-gated sodium channels (Nav). SKL24741 is a chiral compound with an R-configuration; SKL24741 displays more potent efficacy in a refractory partial-onset seizure (rPOS) animal model and a broader safety margin in animal studies compared to the (S)-enantiomer (SKL24742).

The first-line treatment for epilepsy includes antiepileptic drugs (AEDs) of which over 20 drugs have been approved by the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA). However, despite the availability of many AEDs, approximately one-third of patients fail to achieve seizure control (Devinsky et al., 2018). Therefore, the key unmet needs are: effective drugs for drug-resistant epilepsy, improved tolerability of drug treatment, development of individualized treatments based on epilepsy syndrome, and disease-modifying therapies. Based on the results for SKL24741 in *in vitro* studies and animal models of rPOS and other types of epilepsy, this compound has the potential to address these unmet needs.

Further details regarding the SKL24741 studies are discussed in the Investigator's Brochure.

4.1.1. Nonclinical Experience

In vitro and *in vivo* nonclinical studies were conducted to investigate primary and safety pharmacology properties; absorption, distribution, metabolism, and excretion (ADME) properties, pharmacokinetic drug interactions; and toxicology of SKL24741 according to the current regulatory guidance. All definitive *in vitro* safety pharmacology and pivotal toxicology studies were conducted in compliance with Good Laboratory Practice (GLP) regulations. As with many neurological compounds, SKL24741 has a steep dose response with respect to adverse central nervous system (CNS) clinical signs in rats and dogs (Section 4.1.1.3).

4.1.1.1. Pharmacology

A range of *in vitro* mechanism of action and *in vivo* efficacy studies have been conducted to characterize the primary pharmacodynamics of SKL24741. *In vitro* mechanism of action studies were conducted with SKL24741, including radioligand binding assays, functional assays, and ion channel patch clamp assays to evaluate the selectivity of SKL24741 and the potential for off-target effects. An extensive series of *in vitro* studies were conducted to evaluate the effects on synaptic ion channels, including sodium, calcium, and potassium ion channels, as well as its effects on gamma-aminobutyric acid (GABA), N-methyl-D-aspartate (NMDA), and hyperpolarization-activated cAMP-regulated cation 1 (HCN1) currents. Functional assays evaluating the effects of SKL24741 on serotonin 5-hydroxytryptamine (5-HT) receptor subtypes showed that SKL24741 significantly (i.e., ≥50%) inhibited 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_{1D} with half-maximal inhibitory concentration (IC_{50}) values of 5.6, 2.8, 66, and 81 μM, respectively. In *in vitro* electrophysiology assays with sodium channels, SKL24741 exhibited state-dependent inhibition of the voltage-gated sodium channel (Nav) 1.6 current amplitude with an IC_{50} value of 0.47 μM in the inactivated phase. SKL24741 also inhibited other subtypes of human voltage-gated sodium channels (hNav) in a state-dependent manner, including hNav1.1 (IC_{50}=1.7 μM), hNav1.2 (IC_{50}=0.7 μM), hNav1.3

(IC_{50}=1.1 μM), hNav1.7 (IC_{50}=0.59 μM), and Nav1.8 (IC_{50}=0.89 μM). SKL24741 has a much higher affinity for the inactivated state rather than the resting state of Nav channels. A higher affinity of SKL24741 for the inactivated state compared to the tonic state of Nav channels would contribute towards a preferential selectivity targeting the pathological conditions of epilepsy with potentially less adverse side effects (Eijkelkamp et al., 2012). In a kinetic study using human Nav1.6 channels, SKL24741 (1 μM) significantly slowed the recovery time from fast inactivation of Nav1.6 channels. These profiles of SKL24741 on voltage-gated sodium channels may contribute to its antiepileptic activity against bursting neurons under epileptic conditions. In a preliminary study, SKL24741 displayed an enhancement effect of Big Potassium (BK) channels in stably expressed human embryonic kidney (HEK) cell line.

In vivo pharmacology studies have demonstrated the efficacy of SKL24741 in various rodent models of refractory partial-onset seizures (rPOS), generalized tonic-clonic seizures (GTCS), and generalized myoclonic seizures (GMS). SKL24741 demonstrated efficacy in three mouse and one rat models of rPOS. SKL24741 produced a dose-dependent protective effect on electroshock-induced seizures in mice following intraperitoneal (IP) and oral administration. Although less potent than SKL24741, (S)-enantiomer chiral compound (SKL24742) and the racemate compound (SKL24505) also protected against seizures induced by 6-Hz electrical stimulation at 44 mA in a dose-dependent manner in mice. IP administration of SKL24741 also produced a dose-dependent protective effect on amygdala-kindled seizures in male Wistar rats and significantly reduced both seizure scores and electroencephalographic (EEG) after-discharge durations (ADD). In the pentylenetetrazol (PTZ)-induced kindling seizure test in mice, SKL24741 resulted in a significant reduction in seizure score by 42.9%. In a pilocarpine-induced spontaneous recurrent seizure (SRS) model, the maximal protection rate for SKL24741 was 50% at the highest dose tested. In a GTCS model using the maximal electroshock seizure (MES) test, SKL24741 produced a dose-dependent seizure protection effect in both mice and rats.

Finally, the efficacy of SKL24741 was further demonstrated in two GMS models in male mice. These models were induced by administration of PTZ, a non-competitive $GABA_A$ receptor antagonist, or methyl 6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate hydrochloride (DMCM), which binds specific benzodiazepine binding sites with high affinity; both are potent convulsants. In both models, SKL24741 had dose-dependent protective effects. Overall, SKL24741 displays a broad spectrum of efficacy in antiepileptic animal models. The results of *in vivo* efficacy studies suggest that, at doses devoid of behavioral toxicity, SKL24741 possesses a broad anticonvulsant spectrum in rat and mouse seizure models predictive of efficacy against generalized seizures, partial seizures and especially rPOS.

When tested against 112 CNS targets in radioligand binding assays and 34 CNS targets in functional assays, SKL24741 (50 μM) showed no significant (i.e., ≥50%) binding affinity for receptors and enzymes located in the CNS with the exception of human dopamine D4.2 (66% inhibition), rat peripheral benzodiazepine receptor (PBR) (51% inhibition), human sigma 2 (54% inhibition), human dopamine transporter (hDAT) (63% inhibition), and human norepinephrine transporter (hNET) (63% inhibition). In functional assays, SKL24741

showed half-maximal inhibitory concentration (IC_{50}) of 5.6, 2.8, 65.5 and 81 μM for 4 serotonin receptor subtypes (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_{1D}).

In an *in vitro* human ether-á-go-go related gene (hERG) assay in HEK293 cells, SKL24741 inhibited hERG potassium channel currents in a concentration-dependent manner, with an IC_{50} of 21.1 μM. Overall, this result indicates low potency for the hERG channel as there was a substantial safety margin based on SKL24741 exposures at efficacious doses in rodent seizure models (i.e., $C_{max} \approx 2.53$ μM; plasma protein binding = 96.2%). Further evaluations using cardiac ion channels to determine cardiovascular risk showed that SKL24741 inhibited (concentration-dependent) peak hNav1.5 (IC_{50}=20.2 μM) and late hNav1.5 (IC_{50}=4.91 μM) currents in HEK293 cells stably expressing hSCN5A and hCav1.2 currents (IC_{50}=17.2 μM) in Chinese hamster ovary (CHO)-K1 cells. Cardiovascular effects were also evaluated *in vivo* in a GLP study in telemetered male dogs; after single oral doses of SKL24741, there were no unscheduled mortalities and no SKL24741-related changes in any of the parameters evaluated with the exception of decreased QTc intervals at ≥10 mg/kg from 0.5 to 18 hours post-dose (up to -9 msec [-4%]).

SKL24741-related neurotoxicity was evaluated in non-GLP studies in mice and rats using the rotarod test after oral or IP administration. Following single IP administration of SKL24741 in mice and rats, the peak toxicity time was 0.5-hour post-dose with a median neurotoxic dose (NTD_{50}) of 17.3 mg/kg. Following single oral administration of SKL24741 in rats, the peak toxicity time was 1-hour post-dose with an NTD_{50} of 177.5 mg/kg. The effects of SKL24741 on locomotor activity (LMA) were evaluated in male rats. There were no significant effects of SKL24741 on LMA up to a single oral administration of 100 mg/kg. In a GLP study, the modified Irwin battery of assessments was used to evaluate the CNS effects of SKL24741 administered up to 40 mg/kg in male rats. Following oral administration, decreased extensor thrust and dilated pupils of both eyes were noted in rats administered ≥30 mg/kg, and moderate grasping loss, moderate piloerection, and lower body temperature (up to -1.0°C) were noted in rats administered with 40 mg/kg. Based on these findings, the no observed effect level (NOEL) for neurological function in this oral study was 15 mg/kg.

In a GLP study, the respiratory effects of SKL24741 were evaluated in male rats using head-out plethysmography. SKL24741 had no significant effects on tidal volume. However, there was a decrease in respiration rates up to 28 breaths/minute (-22%) and a decrease in minute volume up to 62 mL/minute (-28%). All doses had similar respiratory effects, and no NOEL dose was observed. These observations are considered to be related to the pharmacological action of SKL24741, and the temporal response was consistent with the extended exposure profile of SKL24741 in rats.

4.1.1.2. Pharmacokinetics

The pharmacokinetics (PK) of SKL24741 have been studied both i*n vitro* and *in vivo.* Toxicokinetic (TK) evaluations were performed as a part of oral repeated-dose toxicity studies in rats and dogs for up to 28 days. SKL24741 is intended for oral administration, therefore its absorption PK properties were evaluated in an *in vitro* permeability assay and following single oral and intravenous (IV) dosing in male mice, rats, and dogs. Plasma

samples were analyzed for SKL24741 levels using high performance liquid chromatography coupled with tandem mass spectrometry.

SKL24741 demonstrated high permeability with efflux ratios of 0.916 to 0.985 in Caco-2 cell monolayers. Assessments with breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) inhibitors indicated that SKL24741 may be a substrate of BCRP and P-gp. However, given the large passive permeability of SKL24741, it is unlikely that the *in vivo* absorption of SKL24741 would be impacted by efflux due to these transporters.

In single-dose bioavailability and PK studies in male mice, rats, and dogs, SKL24741 was administered by IV bolus or oral gavage. The elimination kinetics of SKL24741 following a single IV bolus dose varied slightly across species. The highest clearance (CL) and shortest half-life ($t_{½}$) were observed in mice, the lowest CL was observed in dogs and the longest $t_{½}$ was observed in rats. Across species tested in the nonclinical program (mice, rats, dogs), CL values were 3- to 4-fold lower than the calculated values of liver plasma flow (i.e., 3.0, 1.8, and 1.1 L/hr/kg, respectively) (Davies and Morris, 1993), indicating that SKL24741 was cleared slowly from the body. Volume of distribution was comparable in mice and dogs and both were less than that observed in rats; Such data also indicated SKL24741 distributed outside of the central compartment. For fed and fasted rats given SKL24741 orally, the exposures were similar between the two feeding states. The relative bioavailability (F_{rel}) of SKL24741 after oral administration in mice, fed and fasted rats, and dogs was high (F_{rel}≥82.9%). Based on a single-dose radiolabeled PK study, male and female rats had similar exposures, indicating no sex differences following both IV and oral doses.

TK parameters were evaluated in non-GLP and GLP oral toxicity studies of up to 28-day duration. In general, sex differences in SKL24741 exposure, in terms of C_{max} and area under the concentration-time curve from time zero to 24 hours post-dose (AUC_{24hr}), were less than 2-fold in both rats and dogs, indicating no gender differences. In both species, exposure tended to increase with increasing dose levels, but dose-proportionality varied depending on species and dose levels. No accumulation was observed in rats and dogs following 28 days of oral administration.

SKL24741 was highly bound to plasma proteins across species (mouse: 98%, rat: 96%; rabbit: 96%; dog: 98%; monkey: 97%; and human: 96%; all values are approximate means). Blood-to-plasma concentration ratios were approximately 0.8 to 1.0 for all species and concentrations, indicating SKL24741 primarily partitioned into the plasma. In a quantitative whole-body autoradiography study with [^{14}C]-SKL24741 in rats, [^{14}C]-SKL24741 was widely distributed to most tissues. Although tissue concentrations of radioactivity were still detectable in all tissues at 72 hours post-dose, concentrations decreased steadily between 120 through 672 hours post-dose with most tissues at below the limit of quantitation (BLQ) by 672 hours post-dose. Tissue-to-blood exposure ratios in the cerebellum were 2.3 to 3.8-fold indicating [^{14}C]-SKL24741 partitioned into the brain tissue regardless of sex or rat strain (same trend noted in other brain regions). The concentration of radioactivity in pigmented tissues, specifically the uveal tract, had greater exposures than those observed for all other tissues, suggesting an apparent association of [^{14}C]-SKL24741 with tissues containing melanin.

In vitro metabolism studies indicated that SKL24741 had high metabolic stability in rat, rabbit, dog, monkey and human microsomes, and moderate metabolic stability in mouse microsomes. In hepatocytes, SKL24741 showed high metabolic stability in rats and rabbits and moderate stability in mice, dogs, humans, and monkeys. In a separate hepatocyte assay, SKL24741 showed notably greater metabolism in monkeys, compared to other species. A total of six SKL24741 metabolites were found following incubation with mouse, rat, rabbit, dog, monkey, and human hepatocytes. Similar metabolic profiles were observed in hepatocytes from rats, rabbits, dogs, and humans, with no unique human metabolites. Metabolite M1 was not observed in monkey hepatocytes but was seen in human hepatocytes and all other species. SKL24741 showed low potential for covalent binding to liver proteins and low potential to form reactive metabolites that could bind to liver proteins. At a concentration up to 100 μM, SKL24741 had no inhibitory effect on cytochrome P450 (CYP) 2B6, CYP2C8, CYP2D6, and CYP3A4 (i.e., IC_{50} >100 μM for isozymes). The IC_{50} values CYP1A2, CYP2C9, and CYP2C19 were 21.1 μM, 99 μM, and 58.7 μM, respectively.

Excretion of SKL24741 was evaluated following single oral administration of [^{14}C]-SKL24741 in rats. The primary route of elimination of radioactivity was in the feces, with high levels being recovered in the bile of cannulated rats, suggesting that hepatic clearance and biliary excretion play an important role in the elimination of [^{14}C]-SKL24741.

4.1.1.3. Nonclinical safety

Nonclinical toxicology studies have been conducted in Sprague-Dawley rats and Beagle dogs to support oral administration of SKL24741 in humans. *In vitro* metabolite profiling data supported the selection of rats and dogs as the rodent and non-rodent toxicology species. All pivotal studies were performed in compliance with GLP regulations (21 Code of Federal Regulations (CFR) 58). All doses were given once daily via oral administration to support clinical dosing.

In a non-GLP study in male and female rats, single administration of ≥120 mg/kg SKL24741 resulted in severe clinical signs of hypoactivity and ataxia with low body carriage and/or lateral recumbency and led to the unscheduled euthanasia of the 120 and 200 mg/kg animals. Administration of 40 or 80 mg/kg SKL24741 resulted in animals that were ataxic or had low body carriage, but fully recovered by Day 2. Administration of 80 mg/kg also led to decreased body weight gain and food consumption. As clinical signs and body weight effects for 80 mg/kg were generally tolerable, the maximum tolerated dose (MTD) following single oral administration in rats was 80 mg/kg.

In a non-GLP 7-day repeat-dose toxicity and TK study, male and female rats were administered doses of 0, 20, 40, or 80 mg/kg/day SKL24741. Due to severe clinical signs of hypoactivity and ataxia with low body carriage and/or sternal or lateral recumbence, all animals (main and TK animals) dosed at 80 mg/kg/day were euthanized on Day 1 within 3 hours post-dose. Treatment-related clinical signs of hypoactivity, ataxia, hunched posture, piloerection, thin appearance, or limited use of hind limbs were noted for most animals administered 40 mg/kg/day beginning on Day 5. Treatment-related weight loss and decreased food consumption were also observed at this dose level following the first few doses of SKL24741. SKL24741-related reduced reticulocytes and increased cholesterol were

observed in all animals administered 40 mg/kg/day. Based on these findings, the 7-day MTD in rats was 40 mg/kg/day (Day 7 C_{max} and AUC_{24hr} values of 7.40 µg/mL and 111 µg*h/mL, respectively, in males and 12.5 µg/mL and 269 µg*h/mL, respectively, in females).

In a GLP 28-day repeat-dose study toxicity and TK study, male and female rats were administered 0, 15, 30, or 40 mg/kg/day SKL24741. No unscheduled mortalities were observed. Clinical observations were dose-responsive and included transient ataxia and hypoactivity for both sexes administered ≥30 mg/kg/day and low body carriage for animals administered 40 mg/kg/day. Isolated incidences of hunched appearance and lateral recumbency were also observed at 40 mg/kg/day. Clinical signs were considered adverse at 40 mg/kg/day due to the nature and severity of the observations. Dose-dependent decrease in body weight, correlating with decreased food consumption, was observed at ≥30 mg/kg/day; however, these observations were not considered adverse due to their transient nature and reversibility. Clinical chemistry changes included mild, reversible, higher cholesterol concentration in males and females administered ≥15 mg/kg/day and ≥30 mg/kg/day, respectively, which were not considered adverse. SKL24741-related increased liver weights were observed in males administered ≥30 mg/kg/day and females administered ≥15 mg/kg/day. Microscopic liver findings of minimal centrilobular hepatocyte hypertrophy were observed in males and females administered ≥30 mg/kg/day. These findings were consistent with potential microsomal enzyme induction in the liver, an adaptive response, and were considered non-adverse due to their minimal severity and partial recovery following the 2-week recovery phase. Based on FDA recommendation, a NOAEL of 15 mg/kg/day was considered for calculating the starting dose (mean combined sex C_{max} values was 3.32 µg/mL and AUC_{24hr} 61.2 µg*h/mL).

In a non-GLP toxicity study, male and female dogs were administered a single dose of 20, 60, 100, or 300 mg/kg SKL24741. At doses ≥100 mg/kg, clinical signs of lateral (only 300 mg/kg female) and sternal recumbency, ataxia, hypoactivity, emesis, and/or foamy white vomitus, and excessive salivation were observed. Decreased food consumption was noted in animals administered ≥60 mg/kg with full recovery before the next dosing occasion. The MTD following single oral administration in dogs was 100 mg/kg.

In a non-GLP 7-day repeat-dose toxicity and TK study, male and female dogs were administered 50/10, or 100/30 mg/kg/day SKL24741. Animals were initially administered 50 or 100 mg/kg/day. For the 100 mg/kg/day animals, the moribund condition of one male and one female on Day 3 resulted in the unscheduled euthanasia of these two animals. Together with clinical observations of body tremors, rigidity, decreased responsiveness, motor impairment, hypoactivity, ataxia, emesis and vomitus, and excessive salivation in the other animals dosed at 50 and 100 mg/kg/day, all surviving 50 and 100 mg/kg/day animals had a 9-day non-dosing period followed by dose level reduction to 10 and 30 mg/kg/day, respectively. Clinical signs at these reduced dose levels were limited to a single incidence of emesis and vomitus in one female administered 30 mg/kg/day. SKL24741-related excessive salivation was noted after dosing at ≥10 mg/kg/day. SKL24741-related changes in absolute and/or relative organ weights were noted in animals administered ≥50/10 mg/kg/day, including the adrenals, epididymis, heart, kidney, liver, ovaries, pituitary, prostate, spleen, testes, thymus, thyroid, and uterus/cervix. Based on these findings, the 7-day MTD for

SKL24741 in dogs was 30 mg/kg/day (Day 7 mean combined sex C_{max} and AUC_{24hr} values of 3.20 µg/mL and 32.2 µg*h/mL, respectively).

In a GLP 28-day repeat-dose toxicity and TK study, male and female dogs were administered 0, 10, 20, or 40 mg/kg/day SKL24741. Clinical observations included ataxia and/or hypoactivity, emesis and/or vomitus, and excessive salivation in animals administered ≥10 mg/kg/day; intermittent tremors in animals administered ≥20 mg/kg/day; decreased reactivity, retching, and clear oral discharge in animals administered 40 mg/kg/day; and sternal recumbency on a single day in one animal administered 10 mg/kg/day. Severity and frequency of clinical findings increased in a dose-proportional manner; however, the clinical observations were not severe enough to be considered adverse and showed evidence of reversibility during the 2-week recovery phase. Based on FDA recommendation, a NOAEL of 10 mg/kg/day was considered for calculating the starting dose (mean combined sex C_{max} values was 2.61 µg/mL and AUC_{24hr} 21.7 µg*h/mL).

SKL24741 did not show any genotoxic potential in a GLP bacterial reverse mutation (Ames) assay or in a GLP *in vitro* human lymphocyte micronucleus assay. After oral administration up to 40 mg/kg SKL24741 to male Sprague-Dawley rats, there was no increase in micronucleated polychromatic erythrocytes. Additionally, SKL24741 absorption data indicated that SKL24741 was not sufficiently photoreactive to result in direct phototoxicity in humans.

4.1.2. Clinical Experience

SKL24741 has not been studied in humans.

4.2. Rationale for Present Study

The rationale for developing SKL24741 is based on the nonclinical evidence indicating that SKL24741 is a potent inhibitor of voltage-gated sodium channels and a possible activator of Big Potassium (BK) channels. SKL24741 was shown to have a broad anticonvulsant spectrum in rat and mouse seizure models predictive of efficacy against epilepsy, including generalized seizures, partial seizures and especially rPOS (Section 4.1.1.1).

To date, nonclinical safety and pharmacokinetic findings indicate that SKL24741 has a favorable safety profile (Section 4.1.1.3) and dose-dependent drug exposure (Section 4.1.1.2).

This single and multiple ascending dose study is designed to evaluate the safety, tolerability, and PK of SKL24741 administered orally to healthy adult subjects.

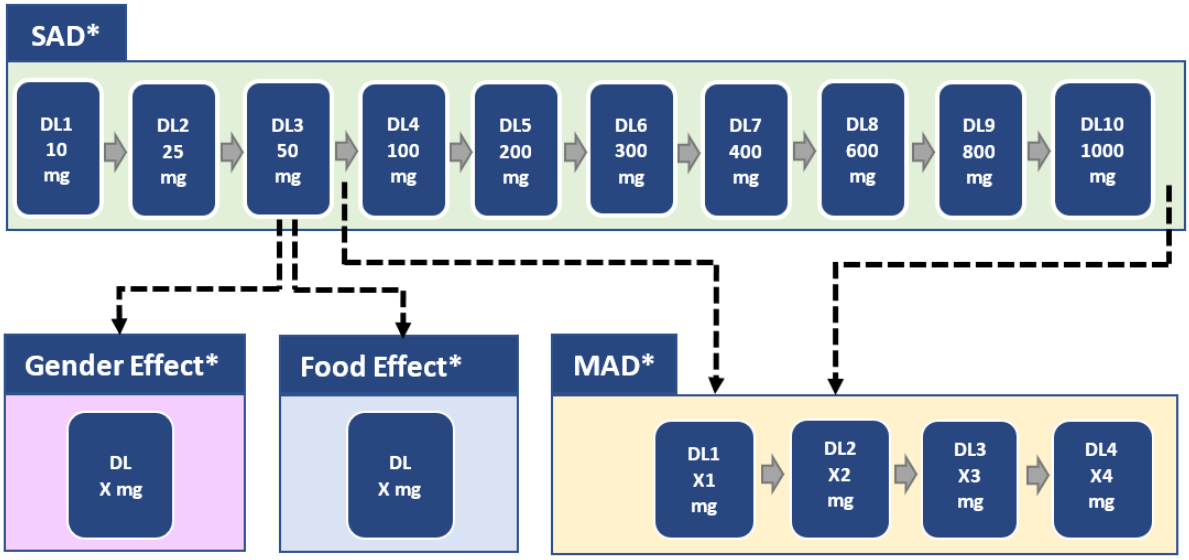
4.2.1. Study Design Rationale

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

The study includes a sequential cohort design that is intended to optimize subject safety and assess tolerability, safety, and PK of SKL24741. In the single-dose escalation part of the study (Part A), tolerability, safety, and PK of SKL24741 will be assessed in healthy male subjects under fasting condition. At an appropriate dose based on PK results, one dose

cohort will be repeated with the subjects under fed condition, in order to evaluate the magnitude of the food effect on the disposition of SKL24741. To assess the gender effect on the disposition of SKL24741, female subjects will be treated at one dose level under fasting condition.

Figure 1: Schematic of study design



Dotted lines and arrows represent the timing of dosing decision.
*Dose may be adjusted or confirmed based on safety/tolerability and PK data (applicable).

The multiple dose portion of the study (Part B) will evaluate the tolerability, safety, and PK of SKL24741 after 14 days of dosing in healthy male subjects. Doses, dosing regimen, and food status (fasting vs. fed) used in Part B will be determined based on the outcome of Part A. The selection of the first dose level of SKL24741 in Part B will be determined based on safety and PK information from Part A.

During Part A and Part B, a sentinel dosing strategy will be used (Section 7.2). Safety reviews will be performed prior to dose escalation from one cohort to another (dose level increase). Dose escalation criteria and dose stopping rules (Section 7.3) will be applicable at any time.

4.2.2. Dosing Rationale

As this study is the first-in-human (FIH) study, the initial dose of SKL24741 has been conservatively selected according to the United States Food and Drug Administration (FDA) guidance document entitled "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (FDA Guidance for Industry, 2005).

The dose levels planned for the Phase 1 clinical trial are based on the overall safety and tolerability profile of SKL24741 established in the nonclinical program. In the GLP 28-day oral toxicity studies, the FDA-recommended no observed adverse effect level (NOAEL) doses of 15 mg/kg/day for rats and 10 mg/kg/day for dogs were used for the human starting dose calculations. Based on the results of the SKL24741 toxicology studies, rats were

considered the most sensitive species. On a body surface area (BSA) basis, human equivalent dose (HED) in rats is 15 mg/kg/day ÷ 6.2 = 2.42 mg/kg/day; HED based on the NOAEL in dogs is 10 mg/kg/day ÷ 1.8 = 5.56 mg/kg/day. By applying a 10-fold safety factor to the HED of 2.42 mg/kg/day for rat NOAEL, the maximum recommended starting dose (MRSD) for a Phase 1 clinical study in healthy volunteer is 0.242 mg/kg (or 14.5 mg based on an assumed human weight of 60 kg [calculation = 2.42 mg/kg/day ÷ 10 (safety factor) × 60 kg]).

Table 3 provides an overview of the NOAELs from the 28-day GLP repeated-dose toxicology studies and the systemic exposures at the NOAEL dose levels. The HED, MRSD, and calculated human starting dose are also presented.

Table 3: Summary of NOAELs, systemic exposure at the NOAEL dose levels, MRSD and human starting dose

Study No. / Species	NOAEL (mg/kg/day)	AUC at NOAEL Day 28 (µg*hr/mL)	C_{max} at NOAEL Day 28 (µg/mL)	Scaling Factor	HED (mg/kg)	MRSD (10X Safety Margin = HED÷10) (mg) (60-kg human weight)
22T0022 / Rat	15*	61.2	3.32	6.2	2.42	14.5
22T0023 / Dog	10*	21.7	2.61	1.8	5.56	33.3

AUC = area under the concentration-time curve; C_{max} = maximum concentration; HED = human equivalent doses; MRSD = maximum recommended starting dose; NOAEL = no observed adverse effect level.
*NOAELs based on FDA recommendation

Based on these data from the most sensitive species (rat), the MRSD is approximately 14.5 mg with a 10-fold safety factor applied to the HED (HED ÷ 10). However, a larger safety factor of approximately 15 was applied to the HED (HED ÷15) due to steep dose-toxicity profile in rats and dogs (Section 4.1.1). Therefore, the starting dose of this FIH clinical study will be a single oral dose of 10 mg of SKL24741. With this starting dose, a safety factor would be approximately 33 from the HED derived from the dog.

The first cohort of the single ascending dose (SAD) study will receive a single dose at the Dose 1 level (i.e., 10 mg) and subsequent cohorts will receive doses up to 1000 mg (as a single dose) based on the prediction from allometric scaling and in silico assessment. However, dose levels of SKL24741 will be adjusted if needed based on plasma exposure, safety and tolerability observed at each dose level during the study.

The single-dose escalation scheme (Part A) is designed to explore a range of doses up to the plasma exposure observed at the NOAEL of 10 mg/kg/day in dogs (Day 28 mean combined sex C_{max} and AUC values of 2.61 µg/mL and 21.7 µg*hr/mL, respectively; Table 3) if the safety and tolerability allow reaching this plasma exposure. A few additional single dose levels beyond the dog NOAEL exposures may be considered if the safety and tolerability warrant a higher dose of SKL24741. However, the dose escalation increment will not exceed 1.5-fold between each dose level due to the steep dose response observed in toxicology species (Section 4.1.1). The institutional review board (IRB) will be notified prior to initiating these additional cohorts. In any case, the plasma exposure in humans will not

exceed the exposure observed at the NOAEL of 15 mg/kg/day in rats (Day 28 mean combined sex C_{max} and AUC values of 3.32 µg/mL and 61.2 µg*hr/mL, respectively).

After the first dose level, if drug exposure in humans differ from what is expected from nonclinical studies, the dose-escalation scheme may be re-evaluated. The dose level selected to assess the preliminary food and gender effects may also be re-evaluated. Any changes to the dose escalation scheme will be reviewed and approved by the Sponsor and submitted to the IRB.

5. STUDY OBJECTIVES

Part A

Primary:

- To evaluate the safety and tolerability of single oral ascending doses of SKL24741 capsule(s) administered to healthy male subjects

Secondary:

- To evaluate the PK of SKL24741 (R-enantiomer), SKL24742 (S-enantiomer) (if appropriate), and its possible metabolites (if deemed necessary) following administration of single oral ascending doses of SKL24741 capsule(s) administered to healthy male subjects
- To assess the food effect on the PK of SKL24741 and SKL24742 (if appropriate) following administration of a single oral dose of SKL24741 capsule(s) administered to healthy male subjects
- To assess the gender effect on the PK of SKL24741 and SKL24742 (if appropriate) following administration of a single oral dose of SKL24741 capsule(s) administered to healthy female subjects

Part B

Primary:

- To evaluate safety and tolerability of multiple oral ascending doses of SKL24741 capsule(s) administered for 14 days to healthy male subjects

Secondary:

- To evaluate the PK of SKL24741, SKL24742 (if appropriate), and its possible metabolites (if deemed necessary) following administration of multiple oral ascending doses of SKL24741 capsule(s) administered to healthy male subjects

6. STUDY ENDPOINTS

6.1. Primary Endpoint

Safety and tolerability will be based on assessment of adverse events, clinically significant laboratory assessments, electrocardiograms (ECGs), vital signs (blood pressure, heart rate, body temperature, respiratory rate, arterial oxygen saturation (SaO_2) (using pulse oximetry)), physical examinations, peak expiratory flow rate (PEFR), and Columbia-Suicide Severity Rating Scale (C-SSRS) (Part B only).

6.2. Secondary Endpoints

PK parameters will be calculated for SKL24741 and SKL24742 (if appropriate) from plasma and urine PK data.

7. STUDY DESIGN

7.1. Overview of Study Design

This is a two-part, double-blinded, randomized study of SKL24741. The schematic of study design is shown in Figure 1. Table 4 further outlines the study design.

Part A is a single-dose escalation study in healthy male subjects, except for the gender effect cohort in healthy female subjects. It is expected that a total of 66 subjects (60 male and 6 female subjects) will be enrolled in Part A. Each subject will be given a single oral dose of study drug capsule (SKL24741 or placebo) on one occasion. There will be 6 new subjects at each dose level (4 subjects randomized to SKL24741 and 2 to placebo) during single-dose escalation. Study drug will be administered under fasting condition, except for one cohort utilized for the food effect assessment at one of the dose levels.

To evaluate the magnitude of the food effect on the disposition of SKL24741, a cohort of subjects will receive a second dose of study drug under fed condition (Period 2) at an appropriate dose level based on PK results. After completing Period 1 (fasting) as part of single dose escalation, these subjects will return to the clinical research unit (CRU) for a second confinement to receive a second single dose (same dose level) of study drug under fed condition. A washout period of at least 14 days is planned between fasting and fed cohorts (i.e., between Period 1 and Period 2). As subjects complete the Follow-up visit of Period 1 and then return to the CRU for re-admission (Day -1 of Period 2), the same study procedures will apply again (including Day -1 procedures) in order to initiate Period 2.

To assess the gender effect on the disposition of SKL24741, a set of 6 female subjects of non-childbearing potential will be treated at one dose level under fasting condition.

At each dose level, except for the food and gender effect cohorts, a sentinel dosing strategy will be used as described in Section 7.2.

Part B is a multiple-dose escalation study in 32 healthy male subjects. Doses, dosing regimen, and food status (fasting vs. fed) used in Part B will be determined based on the outcome of Part A. Dosing will extend over a 14-day period at each dose level. Four dose levels will be assessed, and subjects will be randomized into one of the four dose levels. Each dosing cohort will have 8 new subjects (6 subjects randomized to SKL24741 and 2 to placebo) dosed each day for 14 days (Table 4). Daily dose level in Part B will not exceed the maximum dose level used in Part A.

At each dose level, a sentinel dosing strategy will be used as described in Section 7.2.

Table 4: Study Design

Part A: Single Ascending Doses (SAD)			
Total Number of Subjects	**Randomized Stratification (Active/Placebo)**	**Number of Subjects per Cohort**	**Food Status (Fasting/Fed)**
60 Male Subjects	10 mg SKL24741/Placebo	4 SKL24741/ 2 Placebo	Fasting

	25 mg SKL24741/Placebo	4 SKL24741/ 2 Placebo	Fasting
	50 mg SKL24741/Placebo	4 SKL24741/ 2 Placebo	Fasting
	100 mg SKL24741/Placebo	4 SKL24741/ 2 Placebo	Fasting
	200 mg SKL24741/Placebo	4 SKL24741/ 2 Placebo	Fasting
	300 mg SKL24741/Placebo	4 SKL24741/ 2 Placebo	Fasting
	400 mg SKL24741/Placebo	4 SKL24741/ 2 Placebo	Fasting
	600 mg SKL24741/Placebo	4 SKL24741/ 2 Placebo	Fasting
	800 mg SKL24741/Placebo	4 SKL24741/ 2 Placebo	Fasting
	1000 mg SKL24741/Placebo	4 SKL24741/ 2 Placebo	Fasting
Part A: Food Effect Assessment			
Total Number of Subjects	**Dose**	**Number of Subjects per Cohort**	**Food Status (Fasting/Fed)**
6 Male Subjects*	Based on the outcome of Part A	6 SKL24741	Fed
Part A: Gender Effect Assessment			
Total Number of Subjects	**Dose**	**Number of Subjects per Cohort**	**Food Status (Fasting/Fed)**
6 Female Subjects (non-childbearing potential)	Based on the outcome of Part A	6 SKL24741	Fasting
Note: • All doses are in a capsule formulation. • Subjects will remain in the clinic for a 4-night stay (discharged on Study Day 4). • A sentinel dosing strategy (Section 7.2) will be used for all cohorts, except for food and gender effect cohorts, in Part A. * Refer to Section 7.1 regarding the subjects returning to the CRU for the food effect assessment.			
Part B: Multiple Ascending Doses (MAD)			

Total Number of Subjects	Randomized Stratification (Active/Placebo)	Number of Subjects per Cohort	Food Status (Fasting/Fed)
32 Male Subjects	SKL24741 Dose 1/Placebo	6 SKL24741/2 Placebo	Based on the outcome of Part A
	SKL24741 Dose 2/Placebo	6 SKL24741/2 Placebo	Based on the outcome of Part A
	SKL24741 Dose 3/Placebo	6 SKL24741/2 Placebo	Based on the outcome of Part A
	SKL24741 Dose 4/Placebo	6 SKL24741/2 Placebo	Based on the outcome of Part A

Note:

- All doses are in a capsule formulation.
- Each cohort of 8 subjects will receive the study drug each day for 14 days. Subjects will remain in the clinic for a 17-night stay (discharged on Study Day 17).
- Doses, dosing regimen, and food status (fasting vs. fed) used in Part B will be determined based on the outcome of Part A.
- A sentinel dosing strategy (Section 7.2) will be used for all cohorts in Part B.

A cohort of female subjects will be added to **Part A** for the preliminary gender effect assessment as shown in Table 4. These female subjects will need to be of non-childbearing potential, 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.

7.2. Dosing strategy

A sentinel dosing strategy will be used in both Part A (SAD) and Part B (MAD), except for the food and gender effect cohorts. The investigator and the Sponsor will assess safety and tolerability data and determine whether it is acceptable to continue dosing (within cohorts) or to dose escalate (between cohorts).

Table 5 summarizes the sentinel dosing strategy as the following. The first 2 subjects (1 on SKL24741 and 1 on placebo) within each cohort may be dosed at the same time. Randomization will ensure that one of these 2 subjects (sentinel subjects) receives placebo. If the doses are safe and tolerated, as determined by the investigator and the Sponsor, dosing of the remaining subjects will occur after the observation period as specified in Table 5.

Table 5: Sentinel Dosing Strategy

Dose level (Part A and Part B)	**Observation Period and Safety Review**
First dose level	1) Two sentinel subjects (1 on SKL24741 and 1 on placebo)
	2) 14-day observation period after dosing the first subject with SKL24741
	3) The investigator and the Sponsor review all available blinded safety data at the end of observation period.
	4) The remaining subjects dosed within the cohort
Second dose level and higher	1) Two sentinel subjects (1 on SKL24741 and 1 on placebo)
	2) 7-day observation period after dosing the first subject with SKL24741
	3) The investigator and the Sponsor review all available blinded safety data at the end of observation period.
	4) The remaining subjects dosed within the cohort

Dose escalation between the cohorts (dose increase) will only proceed if the safety and tolerability of the previous dose(s) are acceptable as judged by the investigator and the Sponsor. If available/needed, PK analysis results will also be considered. The investigator and the Sponsor may adjust the observation period based on the disposition of SKL24741.

The initiation and the final choice of the dose level for the food and gender effect cohorts (single dose administration) will not be performed until the PK and safety/tolerability are considered to be acceptable for the dose level provided under fasting condition and in healthy male subjects, respectively (Part A, single dose administration) (Figure 1 and Section 7.1).

The investigator and the Sponsor will take all precautions necessary for studies at an early stage in the development of a new chemical entity. Dose escalation criteria and dose stopping rules (Section 7.3) will be applicable at any time.

7.3. Dose Escalation Criteria

The investigator and the Sponsor will review all available blinded safety (and applicable PK) data in a blinding fashion at the end of each dose group before deciding to escalate to the next dose level. Dose escalation decision will be jointly made by the investigator and the Sponsor. The dose level may be adjusted from the protocol planned dose, if deemed necessary.

The investigator will stop dose escalation or recommend modification of the dose escalation if in his/her judgment, and in consultation with the Sponsor, such action is medically prudent to protect safety of the subjects.

Study drug administration and dose escalation will be discontinued if, within a cohort, 2 or more subjects (for Part A) or 3 or more subjects (for Part B) experience a laboratory

abnormality or significant clinical event (severe or life-threatening), considered by the investigator to be related or possibly related to the study drug.

The initiation and the final choice of the first dose level of Part B (multiple dose administration) will not be performed until the PK, safety, and tolerability at such corresponding dose level after single dose administration (Part A) are assessed and considered to be acceptable.

Dose escalation in Part A and Part B will be stopped based on the dose stopping rules. The situations where the dose stopping rules apply are outlined in Table 6. If one of the following situations occurs, dose will not be escalated.

Table 6: Dose Stopping Rules (Part A and Part B)

Situation 1	PK futility where the magnitude of plasma exposure (AUC) of SKL24741 increase is disproportionate and not considered meaningful regarding the dose increase.
Situation 2	Safety/tolerability profile does not warrant a higher dose to be investigated.
Situation 3	The plasma exposure of SKL2474 exceeds the dose range justified in the dosing rationale (Section 4.2.2).

8. SELECTION OF STUDY POPULATION

Subjects must meet all inclusion and exclusion criteria.

8.1. Inclusion Criteria

1. Male subjects of 18 to 50 years of age (inclusive) except for the gender effect cohort.
2. Able to read, understand, sign, and date a written informed consent form (ICF) before study participation at screening
3. Agree to use 2 highly effective methods of contraception, including at least one barrier method (Section 10.6.7 for details)
4. Body mass index (BMI) between 18.0 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. 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
7. Able to understand and comply with protocol requirements and instructions and likely to complete the study as planned
8. For Part A (gender effect cohort): Female 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 and serum pregnancy test at screening and upon admission with a negative result as per Principal Investigator's judgment

8.2. Exclusion Criteria

1. History of any illness or condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subjects
2. Smokers (subjects who have smoked within 6 months at screening or those with positive results from smoking screening)
3. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with pharmacokinetics of the trial medication (except appendectomy and simple hernia repair).
4. Regular treatment with prescription medications. Subjects should have ended any prescription medications at least 14 days before the first dosing of the study drug. Potential subjects should only stop any prescribed medication at the direction of a physician.

5. Regular treatment with nonprescription medications. Subjects should have ended any nonprescription medications at least 14 days before the first dosing of the study drug. Potential subjects should consult a physician before stopping any regular treatment with nonprescription medication.
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), vitamins, and grapefruit or grapefruit juice, or Seville oranges at least 14 days before the first dosing of study drug.
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. Subjects may not consume any alcohol from 72 hours before the first dosing of study drug through the completion of the last PK sampling.
9. Consumption of an average of more than 5 servings (8 ounces per serving) per day of coffee, cola, or other caffeinated beverage before screening. Subjects may not consume any caffeinated beverages from 48 hours prior to dosing until the collection of the last PK sample.
10. 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.
11. 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.
12. 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)
13. 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])
14. History of any known relevant allergy/hypersensitivity (including allergy to the trial medication or its excipients)
15. Subject who is judged not eligible for study participation by investigator

8.3. Life Style Guidelines

8.3.1. Meals and Dietary Restrictions

Subjects will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (e.g., Seville oranges, and pomelos) from 14 days prior to the first dose (Exclusion criteria (Section 8.2) and Appendix B) of study medication until the Follow-up visit.

Clinical Chemistry Assessments:

- Clinical laboratory specimens are to be collected under fasting condition. Subjects should not take food or fluids, except of water, for at least 6 hours prior to specimen collection (Section 10.6.2).

Dosing Days:

- Food and fluid intake restrictions associated with study drug administration are described in Section 9.3.
- Meal intake should be avoided within 1 hour of ECG data collection during the extensive triplicate 12-lead ECG.
- Lunch will be provided approximately 4 to 5 hours after dosing.
- Dinner will be provided approximately 9 to 10 hours after dosing.
- An evening snack will be permitted.

8.3.2. 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.

A table of study restrictions is provided in Appendix B.

8.3.3. 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.

8.4. Removal of Subjects in the Study

A subject may be discontinued from the study at any time if the subject, investigator, or Sponsor determines that it is not in the best interest of the subject to continue participation. A subject who prematurely discontinues treatment will be asked to return for a Follow-up visit at 14 to 16 days following administration of the last dose of study drug.

Subjects will be discontinued from the study if:

- they develop a medical condition that requires concomitant therapy with a prohibited medication,

- they develop a serious or life-threatening adverse reaction that places them at immediate risk,
- they develop severe nausea or vomiting,
- their female partner becomes pregnant or if the subject/partner is noncompliant with contraception requirements,
- they are noncompliant with study requirements as determined by the investigator,
- they withdraw consent.

In the event that a subject chooses to withdraw from the study, the investigator should make a reasonable effort to ascertain the reason(s) for withdrawal, while fully respecting the subject's rights.

- If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.
- If a subject discontinues due to an adverse event or other medical reason, the subject must continue to be followed at regular intervals until the adverse event normalizes or returns to the subject's baseline condition. SK Life Science, Inc. and the investigator will agree to an acceptable follow-up schedule for these subjects.

8.5. Replacement of Subjects

Subjects who withdraw or are withdrawn during one of the study drug administration periods for reasons unrelated to safety may be replaced in order to have 6 subjects completing each dose level in Part A and 8 completing each dose level in Part B. The numbering of replacement subjects is described in Section 9.4.2.

9. STUDY DRUG ADMINISTRATION AND MANAGEMENT

9.1. Identification of Investigational Product

Three different strengths of oral capsule of SKL24741 (i.e., 5, 25 and 100 mg) will be used at various dose levels. For the dose levels at 200 mg or higher, a new oral capsule formulation strength may be developed.

Placebo-matching capsules will be used for both Part A and Part B, except for the food and gender effect cohorts.

9.2. Preparation and Dispensing

Based on the treatment allocation, the appropriate dose of SKL24741 or matching placebo will be prepared and dispensed by an unblinded pharmacist at the clinical site.

9.3. Administration

The study drug (active) and placebo listed in Table 7 will be administered according to the randomization scheme. The doses listed may require adjustment for safety considerations.

All subjects will be admitted to the clinical research unit (CRU) the day before dosing.

Table 7: Study Treatment

Part	Doses
A	A single oral dose of 10, 25, 50, 100, 200, 300, 400 mg, 600 mg, 800 mg, and 1000 mg of SKL24741 or placebo will be administered to subjects in the morning of the first day, following an overnight (10 hour) fast (all doses) or approximately 30 minutes after the start of a high-calorie, high-fat breakfast (Food effect cohort).
B	Multiple oral administrations of 4 dose levels of SKL24741 or placebo administered to male subjects each day for 14 days. Doses, dosing regimens, and food status (fasting vs. fed) used in Part B will be determined based on the outcome of Part A.

The study drug will be administered as an oral capsule formulation given with water (approximately 240 mL), as described in the Pharmacy Manual. An unblinded pharmacist will be responsible for providing SKL24741 or placebo in appropriate containers for each subject, as per the randomization scheme, to the blinded study personnel for administration.

Study drug will be administered according to the following guidelines.

Part A - Single Dose Administration:

A single oral dose of study drug will be administered to subjects in the morning after a 10-hour overnight fast. 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 for water used for the study drug administration.

Part A - Food Effect Cohort Only

Subjects will receive a high-calorie, high-fat breakfast as follows:

- FDA-recommended breakfast consisting of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast (30 gram) with 2 pats of butter, 4 ounces of hash brown potatoes, and 240 mL (8 fluid ounces) of whole milk (total calories are approximately 1000 kcal; 50% from fat, approximately 55 grams of fat).
- Study drug will be administered to subjects assigned to the non-fasting regimen approximately 30 minutes after the start of a high-fat, high-calorie breakfast.
- The meal will be taken about 30 minutes prior to the study drug administration.
- The meal will be eaten in 30 minutes or less.
- No fluids except those required for breakfast and dose administration will be allowed for two hours before and two hours after dose administration.

Part B – Multiple Dose Administration:

Subjects will be dosed each day for 14 days. Doses, dosing regimen, and food status (fasting vs. fed) will be based on the outcome of Part A.

In both Part A and Part B, study drug administration instructions are as follows:

- Study drug will be administered only after the indwelling catheter is placed (if applicable) and after pre-dose vital signs, peak expiratory flow rate (PEFR), and ECG are performed,
- In Part B, study drug will be given at approximately the same time (within a 1-hour window) on each dosing occasion,
- Study drug will be given as an oral capsule. Subjects will receive the study drug in an upright position. Subjects will be instructed not to lie down for 4 hours after taking the study drug, with the exception of study-specific events or assessments (sitting in an upright or reclining position [at least 45 degrees] is acceptable),
- The investigator (or his/her designee) will supervise dosing and conduct a mouth inspection of each subject to ensure that the study drug was taken.

9.4. Method of Assigning Subjects to Treatment Groups

9.4.1. Randomization

The randomization list will be generated by the clinical research organization (vendor) and will be provided to the site pharmacist. The pharmacist will keep the randomization list in a secure location.

Subjects who have completed screening evaluations and are eligible for the study participation will be randomized for study drug administration.

Each randomized subject will be assigned with a unique randomization number.

9.4.2. Allocation of Randomization Numbers

Subjects fulfilling the eligibility criteria will be randomized to receive their treatment according to the randomization list.

Randomized subjects will be assigned with a 6-digit randomization number in the order in which they are enrolled. The first digit of the randomization number will refer to the part A or B (1 or 2). The second and third digits will refer to the Cohort number. For example, subjects in Cohort 1 of part A will have the randomization numbers 101xxx; subjects in Cohort 2 of part A will have the randomization numbers 102xxx. In a case where a subject needs to be replaced, the last 2 digits of the randomization number for replacement participants will be identical to those of the original participant's randomization number. The fourth digit, however, will be replaced with a 2. For example, if the original participant's randomization number is 110101, then the randomization number for the replacement participant will be 110201. Participants who prematurely discontinue from the study may be replaced at the sponsor's discretion.

9.5. Packaging and Labeling

For each dose level in the study, SKL24741 study drug and placebo will need to be prepared in the pharmacy at the CRU according to detailed instructions provided by SK Life Science, Inc. 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. The study drug and placebo will be available in 50cc HDPE bottle with induction sealed child resistant cap and are packaged as 30 count per bottle. Refer to the Pharmacy Manual for detailed packaging and labeling information.

9.6. Study Drug Supply, Storage, and Handling

SKL24741 study drug will be provided to the site as oral capsule formulation at a dosage of 5, 25, and 100-mg strength. If SKL24741 needs to be investigated at the dose levels of 200 mg or higher, a larger strength of SKL24741 may be developed for such purpose.

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 at room temperature in a dry area, protected from light.

The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final Clinical Study Report (CSR).

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drugs will be retained by CRO, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

All investigational products will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions supplied to the clinical site and its designated pharmacy, the site's standard operating procedures (SOPs), and applicable regulations. Appropriate storage temperature and transportation conditions will be

maintained for the investigational product from the point of manufacture until delivery to the site.

The pharmacy staff will examine the shipment to verify that the investigational products were received in acceptable condition. Once inspected, the investigational products will be stored in a secure area with access restricted only to authorized staff, under physical conditions consistent with the investigational product requirements. The site pharmacist or delegate is responsible for ensuring that all investigational products received at the site is inventoried and accounted for throughout the study, according to the applicable regulations and the site's SOPs. Details of the receipt, storage, dispensing, and destruction will be recorded and maintained in the pharmacy log book by the pharmacy staff.

The Sponsor will provide written instructions regarding the final disposition of the unused study treatments. Copies of the study treatment accountability records will be provided to the Sponsor at the completion of the study and will be made available for review by the Site Monitor, if applicable, during the course of the study.

9.7. Drug Accountability

Study drug may be dispensed only under the supervision of the investigator or designee and only to study subjects. The pharmacist or designated site staff will maintain the information regarding the date and amount of study drug received and dispensed to the subjects. These materials will be retained at the site according to instructions provided by the Sponsor or designee, and until inventoried by the study monitor. The study monitor will review the study drug records and inventory throughout the study.

9.8. Disposal or Retention of Unused Drug

At the end of the study, SK Life Science, Inc. will provide instructions as to disposal of any unused investigational product. If SK Life Science, Inc. authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by SK Life Science, Inc. Destruction must be adequately documented.

9.9. Compliance

All doses of the study drug will be administered within the CRU under the direct supervision of the investigator or designee. A mouth check will be performed after each study drug administration.

9.10. Blinding and Unblinding

This study will be double-blinded: participating subjects, study personnel, and SK Life Science, Inc. personnel will not be aware of which treatment (SKL24741 or a matching placebo) has been given to each subject (Section 9.10.1).

9.10.1. Blinding

For each part (Part A and Part B) of the study, eligible subjects will be assigned to their randomization number linked to the dosing group by an unblinded pharmacist at the clinical site. During the conduct of the study, all study personnel will be blinded to subject treatment assignments except for the following individuals: the bioanalytical laboratory (SK Life Science, Inc. Toxicology group or designated contract research organization [CRO]), the statistician preparing the randomization list (CRO), the dispensing pharmacist and the pharmacy QC/quality assurance (QA) personnel, as applicable. If a subject is unblinded for safety-related regulatory reporting reasons (Section 9.10.2), SK Life Science, Inc. will become aware of the subject's treatment assignment.

To maintain the blinding, the study drug will be administered in an appropriate manner (amber container, for instance). The dispensing of the study drug will be carried out by the unblinded clinical site personnel in a way that maintains blinding of the study. The unblinded clinical site personnel will not, otherwise, participate in the study and are not permitted to reveal any information to the study team, other study personnel and subjects.

A copy of the randomization assignment list will be made available to the pharmacist to allow the dispensing of the investigational product to take place. This documentation will be kept in a secure location until the clinical database has been locked. One set of sealed envelopes containing the randomization list will be available to the Principal Investigator at the start of the study.

9.10.2. Unblinding

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be either a manual or electronic process.

Unblinding of individual subject’s treatment by the investigator should be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, the investigator must first attempt to contact the study Medical Monitor (see relevant telephone contact number provided in Section 12.1.3 or separate contact information document), to discuss the need for unblinding. In situations in which the investigator has tried, but is unable to reach the study Medical Monitor, he/she should use his/her best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the study Medical Monitor. In this case, the investigator will notify the Sponsor immediately after or as soon as possible.

Once a subject's treatment assignment has been unblinded, the medical monitor and study coordinator should be notified within 24 hours of unblinding of the treatment. Information relating to unblinding (e.g., reason, date) shall be clearly recorded in the subject’s study file, as part of relevant standard operating procedures (SOPs). In addition, the investigator should consider whether the clinical event prompting unblinding should be considered a serious adverse event (SAE), according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to SK Life Science, Inc. within 24 hours (Section 12.1).

SK Life Science, Inc. retains the right to break the blinding for subjects who experience SAEs suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. In addition, SK Life Science, Inc. may, for matters relating to safety concerns, unblind individual subjects at any time.

After dosing each cohort, the safety and preliminary PK data will be provided to the Sponsor in a blinding fashion. If needed, preliminary dataset of drug concentration may be disclosed in an unblinding fashion to the Sponsor under restricted conditions (e.g., data quality control).

9.11. Prior and Concomitant Medications

A table of prior and concomitant medication restrictions is provided in Appendix B.

9.11.1. Prohibited and Prior Medications

Subjects should stop taking any prescription, nonprescription, and herbal medications as well as any dietary supplements and specific fruit products at least 14 days before the first dose of the study drug, per exclusion criterion 6 in Section 8.2. Potential subjects should only stop taking any prescribed medications at the direction of a physician and consult a physician before stopping any regular treatment with nonprescription medications.

If any medication has been taken between the screening and the dose of study drug in Part A, and between the screening and the first dose of study drug in Part B, regardless of when dosing of the medication ended, the name, dose, route, regimen, start/stop dates, and reason for its use will be documented in the subject's electronic case report form (eCRF).

9.11.2. Concomitant Medications

Subjects will not take any prescription, nonprescription, or herbal medications, dietary supplements, or fruit products listed in exclusion criteria (Section 8.2) during the study until completion of the Follow-up visit assessments.

Acetaminophen is an acceptable concomitant medication. A maximum of 1000 mg within 24 hours may be prescribed by the investigator or designee when necessary. Other medication to treat adverse events may be prescribed only after consultation with the SK Life Science, Inc. Medical Monitor unless the medication is necessary to eliminate an apparent immediate hazard to a subject. The investigator will notify the SK Life Science, Inc. Medical Monitor within 24 hours of prescribing medications to treat adverse events, if indicated.

All concomitant medications (including drug name, dose, route, regimen, start/stop dates, and reason for its use) administered for the time period from administration of the dose of the study drug in Part A or the first dose of study drug in Part B through to the Follow-up visit will be documented in the subject’s eCRF.

10. ASSESSMENTS

10.1. Timing of Assessments

The timing of assessments is shown in Table 1 and Table 2.

10.2. Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, weight, and BMI.

10.3. Pharmacokinetics

An overview of the schedule of PK assessments is given in Table 1 and Table 2.

10.3.1. Blood Sampling

Part A

- Pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 18, 24, 36, 48, 60, and 72 hours post-dose following the single dose administration

Part B

- **Study Days 1 and 7:** Pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose. The 24-hour post-dose blood PK samples for Days 1 and 7 should be taken before dosing on Days 2 and 8, respectively.
- **Study Days 3 to 6 and 9 to 13**: Pre-dose only
- **Study Day 14**: Pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 18, 24, 36, 48, 60, and 72 hours post-dose

Directions for blood PK collection and sample shipment will be provided in the Sample Handling Guidelines.

Windows for blood PK sampling are described in Table 8. PK samples collected outside of these windows will be considered protocol deviations.

Table 8: Acceptable Windows for PK Blood Sampling (Part A and Part B)

Sampling Time	Acceptable Window
Pre-dose	-30 mins before dose or immediately before breakfast (if under fed condition)
0.25 to 1 hour post-dose	± 2 minutes
2 to 18 hours post-dose	± 10 minutes
24 to 72 hours post-dose	± 20 minutes

10.3.2. Urine Sampling

Part A

- Pre-dose and 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 72 hours post-dose following the dose administration.
- No urine collection for PK analysis in the food and gender effect cohorts

Part B

- No urine collection for PK analysis in Part B

Table 9: Acceptable Windows for PK Urine Sampling (Part A - SAD only)

Sampling Time	Acceptable Window
Pre-dose	-30 mins before dose
0 to 72 hours post-dose	± 15 minutes

10.3.3. Sample Collection, 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., Sample Handling Guidelines). The following Sections (Section 10.3.3.1 and Section 10.3.3.2) briefly summarize the sample processing and handling for blood and urine.

The shipment address and assay lab contact information will be provided to the investigational site prior to initiation of the trial.

Blood and urine samples may be used for metabolite and biomarker exploratory analyses. Possible results from these exploratory analyses may be reported in standalone report(s) if deemed necessary.

10.3.3.1. Blood Sample Processing

Blood (whole blood) will be collected via direct venipuncture or by an indwelling catheter at each scheduled sample time point. Blood samples will be collected into blood collection tubes containing K_2EDTA anticoagulant. The content of the tube will be mixed gently by inverting 6 to 8 times (without shaking), and the sample will be placed in an upright position on wet ice until ready for centrifugation. Blood samples should be processed to harvest plasma within 30 minutes of collection. Blood samples will be centrifuged at 4 ^{o}C for 10 minutes at approximately 2000 xg to separate plasma. Plasma will be aliquoted into labeled cryogenic storage vials, followed by storage at -70 ^{o}C in an upright position until shipment to the bioanalytical laboratory. Refer to the Sample Handling Guidelines for detailed sample collection, processing and handling.

10.3.3.2. Urine Sample Processing

Urine collection for PK analysis at a given time interval should be collected into a urine container maintained in ice or refrigerated for the duration of collection. At the end of each collection time interval, the total volume of urine collected over the given time interval

should be recorded as part of PK data. Refer to the Sample Handling Guidelines for detailed sample collection, processing and handling.

10.3.4. Bioanalysis

Concentration of SKL24741 (R-enantiomer) and SKL24742 (S-enantiomer) in plasma and urine will be determined using validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) methods.

Residual and/or backup plasma and/or urine samples may be assessed for additional SKL24741 metabolites and/or other exploratory assessments, if deemed necessary. If performed, data from these assessments will be documented separately in standalone report(s).

10.4. Pharmacogenomics

Pharmacogenomic (PGX) investigations explore the role of genetic variation in determining an individual's response to drugs. A separate informed consent for genotyping will be obtained from each subject prior to sampling. These PGX investigations allow evaluation of genes coding for proteins 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). The pharmacogenomic data may be included in the final study report, if deemed necessary.

10.4.1. Blood collection for PGX samples

Blood (whole blood) will be collected into blood collection tubes containing K_2EDTA anticoagulant at the pre-dose stage (prior to any drug administration) from each subject who consented for genotyping. The content of the tube will be mixed gently by inverting 6 to 8 times (without shaking), and the sample will be stored in its original sample tube in an upright position until shipment to the pharmacogenomic laboratory or biorepository. Whole blood will be stored at -70ºC for the subsequent DNA extraction and genotyping. Refer to Sample Handling Guidelines for detailed sample collection, processing and handling.

10.5. Efficacy

Not applicable.

10.6. Safety

Safety evaluations will include clinical laboratory assessments, vital signs, physical examinations, ECGs, peak expiratory flow rate (PEFR), Columbia-Suicide Severity Rating Scale (C-SSRS) (Part B only), and reporting of adverse events. The SK Life Science, Inc. Medical Monitor will review these parameters on an ongoing basis during the study, in order to evaluate the safety of study drug dosing.

Physical examination information collected at screening will be captured for inclusion into the clinical database. Any untoward findings identified during physical examinations will be

captured as adverse events, if those findings meet the definition of an adverse event. Demographic data collected at screening will be included in the clinical database.

10.6.1. Adverse Events

Adverse events (serious and non-serious) will be assessed, documented, and reported in accordance with International Conference on Harmonization Good Clinical Practice (ICH-GCP). Section 12.1 briefly outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting of all adverse events. A separate document will be provided for the detailed eCRF completion guidelines for adverse events for investigators, and training will be provided.

10.6.2. Clinical Laboratory Assessments

Clinical laboratory assessments to be conducted in this study are shown in Table 10. Blood and urine specimens will be analyzed at the CRU or its designated laboratory as appropriate. Clinical laboratory specimens are to be collected under fasting condition (subjects should not take food or fluids, except of water, for at least 6 hours prior to specimen collection).

The investigator or designee will perform an assessment of all clinical laboratory data for clinical significance. Clinical laboratory parameters will be determined for all subjects using the CRU's or designated laboratory's routine clinical laboratory methods. Laboratory test results that are abnormal and considered clinically significant must be reported as adverse events (Section 12.1.4).

Monitoring of Laboratory Abnormalities

In the event of unexplained or unexpected clinically significant laboratory test values, the investigator may choose to repeat the test(s) as soon as possible and follow until the results have returned to the normal range and/or an adequate explanation for the abnormality is found. The investigator will clearly mark all laboratory test values that are outside the normal range on the laboratory reports and will indicate which of these deviations are clinically significant. Any abnormal laboratory result judged by the investigator to be clinically significant will be classified as an adverse event and will be recorded on the adverse event eCRF. The investigator will also determine the severity and causality.

Table 10: Clinical Laboratory Assessments

Hematology
Leukocytes
Erythrocytes
Hemoglobin
Hematocrit
Platelets
Partial automated differential: lymphocytes monocytes eosinophils

basophils
neutrophils
MCV
MCH
MCHC
Coagulation
PT
aPTT
PT INR
Clinical Chemistry
Total bilirubin
Direct bilirubin
Indirect bilirubin
Gamma-GT
AST
ALT
LDH
Creatinine
Urea
Total protein
Glucose
Inorganic phosphate
Sodium
Potassium
Calcium
Chloride
Albumin
Magnesium
Urinalysis
pH
Color
Appearance
Specific gravity
Glucose
Ketones
Protein
Blood
Standard microscopy:

Casts
Bacteria
RBCs
WBCs
Smoking Screen (Screening and Admission Only)
Cotinine
Follicle-Stimulating Hormone (FSH) Test (Screening Only) for Female Subjects for Gender Assessment Group[a]
FSH
Serology (Screening Only)
HBsAg
HIV Ag and Ab
HCV Ab
Drugs of Abuse / Alcohol Screen (Screening and Admission Only)
Amphetamine
Barbiturate
Benzodiazepine
Cocaine
Methadone
Opiates
Oxycodone
Phencyclidine
Propoxyphene
Cannabinoid (THC)
MDMA (Ecstasy)
Methaqualone
Ethanol (Alcohol) (Both urine and breath tests)
Tricyclic Antidepressant (TCA)
Other Assessments
Alpha-1-acid glycoprotein
Total cholesterol
LDL cholesterol
HDL cholesterol

[a] Postmenopausal status for females of non-childbearing potential will be further confirmed with follicle-stimulating hormone (FSH) serum levels that are consistent with postmenopausal status. Refer to Inclusion Criteria for details (Section 8.1).

ALT: alkaline transaminase; aPTT: activated partial thromboplastin time; AST aspartate transaminase; Gamma-GT: glutamyl transpeptidase; FSH, follicle-stimulating hormone (FSH); HbsAg: hepatitis B surface

antigen; HCV Ab: hepatitis C antibody; HDL: high density lipoprotein; HIV Ab: human immunodeficiency virus antibody; LDH: Lactic dehydrogenase; LDL: low density lipoprotein; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; PT: prothrombin time; PT INR: PT international normalized ratio; RBC: red blood cell; TCA: tricyclic antidepressant ; THC: cannabinoid; WBC: white blood cell.

10.6.3. Physical Examinations and Vital Signs

A full physical examination (review of all body systems), an abbreviated (symptom-directed) physical examination, and vital sign evaluation will be performed at select study visits, as specified in Table 1 and Table 2.

A full physical examination includes a review of the following systems: head/neck/thyroid, eyes/ears/nose/throat, respiratory, cardiovascular, lymph nodes, abdomen, skin, musculoskeletal, and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. For the conduct of the eye examination, the site's standard procedures should be followed.

Physical examinations are to be performed by the Principal Investigator or designee (physician, physician assistant, or nurse practitioner) listed on the Form FDA 1572.

Vital sign evaluations include blood pressure (systolic and diastolic measurements in supine and standing in the same sequence in each subject, in order to allow orthostatic measurements), temperature, heart rate, respiratory rate, and arterial oxygen saturation (SaO_2) (using pulse oximetry). Additional vital sign assessments may be performed if clinically indicated, in the opinion of the investigator. Clinically significant abnormal findings in vital signs and physical examination will be reported as adverse events.

10.6.4. Electrocardiograms

For study conduct, electrocardiograms (ECGs) will be classified as either safety or triplicate ECGs at the time points indicated in Table 1 and Table 2. Electrocardiograms will be recorded using the site's standard ECG equipment. All ECGs will be obtained using instruments that analyze data using the same algorithms and produce the same data for interpretation. Digital ECGs will be captured and transferred to the designated core cardiology laboratory for ECG analysis. Collection of additional ECGs for routine safety monitoring at additional time points or days is at the discretion of the investigator based on GCP.

ECGs will be obtained using a Mortara continuous 12-lead digital ECG recorder. The ECG will include all 12-standard leads and will be recorded at a paper speed of 25 mm/sec. Standard ECG parameters will be measured, including heart rate (HR), RR, PR, QT, QTc intervals, and QRS duration. All ECGs should be collected after at least 5 minutes of supine rest and prior to blood sample collection. The device will remain connected to the subject during the collection periods as appropriate. The ECG data will be transmitted wirelessly to the Surveyor system, which will extract ECG recordings at the protocol specified time points.

Triplicate ECGs will be extracted approximately 1 minute apart reviewed and analyzed by the central ECG laboratory. The ECG extractions will be time-matched to the PK samples but obtained before the actual sampling time to avoid changes in autonomic tone associated

with the psychological aspects of blood collection as well as the reduction in blood volume subsequent to blood collection. The continuous ECG data will be sent to the central ECG laboratory for a high-resolution measurement of the cardiac intervals and morphological assessment. The ECG core laboratory staff will be blinded to treatment, time, and study day identifiers.

10.6.4.1. Safety 12-Lead ECGs

Standard 12-lead ECGs should be performed at the time points indicated in Table 1 and Table 2, in addition to any other times, if clinically indicated. The following guidelines must be followed:

- The subject will be instructed to rest in the supine position for at least 5 minutes before having an ECG performed,
- The ECG will be performed prior to any other procedures that may affect heart rate (e.g., blood draws).

The ECG data traces will be made for safety review by the investigator and maintained with source documentation. Any clinically significant ECG abnormalities at screening will exclude the subject's participation in the study. Thereafter, clinically significant abnormal findings will be reported as adverse events.

To ensure safety of the subjects, the Principal Investigator or designee will make comparisons to Day -1 (baseline) measurements. If the QTc is increased by >60 msec from the Day 1 pre-dose value or an absolute QTc value is >500 msec for any scheduled ECG, 2 additional ECGs will be collected, approximately 2 to 4 minutes apart, to confirm the original measurement. If either of the QTc values from these repeated ECGs remain above the threshold value (>60 msec increase from the Day 1 pre-dose; or is >500 msec), a single ECGs must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

10.6.4.2. Extensive Triplicate ECGs

Extensive triplicate 12-lead ECGs, except for the food effect cohort, will be obtained to collect continuous 12-lead ECG data from pre-dose until 24 hours post-dose at the specified time points (Table 1 and Table 2). Triplicate 10-second, 12-lead ECG recordings (digital ECGs) will be obtained within a 5-minute time window around the targeted time points outlined in the Schedule of Assessments described in Table 1 for Part A (single dose administration) and Table 2 for Part B (multiple dose administration). During the extensive triplicate 12-lead ECG assessment, meal intake should be avoided within 1 hour of ECG data collection.

Timing and recording technique for ECGs will be standardized for all subjects. Subjects will be required to lie quietly in a supine position with minimal movement and minimal exposure to noise and other environmental stimuli for at least 5 minutes before the ECG time point in order to allow for quality ECG data. All ECG data should occur in a 5-minute time window around the targeted time. If digital ECGs are artifactual and of poor quality, analyzable 10-

second ECGs will be repeated as close as possible to targeted time points. Actual time of the ECG recording will be used for the analysis.

The triplicate 10-second, 12-lead ECG time points post-dose are guided by PK animal data and are based around the estimated T_{max}. The time points may be changed depending on PK information obtained during the study from previous cohorts.

10.6.5. Columbia-Suicide Severity Rating Scale

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 C-SSRS will be assessed only after multiple dose administration (Part B). The "Baseline (Lifetime/Recent)" version of the C-SSRS will be assessed at screening (Appendix C). The C-SSRS "Since Last Visit" version will be assessed on other study days (Appendix D).

10.6.6. Peak Expiratory Flow Rate (PEFR) Measurement

Peak expiratory flow rate (PEFR) will be measured within a 30-minute time window around the targeted time points as outlined in the Schedule of Assessments in Table 1 for Part A (single dose administration) and Table 2 for Part B (multiple dose administration). The peak expiratory flow rate (PEFR, also known as a peak flow) is the maximum rate that a person can exhale during a short maximal expiratory effort after a full inspiration. Measurements will be performed in an upright position, with lips tightly closed around the mouth piece of the peak flow meter and blowing out as hard and as fast as possible into the meter.

10.6.7. Contraception and Pregnancy

The effects of SKL24741 on conception, pregnancy, and lactation in humans are not known. SKL24741 did not show any genotoxic potential in a standard battery of *in vitro* (Ames, human lymphocyte micronucleus) and *in vivo* (rat bone marrow micronucleus) studies (see Investigator's Brochure).

10.6.7.1. Contraception

Subjects who can father a child must agree to use 2 highly effective methods of contraception, including at least one barrier method, as follows. Male subjects must use a condom with spermicide and if subject's female partner is of childbearing potential, she must use 1 of the following highly effective methods of contraception:

- Hormonal contraception,
- Occlusive cap (cervical cap or diaphragm) with spermicide,
- Intrauterine device.

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

For all study subjects who can father a child with partners of child-bearing potential, all methods of contraception, including abstinence, must be used from the time of consent through 90 days after the last dose of study drug. Subjects whose partners become of child-bearing potential during the study must agree to the contraceptive requirements.

10.6.7.2. Pregnancy

If the female partner of a subject becomes pregnant, the subject must permanently discontinue study treatment. The investigator must notify the Medical Monitor, SK Life Science, Inc., and IQVIA by completing the Pregnancy Report form, faxing and emailing the form as per the Table of Contact (Table 13 and Table 14), within 24 hours of the site's knowledge of the partner's pregnancy. The subject's treatment assignment will be unblinded, and if the subject was taking the active drug, the subject's partner will be followed until the end of pregnancy (e.g., delivery, miscarriage) and the infant exposed in-utero will be followed for 1 year after birth, provided consent is obtained. An ICF will be provided to explain these follow-up activities. Pregnancy does not constitute an adverse event.

11. 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, and clinical pharmacologic analysis details (including the definition of the PK population) will be provided in the Clinical Pharmacology Data Analysis Plan (CPAP), both of which 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.

11.1. Sample Size and Power

No formal sample size calculations have been performed. This study utilizes the sample size, or the number of subjects, that is commonly employed in early clinical pharmacology studies, in order to achieve the study objectives. Subjects who do not complete all the treatments and assessments specified in this protocol may be replaced.

11.2. Analysis Populations

- **Safety Population**: All subjects who were randomized and received at least 1 dose of study drug.
- **PK Population**: All subjects who received at least 1 dose of study drug and have sufficient PK data without any major protocol deviations.

All subject (randomized or dosed) data will be presented in the subject data listings.

11.3. Clinical Pharmacology Analysis

11.3.1. Pharmacokinetic Analysis

The PK analysis of SKL24741 (R-enantiomer) and SKL24742 (S-enantiomer) (if appropriate) will be performed using non-compartmental analysis (NCA) method.

The following PK parameters will be calculated for SKL24741 and SKL24742 (if appropriate) for the plasma concentration-time profile: Maximum concentration (C_{max}), time to maximum concentration (t_{max}), area under the concentration-time curve (AUC) from 0 to infinity (AUC_{∞}), AUC from time 0 to a given time t (AUC_t), AUC over the dosing interval ($AUC\tau$), apparent clearance (CL/F), apparent volume of distribution (V_d/F), half-life ($t_{½}$), and accumulation ratio (R_{acc}). In addition, the fraction excreted unchanged in the urine (f_e) and renal clearance (CL_R) will be calculated, if deemed appropriate. If SKL24741 metabolites are quantified in this study, appropriate PK parameters will be calculated for metabolites. Other PK parameters will be determined, as deemed appropriate.

A detailed description of the planned PK analysis will be presented in the CPAP. Statistical analyses on PK data may be performed if deemed appropriate.

11.4. Statistical Analysis

This section presents a summary of the planned statistical analyses of safety for this study. Statistical analysis details will be provided in the SAP for this study, which will be finalized prior to clinical database lock.

11.4.1. General Considerations

The SK Life Science, Inc. Biometrics designated CRO will analyze the safety data derived from this study. Only descriptive analyses will be performed; no statistical hypothesis testing will be done. Continuous variables (e.g., age) and PK parameters will be summarized by means of descriptive statistics (e.g., number of subjects (*n*), arithmetic mean, arithmetic standard deviation (SD), standard error of the mean (SEM), coefficient of variation (CV), geometric mean, geometric CV, median, first and third quartiles, minimum, and maximum). If the measurements in the source (raw) data are integers, then the corresponding mean and median will be presented to 1 decimal place and the SD to 2 decimal places; if the measurements are obtained to 1 decimal place, then the mean and median will be presented to 2 decimal places and the SD to 3 decimal places; and so forth. Minimum and maximum will be displayed as reported in the source (raw) data. Categorical variables (e.g., presence of an adverse event) will be summarized using counts and percentages. Percentages will be presented to 1 decimal place unless otherwise specified. Statistical analysis results will be presented by treatment group and as appropriate.

All subject data, including derived, will be presented in the subject data listings; listings will display all subjects who were randomized and/or dosed with the study drug.

11.4.2. Background Characteristics

11.4.2.1. Subject Disposition

The number and percentage of subjects in each disposition category (e.g., randomized, completing treatment period, completing the Follow-up visit, and discontinuing study with a breakdown of the reasons for discontinuation) will be summarized by the treatment group.

11.4.2.2. Demographics and Baseline Characteristics

Demographic, parameters and baseline characteristics will be summarized for the Safety Population. Continuous variables will be summarized by descriptive summary statistics and categorical variables by the number and percentage of participants.

11.4.2.3. Medical History

Medical history encompassing abnormalities and surgeries reported before the Screening visit will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0 or newer.

11.4.2.4. Prior and Concomitant Medications

Medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) and summarized by medication class and preferred term for the Safety Population as frequency tables in 2 parts:

- **Prior medication:** medication received between the Screening visit and the dose of study drug in Part A, and between the Screening visit and the first dose of study drug in Part B, regardless of when dosing of the medication ended,
- **Concomitant medication:** medication received at or after the dose of the study drug in Part A or the first dose of study drug in Part B.

If the medication start date is **on or after** the date of initial dosing of the study drug, then medication will be summarized as concomitant medication regardless of the medication end date. If the medication end date is **before** the date of initial dosing of the study drug, then medication will be summarized as prior medication regardless of the medication start date. The prior and concomitant medications will be summarized separately.

11.4.2.5. Study Drug Exposure

Exposure to study drug in Part B (multiple dose administration) will be defined as total number of days treated with study drug during the study, with total days calculated as last day of study drug minus first day of study drug plus 1 day.

11.4.2.6. Study Drug Compliance

As the study drug will be administered under direct supervision at the study site, no analysis of compliance will be performed.

11.4.3. Efficacy Analysis

As efficacy is not being measured in this study, no efficacy analysis will be performed.

11.4.4. Safety Analysis

The overall safety profile of SKL24741, relative to placebo, will be assessed in terms of the following safety endpoints:

- Incidence of treatment-emergent adverse events
- Clinical laboratory values (hematology, coagulation, clinical chemistry, urinalysis and cholesterol)
- ECG outcomes
- Vital signs
- Peak expiratory flow rate (PEFR)
- Columbia-Suicide Severity Rating Scale (C-SSRS) (Part B only)

Statistical analysis details will be provided in the SAP. Safety analyses will be based on the Safety analysis set.

All safety data will also be presented in individual subject data listings.

11.4.4.1. Adverse Events

Adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing an adverse event will be summarized by the MedDRA system organ class and preferred term, as well as by dose received. Adverse events will be classified as pre-treatment or treatment-emergent.

Pre-treatment adverse events are defined as adverse events that were reported or worsened after signing the ICF up to start of study medication.

Treatment-emergent adverse events are defined as adverse events that were reported or worsened on or after start of study medication through the Follow-up visit.

Only treatment-emergent adverse events will be summarized in tables. Treatment-emergent adverse events will hereafter be referred to as "adverse events."

The incidence of adverse events will be summarized. Adverse event summaries will include the following:

- All adverse events (regardless of severity or relationship to study drug)
- SAEs
- Adverse events by severity
- Adverse events by relationship to study drug
- Adverse events leading to discontinuations
- Adverse events leading to deaths

Adverse event summaries will be presented by MedDRA System Organ Class and Preferred Term. A subject with multiple occurrences of the same adverse event or a continuing adverse event will be counted once, and only the maximum severity level will be presented in the severity summaries, and the worst relationship level in the relationship summaries. Adverse events will be listed separately for those leading to death, SAEs, dose interruption, and permanent discontinuation.

All adverse events through the Follow-up visit will be listed in an individual subject data listing, including pre-treatment adverse events.

11.4.4.2. Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using International System of Units (SI). Hematology, coagulation, clinical chemistry, urinalysis, and cholesterol panel results will be summarized by dose received and by part of the study at each scheduled time point.

The raw values, changes from baseline, percentage change from baseline (for selected laboratory parameters), shifts from baseline (categorical change from baseline), and clinical abnormalities will be summarized as appropriate. Baseline will be defined in the study SAP. Clinically significant abnormal findings will be reported as adverse events.

11.4.4.3. Electrocardiogram

A summary of raw values and change from baseline values (as specified in the study SAP) will be provided by treatment group, dose received, and by part of the study at each scheduled visit for the following ECG measurements: heart rate (HR), RR, PR, QT, QTc intervals, and QRS duration. In addition, the number and percentage of subjects by maximum on-treatment value of QT/QTc intervals, categorized as ≤450 msec, >450 msec and ≤480 msec, >480 msec and ≤500 msec, and >500 msec, as well as maximum on-treatment change from baseline value of QT/QTc intervals, categorized as ≤30 msec, >30 msec and ≤60 msec, and >60 msec, will be provided. Baseline will be defined in the study SAP. Correction of the QT values will be done using Fridericia formula. Clinically significant abnormal findings will be reported as adverse events.

11.4.4.4. Vital Signs

The following vital signs will be summarized by treatment group at each scheduled time point: systolic and diastolic blood pressure (mmHg) measurements (in supine and standing in the same sequence in each subject, in order to allow orthostatic measurements), body temperature (°C), heart rate (beats per minute [bpm]), respiratory rate (breaths per minute), and arterial oxygen saturation (SaO_2) (using pulse oximetry). The raw values, changes from baseline, percentage change from baseline (for selected parameters), shifts from baseline (categorical change from baseline), and clinical abnormalities will be summarized as appropriate. Baseline will be defined in the study SAP. Clinically significant abnormal findings in vital signs will be reported as adverse events.

11.4.4.5. Physical Examination

Physical examination findings at screening will be presented as a listing only. At post-screening assessments, any untoward findings identified during physical examinations will be captured as adverse events, if those findings meet the definition of an adverse event.

11.4.4.6. Peak Expiratory Flow Rate

Peak expiratory flow rate (PEFR) results will be summarized by treatment group and by part of the study at each scheduled time point. The raw values, changes from baseline, percentage change from baseline, shifts from baseline (categorical change from baseline), and clinical abnormalities will be summarized as appropriate. Baseline and unit (e.g., L/min) will be defined in the study SAP. Clinically significant abnormal findings will be reported as adverse events.

11.4.4.7. Columbia-Suicide Severity Rating Scale (Part B only)

Columbia-Suicide Severity Rating Scale (C-SSRS) results will be summarized by treatment group and by part of the study at each study day of assessment. The raw values, changes from baseline, and clinical abnormalities will be summarized as appropriate. Baseline will be defined in the study SAP. Clinically significant abnormal findings will be reported as adverse events.

11.4.4.8. Other Safety Analysis

Not applicable.

11.4.5. Other Analysis

Not applicable.

11.4.6. Interim and Independent Data Monitoring Committee Analyses

11.4.6.1. Interim Analysis

Not applicable.

11.4.6.2. Independent Data Monitoring Committee Analysis

Not applicable.

12. PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

12.1. Adverse Event

12.1.1. Definition

An **adverse event (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.

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.

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 **serious adverse event (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.
- 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.

12.1.1.1. 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 11.

Table 11: 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.

12.1.1.2. 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 12.

Table 12: 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)

Adverse events must be followed until resolution by the Principal Investigator. Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic. Adverse events that are not serious and are ongoing at the subject's last visit will be followed for a maximum of 30 days. Serious adverse events that are not resolved or stabilized during this time period will be followed until resolution or stabilization.

12.1.2. 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, peak expiratory flow rate (PEFR), Columbia-Suicide Severity Rating Scale (C-SSRS), 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 latest version of Medical Dictionary for Regulatory Activities (MedDRA) at the start of the study.

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.

12.1.3. 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 13 and Table 14).

Table 13: Contact Information for IQVIA

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

Table 14: Contact Information for Sponsor Medical Monitor

Name	Jimmy Schiemann
Email	jschiemann@sklsi.com
Telephone	+1 (404) 509-4293
Fax	+1 (201) 421-3884

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

The Sponsor 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 the Sponsor during the clinical portion of this study (related or not to the present study), the Sponsor has to advise the clinical site, through its Principal Investigator, of those events.

12.1.4. Laboratory Results as Adverse Events

The determination of whether laboratory test results are clinically significant should be made by a physician or by a clinical study staff member (listed on Form FDA 1572) who is qualified to review and assess laboratory tests. This determination is important, as a clinically significant laboratory abnormality must be associated with an adverse event, either directly or indirectly as explained below.

The criteria for determining whether an abnormal laboratory test finding should be clinically significant are as follows:

Test result is associated with clinical signs or symptoms. If the signs or symptoms are related to a diagnosis that has already been documented as an adverse event, the lab abnormality itself generally does not have to be reported as an additional adverse event (e.g., hyperglycemia with an adverse event of new-onset diabetes; if diabetes is documented as an adverse event, hyperglycemia does not need to be documented separately as it is a common finding as part of the diabetes diagnosis).

Test result requires additional diagnostic testing or medical/surgical intervention.

Test result leads to a change in study drug dosing or to discontinuation from the study.

Test result is considered by the investigator to be an adverse event (i.e., any new unfavorable sign/symptom, or previous condition that has increased in severity or frequency during the study).

Laboratory abnormalities that are associated with a chronic, stable medical condition (e.g., slightly elevated ALT in a subject with hepatitis C that is unchanged or decreased from baseline) do not have to be considered clinically significant, but this judgment is left to the investigator.

Note that repeating a test to confirm an abnormal result, in the absence of any of the above, does not mean that a lab must be clinically significant. An abnormal result that is found to be in error is not clinically significant and should not be reported as an adverse event.

12.2. Administrative Requirements

12.2.1. Ethical Considerations

The study will be conducted in accordance with the current ICH-GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and according to local regulations. The 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, Investigator's Brochure, 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.

12.2.2. 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 SK Life Science, Inc.

A subject identification number (subject ID) will be assigned to each subject at the time that informed consent is obtained; this subject ID will be used throughout the study.

12.2.3. Investigator Compliance

No modifications to the protocol will be made without the approval of SK Life Science, Inc. 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. 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 SK Life Science, Inc. 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.

12.2.4. Access to Records

The investigator must make the source documents of subjects enrolled in this study available for inspection by SK Life Science, Inc. 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.

12.2.5. 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 SK Life Science, Inc. 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.

12.2.6. Record Retention

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 SK Life Science, Inc. must be notified.

12.2.7. Study Termination

SK Life Science, Inc. 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.

12.3. Data Quality Assurance

SK Life Science, Inc. or its designated representative will conduct a study site visit to verify the qualifications of each investigator, inspect trial site facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each enrolled subject will be entered into an eCRF by site personnel using a secure, validated web-based electronic data capture (EDC) application (Section 12.5).

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via a database query. An audit trail for all changes will be maintained within the clinical database.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

12.4. Monitoring

Monitoring and auditing procedures developed or approved by SK Life Science, Inc. will be followed, in order to comply with 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 SK Life Science, Inc. 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.

12.5. Electronic Data Capture

The Sponsor 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.

The Sponsor 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.

12.6. Report and Publications

12.6.1. Publication of Study Results

Any and all scientific, commercial, and technical information disclosed by SK Life Science, Inc. in this protocol or elsewhere should be considered confidential and proprietary property of SK Life Science, Inc. 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 SK Life Science, Inc. 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 SK Life Science, Inc. 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 SK Life Science, Inc. and the investigator and/or the investigator's institution.

12.6.2. Clinical Study Report

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

13. REFERENCES

Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE Official Report: A practical clinical definition of epilepsy. Epilepsia, 2014; 55: 475–482.

Devinsky O, Vezzani A, O'Brien TJ, Jette N, Scheffer IE, de Curtis M, et al. Epilepsy. Nat Rev Dis Primers. 2018; 4:18024.

Hauser WA, Beghi E. First seizure definitions and worldwide incidence and mortality. Epilepsia 2008; 49(Suppl 1):8–12.

Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton, C. R. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia 2010; 51(5):883–890.

Stafstrom CE, Carmant L. Seizures and epilepsy: an overview for neuroscientist. Cold Spring Harb Perspect Med. 2015; 5(6):a022426.

Meinardi H, Binnie CD and Meijer JW. Assessment of effects of antiepileptic drugs. Electroencephalogr. Clin. Neurophysiol. Suppl., 1985; 37: 201-214.

Eijkelkamp N, Linley JE, Baker MD, Minett MS, Cregg R, Werdehausen R, et al. Neurological perspectives on voltage-gated sodium channel. Brain, 2012; 135(9):2585-2612.

Davies B, Morris T. Physiological parameters in laboratory animals and humans. Pharm Res. 1993; 10(7):1093-1095

APPENDIX A. CALCULATION OF BODY MASS INDEX

The BMI will be calculated during screening to determine a subject's eligibility, using the subject's height and weight measurements. The equation for calculating BMI is:

BMI (kg/m^2) = Body weight (kg) ÷ Height^2 (m^2)

APPENDIX B. PRIOR AND CONCOMITANT MEDICATIONS AND OTHER STUDY RESTRICTIONS

Study Restrictions		
Restricted	**Study Period**	
Medication/Food/Activity	**Screening**	**Dosing and Follow-up**
Prescription medications	None for 14 days before the first dosing	None through Follow-up visit
Nonprescription medications	None for 14 days before the first dosing	None through Follow-up visit, except occasional, limited acetaminophen
Vitamins	None for 14 days before the first dosing	None through Follow-up visit
Herbal medications Grapefruit/grapefruit juice Seville (blood) oranges	None for 14 days before the first dosing	None through Follow-up visit
Alcoholic beverages	Not more than 2 units of alcoholic beverages per day or more than 14 units per week[a]	None within 72 hours of the first dose through collection of last pharmacokinetic sample
Coffee, cola, or other caffeinated beverage	Not more than five 8 oz servings/day	None within 48 hours of the first dose through collection of last pharmacokinetic sample
Smoking	Non-smokers only[b]	Not allowed

[a] 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
[b] Subjects who have stopped smoking at least 6 months before screening are considered non-smokers

APPENDIX C. SUMMARY OF CHANGES TO PROTOCOL

None

APPENDIX D. COLUMBIA-SUICIDE SEVERITY RATING SCALE (BASELINE/SCREENING)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ____ (***Type # (1-5)***) ____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** ____ (***Type # (1-5)***) ____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

APPENDIX E. COLUMBIA-SUICIDE SEVERITY RATING SCALE (SINCE LAST VISIT)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION

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

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

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

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could /can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others.
(2) Mostly to get attention, revenge or a reaction from others.
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(0) Does not apply

____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Completed Suicide:	**Yes** **No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____