A First-in-Human, Randomized, Double-blind, Dose Escalation Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Following Single and Multiple Oral Doses of KM-819 in Healthy Young Adult and Elderly Subjects

Sponsor:	Kainos Medicine, Inc. 16, 712 beon-gil, Daewangpankyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, 13488, Korea
Clinical Research Organization:	PAREXEL International
Principal Investigator	Kyoung Soo Lim, MD, PhD Assistant Professor Department of Clinical Pharmacology and Therapeutics CHA University School of Medicine and CHA Bundang Medical Center
Sponsor Protocol No.:	KMCP-819-K101
IND No.:	Not Applicable
EudraCT No.:	Not Applicable
Study Drug Name:	KM-819
Development Phase:	Phase 1
Date of Protocol:	13 Feb 2017, Final 5.0
Date of Previous Protocol:	28 Dec 2016, Final 4.0

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki,[1] and with other applicable regulatory requirements.

SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: A First-in-Human, Randomized, Double-blind, Dose Escalation Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Following Single and Multiple Oral Doses of KM-819 in Healthy Young Adult and Elderly Subjects

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 2013 and the guidelines on Good Clinical Practice (GCP).

_____ _____

Name
Title
Institution

Date

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Name
Title
Institution

Date

Declaration of the Principal Investigator

Title: A First-in-Human, Randomized, Double-blind, Dose Escalation Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Following Single and Multiple Oral Doses of KM-819 in Healthy Young Adult and Elderly Subjects

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in 2013 and the guidelines on Good Clinical Practice.

Principal Investigator

_____ _____

Name
Title
Institution

Date

PROTOCOL SYNOPSIS

Title	A First-in-Human, Randomized, Double-blind, Dose Escalation Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Following Single and Multiple Oral Doses of KM-819 in Healthy Young Adult and Elderly Subjects
Sponsor Study No.	KM-819
Phase	1
Sponsor	Kainos Medicine, Inc.
Principal Investigator	Kyoung Soo Lim Assistant Professor Department of Clinical Pharmacology and Therapeutics CHA University School of Medicine and CHA Bundang Medical Center
Study Center	This study will be conducted in site CHA Bundang Medical Center, Korea.
Objectives	**Primary objective:** To evaluate the safety and tolerability of single and multiple ascending oral doses of KM-819 in healthy young adult male subjects. **Secondary objectives:** • To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of single and multiple ascending oral doses of KM-819 in healthy young adult male subjects. • To evaluate the safety and tolerability of single and multiple oral doses of KM-819 in elderly male or post-menopausal female subjects. • To evaluate the PK and PD of single and multiple oral doses of KM-819 in elderly male or post-menopausal female subjects.
Design	This first-in-human, single-center, randomized, placebo-controlled, double-blind, sequential group Phase 1 study in healthy subjects will be conducted to evaluate the safety, tolerability, PK, and PD following the escalation of single and multiple doses of KM-819. The study will consist of 2 parts. In Part A, up to 5 cohorts of young adult male subjects, and 1 single-dose cohort of elderly male or post-menopausal female subjects will receive escalating single doses of KM-819. In Part B, up to 4 cohorts of healthy young adult male subjects and 1 multiple-dose cohort of elderly male or post-menopausal female subjects will receive escalating multiple doses of KM-819. Part B will be conducted after completion of all cohorts of young adult male subjects in Part A. Dose escalation to the next level will be determined using safety, tolerability, and PK data of the previous cohort. *Part A, Single Ascending Dose (SAD)* Up to 40 healthy young adult male subjects and 8 healthy elderly male or post-menopausal female subjects will be enrolled and randomized to receive either KM-819 or placebo. Each of the 5 dose escalation cohorts consists of 8 healthy young adult male subjects; 6 subjects will receive 10, 30, 100, 200, or 400 mg of KM-819 and 2 subjects will receive placebo. In each single dose cohort, dosing of subjects will be sentinel, i.e., 2 subjects will be dosed on the first day (1 subject will receive active treatment and 1 subject will receive placebo) and the remaining 6 subjects will be dosed at least 24 hours after the first 2 subjects. Cohorts will be dosed sequentially with escalating doses. Eight elderly male or post-menopausal female subjects will be enrolled into

	an additional cohort; 6 subjects will receive 200 mg KM-819 and 2 subjects will receive placebo. Part A consists of a Screening period of up to 28 days, and a 3-day Confinement period when subjects are hospitalized for study activities. Subjects are required to return for outpatient visits on Day 4, 7 and for the Follow-up Visit on Day 14. *Part B, Multiple Ascending Dose (MAD)* Up to 32 healthy young adult male subjects and 8 healthy elderly male or post-menopausal female subjects will be enrolled and randomized to receive either KM-819 or placebo. Each of the 4 dose escalation cohorts consists of 8 healthy young adult male subjects; 6 subjects will receive 30, 100, 200, or 400 mg of KM-819 once a day (QD) for 7 days and 2 subjects will receive placebo. Cohorts will be dosed sequentially with escalating doses. Eight elderly male or post-menopausal female subjects will be enrolled into an additional cohort; 6 subjects will receive 200 mg KM-819 QD for 7 days and 2 subjects will receive placebo. Part B consists of a Screening period of up to 28 days and an 8-day confinement period when they are hospitalized for study activities. Subjects are required to return for a Follow-up Visit on Day 14.
Treatment	The following treatments will be administered orally to subjects in this study: Part A: KM-819: 10 mg (1 × 10 mg tablet), 30 mg (3 × 10 mg tablet), 100 mg (1 × 100 mg tablet), 200 mg (2 × 100 mg tablet), or 400 mg (4 × 100 mg tablet) Placebo: KM-819-matched placebo tablet Part B: KM-819: 30 mg (3 × 10 mg tablet), 100 mg (1 × 100 mg tablet), 200 mg (2 × 100 mg tablet), or 400 mg (4 × 100 mg tablet) Placebo: KM-819-matched placebo tablet
Number of Subjects	Part A: up to 40 healthy young adult male and 8 healthy elderly male or post-menopausal female subjects will be enrolled. Part B: up to 32 healthy young adult male and 8 healthy elderly male or post-menopausal female subjects will be enrolled.
Population	For Parts A and B: healthy young adult male (19 to 45 years old) or healthy elderly male or post-menopausal female (over 60 years old). **Inclusion/Exclusion Criteria:** Waivers for inclusion/exclusion criteria will not be granted. **Inclusion:** 1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable). 2. Male subject should be 19 to 45 years old (for young adult cohorts) or over 60 years old (for elderly cohorts). 3. Subject has a body mass index (BMI) range of 18.5 to 30 kg/m^2 inclusive at Screening.

4. Male subject and his female spouse/partner who is of childbearing potential must be using highly effective contraception consisting of 2 forms of birth control (at least one of which must be a barrier method) starting at Screening and continuing throughout the study period and for 90 days after final study drug administration.
   Highly effective contraception is defined as:
   - Established use of oral, injected, or implanted hormonal methods of contraception
   - Placement of an intrauterine device or intrauterine system
   - Barrier methods of contraception: condom with spermicidal foam, gel, film, cream, suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam, gel, film, cream, or suppository
5. Male subject must not donate sperm starting at Screening, throughout the study period and for at least 90 days after final study drug administration.
6. Female subject must be over 60 years old and post-menopausal (defined as at least 1 year without any menses) prior to Screening.
7. Subject agrees not to participate in another investigational study while on study treatment.

Exclusion:

For all subjects:

1. Subject has a known or suspected hypersensitivity to KM-819, or any components of the formulation(s) used.
2. Subject has previously participated in a clinical study with KM-819.
3. Subject has any of the liver enzymes (aspartate aminotransferase [AST], alanine transaminase [ALT], alkaline phosphatase, γ-glutamyl transferase) or total bilirubin (TBIL) above the upper limit of normal (ULN). If any liver enzyme is > 1 × ULN but < 1.5 × ULN, the assessment may be repeated once during the Screening period or on check-in. If the repeated assessment is above the ULN, it is exclusionary. If the initial value is > 1.5 × ULN, it cannot be repeated and is exclusionary.
4. Subject has any clinically significant history of allergic conditions (including drug allergies, asthma, eczema, or anaphylactic reactions, but excluding untreated, allergic rhinitis or rhino-conjunctivitis, or house dust mite allergy at time of dosing).
5. Subject with a history of a suicide attempt or suicidal behavior. Any recent suicidal ideation (a level of 4 or 5) within the last 3 months, or having a positive Columbia Suicide Severity Rating Scale (C-SSRS) at check-in (Day -1), or who is at significant risk to commit suicide, as judged by the Investigator using the C-SSRS at Screening.
6. Subject has/had febrile illness or symptomatic viral, bacterial (including upper respiratory infection) or fungal (non-cutaneous) infection within 1 week before site check-in.
7. Subject has any clinically significant abnormality following the Investigator's review of the physical examination, electrocardiogram (ECG), and protocol-defined clinical laboratory tests at Screening or site check-in.
8. Subject has a mean pulse < 40 or > 90 beats per minute (bpm); mean systolic blood pressure (SBP) > 140 mmHg; or mean diastolic blood pressure (DBP) > 90 mmHg (measurements taken in triplicate after

subject has been resting in the supine position for 5 minutes; pulse will be measured automatically) at Screening or check-in. If the mean pulse, mean SBP, or mean DBP is out of the range specified above, 1 additional triplicate measurement may be taken at Screening and check-in.

9. Subject has a mean QTcF interval of > 430 msec (for males) and > 450 msec (for females) at Screening or check-in. If the mean QTcF exceeds the limits above, 1 additional triplicate ECG can be taken. If this triplicate also gives an abnormal result, the subject should be excluded.
10. Subject has a history of unexplained syncope, cardiac arrest, unexplained cardiac arrhythmias or *torsade de pointes*, structural heart disease, or a family history of Long QT Syndrome.
11. Subject has use of any prescribed or non-prescribed drugs (including vitamins, hormone replacement therapy, natural and herbal remedies, e.g., St. John's Wort) in the 2 weeks before study drug administration. Acetaminophen up to 2000 mg/day is allowed.
12. Subject has had any use of tobacco- or nicotine-containing products within 6 months prior to Screening.
13. Subject has history of consuming more than 14 units of alcoholic beverages per week within 6 months prior to Screening or has a history of alcoholism or abuse of amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates (drugs-of-abuse) within the past 2 years prior to Screening (Note: 1 unit = 355 mL of beer, 118 mL of wine, or 29 mL of spirits/hard liquor) or the subject tests positive at Screening or site admission for alcohol or drugs-of-abuse.
14. Subject has used any drugs-of-abuse within 3 months before check-in.
15. Subject has used any inducers of metabolism (e.g., barbiturates, rifampin) in the 3 months prior to check-in.
16. Subject has any significant blood loss, donated 1 unit (450 mL) of blood or more, or received a transfusion of any blood or blood products within 60 days, or donated plasma within 7 days before check-in.
17. Subject has a positive serology test for hepatitis B surface antigen (HbsAg), anti-hepatitis A virus Immunoglobulin M (HAV IgM), anti-hepatitis C virus (HCV Ab), or anti-human immunodeficiency virus (HIV Ab).
18. Subject has participated in any interventional clinical study or has been treated with any investigational drugs within 3 months or 5 half-lives, whichever is longer, before the initiation of Screening.
19. Subject has (recent history of) any other condition which, in the opinion of the Investigator, precludes the subject's participation in the trial.
20. Subject is an employee of the Kainos Medicine, Inc. or vendors involved in the study.

Additional Exclusion Criteria for Young Adult Subjects

21. For young adult cohorts, subject has any history or evidence of any clinically significant cardiovascular, gastrointestinal, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, renal, and/or other major disease or malignancy, as judged by the Investigator or designee.

Exclusion Criteria for Elderly Subjects

Replacement for Exclusion No. 8 above

8. Subject has a mean pulse < 50 or > 90 bpm; mean SBP > 160 mmHg; mean DBP > 100 mmHg (measurements taken in triplicate after subject has been resting in supine position for 5 minutes; pulse will be measured automatically).

Replacement for Exclusion No. 21 above

21. For elderly cohorts, subject has any history or evidence of any clinically significant cardiovascular, gastrointestinal, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, renal, and/or other major disease or malignancy that is not well managed and stable, as judged by the Investigator or designee.

Additional Exclusion Criteria

22. Elderly subject is excluded if the Glomerular Filtration Rate (calculated based on Cockcroft-Gault formula) is < 60 mL/min/1.73 m^2.
23. Clinically significant abnormal findings in the lumbar X-ray examination (only for elder subjects for MAD study).

Dose Escalation Criteria:

In Part A, escalation to the next dose level will take place only after the safety and tolerability data for all subjects in the cohort (through Day 4) and available plasma PK data (through the 72-hour sample postdose) from the previously administered dose cohort has been reviewed. Data from exploratory PD assessments and central nervous system (CNS) scales will not be included in the review for dose escalation decisions. Within the planned dose range a dose lower than the next planned dose level may be tested, depending on the emerging safety, tolerability and/or other relevant data (e.g., plasma PK data).

Stopping Criteria for Dose Escalation:

Dosing will be stopped if 1 (or more) of the following apply. Depending on the nature of the adverse events (AE)s, it could be decided to investigate a lower dose level (intermediate between the current and the prior one) in the next group.

1. If 1 or more subjects experiences a study drug-related serious adverse event (SAE), unblinding of the subject(s) will be done. If the subject(s) was (were) on active treatment, dosing will be stopped.
2. If 2 subjects in 1 dose group show the following findings in 2 consecutive postdose measurements within 24 hours and if unblinding reveals that both subjects received active treatment, dosing will be stopped:
    a. ALT or AST ≥ 3 x ULN or,
    b. ALT or AST ≥ 2 x ULN and ALT or AST ≥ 5 x baseline value or,
    c. TBIL ≥ 2 x ULN
3. If 2 or more subjects in 1 cohort experience AEs of severe intensity or 4 or more subjects in 1 cohort experience AEs of moderate intensity, which are considered by the Principal Investigator (PI) and/or Sponsor to be possibly or probably related to the investigational product, and of clinical concern, and if unblinding reveals that these subjects received active treatment, dosing will be

stopped.

PK stopping criteria

The decision to escalate to the next planned dose will also be based on review of PK exposure data from previous dose cohort(s). All available PK data will be used to estimate the expected exposures (AUC and C_{max}) of the next dose level using modeling. If predicted mean AUC and C_{max} for the next dose level is higher than 41.3 ug.h/mL and 9.3 ug/mL, respectively, then the dose escalation will stop and the Sponsor and PI will need to review the totality of data, including safety and PK before make any dose escalation decision.

Discontinuation of Individual Subject(s):

A discontinued subject is a subject who is enrolled in the clinical study and for whom study treatment is permanently discontinued prematurely for any reason.

A subject may withdraw from the study at any time without penalty and for any reason without prejudice to his/her future medical care. Participation of subjects may also be discontinued based on the medical judgment of the PI in conjunction with the Sponsor for any of the following reasons:

- ECG abnormalities:
  Any increases in QTcF > 500 msec or increase > 60 msec from baseline as confirmed with 3 consecutive ECGs taken within 5 minutes, with at least a 1-minute interval.
- Suicidality:
  Any suicide attempt or any recent suicidal ideation (a level of 4 or 5) since the last assessment, or a significant risk to commit suicide, as judged by the PI using the C-SSRS.
- Liver Safety Monitoring:
  Please refer to Stopping Criteria No. 2.
- After enrolment, the subject is found to violate the inclusion and/or exclusion criteria
- AE(s)
- Subject lost to follow-up
- Major protocol violation
- Use of prohibited medications
- Any serious safety concern
- Premature termination of the study
- Others

A clear and concise reason for discontinuation will be recorded in the electronic case report form (eCRF). Subjects who are discontinued will have an Early Discontinuation (ED) Visit per the Schedules of Assessments.

Criteria for Evaluation of Pharmacokinetic and Pharmacodynamic

Pharmacokinetic Endpoints:

KM-819

Plasma PK parameters for KM-819 include the following for single dose and/or multiple dose analysis: $AUC_{tau,}$ AUC_{inf}, AUC_{inf} (%extrap), AUC_{last}, CL/F, C_{max}, C_{trough}, λ_z, R_{ac} (AUC), R_{ac} (C_{max}), $t_{1/2}$, t_{lag}, t_{max}, V_z/F, and other parameters, as appropriate, including dose-adjusted parameters.

Cerebrospinal fluid (CSF) PK parameters for KM-819 include the following for multiple dose analysis: KM-819 concentration in CSF.

Pharmacodynamic Endpoints:

In both Parts A and B, mean and absolute value change from baseline at each post-baseline measurement for Bond and Lader Visual Analogue Scale (VAS), Profile of Mood States (POMS), Korean Wechsler Adult Intelligence Scale-IV (K-WAIS-IV), and C-SSRS.

In Part B only, PD parameters in plasma and CSF including: alpha synuclein oligomer, total Tau, phospho-Tau, and ratio of CSF concentration/Plasma C_{max}.

Criteria for Evaluation of Safety

Safety Endpoints:

Parts A and B

- Reporting AEs (nature, frequency, severity, time of onset/offset)
- Standard clinical laboratory evaluations
- Vital signs measurements (tympanic temperature, supine pulse, and supine blood pressure [BP])
- 12-lead ECGs

Statistical Methods

Study Part A and B will be analyzed separately. Three analysis sets will be used.

- The safety analysis set (SAF) will be the primary analysis set for all safety displays and consists of all subjects who received at least one dose.
- The PK analysis set (PKAS) will be the primary analysis set for all PK displays and analyses, consists of all subjects from the SAF for whom sufficient plasma concentration data are available to facilitate the calculation of at least one PK parameter and no important protocol deviations affecting the PK variables, as confirmed during a pre-analysis review of the data prior to database lock.
- The PD analysis set (PDAS) consists of all subjects from the SAF for whom sufficient data for neuropsychologic testing (Parts A and B) or plasma and CSF concentration data are available (Part B) to facilitate the calculation of at least one PD parameter and had no important protocol deviations affecting the PD analysis, as confirmed during a pre-analysis review of the data prior to database lock.

Continuous variables will be summarized using descriptive statistics (number of observations, mean, standard deviation [SD], minimum, median, maximum, geometric mean, and coefficient of variation [CV]). Categorical variables will be described using absolute and relative frequency.

Dose-proportionality analysis will be performed as an exploratory analysis.

Dose proportionality for primary PK parameter (C_{max} and AUC_{inf} will be examined via the power model and will be summarized and reported graphically. The PK parameters and the dose will be logarithmically (ln) transformed prior to analysis. An alpha level of 5% will be used.

Additionally, an analysis of variance (ANOVA) of the natural log-transformed dose-normalized PK parameters AUC_{inf}/dose and C_{max}/dose with log-transformed KM-819 dose as a covariate and subject as random effect, will be performed to estimate the slope of the effect of dose level on the PK parameter and its 95% Confidence Interval (CI).

The PK parameters will be plotted versus dose level of KM-819 including the regression line from the statistical analysis. Plots will be presented for dose-normalized parameters based on absolute dose.

Sample Size Justification:
The sample size of 8 subjects each cohort in both parts is standard in First-in-Human studies for dose escalation. The number of subjects planned for both parts of this study is considered sufficient to achieve the study objectives (safety, tolerability, PK, and PD).

Subjects who discontinue from study may be replaced at the discretion of the Sponsor.

Efficacy:
Efficacy will not be tested in this study.

Pharmacokinetics:
Descriptive statistics (number of subjects, mean, SD, CV%, median, minimum, and maximum) will be used to summarize plasma KM-819 PK continuous parameters and plasma KM-819 concentrations by dose group where appropriate. Geometric means will also be provided for AUC_{tau}, AUC_{last}, AUC_{inf}, and C_{max}. Individual and mean plasma KM-819 concentration-time curves on normal and semi-logarithmic scales will be provided. Overlay plots by treatment group will also be provided.

Pharmacodynamics:
Part A and B:
To evaluate the effect of KM-819, descriptive statistics for continuous and categorical variables will be used to summarize PD parameters: VAS, POMS, K-WAIS-IV, and C-SSRS.
Part B:
Descriptive statistics variables will be used to summarize PD parameters by dose group where appropriate. Modeling of PK/PD variables may be performed if considered necessary.
No formal interim analysis is planned.

Details of the statistical analysis will be provided in Statistical Analysis Plan (SAP).

Schedule of Procedures Schedule of Procedures for Part A and for Part B are described in Section 7.1.

LIST OF STUDY PERSONNEL

Sponsor	Kainos Medicine, Inc. 16, 712 beon-gil, Daewangpankyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, 13488, Korea
Principal or Global Coordinating Investigator	Kyoung Soo Lim, MD, PhD Assistant Professor Department of Clinical Pharmacology and Therapeutics CHA University School of Medicine and CHA Bundang Medical Center
Contract Research Organization	PAREXEL International 70 Sir John Rogerson's Quay, Dublin 2, Ireland Telephone number: +3531 473 9500
Adverse Event Reporting	PAREXEL International Room 1505, 15F, KunTai International Mansion, Yi No. 12, Chao Yang Men Wai Street, Chaoyang District, Beijing, 100020, China Telephone number: +65-62218582 Toll free fax number: 00308-13-2766
Specific Laboratory 1	Bioinfra 7F, Kyunggi Bio-Center, 147, Gwanggyo-ro, Yeongtong-gu, Suwon-si, Gyeonggi-do, 16229, Korea Telephone number: +82-31 888 6270
Specific Laboratory 2	Green Cross Lab. Cell Corp. 107 (Bojeong-dong), 30, Ihyeon-ro, Giheung-gu, Yongin-si, Gyeonggi-do, 16924, Korea Telephone number: +82-2 2669 0481

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AEI	Adverse event of interest
ALD	Approximate lethal dose
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CNS	Central nervous system
CRF	Case report form
CSF	Cerebrospinal fluid
CV	Coefficient of variation
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
ED	Early discontinuation
EDC	Electronic data capture
FAF1	Fas (TNFRSF6)-associated factor 1
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAV	Hepatitis A virus
HCV	Hepatitis C virus
HED	Human equivalent dose
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization

IEC	Independent Ethics Committee
IRB	Institutional Review Board
K-WAIS-IV	Korean Wechsler Adult Intelligence Scale-IV
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NOAEL	No Observed Adverse Effect Level
PD	Pharmacodynamics
PK	Pharmacokinetics
PI	Principal Investigator
PO	Per oral
PPS	Per-Protocol Set
SAD	Single Ascending Dose
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VAS	Visual Analogue Scale

1 INTRODUCTION

1.1 Background

There are approximately 90 million patients with central nervous system (CNS) disease worldwide in 2005, and it is expected to increase up to 130 million in 2030. Parkinson's disease and Alzheimer patients are expected to increase by 66% from 2005 to 2030.[2] High number of new incidents of both diseases is expected in 7 countries (US, Japan, France, Germany, Italy, Spain, and England), estimated to be more than 1.5 million.[3] In the US, the incidence is 50,000-60,000 every year, and in Korea it is also increasing rapidly due to recent increase of the aging population. In Korea, the number of Parkinson's disease patients was 39,000 in 2004, increased 1.7 folds to 66,000 in 2008, and has increased further to between 100,000 and 150,000 in 2010. Ninety-five percent of patients are over 50 years old.[4]

Parkinson's disease is a progressive neurodegenerative disease caused by loss of dopaminergic neurons in substantia nigra in mid brain. The symptoms include bradykinesia, resting tremor, rigidity, unstable posture, and postural reflex impairment. The therapeutic drugs for its cause and progression are limited and not sufficient for medical needs.

Although mechanism for the neuron loss is unknown, the movement control ability can be temporally improved by the dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA). Current drugs are classified largely into 4 classes (dopamine supplements, dopamine catechol-O-methyl transferase (COMT) inhibitor, dopamine precursors, and MAO-B inhibitors). These medicines supplement dopamine or help for relieving symptoms, but there is no remedy for the cause of disease such as inhibiting the death of dopaminergic neuron cells. Also, the current medicines require increasing dose over time and have serious side effects such as insomnia, movement impairment, and tremors.

1.2 KM-819

KM-819 is an innovative new drug that protects neuron cells from death through inhibition of the function of Fas (TNFRSF6)-associated factor 1 (FAF1), a cell death inducing protein in dopamine neuron cells.

It has been reported that the expression of FAF1 is increased in Parkinson's patient's brain tissue.[5] Animal models relevant to Parkinson's disease have confirmed a significant increase of FAF1 in the midbrain. Parkinson's disease cell and animal models have confirmed an inhibition of cell death when FAF1 expression is reduced.[6] Therefore, FAF1 is validated as a potential novel target for new drug discovery for Parkinson's disease. KM-819 has been developed as a compound targeting FAF1 as a therapy drug for Parkinson's disease.

KM-819 not only protects dopaminergic neuron cell from death (neuroprotection), but may also improve behavior similar to other drugs. Therefore, if KM-819 becomes successful as a new drug, it is expected to replace the current market and create new market by fulfilling unmet medical needs.

1.2.1 Non-clinical Data

1.2.1.1 Pharmacology

KM-819 is a drug candidate with EC_{50} value of nM range for in vitro cell death protection assay study (in human neuronal cell line 200.3 nM and rat primary neuron 134.5 nM), and confirmed to exhibit dopaminergic neuron cell protection in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease animal models, and to have a superior neuron cell protection effects and the similar behavioral improvement effects compared to L-dopa. In addition, it demonstrates specific binding to the target protein FAF1 upon cell death related to Parkinson's disease.

In vitro efficacy of the FAF1 inhibitor KM-819 in Parkinson's disease cell model was evaluated using dopaminergic neuron cells obtained from rat substantia nigra. The cells treated with KM-819 showed better protection from death to MPTP compared to untreated cells in a dose-dependent manner (0.1, 1, and 10 uM).

Inhibitory effect of KM-819 on FAF1 signaling in Parkinson's disease cell model was evaluated using the human neuroblast cell line SH-SY5Y. Treatment with KM-819 inhibited the interaction of FAF1 with Caspase-8 and JNK1, 2 downstream targets of FAF1, in Parkinson's disease cell model induced by H_2O_2, and the subsequent studies done by Western blotting gave results that the drug inhibited the activation of Caspase-8 and JNK1 from 100 nM to 10 uM in a dose-dependent manner.

In acute Parkinson's disease models induced by MPTP in vivo, treatment with KM-819 at 20 mg/kg for 6 consecutive days orally protected dopaminergic neuron cells both in substantia nigra and striatum, compared to non-treated controls, and also improved the behavioral impairments in these models. These effects were dose-dependent at 1, 10, and 20 mg/kg.

In sub-acute Parkinson's disease models induced by MPTP, the effects of KM-819 were compared to a current Parkinson's disease drug L-dopa. Treatment with KM-819 at 20 mg/kg for 6 consecutive days orally protected dopaminergic neuron cells better than treatment with L-dopa which was injected into abdominal cavity at 20 mg/kg. And the improvement of behavior was very similar in these 2 groups. The effects of KM-819 on neuron cells in brain was also studied by MRI imaging and compared with a current Parkinson's disease drug ropinirole. Treatment with KM-819 for one week orally gave results in higher Fractional Anisotrophy (FA) value from KM-819 than ropinirole, demonstrating the superior cell protection effects of KM-819 compared with ropinirole. Also, detecting dopamine transporters (DAT) scanning data by positron emission tomography (PET) imaging showed that both KM-819 and ropinirole treatments gave the higher Standardized Update Value (SUV) compared to non-treated controls, demonstrating the protective effects in dopaminergic neuron cells in striatum.

In chronic Parkinson's disease models induced by MPTP, pre- or post-treatment with KM-819 at 30 mg/kg for 3 months orally protected dopaminergic neuron cells both in substantia nigra and striatum, compared to non-treated controls.

Therefore, the efficacy of KM-819 in the protection of cell protection and behavior improvement were found in both in vitro and in vivo Parkinson's disease animal models.

1.2.1.2 Safety Pharmacology

Safety of KM-819 on various organs was evaluated by core battery of safety pharmacology tests. No changes in various neuronal behaviors and body temperature at up to 1000 mg/kg of KM-819

in male and female rats were observed. No changes in heart rate, blood pressure (BP), and electrocardiogram (ECG) variables including QT intervals at up to 500 mg/kg per oral (PO) dose in male dogs were observed. KM-819 did not inhibit the human ether-a-go-go related gene (hERG potassium channel) at up to 10 uM. KM-819 did not inhibit any respiratory functions in rats at up to 1000 mg/kg PO dose.

1.2.1.3 Pharmacokinetics

A pharmacokinetic (PK) study in male rats, by administering single intravenous (IV) injection of 5 mg/kg KM-819 showed: C_{max}: 62.73 ug/ml, t_{max}: 0.083 hr, and $t_{1/2}$: 7.08 hr. Single dose oral administration of 5 mg/kg KM-819 resulted in: C_{max}: 3.89 ug/ml, t_{max}: 3 hr, and $t_{1/2}$: 6.06 hr. Oral bioavailability assessed by comparing $AUC_{0-\infty}$ for oral and IV administration was 35.97%.

A PK study in male dogs, by administering single IV injection of 1 mg/kg KM-819 showed: t_{max}: 0.08 hr, C_{max}: 11.91 ug/ml, and $t_{1/2}$: 8.61 hr. Single dose oral administration of 5 mg/kg and 10 mg/kg KM-819 resulted in: t_{max}: 0.83 hr and 0.58 hr, C_{max}: 6.01 ug/ml and 9.48 ug/ml, and $t_{1/2}$: 4.96 hr and 5.03 hr, bioavailability: 32.3% and 28.9%, respectively.

In vitro plasma protein binding is 99.96 %, 99.79%, and 99.96% in rat, dog and human, respectively. KM-819 at 10 uM did not inhibit CYP450s (including 1A2, 2C9, 2C19, 2D6, 3A4) and P-gp.

1.2.1.4 Toxicology

Toxicity of KM-819 was evaluated in rats (up to 28 days) and dogs (up to 14 days) by single and multiple PO dose. The toxicity was also tested by single IV injection in rats.

Repeated dose toxicity test in rats and dogs did not reveal any drug-related pathological tissue changes (including reproductive organ) or significant clinical symptoms at tested highest dose.

Single dose toxicity test in SD rats with oral doses of KM-819 at 500, 1000, and 2000 mg/kg did not result in any death, change in clinical observations, body weight, or biopsy results. Therefore, the approximate lethal dose (ALD) is above 2000 mg/kg. And from the test of KM-819 for 4 week repeated oral dose (2 weeks recovery) in SD rats, No Observed Adverse Effect Level (NOAEL) is 500 mg/kg/day.

Single IV injection of KM-819 at 25, 50, and 100 mg/kg did not result in any death, change in clinical observations, BW change, or biopsy results in SD rats.

In beagle dogs, single oral doses of KM-819 at 500, 1000, and 2000 mg/kg did not result in any death, or changes in clinical observations, body weight, or biopsy results except contamination of test materials in feces, therefore, the ALD is above 2000 mg/kg/day. During a 2-Week repeated dose study in male and female Beagle dogs (with 1 week recovery), KM-819 at 50, 250, and 1000 mg/kg did not result in any death, or changes in clinical observations, body weight, or biopsy results except contamination of test materials in feces. Liver damage (higher ALT, ALP, GGT, and enlargement in common bile duct in liver) was reported in one male dog following multiple dosing at 2000 mg/kg for 7 days. Therefore, NOAEL is 1000 mg/kg/day for both male and female Beagle dogs.

KM-819 did not show any genotoxicity from mutation reversion test, chromosome abnormality test, and bone marrow micronucleus test.

1.2.2 Clinical Data

KM-819 has not been investigated in humans yet, therefore, no clinical study data is available.

1.3 Rationale

KM-819 has not previously been administered to humans. This First-in-Human study is therefore designed to provide safety, tolerability, PK, and pharmacodynamic (PD) data of KM-819 in healthy young adult male and elderly male or female subjects following ascending single and multiple dose administration. Data from this study will be used to guide rational drug dosing and therapeutic regimen choices in subsequent clinical studies.

1.4 Risk-Benefit Assessment

Given the favorable toxicity profile and the positive results of in vitro and animal models, it is suggested that the present clinical study has an acceptable risk-benefit ratio.

The safety monitoring practices employed by this protocol are standard for a First-in-Human, single and multiple ascending dose study and are considered adequate to protect the subjects' safety. Subjects will be admitted to the Clinical Study Unit, where they will be monitored to detect adverse events (AE)s during the study and followed appropriately to ensure resolution of AEs. Sentinel dosing will be employed within each single dose cohort, and available safety and PK data will be assessed after each dose level to determine if it is safe to escalate the dose.

Subjects participating in this study will not benefit from administration of KM-819. None of the findings in non-clinical safety pharmacology or toxicology studies precludes further development of KM-819 in Phase 1 First-in-Human clinical trials.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the safety and tolerability of single and multiple ascending oral doses of KM-819 in healthy young adult male subjects.

2.2 Secondary Objectives

- To evaluate the pharmacokinetics and pharmacodynamics of single and multiple ascending oral doses of KM-819 in healthy young adult male subjects.
- To evaluate the safety and tolerability of single and multiple oral doses of KM-819 in elderly male or post-menopausal female subjects.
- To evaluate the PK and PD of single and multiple oral doses of KM-819 in elderly male or post-menopausal female subjects.

3 OVERALL DESIGN AND PLAN OF THE STUDY

3.1 Overview

This is a first-in-human, single-center, randomized, placebo-controlled, double-blind, sequential group Phase 1 study in healthy subjects. The aim of this study is to evaluate the safety, tolerability, PK, and PD following the escalation of single and multiple doses of KM-819.

The study will consist of 2 parts (Part A and Part B).

- Part A includes up to 5 cohorts of healthy young adult male subjects receiving single ascending doses (SAD)s of KM-819, and 1 additional single-dose cohort of elderly male or post-menopausal female subjects.
- Part B includes up to 4 cohorts of healthy young adult male subjects receiving multiple ascending doses (MAD)s of KM-819, and 1 additional multiple-dose cohort of elderly male or post-menopausal female subjects.

Dose escalation to the next level will be determined using the safety, tolerability, and PK data of the previous cohort.

Part A, Single Ascending Dose (SAD)

Up to 40 healthy young adult male subjects and 8 healthy elderly male or post-menopausal female subjects will be enrolled and randomized to receive either KM-819 or placebo.

Each of the 5 dose escalation cohorts consists of 8 healthy young adult male subjects; 6 subjects will receive single dose of 10, 30, 100, 200, or 400 mg KM-819 and 2 subjects will receive placebo.

Cohorts will be dosed sequentially with escalating doses, escalation to the next dose level will take place only after the safety, tolerability data, and available PK data from the previously treated dose cohort has been reviewed; see Section 3.4 for dose escalation criteria. In each of the 5 single dose cohorts, dosing of subjects will be sentinel, i.e., 2 subjects will be dosed on the first day (1 subject will receive active treatment and 1 subject will receive placebo) and the remaining 6 subjects will be dosed at least 24 hours after the first 2 subjects.

After completion of the 5 dose escalation cohorts, 8 elderly male or post-menopausal female subjects will be enrolled into an additional cohort; 6 subjects will receive 200 mg KM-819 and 2 subjects will receive placebo.

See Table 3-1 for Part A dose groups.

Table 3-1: Dose Groups for Part A

KM-819 Dose (mg)	Subjects on KM-819 (n)	Subjects on Placebo (n)	Total Subjects in Group (n)	Age Group
10†	6	2	8	Young adult male subjects
30†	6	2	8	
100†	6	2	8	
200†	6	2	8	
400†	6	2	8	
200	6	2	8	Elderly male or post-menopausal female subjects

† Doses between the current planned range may be assigned or a dose may be repeated depending on safety, tolerability, and pharmacokinetic data from previous subjects and cohorts.

All subjects will undergo a Screening period of up to 28 days and a 3-day Confinement period when they are hospitalized for study activities (Day -1 to Day 3). Subjects are required to return for outpatient visits on Day 4, Day 7, and for Follow-up Visit on Day 14. See Figure 3-1 for Part A SAD study design.

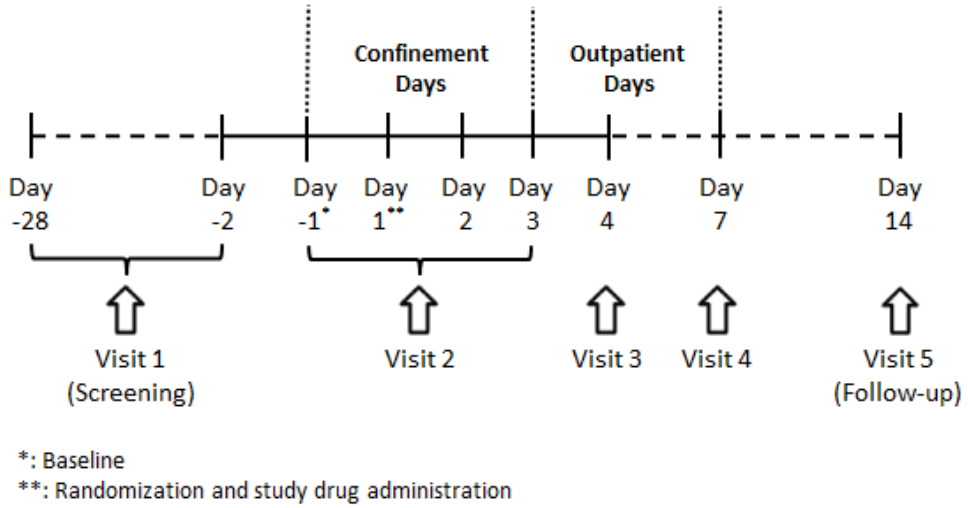

Figure 3-1: Part A Single Ascending Dose Study Design

Part B, Multiple Ascending Dose (MAD)

Part B will be conducted after completion of all cohorts of young adult male subjects in Part A.

Up to 32 healthy young adult male subjects and 8 healthy elderly male or post-menopausal female subjects will be enrolled and randomized to receive either KM-819 or placebo.

Each of the 4 dose escalation cohorts will consist of 8 healthy young adult male subjects; 6 subjects will receive 30, 100, 200, or 400 mg of KM-819 once a day (QD) for 7 days and 2 subjects will receive placebo. Cohorts will be dosed sequentially with escalating doses.

After completion of the 4 dose escalation cohorts, 8 elderly male or post-menopausal female subjects will be enrolled into an additional cohort; 6 subjects will receive 200 mg KM-819 QD for 7 days and 2 subjects will receive placebo.

See Table 3-2 for Part B dose groups.

Table 3-2: Dose Groups for Part B

KM-819 Dose (mg)	Subjects on KM-819 (n)	Subjects on placebo (n)	Total Subjects in Group (n)	Age Group
30†	6	2	8	Young adult male subjects
100†	6	2	8	
200†	6	2	8	
400†	6	2	8	
200	6	2	8	Elderly male or post-menopausal female subjects

† Doses between the current planned range may be assigned depending on safety, tolerability, and pharmacokinetic data from previous subjects and cohorts.

All subjects will undergo a Screening period of up to 28 days and an 8-day Confinement period when they are hospitalized for study activities (Day -1 to Day 8). Subjects are required to return for a Follow-up Visit on Day 14. See Figure 3-2 for Part B MAD study design.

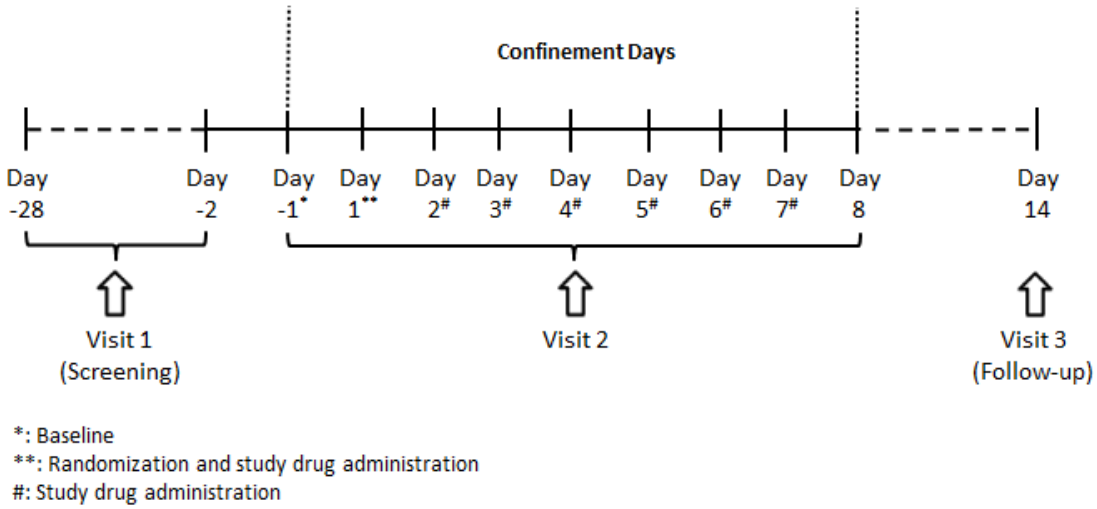

Figure 3-2: Part B Multiple Ascending Dose Study Design

3.2 Criteria for Evaluation of the Study

The study involves safety, PK, and PD assessments. The specific endpoints are listed below.

3.2.1 Safety Endpoints

Parts A and B

- Reporting AEs (nature, frequency, severity, time of onset/offset)
- Standard clinical laboratory evaluations
- Vital signs measurements (tympanic temperature, supine pulse, and supine BP)
- 12-lead ECGs

3.2.2 Pharmacokinetic Endpoints

KM-819

Plasma PK parameters for KM-819 include the following for single dose and/or multiple dose analysis:

Single Dose and Day 1 of multiple doses

- AUC_{last}: area under the plasma concentration-time from predose (time 0) to the last quantifiable concentration
- AUC_{inf}: area under the plasma concentration-time curve from predose (time 0) extrapolated to infinity
- AUC_{inf} (%extrap): Percentage of AUC_{inf} that is due to extrapolation beyond t_{last}
- CL/F: apparent oral clearance
- C_{max}: maximum plasma concentration determined directly from the concentration-time profile
- λ_z: terminal elimination rate constant
- $t_{1/2}$: apparent terminal elimination half-life
- t_{lag}: lag time

- t_{max}: time to achieve maximum observed plasma concentration determined directly from the concentration-time profile
- V_z/F: volume of distribution
- Other parameters, as appropriate, including dose-adjusted parameters.

Day 7 of multiple doses

- AUC_{tau}: area under the plasma concentration-time curve for a dosing interval
- AUC_{last}: area under the plasma concentration-time from predose (time 0) to the last quantifiable concentration
- CL/F: apparent oral clearance
- C_{max}: maximum plasma concentration determined directly from the concentration-time profile
- C_{min}: minimum plasma concentration determined directly from the concentration-time profile
- C_{trough}: observed plasma concentration before dosing
- R_{ac} (AUC): observed accumulation by AUC
- R_{ac} (C_{max}): observed accumulation by C_{max}
- t_{lag}: lag time
- t_{max}: time to achieve maximum observed plasma concentration determined directly from the concentration-time profile
- V_z/F: volume of distribution
- Other parameters, as appropriate, including dose-adjusted parameters

Cerebrospinal fluid (CSF) PK parameter for KM-819 includes the following after multiple dose CSF sample collection:

- KM-819 concentration in CSF

3.2.3 Pharmacodynamic Endpoints

In both Parts A and B, mean and absolute value change from baseline at each post-baseline measurements for:

- Bond and Lader Visual Analogue Scale (VAS)
- Profile of Mood States (POMS)
- Korean Wechsler Adult Intelligence Scale-IV (K-WAIS-IV)
- C-SSRS

In Part B only, PD parameters in plasma and CSF including:

- alpha synuclein oligomer
- total Tau
- phospho-Tau
- ratio of CSF concentration/Plasma C_{max}

3.3 Justification of the Study Design

This is a study of safety, tolerability, PK, and PD of KM-819 administered orally to healthy adult and elderly subjects. A double-blind, placebo-controlled study is appropriate and standard for a SAD and MAD study. This design will minimize bias and provide reference data (i.e., data from placebo-treated subjects) which will aid in the interpretation of results.

Five SAD levels and four MAD levels are planned. The Principal Investigator (PI) and the Sponsor (both in a blinded state) will review available safety and PK data after each cohort to confirm whether it is safe to proceed with the next planned ascending dose, dose escalation should be stopped or the dose should be lowered or repeated in the subsequent cohort.

The safety assessments for the study are accepted measures for ensuring safety of patients during a clinical study. The times allowed for collection of PK/PD samples for KM-819 concentration are considered appropriate given the information available.

3.4 Dose Escalation Criteria

In Part A, escalation to the next dose level will take place only after the safety and tolerability data for all subjects in the cohort (through Day 4) and available plasma PK data (through the 72-hour sample postdose) from the previously administered dose cohort has been reviewed. Data from exploratory PD assessments and CNS scales will not be included in the review for dose escalation decisions. Within the planned dose range a dose lower than the next planned dose level may be tested, depending on the emerging safety, tolerability, and/or other relevant data (e.g., plasma PK data).

3.5 Stopping Criteria for Dose Escalation

Dosing will be stopped if 1 (or more) of the following apply. Depending on the nature of the AEs, it could be decided to investigate a lower dose level (intermediate between the current and the prior one) in the next group.

1. If 1 or more subjects experiences a study drug-related serious adverse event (SAE), unblinding of the subject(s) will be done. If the subject(s) was (were) on active treatment, dosing will be stopped.
2. If 2 subjects in 1 dose group show the following findings in 2 consecutive postdose measurements within 24 hours and if unblinding reveals that both subjects received active treatment, dosing will be stopped:
    a. ALT or AST $\geq$ 3 x upper limit of normal (ULN) or,
    b. ALT or AST $\geq$ 2 x ULN and ALT or AST $\geq$ 5 x baseline value or,
    c. TBIL $\geq$ 2 x ULN
3. If 2 or more subjects in 1 cohort experience AEs of severe intensity or 4 or more subjects in 1 cohort experience AEs of moderate intensity, which are considered by the PI and/or Sponsor to be possibly or probably related to the investigational product, and of clinical concern, and if unblinding reveals that these subjects received active treatment, dosing will be stopped.

3.5.1 PK stopping criteria

Due to the liver damage (higher ALT, ALP, GGT, and enlargement in common bile duct in liver) reported in one male dog following multiple dosing at 2000 mg/kg for 7 days, and NOAEL in male and female beagle dog at 1000 mg/kg/day for 14 days, the decision to escalate to the next planned dose will be based on review of PK exposure data from previous dose cohort(s). This will involve use of best available modeling practices of the observed AUC (i.e., AUC_{tau} or AUC_{0-inf}) and C_{max} from each dose, resulting in a predictive distribution of AUC and C_{max} at higher dose levels. If predicted mean AUC and C_{max} for the next dose level is higher than 41.3 ug.h/mL and 9.3 ug/mL, respectively, then the dose escalation will stop and the Sponsor and PI will need to review the totality of data, including safety and PK before make any dose escalation decision. This PK stopping criteria are based on dog 2-Week study NOAEL exposure at 1000 mg/kg/day (the most conservative species and gender).

4 STUDY POPULATION

For Parts A and B: healthy young adult male (19 to 45 years old) or healthy elderly male or post-menopausal female (over 60 years old).

The study population will consist of healthy subjects. Subjects must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

Waivers for inclusion/exclusion criteria will not be granted.

4.1 Inclusion Criteria

Subjects will be entered into this study only if they meet all of the following criteria:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Male subject should be 19 to 45 years old (for young adult cohorts) or over 60 years old (for elderly cohorts).
3. Subject has a body mass index (BMI) range of 18.5 to 30 kg/m^2 inclusive at Screening.
4. Male subject and his female spouse/partner who is of childbearing potential must be using highly effective contraception consisting of 2 forms of birth control (at least one of which must be a barrier method) starting at Screening and continuing throughout the study period and for 90 days after final study drug administration. Highly effective contraception is defined as:
    - Established use of oral, injected, or implanted hormonal methods of contraception
    - Placement of an intrauterine device or intrauterine system
    - Barrier methods of contraception: condom with spermicidal foam, gel, film, cream, suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam, gel, film, cream, or suppository
5. Male subject must not donate sperm starting at Screening, throughout the study period and for at least 90 days after final study drug administration.
6. Female subject must be over 60 years old and post-menopausal (defined as at least 1 year without any menses) prior to Screening.
7. Subject agrees not to participate in another investigational study while on study treatment.

4.2 Exclusion Criteria

Subjects will be entered into this study only if they meet none of the following criteria:

1. Subject has a known or suspected hypersensitivity to KM-819, or any components of the formulation(s) used.
2. Subject has previously participated in a clinical study with KM-819.

3. Subject has any of the liver enzymes (aspartate aminotransferase [AST], alanine transaminase [ALT], alkaline phosphatase, γ-glutamyl transferase) or total bilirubin (TBIL) above the ULN. If any liver enzyme is > 1 × ULN but < 1.5 × ULN, the assessment may be repeated once during the Screening period or on check-in. If the repeated assessment is above the ULN, it is exclusionary. If the initial value is > 1.5 × ULN, it cannot be repeated and is exclusionary.
4. Subject has any clinically significant history of allergic conditions (including drug allergies, asthma, eczema, or anaphylactic reactions, but excluding untreated, allergic rhinitis or rhino-conjunctivitis, or house dust mite allergy at time of dosing).
5. Subject with a history of a suicide attempt or suicidal behavior. Any recent suicidal ideation (a level of 4 or 5) within the last 3 months, or having a positive C-SSRS at check-in (Day -1), or who is at significant risk to commit suicide, as judged by the Investigator using the C-SSRS at Screening.
6. Subject has/had febrile illness or symptomatic viral, bacterial (including upper respiratory infection) or fungal (non-cutaneous) infection within 1 week before site check-in.
7. Subject has any clinically significant abnormality following the Investigator's review of the physical examination, ECG, and protocol-defined clinical laboratory tests at Screening or site check-in.
8. Subject has a mean pulse < 40 or > 90 beats per minute (bpm); mean systolic blood pressure (SBP) > 140 mmHg; or mean diastolic blood pressure (DBP) > 90 mmHg (measurements taken in triplicate after subject has been resting in the supine position for 5 minutes; pulse will be measured automatically) at Screening or check-in. If the mean pulse, mean SBP, or mean DBP is out of the range specified above, 1 additional triplicate measurement may be taken at Screening and check-in.
9. Subject has a mean QTcF interval of > 430 msec (for males) and > 450 msec (for females) at Screening or check-in. If the mean QTcF exceeds the limits above, 1 additional triplicate ECG can be taken. If this triplicate also gives an abnormal result, the subject should be excluded.
10. Subject has a history of unexplained syncope, cardiac arrest, unexplained cardiac arrhythmias or *torsade de pointes*, structural heart disease, or a family history of Long QT Syndrome.
11. Subject has use of any prescribed or non-prescribed drugs (including vitamins, hormone replacement therapy, natural and herbal remedies, e.g., St. John's Wort) in the 2 weeks before study drug administration. Acetaminophen up to 2000 mg/day is allowed.
12. Subject has had any use of tobacco- or nicotine-containing products within 6 months prior to Screening.
13. Subject has history of consuming more than 14 units of alcoholic beverages per week within 6 months prior to Screening or has a history of alcoholism or abuse of amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates (drugs-of-abuse) within the past 2 years prior to Screening (Note: 1 unit = 355 mL of beer, 118 mL of wine, or 29 mL of spirits/hard liquor) or the subject tests positive at Screening or site admission for alcohol or drugs-of-abuse.
14. Subject has used any drugs-of-abuse within 3 months before check-in.

15. Subject has used any inducers of metabolism (e.g., barbiturates, rifampin) in the 3 months prior to check-in.
16. Subject has any significant blood loss, donated 1 unit (450 mL) of blood or more, or received a transfusion of any blood, or blood products within 60 days or donated plasma within 7 days before check-in.
17. Subject has a positive serology test for hepatitis B surface antigen (HbsAg), anti-hepatitis A virus Immunoglobulin M (HAV IgM), anti-hepatitis C virus (HCV Ab), or anti-human immunodeficiency virus (HIV Ab).
18. Subject has participated in any interventional clinical study or has been treated with any investigational drugs within 3 months or 5 half-lives, whichever is longer, before the initiation of Screening.
19. Subject has (recent history of) any other condition which, in the opinion of the Investigator, precludes the subject's participation in the trial.
20. Subject is an employee of the Kainos Medicine, Inc. or vendors involved in the study.

Additional Exclusion Criteria for Young Adult Subjects

21. For young adult cohorts, subject has any history or evidence of any clinically significant cardiovascular, gastrointestinal, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, renal, and/or other major disease or malignancy, as judged by the Investigator or designee.

Exclusion Criteria for Elderly Subjects

Replacement for Exclusion No. 8 above

8. Subject has a mean pulse < 50 or > 90 bpm; mean SBP > 160 mmHg; mean DBP > 100 mmHg (measurements taken in triplicate after subject has been resting in supine position for 5 minutes; pulse will be measured automatically).

Replacement for Exclusion No. 21 above

21. For elderly cohorts, subject has any history or evidence of any clinically significant cardiovascular, gastrointestinal, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, renal, and/or other major disease or malignancy that is not well managed and stable, as judged by the Investigator or designee.

Additional Exclusion Criteria

22. Elderly subject is excluded if the Glomerular Filtration Rate (calculated based on Cockcroft-Gault formula) is < 60 mL/min/1.73 m^2.
23. Clinically significant abnormal findings in the lumbar X-ray examination (only for elder subjects for MAD study).

4.3 Subject Withdrawal and Replacement

A subject may withdraw from the study at any time without penalty and for any reason without prejudice to his/her future medical care. Participation of subjects may also be discontinued based on the medical judgment of the PI in conjunction with the Sponsor for any of the following reasons:

- ECG abnormalities:

  Any increases in QTcF > 500 msec or increase > 60 msec from baseline as confirmed with 3 consecutive ECGs taken within 5 minutes, with at least a 1-minute interval.
- Suicidality:

  Any suicide attempt or any recent suicidal ideation (a level of 4 or 5) since the last assessment, or a significant risk to commit suicide, as judged by the PI using the C-SSRS.
- Liver Safety Monitoring:

  Please refer to Stopping Criteria No. 2.
- After enrolment, the subject is found to violate the inclusion and/or exclusion criteria
- AE(s)
- Subject lost to follow-up
- Major protocol violation
- Use of prohibited medications mentioned in Section 5.8
- The Investigator may, after discussion with the subject, withdraw the subject due to any serious safety concerns
- The study is terminated prematurely
- Other

In all cases, the reason(s) for withdrawal, and the primary reason, must be recorded on the electronic case report form (eCRF). Subjects who are withdrawn will have an Early Discontinuation (ED) Visit per the Schedules of Assessments (see Table 7-1 and Table 7-2).

A subject may also be withdrawn from study by the Sponsor, Regulatory Authorities, or IECs/IRBs.

Subjects will also be withdrawn if the entire study is terminated prematurely as described in Section 9.10.

Withdrawn subjects may be replaced at the discretion of the Sponsor with agreement of the Investigator. Subjects who are discontinued because of treatment-emergent AE (TEAE) or possible toxic effects of the drug will not be replaced.

4.4 Planned Sample Size and Number of Study Centers

It is planned to recruit in total 72 healthy young adult subjects and 16 healthy elderly subjects at 1 center in Korea for this study.

Part A: up to 40 healthy young adult male and 8 healthy elderly male or post-menopausal female subjects will be enrolled.

Part B: up to 32 healthy young adult male and 8 healthy elderly male or post-menopausal female subjects will be enrolled.

See Section 8.10 for a discussion of sample size.

4.5 Subject Identification and Randomization

4.5.1 Subject Identification

Upon enrolment, each subject will receive a unique screening number. Enrolled subjects who drop out of the study before randomization will retain their screening number.

4.5.2 Randomization Scheme

In each dose cohort, 8 subjects will be randomized to have 6 subjects receiving KM-819 and 2 subjects receiving placebo in both Part A and Part B.

In each single dose cohort (Part A), dosing of subjects will be sentinel, i.e., 2 subjects will be dosed on the first day (1 subject will receive active treatment and 1 subject will receive placebo) and the remaining 6 subjects will be dosed at least 24 hours after the first 2 subjects.

Randomization will occur on Day 1 (of the first treatment period for Part A) after all predose procedures have been performed and eligibility for the clinical study has been confirmed. Each eligible subject will receive a 4-digit randomization number. Randomization numbers will be sequential and will be assigned as follows:

Part A:

Cohort 1: 1101-1108

Cohort 2: 1201-1208

Cohort 3: 1301-1308

Cohort 4: 1401-1408

Cohort 5: 1501-1508

Cohort 6: 1601-1608

Replacement subjects will be assigned the same randomisation number as the subject they are replacing plus 50, i.e., a subject replacing Subject 1101 will be assigned the subject number 1151.

Part B:

Cohort 1: 2101-2108

Cohort 2: 2201-2208

Cohort 3: 2301-2308

Cohort 4: 2401-2408

Cohort 5: 2501-2508

4.5.3 Allocation/Randomization of Subjects to Treatment

Prior to dosing on Day 1, subjects will be assigned a randomization number in accordance with the randomization code generated by PAREXEL using PROC PLAN method of SAS. The assigned randomization number will determine the treatment the subject receives.

Once a randomization number has been allocated to one subject, it may not be assigned to another subject. If subjects withdraw prematurely from the study and are replaced under the direction of the Sponsor, a replacement randomization number will be assigned. A replacement

randomization code will be generated such that replacement subjects are assigned to the same treatment as the discontinued subjects.

5 STUDY DRUG

5.1 Identity

The Sponsor will provide the Investigator with adequate quantities of the study drugs, as described in Table 5-1.

Table 5-1: Identity of the Study Drugs

Study Drug	Formulation	Strength	Route	Manufacturer
KM-819	White circular tablet	10 mg	Oral	HanAll BioPharma Co., Ltd.
		100 mg		
Placebo	White circular tablet	0 mg	Oral	HanAll BioPharma Co., Ltd.

The composition of each KM-819 tablet is presented below (see Table 5-2):

Table 5-2: Composition of Each Study Drug Tablet

Ingredient	Function	Quantity		
		KM-819 10 mg strength	KM-819 100 mg strength	Placebo
KM-819	Main ingredient	10 mg	100 mg	0 mg
Crystallized cellulose	Diluting agent	245 mg	157 mg	216 mg
Pre-gelatinized starch	Diluting agent	44 mg	44 mg	55 mg
Povidone	Bonding agent	24 mg	22 mg	27 mg
Crosscarmellose sodium	Disintegrating agent	11 mg	11 mg	29 mg
Colloidal silicone dioxide	Fluidizing agent	15 mg	15 mg	19 mg
Stearic magnesium	Lubricant Agent	11 mg	11 mg	14 mg

5.2 Administration

Study drug (KM-819 or placebo) will be administered orally at the study center.

The study drug should be administered with approximately 240 mL of water (room temperature), after an overnight fasting for a minimum of 8 hours. No food should be allowed for at least 4 hours postdose. Water will be allowed as desired except for 1 hour before and after drug administration.

For Part B (MAD) study, on Day 2 to Day 6, the study drug should be administered with approximately 240 mL of water (room temperature), after an overnight fasting for a minimum of 8 hours. No food should be allowed for at least 2 hours postdose. Water will be allowed as desired except for 1 hour before and 2 hours after drug administration.

Each dispensing of study drug will be documented in the eCRF.

5.3 Rationale for Selection of Starting Dose

The FDA Guidance "Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers"[7] and allometric scaling modeling and simulation were used for the initial calculation of the starting human dose in this study. Based on the FDA Guidance document and the 4-week rat toxicology study NOAEL of 500 mg/kg/day, the human equivalent dose (HED) is estimated to be 5600 mg for a 70 kg human subject. A 10-fold safety factor is applied to the HED, resulting in an estimated Maximum Recommended Starting Dose (MRSD) was 560 mg per person for a 70 kg person. In addition to the FDA Guidance method, an allometric scaling method was used to predict human PK. The human PK parameters were predicted as followed: CL= 2.93 L/h, V = 39.2 L, and half-life =9.27 hours. Using these predicted human PK parameters, simulation was conducted based on the assumption that human PK behaves with one compartment model with first order absorption and first order elimination rate and the bioavailability was assumed to be 35% (mean F from animal data).

Based on simulated human PK profile and animal efficacy data, a lower dose was chosen for the starting dose.

The first-in-human Phase 1 single ascending dose study will have an initial starting dose of 10 mg, which is x56-fold below the estimated MRSD derived from the rat NOAEL.

5.4 Packaging, Labeling and Storage

Study drug will be packaged by Kainos Medicine, Inc. according to all local legal requirements. Study drug will be labeled in accordance with applicable regulatory requirements.

All study drug supplies must be stored in accordance with the manufacturer's instructions (stored at a temperature of 1–30ºC). Until dispensed to the subjects, the study drug will be stored in a securely locked area, accessible to authorized personnel only.

5.5 Blinding and Breaking the Blind

The study will be performed in a double-blind manner. All study drugs will be supplied in identical tablets and will be similar in color, smell, taste, and appearance, thereby enabling double-blind conditions.

For this study, the bioanalyst will be unblinded for dose escalation PK analysis.

For each randomized subject, an individual emergency (randomization) code break envelope will be stored in a secure location with access by designated staff members to open in the event of a medical emergency requiring knowledge of a subject's treatment assignment.

The blind must only be broken following discussion on a case-by-case basis, at the discretion of the Sponsor/PI.

If the blind is broken, the date, time, and reason must be recorded in the subject's eCRF, and any associated AE report.

If an emergency unblinding becomes necessary, the Investigator should notify the Sponsor/PI, if possible, prior to unblinding. The Investigator is responsible for opening the specified envelope, in the presence of a witness, both of whom must sign and date the envelope.

All envelopes, whether sealed or opened, must be returned to PAREXEL at the end of the study.

Serious unexpected suspected adverse reactions (SUSARs), which are subject to expedited reporting, should be unblinded before submission to the Regulatory Authorities.

The overall randomization code will be broken only for reporting purposes. This will occur once all final clinical data have been entered into the database and all data queries have been resolved, and the assignment of subjects to the analysis sets has been completed.

5.6 Drug Accountability

The Investigator is responsible for maintaining accurate study drug accountability records throughout the study.

The Investigator is responsible for returning all unused or partially used study drug to the Sponsor and must verify that all unused or partially used drug supplies have been returned by the subject and that no remaining supplies are in the Investigator's possession.

5.7 Compliance

Dosing will take place at the study center. The dose and schedule of study drugs administered to each subject will be recorded on the appropriate form. The administration of KM-819 (or placebo) will be supervised by the Investigator or a medically qualified staff member to ensure treatment compliance. After medication intake, the subject's hands and mouth will be inspected to ensure that the tablets have been swallowed completely. Treatment compliance should be monitored closely and any deviation in compliance should be reported to the Sponsor.

5.8 Previous and Concomitant Medications

Any medication that the subject takes other than the study drug, including herbal and other non-traditional remedies, is considered a concomitant medication. All concomitant medications must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

At Screening, subjects will be asked what medications they have taken during the last 3 months. At each subsequent study visit, subjects will be asked what concomitant medications they are currently taking.

In all study cohorts, no concomitant medications will be allowed, with the exception of acetaminophen (up to 2000 mg/day) (as per Exclusion Criteria 11).

5.9 Restrictions during the Study

- Alcohol use is prohibited from 48 hours prior to check-in and throughout the duration of the study.
- Caffeine-containing products (coffee, tea, chocolate) are prohibited from 48 hours prior to check-in and throughout the duration of the study (except for ambulatory period before Follow-up Visit).
- Grapefruit, Seville oranges, star fruit, or any products containing these items are prohibited within 48 hours days prior to dosing and throughout the duration of the study.

- Subjects will not be allowed to consume food or drinks, which may interact with circulatory, gastrointestinal, liver or renal function (e.g. alcohol, caffeine, or caffeine containing products, or grapefruit juice) throughout the duration of the study. Subjects will be served normal balanced caloric drinks and meals at standardized times during their stay in the study center. Total daily caloric intake will preferably not exceed normal daily limits (2500 kcal).
- Smoking and other nicotine-containing products are prohibited within 6 months prior to Screening and throughout the duration of the study.
- Strenuous activity is prohibited from 48 hours prior to check-in until discharge. After discharge, mild physical activity can be resumed, but strenuous physical activity is prohibited until the Follow-up Visit.
- Blood donation is prohibited throughout the duration of the study.

6 VARIABLES AND METHODS OF ASSESSMENT

6.1 Pharmacokinetics and Pharmacodynamics Assessment

6.1.1 Pharmacokinetics Assessment

Plasma and CSF samples for PK analysis of KM-819 will occur at the time points relative to dosing described on Table 7-1 and Table 7-2.

The actual date and time of PK blood and CSF samples collection will be captured in the eCRFs. Blood and CSF collection, handling, storage, and shipping details will be addressed in the Laboratory Manual.

6.1.2 Pharmacodynamic Assessment

Scales (Bond and Lader VAS, POMS, and K-WAIS-IV) and C-SSRS will be evaluated at the time points described on Table 7-1 and Table 7-2.

CSF and plasma samples for MAD PD analysis will occur at the time points described on Table 7-1 and Table 7-2.

6.2 Pharmacokinetic Variables

6.2.1 KM-819 Pharmacokinetic Blood Sampling

Blood (approximately 6 mL) will be taken by venipuncture or cannulation of a forearm vein(s) and collected into anticoagulant EDTA K2 tubes. Blood will be processed for plasma by centrifuging at 4°C, 3000 rpm for 10 min. The obtained plasma will be transferred into 3 polypropylene tubes (1.5 mL) with a volume of 0.8 mL, respectively. The tubes will be immediately stored at -70°C freezer. Two aliquots of plasma samples will be transferred to Bioinfra Co., Ltd and be analyzed by a validated method for the concentration of KM-819 (Parts A and B); one aliquot will be stored in study center as a back-up until completion of the clinical study report (CSR).

The PK parameters listed in Section 3.2.2 will be calculated from the plasma concentration-actual time profiles. The non-compartmental analysis will be performed using Phoenix® WinNonlin® Software Version 6.3 or higher (Certara, L.P., 9666 Olive Blvd, Suite 425, St. Louis MO 63132).

The total volume of PK blood drawn from each subject will be approximately 72 mL in Part A SAD and 144 mL in Part B MAD.

6.2.2 KM-819 Urine Sampling

Urine samples for possible analysis of KM-819 and qualitative analysis of any metabolites will be collected at intervals relative to study drug dosing as detailed in the Schedule of Procedures (Table 7-1 and Table 7-2). Within 60 minutes prior to dosing on Day 1, each subject will be instructed to void their bladder and no more than 20 mL of this urine sample will be retained as a control. Urine collection will begin immediately following dose administration. A 0 to 24 hour urine collection will be made for each subject and the volume will be recorded. After sampling, urine samples will be transferred into 3 polypropylene tubes (1.5 mL) with a volume of 1 mL, respectively. The tubes will be immediately stored at -70°C freezer.

At the completion of Part A, the urine sample collections obtained from the highest single dose cohort from Part A will be shipped to the analytical site and analysed for KM-819 metabolites. Two aliquots of urine samples will be transferred to Bioinfra Co., Ltd and 1 aliquot will be stored in study center as a back-up until completion of the CSR. Results will be reported under a separate protocol, if metabolite profiling was completed. All other urine samples from earlier periods will be defrosted and discarded by the Clinical Research Unit.

6.2.3 KM-819 Pharmacokinetic CSF Sampling

CSF (approximately 2 mL) will be taken by lumbar puncture between the 3rd and 4th lumbar vertebrae. CSF samples will be transferred into 3 polypropylene tubes (1.5 mL) with a volume of 0.5 mL, respectively. The tubes will be immediately stored at -70°C freezer. Two aliquots of CSF samples will be transferred to Bioinfra Co., Ltd and be analyzed by a validated method for the concentration of KM-819 (Part B only); one aliquot will be stored in study center as a back-up until completion of the CSR.

6.3 Pharmacodynamic Variables

6.3.1 Scales

6.3.1.1 Bond and Lader VAS

The Bond-Lader VAS will be used to rate subjects' feelings in terms of 16 dimensions. The dimensions will be presented as 100 mm lines, the 2 extremes of the emotion (i.e., 'alert' and 'drowsy') written at each end, and subjects will be asked to record their current state on each line.

The Bond-Lader VAS will be analyzed using 3 factor scores: alertness, contentedness, and calmness. Calculation of these 3 scores is based on the main factors resulting from statistical factor analysis. A high score indicates impairment.

1. Alertness (9 subscales): [Q1 + Q3 + (100 – Q4) + Q5 + (100 – Q6) + (100 – Q9) + Q11 + (100 – Q12) + Q15] / 9
2. Contentedness (5 subscales): [Q7 + (100 – Q8) + Q13 + (100 – Q14) + (100 – Q16)] / 5
3. Calmness (2 subscales): [Q2 + (100 – Q10)] / 2

Ratings will be performed at the time points detailed in Schedule of Procedures (Table 7-1 and Table 7-2).

6.3.1.2 Profile of Mood States

POMS will be used to describe subjects' feelings with a questionnaire containing 65 words/statements. Feelings will be scored using different statement: "Not at All", "A Little", "Moderately", "Quite a lot", and "Extremely".

Assessments will be performed at the time points detailed in Schedule of Procedures (Table 7-1 and Table 7-2).

6.3.1.3 Korean Wechsler Adult Intelligence Scale-IV

The K-WAIS-IV consists of an assessment of the cognitive ability using a core battery of 10 unique subtests (Block Design, Similarities, Digit Span, Matrix Reasoning, Vocabulary, Arithmetic, Symbol Search, Visual Puzzles, Information, and Coding) that focus on four specific

domains of intelligence: verbal comprehension, perceptual reasoning, working memory, and processing speed.

Only the Coding subtest will be assessed at the time points detailed in Schedule of Procedures (Table 7-1 and Table 7-2).

6.3.2 Columbia Suicide Severity Rating Scale

The C-SSRS is a scale that captures the occurrence, severity and frequency of suicide-related thoughts and behaviors during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. The C-SSRS must be administered by appropriately trained site personnel. The C-SSRS will be administered at the times specified in Schedule of Procedures (Table 7-1 and Table 7-2).

6.3.3 KM-819 Pharmacodynamic Blood Sampling

Blood (approximately 3 mL) will be taken by venipuncture or cannulation of a forearm vein(s) and collected into appropriate collection tubes (only on Part B). The PD parameters listed in Section 3.2.2 will be calculated.

The total volume of PD blood drawn from each subject will be approximately 6 mL.

6.3.4 KM-819 Pharmacodynamic CSF Sampling

CSF (approximately 1.5 mL) will be taken by lumbar puncture between the 3rd and 4th lumbar vertebrae (only on Part B). The PD parameters listed in Section 3.2.2 will be calculated.

6.4 Safety Variables

6.4.1 Adverse Events

6.4.1.1 Collection of Adverse Events

It is responsibility of the Investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questionings e.g., "How have you felt since I last saw you?"

6.4.1.2 Definitions

An AE is any untoward medical-occurrence that occurs in a subject or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

All AEs, including intercurrent illnesses, occurring during the study will be documented in the eCRF. Concomitant illnesses, which existed before entry into the study, will not be considered AEs unless they worsen during the treatment period. All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, reported by subject), must be documented.

Pre-existing conditions will be recorded in the eCRF on the medical history or appropriate page.

A TEAE will be defined as an AE that begins or that worsens in severity after at least one dose of study drug has been administered.

6.4.1.3 Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to the following categories.

6.4.1.3.1 Seriousness

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;
  This means that the subject is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

6.4.1.3.2 Intensity

The intensity of each AE must be assessed by the Investigator using one of the following categories, and recorded in the eCRF:

- Mild: The AE was transient and easily tolerated by the subject.
- Moderate: The AE caused discomfort and interferes with the subject's general condition.
- Severe: The AE caused considerable interference with the subject's general condition and may have been incapacitating.

6.4.1.3.3 Causality

The Investigator will assess the causality / relationship between the study drug and the AE and record that assessment in the eCRF.

The most likely cause of an SAE (e.g., disease under treatment, concomitant disease, concomitant medication, other) will be indicated on eCRF with details of the concomitant disease or medication or other cause.

The causal relationship of the AE to study drug will be described as one of the following terms:

Table 6-1: Causal Relationship of Adverse Event to Study Drug

Causal relationship	Description
Definite	A clinical event with a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. Response to withdrawal plausible (pharmacologically, pathologically), Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon), Rechallenge satisfactory, if necessary.
Probable	A clinical event with a reasonable time relationship to drug administration is unlikely to be attributed to concurrent disease or other drugs or chemicals. Response to withdrawal clinically reasonable (Rechallenge not required).
Possible	A clinical event with a reasonable time relationship to drug administration, but which could also be explained by concurrent disease or other drugs or chemicals.
Unlikely	A clinical event whose time relationship to drug administration makes a causal connection improbable, which could be plausibly explained by underlying disease or other drugs or chemicals.
Not related	A clinical event with no time relationship to drug administration, or with no causal relationship to drug administration (e.g., definitely induced by the clinical conditions of the subject or by the test procedures/requirements or by external events which are not associated with study treatments).
Unassessable	A clinical event with insufficient or contradictory information to permit assessment and identification of the cause.

The causal relationship of definite, probable, possible and unassessable will be considered as related to study drug.

6.4.1.3.4 Adverse Events of Interest

An adverse event of interest (AEI) is an event which, in the evaluation of safety, has a special focus. An AEI is an AE (SAE or non-serious AE) which fulfils below defined AEI criteria:

- Potential Hy's law cases

  Potential Hy's law, defined as ≥ 3 x ULN ALT with co-existing ≥ 2 x ULN bilirubin in the absence of ≥ 2 xULN ALP, with no alternative explanation for the biochemical abnormality, must always be reported as an AE of interest (i.e., without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

AEI should be reported to the Sponsor/PAREXEL immediately (within 24 hours of the site being aware of the event).

6.4.1.4 Recording Adverse Events

AE reporting will extend from signing of informed consent until completion of Follow-up Visit. AEs occurring after the end of the study should be reported to the Sponsor by the Investigator if the Investigator considers there is a causal relationship with the study drug.

All AEs, regardless of the relationship to study drug, will be recorded in the eCRF.

All AE reports should contain a brief description of the event, date and time of onset, date and time of resolution, intensity, treatment required, relationship to study drug, action taken with the study drug, outcome, and whether the event is classified as serious.

6.4.1.5 Reporting Serious Adverse Events

All SAEs that occur during the period of observation, and all SAEs occurring up to 30 days after receiving the last dose of study drug, whether considered to be associated with the study drug or not, must be reported within 24 hours by telephone, fax, or eCRF to the PAREXEL Safety Contact using the numbers in the List of Study Personnel.

SAEs occurring after the end of the study should be reported to the Sponsor/PAREXEL by the Investigator if the Investigator considers there is a causal relationship with the study drug.

The minimum information required for an initial report is:

- Name of person sending the report (i.e., name, address of Investigator);
- Subject identification (screening/randomization number, initials, NOT subject name);
- Protocol number;
- Description of SAE;
- Causality assessment, if possible.

However, as far as possible all points on the SAE form should be covered in the initial report, or the completed SAE form itself must be faxed to the PAREXEL Safety Contact. The original SAE form must then be sent by mail to the PAREXEL Safety Contact. In addition, the event must be documented in the EDC system.

In case the PAREXEL Safety Contact cannot be contacted (e.g., out of normal working hours or at weekends), an automated reporting service is available. The required information should be faxed and a message should be left on the voicemail service (for phone/fax numbers see the numbers in the List of Study Personnel).

After receipt of the initial report, the safety center will review the information and, if necessary, contact the Investigator, to obtain further information for assessment of the event. PAREXEL will be responsible for all information processing and reporting according to local legal requirements. Where necessary, Investigators will inform Regulatory Authorities in their own countries.

PAREXEL International
Toll free SAE fax number: 00308-13-2766 (24-hour service)
SAE hotline: +65-62218582
Email: Medical_Singapore@parexel.com

6.4.1.6 Follow-up of Adverse Events

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the PI, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until the subject has died.

6.4.1.7 Suspected Unexpected Serious Adverse Reactions

Any AE that is serious, associated with the use of the study drug, and unexpected (SUSAR) has additional reporting requirements, as described below.

- If the SUSAR is fatal or life-threatening, associated with the use of the study drug, and unexpected, Regulatory Authorities and IECs/IRBs will be notified within 7 calendar days after the Sponsor learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total).
- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with the use of the study drug, and unexpected, Regulatory Authorities and IECs/IRBs will be notified within 15 calendar days after the Sponsor learns of the event.

The Sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of subjects. Follow-up information may be submitted if necessary.

The Sponsor will also provide annual safety updates to the Regulatory Authorities and IECs/IRBs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

6.4.1.8 Pregnancy

If a female partner of a male study subject who has been exposed to the study drug becomes pregnant, the pregnancy and outcome of pregnancy should be monitored.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

All pregnancies in female partners of male subjects must be reported by the Investigator to PAREXEL/Sponsor on the initial pregnancy report form within 30 days after becoming aware of the pregnancy. The Investigator must follow-up and document the course and the outcome of all pregnancies even if the study has finished.

All outcomes of pregnancy must be reported by the Investigator to PAREXEL/Sponsor on the pregnancy outcome report form within 30 days after he or she has gained knowledge of the normal delivery or elective abortion.

6.4.2 Laboratory Variables

Laboratory assessments will be performed locally at study center's laboratory by means of their established and validated methods. Before starting the study, the Investigator will supply PAREXEL/Kainos with a list of the normal ranges and units of measurement.

The Investigator may decide to repeat the tests, should the results be outside normal ranges and considered clinically relevant, or if the original sample could not be analyzed.

The following laboratory variables will be determined in accordance with the Schedule of Procedures (Table 7-1 and Table 7-2):

Table 6-2: Laboratory Assessments

Test Group	Analyte/Component	Test Group	Analyte/Component
Hematology:	erythrocytes mean corpuscular volume (MCV) mean corpuscular hemoglobin (MCH) neutrophils eosinophils basophils lymphocytes monocytes platelets leukocytes hemoglobin hematocrit	Urinalysis:	pH protein glucose ketone bilirubin blood nitrite
Clinical chemistry:	albumin creatinine glucose urea uric acid total bilirubin (TBIL) direct bilirubin total protein triglycerides (TG) total cholesterol low-density lipoprotein (LDL) cholesterol high-density lipoprotein (HDL) cholesterol	Liver enzymes:	alkaline phosphatase (ALP) aspartate aminotransferase (AST) alanine aminotransferase (ALT)gamma-glutamyl transpeptidase (GGT)
Electrolytes:	sodium potassium calcium chloride	Serological marker:	Hepatitis B surface antigen (HbsAg) Anti-Hepatitis A Virus Immunoglobulin M (HAV IgM) Anti-Hepatitis C Virus (HCV Ab) Anti-Human immunodeficiency virus (HIV Ab)

Test Group	Analyte/Component	Test Group	Analyte/Component
Urine drug and cotinine screening, alcohol breath test	Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Opiates Cotinine Alcohol		

Clinical significance of out-of-range laboratory findings is to be determined and documented by the Investigator/sub-Investigator who is a qualified physician. Clinically relevant changes will be recorded as AEs in the eCRF (see Section 6.4.1.2).

For safety laboratory tests, the total volume of blood drawn will be approximately 51 mL for subject in Part A SAD and approximately 51 mL for subject in Part B MAD. Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

6.4.3 Vital Signs

The following vital signs will be assessed in accordance with the Schedule of Procedures (Table 7-1 and Table 7-2):

- BP, supine (systolic and diastolic; mmHg)
- Pulse, supine (beats per minute)
- Body temperature (°C) (tympanic)

BP and pulse will be measured using the normal practice at study center; after the subject has been in a supine position for at least 5 minutes.

If the subject experiences any changes during the visits which fulfill the criteria of an AE it must be recorded as such (see Section 6.4.1).

6.4.4 Electrocardiograms

Standard 12-lead ECGs will be performed in accordance with the Schedule of Procedures (Table 7-1 and Table 7-2).

ECG will be performed using an internationally recognized 12-lead cardiograph (10 sec. rhythm strip) after the subject has been resting in a supine position for 5 minutes. All records will be done in triplicate within 5 minutes, with at least a 1-minute interval. ECG printouts will include: date, time, at least 2-3 complexes for 12 leads data, HR, QRS duration, P-R interval, R-R interval, QT interval, and QTcF (QT interval corrected for HR according to Fridericia).

- $QTcF=QT \times R\text{-}R^{1/3}$

ECG recording will be performed according to the relevant site SOP. The review of the ECG must be done by the Investigator or delegate. The interpretation of the ECG result must follow the categories: “normal”, “abnormal, not clinically significant”, or “abnormal, clinically significant”. Clinically significant findings must be recorded as AEs, or if present at Screening, it should be documented as concomitant illness (see Section 6.4.1).

6.4.5 Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Procedures (Table 7-1 and Table 7-2).

The examinations will include:

- General appearance
- Head, ears, eyes, nose, throat, neck
- Lymph node palpation
- Abdomen
- Skin
- Extremities
- Respiratory system
- Cardiovascular system
- Gastrointestinal system
- Musculoskeletal system
- Central and peripheral nervous system

If the subject experiences any changes during the visits which fulfill the criteria of an AE it must be recorded as such (see Section 6.4.1).

6.5 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be assessed at Screening (Visit 1).

6.5.1 Subject Demography

The following demography information will be collected at Visit 1:

- age
- sex
- race

6.5.2 Body Measurements

The following body measurements will be performed at Visit 1:

- Body weight (kg)
- Height (cm)
- BMI

6.5.3 Medical History

Thorough medical examination will be performed by interview and checking medical chart history at Screening (Visit 1); the medical and medication history of subjects should be investigated and recorded in detail.

The medical history will be obtained by interviewing the subject or by inspecting his/her medical records.

For coding of medical history, see Section 9.4.

6.5.4 Previous and Concomitant Medications

Previous and concomitant medication will be documented as described in Section 5.8.

7 STUDY CONDUCT

7.1 Schedule of Procedures

Table 7-1: Schedule of Assessments for Part A (SAD)

Assessments	Screening Period (V1)	Confinement Days (V2)				Outpatient Visit Day (V3-V4)		Follow-up Visit (V5)
	Day -28 to Day -2	-1	1[1]	2	3[2]	Day 4	Day 7	Day 14 (±1 day)
Informed Consent	X							
Randomization and Study Drug Administration[3]			X					
Inclusion/Exclusion Criteria	X	X[4]						
Demography	X							
Medical/Medication History	X							
Assessment of AEs	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Vital Signs[5]	X	X	X	X	X	X	X	X
12-lead ECG[6]	X	X	X	X			X	X
Physical Examination	X	X			X	X	X	X
Height, Weight, BMI[7]	X							
Serology[8]	X							
Drug/Alcohol/Cotinine Screen	X	X						
Safety laboratory: Hematology, Serum Chemistry, Urinalysis[9]	X	X		X			X	X
Blood Pharmacokinetic Sampling[10]			X	X	X	X		
Urine Sampling[11]			X	X				
Scales[12]		X	X	X	X	X		
C-SSRS[13]	X				X			

AE: adverse event; BMI: body mass index; BP: blood pressure; C-SSRS: Columbia Suicide Severity Rating Scale; K-WAIS-IV: Korean Wechsler Adult Intelligence Scale-IV; ECG: electrocardiogram; ED: Early Discontinuation; HCV: hepatitis C virus; HBsAg: hepatitis B surface antigen; HAV: hepatitis A virus; HIV: human immunodeficiency virus; VAS: Visual Analogue Scale; POMS: Profile of Mood States

1. On Day 1, any predose procedures should be performed within 2 hour before study drug administration.
2. Discharge assessments to be performed for ED are the Day 3 assessments supplemented with an ECG and safety labs, see Section 7.2.4.
3. Randomization occurs on Day 1 prior to dosing.
4. Confirmation of inclusion and exclusion criteria.
5. Vital signs include tympanic temperature, supine pulse and supine BP. Vital signs will be collected after the subject has been in a supine position for at least 5 minutes. On Day 1, vital signs will be measured at predose, and at 0.5, 1, 2, and 4 hour postdose.
6. 12-lead ECGs will be obtained in triplicate within 5 minutes, with at least a 1-minute interval. On Day 1, ECGs will be recorded at predose and at 1 hour postdose. ECGs should be performed prior to pharmacokinetic and safety laboratory blood draws.
7. Screening height and weight will be used for BMI calculation for assessment of eligibility.
8. Blood will be tested for HBsAg, anti-HAV IgM, anti-HCV Ab, and anti-HIV Ab.
9. All hematology and serum chemistry labs will be taken after fasting for a minimum of 8 hours.
10. Plasma samples for pharmacokinetics of KM-819 will be obtained on Day 1 predose (within 30 minutes prior

to study drug administration) and 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, and 72 hours postdose.

11. Urine samples will be taken at: Day 1 predose (within 1 hour before study drug administration) and from 0 to 24 hours postdose.
12. Bond and Lader VAS, POMS, and K-WAIS-IV will be performed on Day -1, Day 1 (predose) and at 3, 6, 12, 24, 48, and 72 hours postdose (± 30 minutes for each time point).
13. The version of the C-SSRS to be performed at Screening is the "Baseline-Screening for Phase 1," and the version of the C-SSRS to be performed on Day 3 (or at ED) is the "Since Last Visit".

Table 7-2: Schedule of Assessments for Part B (MAD)

Assessments	Screening Period (V1)	Confinement Days (V2)									Follow-up Visit (V3)
	Day -28 to Day -2	-1	1[1]	2	3	4	5	6	7	8[2]	Day 14 (±1 day)
Informed Consent	X										
Randomization and Study Drug Administration[3]			X	X	X	X	X	X	X		
Inclusion/Exclusion Criteria	X	X									
Demography	X										
Medical/Medication History	X										
Assessment of AEs	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[5]	X	X	X			X				X	X
Physical Examination	X	X								X	X
Height, Weight, BMI[6]	X										
Serology[7]	X										
Drug/Alcohol/Cotinine Screen	X	X									
Safety Laboratory: Hematology, Serum Chemistry, Urinalysis[8]	X	X		X		X				X	X
Spine X-ray examination[9]	X										
Blood Pharmacokinetic Sampling[10]			X	X	X	X	X	X	X	X	
CSF Pharmacokinetic Sampling[11]			X						X		
CSF Pharmacodynamic Sampling[12]			X						X		
Plasma Pharmacodynamic Sampling[13]			X						X		
Scales[14]		X	X	X					X	X	
C-SSRS[15]	X				X					X	

AE: adverse event; BMI: body mass index; BP: blood pressure; CSF: Cerebrospinal fluid; C-SSRS: Columbia Suicide Severity Rating Scale; K-WAIS-IV: Korean Wechsler Adult Intelligence Scale-IV; ECG: electrocardiogram; ED: Early Discontinuation; HCV: hepatitis C virus; HBsAg: hepatitis B surface antigen; HAV: hepatitis A virus; HIV: human immunodeficiency virus; VAS: Visual Analogue Scale; POMS: Profile of Mood States

1. On Day 1, any predose procedures should be performed within 2 hour before study drug administration.
2. Discharge assessments to be performed for ED.
3. Randomization occurs on Day 1 prior to dosing.
4. Vital signs include tympanic temperature, supine pulse, and supine BP. Vital signs will be collected after the subject has been in a supine position for at least 5 minutes. On Day 1 and Day 4, vital signs will be measured at predose and at 1 hour postdose; On Day 2, Day 3, Day 5, Day 6, and Day 7, vital signs will be measured at predose. Timing of vital signs measurements may be shifted and/or added based on the results of Part A.
5. 12-lead ECGs will be obtained in triplicate within 5 minutes, with at least a 1-minute interval. On Day 1 and Day 4, ECGs will be recorded at predose and at 1 hour postdose. ECGs should be performed prior to pharmacokinetic and safety laboratory blood draws.
6. Screening height and weight will be used for BMI calculation for assessment of eligibility.
7. Blood will be tested for HBsAg, anti-HAV IgM, anti-HCV Ab, and anti-HIV Ab.
8. All hematology and serum chemistry labs will be taken after fasting for a minimum of 8 hours.
9. Simple spine X-ray examination will only be conducted at Screening for healthy elderly cohort.
10. Plasma samples for pharmacokinetics of KM-819 will be obtained on Day 1 predose (within 30 minutes prior to study drug administration) and 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hours postdose, predose on Days 2, 3, 4, 5, 6,

and on Day 7 predose (within 30 minutes prior to study drug administration) and 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose.

11. CSF samples for pharmacokinetic of KM-819 will be obtained on Day 1 (at -120 minutes to 0 minute prior to the first dosing) and on Day 7 (at 1 hour after last dosing).
12. CSF samples for pharmacodynamic of KM-819 will be obtained on Day 1 (at -120 minutes to 0 minute prior to the first dosing) and on Day 7 (at 1 hour after last dosing).
13. Plasma samples for pharmacodynamic of KM-819 will be obtained on Day 1 (within 30 minutes prior to study drug administration) and on Day 7 (at 1 hour after last dosing).
14. Bond and Lader VAS, POMS, and K-WAIS-IV will be performed on Day -1, on Day 1 and Day 7 at predose, 3, 6, 12, and 24 hours postdose (± 30 minutes for each time point).
15. The version of the C-SSRS to be performed at Screening is the “Baseline-Screening for Phase 1,” and the version of the C-SSRS to be performed on Day 3 and Day 8 (or at ED) is the “Since Last Visit”.

Table 7-3: Pharmacokinetic Sampling Time points for Part A (SAD)

Visits	Nominal time		Remark
	Sampling time	Sampling windows	
Visit 2, Day 1	Predose	- 30 min	Baseline sample
			Study drug administration
	0.25 hour	+ 2 min	
	0.5 hour	± 3 min	
	1 hour	± 5 min	
	2 hour	± 10 min	
	4 hour	± 10 min	
	6 hour	± 10 min	
	8 hour	± 10 min	
	12 hour	± 15 min	
Visit 2, Day 2	24 hour	± 15 min	
Visit 2, Day 3	48 hour	± 60 min	
Visit 3, Day 4	72 hour	± 60 min	

Table 7-4: Pharmacokinetic Sampling Time points for Part B (MAD)

Visits	Nominal time		Remark
	Sampling time	Sample windows	
Visit 2, Day 1	Predose	- 30 min	Baseline sample
			First study drug administration
	0.25 hour	+ 2 min	
	0.5 hour	± 3 min	
	1 hour	± 5 min	
	2 hour	± 10 min	
	4 hour	± 10 min	
	6 hour	± 10 min	
	8 hour	± 10 min	
	12 hour	± 15 min	
Visit 2, Day 2	Predose	- 30 min	24 hour after first dose
Visit 2, Day 3	Predose	- 30 min	Trough sample
Visit 2, Day 4	Predose	- 30 min	Trough sample
Visit 2, Day 5	Predose	- 30 min	Trough sample
Visit 2, Day 6	Predose	- 30 min	Trough sample
Visit 2, Day 7	Predose	- 30 min	Predose sample
			Last study drug administration
	0.25 hour	+ 2 min	
	0.5 hour	± 3 min	
	1 hour	± 5 min	
	2 hour	± 10 min	
	4 hour	± 10 min	
	6 hour	± 10 min	
	8 hour	± 10 min	
	12 hour	± 15 min	
Visit 2, Day 8	24 hour	± 15 min	

7.2 Procedures by Visit

Visits should occur within visit windows (defined in Table 7-1 and Table 7-2) of the scheduled visits. All times should be recorded using the 24-hour clock (e.g., 23:20, not 11:20 pm).

7.2.1 Screening (Visit 1) for Part A and Part B

The subjects will receive verbal and written information about the study and the procedures involved before Screening. Before any study-related activities are performed, the subject must have given written informed consent to study participation.

The Screening Period may extend up to 27 days from the time the informed consent form (ICF) is signed. The subject may visit the site more than one time during this period.

The assessments to be performed at this visit are listed below:

- inclusion/exclusion criteria assessment
- demographic and medical/medication history data collection
- concomitant medication
- assessment of AE
- vital signs measurement and physical examination
- ECG assessment
- body measurements (weight, height, and BMI)
- hematology and biochemistry blood sampling
- serology blood sampling
- urinalysis sampling
- urine drug/cotinine tests
- alcohol breath test
- C-SSRS assessment
- spine X-ray examination (only for healthy elderly cohort in Part B)

7.2.2 Visits for Part A Single Ascending Dose

7.2.2.1 Confinement Visit (Visit 2)

Visit 2 for SAD will occur within 28 days after Screening.

On Day -1 (check-in), subjects will need to attend the study center, the following assessments will be performed:

- confirmation of inclusion/exclusion criteria
- concomitant medication
- assessment of AE
- vital signs measurement and physical examination
- ECG assessment
- hematology and biochemistry blood sampling
- urinalysis sampling

- urine drug/cotinine tests
- alcohol breath test
- scales assessment

All results necessary for evaluation of the inclusion and exclusion criteria must be available before determining whether or not the subject can continue in the study.

Once verified eligible to the study, the subjects will be required to stay in study center for 3 nights (confined from the evening of Day -1 to Day 3).

On Day 1, the procedures to be performed at predose are listed below:

- Randomization: eligible subjects will be randomized to receive either KM-819 or placebo
- vital signs measurement (predose)
- ECG assessment (predose)
- scales assessments (predose)
- Urine sampling within 1 hour before dosing
- PK blood sampling within 30 minutes before dosing

Study drug will be administered from 8:00 to 10:00.

The procedures to be performed at postdose are listed below:

- postdose PK blood sampling at 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hours (see Table 7-1)
- postdose vital signs measurements at 0.5, 1, 2, and 4 hours
- postdose ECG assessment at 1 hour
- postdose urine sampling from 0 to 24 hours
- postdose scales assessments at 3, 6, and 12 hours

The following assessments will also be performed during Day 1:

- concomitant medication
- assessment of AE

On Day 2 to Day 3, the procedures to be performed are listed below:

- concomitant medication
- assessment of AE
- vital signs measurement
- ECG assessment (only on Day 2)
- hematology and biochemistry blood sampling (only on Day 2)
- urinalysis sampling (only on Day 2)
- postdose PK blood sampling at 24 hour and 48 hours
- postdose scales assessments at 24 hours and 48 hours
- physical examination (only on Day 3)
- C-SSRS assessment (only on Day 3)

Subjects will be allowed to leave the study center after completing all the procedures on Day 3.

7.2.2.2 Outpatient Visits (Visit 3 to Visit 4)

Subjects will need to attend the study center on Day 4 for Visit 3 and on Day 7 for Visit 4. The following assessments will be performed on each visit:

- concomitant medication
- assessment of AE
- vital signs measurement and physical examination
- ECG assessment (only on Visit 4)
- hematology and biochemistry blood sampling (only on Visit 4)
- urinalysis sampling (only on Visit 4)
- postdose PK blood sampling at 72 hours (only on Visit 3)
- postdose scales assessments at 72 hours (only on Visit 3)

7.2.2.3 Follow-up Visit (Visit 5)

Subjects will need to attend the study center on Day 14 for Follow-up Visit (Visit 5). The following assessments will be performed:

- concomitant medication
- assessment of AE
- vital signs measurement and physical examination
- ECG assessment
- hematology and biochemistry blood sampling
- urinalysis sampling

7.2.3 Visits for Part B Multiple Ascending Dose

7.2.3.1 Confinement Visit (Visit 2)

Visit 2 for MAD will occur within 28 days after Screening.

On Day -1 (check-in), subjects will need to attend the study center, the following assessments will be performed:

- confirmation of inclusion/exclusion criteria
- concomitant medication
- assessment of AE
- vital signs measurement and physical examination
- ECG assessment
- hematology and biochemistry blood sampling
- urinalysis sampling
- urine drug/cotinine tests
- alcohol breath test

- scales assessment

All results necessary for evaluation of the inclusion and exclusion criteria must be available before determining whether or not the subject can continue in the study.

Once verified eligible to the study, the subjects will be required to stay in study center for 8 nights (confined from the evening of Day -1 to Day 8).

On Day 1, the procedures to be performed at predose are listed below:

- Randomization: eligible subjects will be randomized to receive either KM-819 or placebo
- vital signs measurement (predose)
- ECG assessment (predose)
- scales assessments (predose)
- CSF PK and PD sampling (at -120 minutes to 0 minutes before dosing)
- PK blood sampling within 30 minutes before dosing
- plasma PD sampling within 30 minutes before dosing

Study drug will be administered from 8:00 to 10:00.

The procedures to be performed at postdose are listed below:

- postdose PK blood sampling at 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hours (see Table 7-2)
- postdose vital signs measurements at 1 hour
- postdose ECG assessment at 1 hour
- postdose scales assessments at 3, 6, and 12 hours

The following assessments will also be performed during Day 1:

- concomitant medication
- assessment of AE

On Day 2 to Day 6, the procedures to be performed on each day are listed below:

- concomitant medication
- assessment of AE
- vital signs measurement (at predose and at 1 hour postdose on Day 4; at predose on Day 2, Day 3, Day 5, and Day 6)
- ECG assessment (at predose and at 1 hour postdose on Day 4)
- hematology and biochemistry blood sampling (only on Day 2 and Day 4)
- urinalysis sampling (only on Day 2 and Day 4)
- PK blood sampling within 30 minutes before each dosing
- study drug administration from 8:00 to 10:00
- scales assessments at 24 hours after first dosing (only on Day 2)
- C-SSRS assessment (only on Day 3)

On Day 7, the procedures to be performed before last dose are listed below:

- vital signs measurement (predose)

- scales assessments (predose)
- PK blood sampling within 30 minutes before dosing

Study drug will be administered from 8:00 to 10:00.

The procedures to be performed at postdose are listed below:

- postdose PK blood sampling at 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hours (see Table 7-2)
- Plasma PD sampling (at 1 hour postdose)
- CSF PK and PD sampling (at 1 hour postdose)
- postdose scales assessments at 3, 6, and 12 hours

The following assessments will be also performed during Day 7:

- concomitant medication
- assessment of AE

On Day 8, the procedures to be performed are listed below:

- concomitant medication
- assessment of AE
- vital signs measurement and physical examination
- ECG assessment
- hematology and biochemistry blood sampling
- urinalysis sampling
- PK blood sampling at 24 hour after last dosing
- scales assessments at 24 hours after last dosing
- C-SSRS assessment

Subjects will be allowed to leave the study center after completing all the procedures on Day 8.

7.2.3.2 Follow-up Visit (Visit 3)

Subjects will need to attend the study center on Day 14 for Follow-up Visit (Visit 3). The following assessments will be performed:

- concomitant medication
- assessment of AE
- vital signs measurement and physical examination
- ECG assessment
- hematology and biochemistry blood sampling
- urinalysis sampling

7.2.4 Early Termination Visit

Subjects who discontinue early from the study should, if possible, have an ED Visit. This visit should take place as soon as possible after the subject stops taking study drug/after it was learned that the subject will not be able to complete Follow-up. The observations and procedures scheduled for Day 3 (Part A, safety laboratory and ECG assessment also needed) or Day 8 (Part

B) should be performed at the ED Visit. For subjects who discontinue early from the study during out-patient period (i.e., after completion of hospitalization period), C-SSRS will not be done at ED visit. Scales (Bond and Lader VAS, POMS, and K-WAIS-IV) will not be assessed for all the early discontinued subjects.

8 STATISTICAL METHODS

All statistical analyses and programming of tables, figures, and listings will be performed by PAREXEL International Early Phase Biostatistics using the latest available version of SAS® (SAS Institute Inc., Cary, North Carolina, USA) version 9.2 or higher. Pharmacokinetic parameters will be calculated by a PK analyst and reviewed by a PK scientist from the PAREXEL Quantitative Clinical Development department, using Phoenix® WinNonlin® (Certara, L.P., 1699 S Hanley Road, St Louis MO 63144 USA) Version 6.2 (or higher).

Before database lock, a Statistical Analysis Plan (SAP) will be issued as a separate document, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses as mentioned in detail in the SAP will be described in a SAP Addendum and justified in the final integrated Clinical Study Report.

8.1 Study Subjects

8.1.1 Disposition of Subjects

The assignment of subjects to analysis populations will be listed and summarized by group for Parts A and B. The tabulation will include the following information: number of subjects dosed, number and percentage of subjects completing the study, number and percentage of subjects who were withdrawn (including reasons for withdrawal), number and percentage of subjects in each of the analysis populations. A listing of withdrawals from the study will be presented.

Disposition data will be presented using the safety population.

8.1.2 Protocol Deviations

Protocol deviations as recorded in the protocol deviations log by Project Management will be listed. Time window deviations as derived by Data Management will also be included in this listing.

8.1.3 Analysis Sets

Safety Analysis Set (SAF): The safety analysis set (SAF) will be the primary analysis set for all safety displays and consists of all subjects who received at least one dose.

Pharmacokinetic Analysis Set (PKAS): The pharmacokinetic analysis set (PKAS) will be the primary analysis set for all PK displays and analyses, consists of all subjects from the SAF for whom sufficient plasma concentration data are available to facilitate the calculation of at least one PK parameter, had no important protocol deviations affecting the PK variables, as confirmed during a pre-analysis review of the data prior to database lock.

Pharmacodynamic Analysis Set (PDAS): The pharmacodynamic analysis set (PDAS) consists of all subjects from the SAF for whom sufficient data for neuropsychologic testing (Parts A and B) or plasma and CSF concentration data are available

(Part B) to facilitate the calculation of at least 1 PD parameter, had no important protocol deviations affecting the PD analysis, as confirmed during a pre-analysis review of the data prior to database lock.

8.2 General Considerations

All statistical tests will be two-sided and will be performed at the 5% level of significance, unless otherwise stated.

Study Part A and Part B will be analyzed separately.

All original and derived parameters as well as demographic and disposition data will be listed and described using summary statistics. Frequency counts (number of subjects [n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, standard deviation [SD], median, minimum, maximum, geometric mean, and coefficient of variation [CV]) will be calculated for each quantitative variable (unless otherwise stated).

The following rules will apply to any repeated safety measurements (including measurements performed in triplicate):

- If the repeated measurement occurs prior to study drug administration (in each treatment period if applicable) then the last obtained value (or last obtained set of triplicate measurements) prior to dosing will be used in the descriptive statistics and in the calculation of changes from baseline (for results measured in triplicate the mean of the triplicates will be used in the calculation of changes from baseline).
- If the repeated measurement occurs after study drug administration (in each treatment period if applicable) then the first (non-missing) value of any repeated measurements (or first set of triplicate measurements) will be used in the descriptive statistics and in the calculation of changes from baseline (for results measured in triplicate the mean of the triplicates will be used in the calculation of changes from baseline).
- If not otherwise specified, baseline refers to the last scheduled measurement (or mean of the set of triplicate measurements) before study drug administration (using the rules described above for repeated measurements). Further details regarding handling of repeated triplicate measurements will be described in the SAP.

8.2.1 Missing Data

Missing dates/times in AE and concomitant medication data will be handled as described in the SAP. There will be no imputation schemes applied to missing PK and/or PD data. Values that are below the limit of quantification (BLQ) in the PK data will be handled as described in the SAP.

8.3 Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

Demographic and anthropometric information (height, weight, BMI, age, race) will be listed and summarized.

Medical history data will be listed by subject. All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Prior medications are defined as those taken from Screening until the time of the first study drug administration. Concomitant medications are defined as those taken at the time of or after the first study drug administration.

Prior and concomitant medication will be coded according to the latest available version of the World Health Organization's Drug Dictionary (WHO-DD) and the Anatomical Therapeutic Chemical (ATC) classification system. Prior and concomitant medication will be listed.

8.4 Treatment Compliance

Exposure to study drug will be listed by subject.

8.5 Efficacy Analyses

Efficacy will not be tested in this study.

8.5.1 Primary Efficacy Analysis

8.5.1.1 Hypothesis to be Tested

Not applicable

8.5.1.2 Statistical Methods

Not applicable

8.5.1.3 Subgroup Analyses

Not applicable

8.5.2 Secondary Efficacy Analyses

Not applicable

8.6 Safety Analyses

Safety data will be summarized by using descriptive statistics (n, mean, SD, minimum, median and maximum). Categorical data will be summarized using frequencies and percentages.

8.6.1 Adverse Events

All AEs will be coded according to MedDRA. All reported AEs will be included in the subject data listings. The following listings will be produced:

- All AEs
- All AEs leading to withdrawal
- SAEs

Treatment-emergent AEs will be summarized by System Organ Class (SOC) and preferred term. In addition, TEAEs will be summarized by intensity and causality. Only AEs with onset during the treatment period (i.e., TEAEs) will be included in summary tables.

8.6.2 Vital Signs and Electrocardiogram

Vital signs and ECG parameters will be listed by subject and time point including changes from baseline and repeat/unscheduled measurements. The baseline for each measurement will be the mean of the triplicate assessments obtained on Day -1. Descriptive statistics will be presented for both absolute values and changes from baseline. The mean of any triplicate assessments performed at a given time point will be used in all calculations of changes from baseline and in all tabulations. Further details will be provided in the SAP.

8.6.3 Safety Laboratory Parameters

Safety laboratory parameters (hematology and clinical chemistry) will be listed by subject and time point including changes from baseline and repeat/unscheduled measurements. The baseline for each of these measurements will be the assessment obtained on Day -1. All values outside the reference ranges will be flagged in the subject data listings. Descriptive statistics (for non-categorical data) will be presented for both absolute values and changes from baseline.

Urinalysis data will be listed by subject and time point including repeat/unscheduled measurements.

Serology and drugs-of-abuse (including alcohol and cotinine) assessments will be listed by subject and time point (where appropriate).

8.6.4 Other Analyses

Abnormal physical examination results will be listed by subject and time point. Listing of spinal X-ray will be provided (if appropriate).

8.7 Pharmacokinetic Analysis

Plasma and CSF KM-819 concentration data will be listed by subject including actual sampling times. Plasma and CSF KM-819 concentrations will be summarized by treatment (dose level) and nominal time point. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: n, arithmetic mean, SD, CV%, median, geometric mean, minimum, and maximum values.

Individual and mean plasma KM-819 concentration time curves on normal and semi-logarithmic scales will be provided. Overlay plots by treatment group will also be provided.

The KM-819 PK parameter data will be listed and summarized by treatment (dose level). Summary statistics will include n, arithmetic mean, SD, CV%, median, geometric mean, minimum, and maximum values.

Further details will be provided in the SAP.

8.7.1 Dose Proportionality (Part A)

Dose proportionality analysis will be performed as an exploratory analysis.

Dose proportionality for C_{max} and AUC_{inf} will be examined via the power model and will be summarized and reported graphically. The PK parameters and the dose will be logarithmically (ln) transformed prior to analysis.[8] An alpha level of 5% will be used.

The power model assumes that the PK parameters are log-normally distributed with equal variances (constant coefficient of variation for untransformed data). A linear model with ln (dose) as continuous independent variable will be estimated. Estimates of $\beta 0$ and $\beta 1$, their standard

errors, 95% Confidence Interval (CI) and the CV for β0 for each PK parameter will be reported. Dose proportionality plots of individual primary PK parameters will be displayed versus dose (log-log scale) along with the regression line and the 95% CI. Plots of dose-normalized parameters versus dose will also be provided.

Additionally, an analysis of variance (ANOVA) of the natural log-transformed dose-normalized PK parameters AUC_{inf}/dose and C_{max}/dose with log-transformed KM-819 dose as a covariate and subject as random effect, will be performed to estimate the slope of the effect of dose level on the PK parameter and its 95% CI.

Further details will be provided in the SAP.

8.8 Pharmacodynamic Analysis

Part A and Part B:

To evaluate the effect of KM-819, descriptive statistics for continuous and categorical variables will be used to summarize PD parameters: VAS, POMS, K-WAIS-IV, and C-SSRS.

Part B:

Descriptive statistics variables will be used to summarize PD parameters by dose group where appropriate. Modeling of PK/PD variables may be performed if considered necessary.

Further details will be provided in SAP.

8.9 Interim Analyses

No interim analysis is planned for this study.

8.10 Determination of Sample Size

The sample size of 8 subjects each cohort in both parts is standard in first-in-human study for dose escalation. The number of subjects planned for both parts of this study is considered sufficient to achieve the study objectives (safety, tolerability, PK, and PD).

9 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1 Data Quality Assurance

The Sponsor or Sponsor's designee will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct 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. All information recorded on the EDC system for this study must be consistent with the subjects' source documentation (i.e., medical records).

9.1.1 Database Management and Quality Control

Case report forms (CRFs) are provided for each subject in electronic format as eCRF. All data generated by the site personnel will be captured electronically at each study center using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the EDC system will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system.

9.2 Case Report Forms and Source Documentation

All data obtained during this study should be entered in the EDC system promptly. All source documents from which EDC entries are derived should be placed in the subject's medical records. Measurements for which source documents are usually available include laboratory assessments and ECG etc.

Data that will be entered directly into the EDC system (i.e., for which there is no prior written or electronic record of data, such as Quality of Life assessments) are considered to be source data.

The original EDC entries for each subject may be checked against source documents at the study site by the PAREXEL site monitor.

After review by the site monitor, completed EDC entries will be uploaded and forwarded to Kainos Medicine, Inc. and PAREXEL. Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

9.2.1 Data Collection

The Investigators (and appropriately authorized staff) will be given access to an online web‑based EDC) system which is 21 CFR Part 11 compliant. This system is specifically designed for

the collection of the clinical data in electronic format. Access and right to the EDC system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the Investigator and authorized staff will be able to enter data and make corrections in the eCRFs.

The eCRF should be completed for each subject included in the study and should reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or immediately after the subject's visit or assessment. The Investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the eCRF.

Computerized data-check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved online. All discrepancies will be solved online directly by the Investigator or by authorized staff. Off-line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the Investigator will be required to electronically sign off the clinical data

Data about all study drugs dispensed to the subject and any dosage changes will be tracked on the eCRF.

9.3 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare EDC entries and individual subject's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. EDC entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

Checking of the EDC entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, Regulatory Authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures PAREXEL and the Sponsor of the necessary support at all times.

9.4 Data Processing

All data will be entered by site personnel into the EDC system (See Section 9.2.1).

The data-review and data-handling document, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. Query/correction sheets for unresolved queries will be sent to the study monitors for resolution with the Investigator. The database will be updated on the basis of signed corrections.

Previous and concomitant medications will be coded using the World Health Organization (WHO) Drug Reference List (DRL), which employs the ATC classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

Previous and concomitant diseases as well as AEs will be coded with MedDRA.

The versions of the coding dictionaries will be provided in the Clinical Study Report.

9.5 Archiving Study Records

According to International Conference on Harmonization (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

9.6 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the GCP guidelines of the ICH, and of the Declaration of Helsinki (2013). The study also will be carried out in keeping with local legal requirements.

9.7 Informed Consent

Before each subject is admitted to the study, informed consent will be obtained from the subject (or his/her legally authorized representative) according to the regulatory and legal requirements of the participating country. This consent form must be dated and retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the EDC system.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB, and signed by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

9.8 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the subject benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

9.9 Duration of the Study

For an individual subject, the maximum duration of the study for each subject will be:

- Part A (SAD): up to 42 days (including up to 28 days for Screening, up to 7 days treatment and up to 7 days Follow-up).

- Part B (MAD): up to 42 days (including up to 28 days for Screening, up to 8 days treatment and up to 6 days Follow-up).

The study will close when all subjects have completed the Final Follow-up Visit.

9.10 Premature Termination of the Study

If the PI and the Sponsor becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study;
- Failure to enroll subjects at an acceptable rate;
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

9.11 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating subjects must be maintained. Subjects will be identified on EDC system and other documents submitted to PAREXEL by their subject number. Documents not to be submitted to PAREXEL that identify the subject (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

9.12 Other Ethical and Regulatory Issues (Optional)

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to all parties – Regulatory Authorities, Investigators, and IRB/IECs.

A significant safety issue is one that has a significant impact on the course of the clinical study or program (including the potential for suspension of the development program or amendments to protocols) or warrants immediate update of informed consent.

9.13 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him or her and the hospital, practice, or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for subjects participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

9.14 Publication Policy

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, Regulatory Authorities will be notified of the Investigator's name, address, qualifications and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance. Details are provided in a separate document.

10 REFERENCE LIST

1 World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, *the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002, Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004, and 59th WMA General Assembly, Seoul, South Korea, October 2008, 64rd WMA General Assembly, Fortaleza, Brazil, October 2013. JAMA 2013; 310(20):2191-2219.*

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4 Health Insurance Evaluation Committee, 2008

5 Betarbet R, Anderson LR, Gearing M, et al. Fas Associated Factor 1 and Parkinson's disease. *Neurobiol Dis.* 2008; 31(3): 309–315.

6 Sul JW, Park MY, Shin J, et al. Accumulation of the parkin substrate, FAF1, plays a key role in the dopaminergic neurodegeneration. *Hum Mol Genet*. 2013; 22(8):1558-1573.

7 Food and Drug Administration. Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, Jul 2005

8 Smith BP, Vandenhende FR, DeSante KA, et al. Confidence interval criteria for assessment of dose proportionality. *Pharm Res.* 2000; 17(10): 1278-1283.