STATISTICAL ANALYSIS PLAN

KMCP-819-K101

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

Version: Final 1.0

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REVISION HISTORY

Version	Version Date	Author	Summary of Changes Made
Final 1.0	14-Nov-2017	Sampath Kalluri	New Document

SIGNATURE PAGE - KAINOS MEDICINE, INC.

Declaration

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study, as presented in this document.

Jae Moon Lee	**Date (DD Mmm YY)**
VP	

SIGNATURE PAGE - PAREXEL

Declaration

The undersigned agree to the statistical analyses and procedures of this clinical study.

If this document has been signed electronically, signature(s) and date(s) are present at the end of the document:

Document prepared and approved by:

Sampath Kalluri **Date (DD Mmm YY)**

Senior Biostatistician

Document prepared and approved by:

Joseph Kim **Date (DD Mmm YY)**

QCD Senior Director

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ABBREVIATION AND ACRONYM LIST

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
$AUC_{(0\text{-}inf)}$	AUC from time zero extrapolated to infinity
AUClast	AUC from time zero to the last quantifiable concentration
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
Bpm	Beats per minute
CI	Confidence interval
CL/F	Apparent clearance following oral administration
CSF	Cerebrospinal Fluid
CSP	Clinical Study Protocol
CSSRS	Columbia Suicide Severity Rating Scale
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration in the dosing interval
CS	Clinically significant
C_{trough}	Concentration immediately prior to dosing
CV	Coefficient of variation
DBP	Diastolic blood pressure
ECG	Electrocardiogram
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IMP	Investigational Medicinal Product
K-WAIS-IV	Korean Wechsler Adult Intelligence Scale-IV
LLOQ	Lower limit of quantification

Abbreviation / Acronym	Definition / Expansion
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
NK	Not known
PD	Pharmacodynamic
PDAS	Pharmacodynamic analysis set
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
POMS	Profile of Mood States
R_{ac}	Accumulation ratio
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation or single dose
SE	Standard error of the mean
SOC	System Organ Class
$t_{½}$	Apparent terminal elimination half-life
t_{last}	Time of last quantifiable concentration
TEAE	Treatment-emergent adverse event
t_{max}	Time corresponding to occurrence of C_{max}
VAS	Visual Analogue Scale
V_z/F	Apparent volume of distribution during terminal phase
WHO-DD	World Health Organisation - Drug Dictionary
λ_z	Terminal elimination rate constant
$\%AUC_{ex}$	Percentage of $AUC_{(0\text{-inf})}$ obtained by extrapolation

STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP).

The analyses described are based on the final CSP 5.0, dated, 13/Feb/2017. The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in a SAP Addendum.

1. STUDY OBJECTIVES

1.1 Primary Objective

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

1.2 Secondary Objective

- 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.

2. STUDY DESIGN

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 Single Ascending Dose (SAD):

This part 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.

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 mg (1 x 10 mg tablet), 30 mg (2 x 10 mg tablet),, 100 mg (1 x 100 mg tablet),,

200 mg (2 x 100 mg tablet),, or 400 mg (4 x 100 mg tablet) 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 of CSP 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.

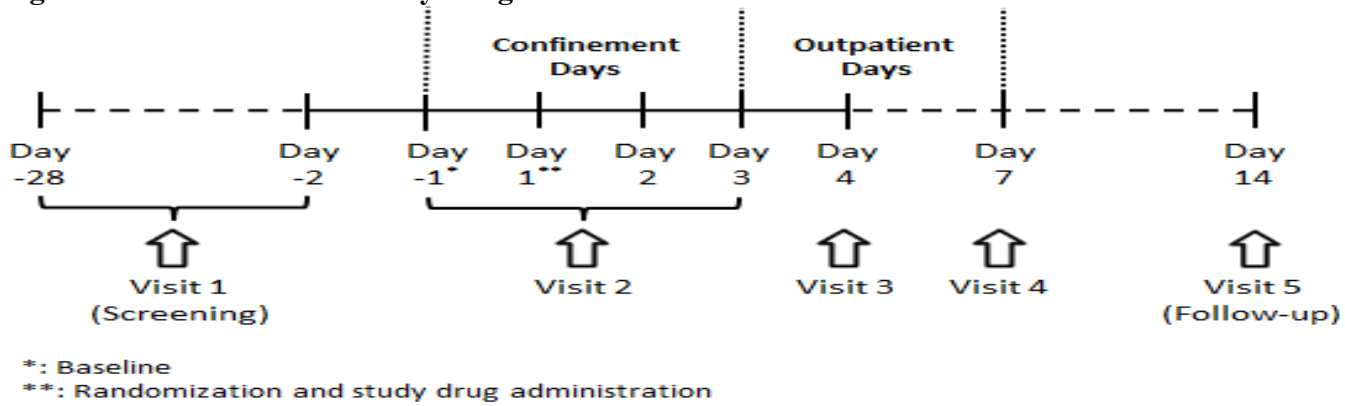
Table 1 Dose Groups for Part A

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.

Figure 1 Part A SAD study design



Part B, Multiple Ascending Dose (MAD):

This part 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.

It includes 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 mg (3 x 10 mg tablet), 100 mg (1 x 100 mg tablet), 200 mg (2 x 100 mg tablet), or 400 mg (4 x 100 mg tablet) 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 KM-819 at a dose level not exceeding the highest dose tested in the young adult male cohorts and 2 subjects will receive placebo. The dose level will be decided by Investigator and Sponsor.

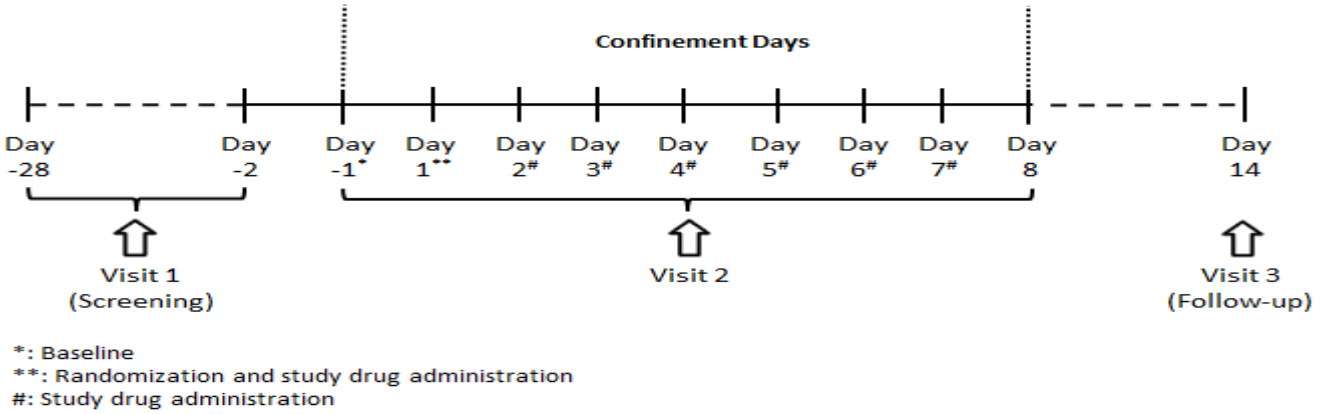
Table 2 Dose Groups for Part B

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.

Figure 3 Part B MAD study design



Criteria for Evaluation of the Study

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

- **Safety Endpoints**

  Parts A and B:

  1. Reporting AEs (nature, frequency, severity, time of onset/offset)
  2. Standard clinical laboratory evaluations
  3. Vital signs measurements (tympanic temperature, supine pulse, and supine BP)
  4. 12-lead ECGs

- **Pharmacokinetic Endpoints**

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

Single Dose, Day 1 of multiple doses:

1. AUC(0-24): area under the plasma concentration-time from predose (time 0) to 24hrs post dose
2. AUClast: area under the plasma concentration-time from predose (time 0) to the last quantifiable concentration
3. AUCinf: area under the plasma concentration-time curve from predose (time 0) extrapolated to infinity
4. AUCinf (%extrap): Percentage of AUCinf that is due to extrapolation beyond tlast (%AUCex)
5. CL/F: apparent oral clearance
6. Cmax: maximum plasma concentration determined directly from the concentration-time profile
7. λz: terminal elimination rate constant
8. $t_{1/2}$: apparent terminal elimination half-life
9. tlag: lag time
10. tmax: time to achieve maximum observed plasma concentration determined directly from the concentration-time profile
11. Vz/F: volume of distribution

12. Other parameters, as appropriate, including dose-adjusted parameters (AUC_D_obs, AUClast_D, Cmax_D).

Day 7 of multiple doses:

1. AUCtau: area under the plasma concentration-time curve for a dosing interval
2. AUClast: area under the plasma concentration-time from predose (time 0) to the last quantifiable concentration
3. CL/F: apparent oral clearance
4. Cmax: maximum plasma concentration determined directly from the concentration-time profile
5. Cmin: minimum plasma concentration determined directly from the concentration-time profile
6. Ctrough: observed plasma concentration before dosing
7. Rac (AUC): observed accumulation by AUC
8. Rac (Cmax): observed accumulation by Cmax
9. tlag: lag time
10. tmax: time to achieve maximum observed plasma concentration determined directly from the concentration-time profile
11. Vz/F: volume of distribution
12. Other parameters, as appropriate, including dose-adjusted parameters (AUCtau_D, AUClast_D, Cmax_D).

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

1. KM-819 concentration in CSF

- **Pharmacodynamic Endpoints**

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

1. Bond and Lader Visual Analogue Scale (VAS)

2. Profile of Mood States (POMS)
3. Korean Wechsler Adult Intelligence Scale-IV (K-WAIS-IV)
4. C-SSRS

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

1. alpha synuclein oligomer
2. total Tau
3. phospho-Tau
4. Ratio of CSF concentration/Plasma Cmax

3. STUDY POPULATION

The study population will consist of for Parts A up to 40 and for Part B up to 32 healthy young adult male (19 to 45 years old) or healthy elderly male or post-menopausal female (over 60 years old). subjects.

For further details of inclusion and exclusion criteria please refer to the sections 4.1 and 4.2 of the CSP.

4. STATISTICAL BASIS FOR SAMPLE SIZE

It is planned to recruit in total 72 healthy young adult subjects and 16 healthy elderly subjects at one center in 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.

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).

5. RANDOMIZATION

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.

For further details of randomization scheme please refer the section 4.5.2 and 4.5.3 of the CSP.

6. STATISTICAL ANALYSIS CONVENTIONS

6.1 Analysis Variables

6.1.1 Demographic and Background Variables

The following demography information will be collected at Visit 1:

- Date of informed consent
- Medical history (including previous and current medical conditions and medications)
- Age
- Sex
- Race
- Ethnicity

The following body measurements will be performed at Visit 1:

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

All medical history will be coded using Version **19.1** of the Medical Dictionary for Regulatory Activities (MedDRA).

6.1.2 Safety Variables

6.1.2.1 Adverse Events

An adverse event 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 will be coded using the latest available version **19.1** of the Medical Dictionary for Regulatory Activities (MedDRA).

A treatment-emergent adverse event (TEAE) is defined as an AE that begins or that worsens in severity after at least one dose of the study drug has been administered.

Any AEs with incomplete start and end dates/times will be treated as follows:

- Adverse events with unknown start and/or end times (but where the date is known) will be imputed with a time of 00:00 h for the tabulations but will be shown as NK:NK in the listings (where NK = Not Known).
- Adverse events with completely unknown start dates will be considered as treatment-emergent for the tabulations and will be shown as NK in the listings.

6.1.2.2 Clinical Laboratory Tests

The following safety laboratory parameters will be measured at the time points mentioned in the table of assessments in the CSP section 7.

- **Clinical chemistry:** albumin, creatinine, glucose, urea, uric acid, TBIL, total protein, triglycerides (TG), total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol.
- **Hematology:** erythrocytes, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), neutrophils, eosinophils, basophils, lymphocytes, monocytes, platelets, leukocytes, hemoglobin, and hematocrit.
- **Urinalysis:** pH, protein, glucose, ketone, bilirubin, blood, and nitrite.

- **Serological marker:** Hepatitis B surface antigen (HbsAg), Anti-Hepatitis A Virus Immunoglobulin M (HAV IgM), Anti-Hepatitis C Virus (HCV Ab) and Anti-Human immunodeficiency virus (HIV Ab).
- **Urine Drug and cotinine screening, alcohol breath test:** Amphetamines, Barbiturates, Benzodiazepines, Cannabinoids, Cocaine, Opiates, Cotinine, and Alcohol.
- **Electrolytes:** sodium, potassium, calcium, and chloride.
- **Liver enzymes:** alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT).

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 of CSP).

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.

6.1.2.3 Vital Signs

The following vital signs measurements will be obtained at the time points mentioned in the table of assessments in the CSP section 7 (Table 7-1 and Table 7-3).

- Blood Pressure (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.

6.1.2.4 Electrocardiograms

The following electrocardiogram (ECG) parameters will be recorded at the time points mentioned in the table of assessments in the CSP section 7 (Table 7-1 to Table 7-3).

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,

- Heart rate (HR) (beats per minute [bpm])
- QRS-duration (msec)
- PR (PQ)-interval (msec)
- RR-interval (msec)
- QT-interval (msec)
- QTcF (QT interval corrected for HR according to Fridericia) (msec)

  Where QTcF is calculated using $QTcF=QT \times R\text{-}R^{1/3}$

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 of CSP).

6.1.2.5 Physical Examination

The following physical examination parameters will be recorded at the time points mentioned in the table of assessments in the CSP section 7.

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 of CSP).

6.1.2.6 Concomitant Medication

Concomitant medication will be coded using the World Health Organization-Drug Dictionary (WHO-DD) (Version WHO-DD **March 2016**) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

Any medication that the subject takes other than the study drug, including herbal and other non-traditional remedies, is considered a concomitant medication. Prior concomitant 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.

Concomitant medication will be coded using the World Health Organization-Drug Dictionary (WHO-DD) (Version WHO-DD **March 2016**) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

6.1.3 Pharmacokinetic Variables

Unless otherwise stated, derivation of pharmacokinetic (PK) parameters will be the responsibility of Quantitative Clinical Development (QCD), PAREXEL International. The following PK parameters will be determined for KM-819 in plasma following single dose administration:

Table 1 Pharmacokinetic Parameters after Single Dose Administration (Part A)

Parameter	Definition
C_{max}	Maximum plasma concentration determined directly from the concentration-time profile
t_{max}	Time to achieve maximum observed plasma concentration determined directly from the concentration-time profile
$t_{½}$	Apparent terminal elimination half life
Tlag	Lag time
λ_z	Terminal elimination rate constant
AUClast	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(0-24)	Area under the plasma concentration-time from predose (time 0) to 24hrs postdose
%AUCex	Percentage of AUCinf that is due to extrapolation beyond tlast
CL/F*	Apparent oral clearance
V_z/F*	Apparent volume of distribution
AUCINF_D_obs	AUC_{inf} divided by dose
AUClast_D	AUClast divided by dose
Cmax_D	Maximum observed concentration divided by dose

*Parent drug only

This Table is applicable for Single ascending dose (Part A) and Day1 of Multiple ascending dose (Part B).

Table 2 Pharmacokinetic Parameters after Multiple Dose Administration

Parameter	Definition
C_{trough}	Observed concentration before dosing
C_{maxs}	Maximum plasma concentration determined directly from the concentration-time profile
C_{min}	Minimum plasma concentration determined directly from the concentration-time profile
t_{max}	Time to achieve maximum observed plasma concentration determined directly from the concentration-time profile
Tlag	Lag time
AUCtau	Area under the plasma concentration-time curve for a dosing interval
AUClast	Area under the plasma concentration-time from predose (time 0) to the last quantifiable concentration
CL/F*	Apparent oral clearance
V_z/F*	Apparent volume of distribution
$C_{av,ss}$	Average concentration at steady-state
R_{ac}(AUC)	Observed accumulation by AUC
Rac (Cmax)	Observed accumulation by Cmax
AUCtau_D	AUCtau divided by dose,
AUClast_D	AUClast divided by dose
Cmax_D	Maximum observed concentration divided by dose

*Parent drug only

This Table is applicable for Day7 of Multiple ascending dose (Part B).

All urine voided will be collected in the following intervals: pre-dose and 0-24 hours post-dose. Urine samples will be used for qualitative analysis of KM-819 and possible metabolic profiling, if appropriate, and will be reported separately. For cerebrospinal fluid (CSF) PK, the concentration of KM-819 will be listed and no other PK parameters will be calculated as there will be only one sample from each subject.

6.1.3.1 Pharmacokinetic Parameter Calculation Methods

PK parameters will be calculated by non-compartmental analysis methods from the concentration-time data using WinNonlin (WNL) Professional (Version 6.3 or higher) following these guidelines:

- Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters.
- There will be no imputation of missing data.
- Any subjects with more than one observed concentration data will be included in the PK analysis set provided that at least C_{max} and $AUC_{(0-t)}$ can be reliably calculated .
- If one or more non-quantifiable (NQ) values occur in a profile before the first measurable concentration, they will be assigned a value of zero concentration. If a single NQ value occurs between measurable concentrations in a profile, the NQ should generally be omitted (set to missing) in the derivation of pharmacokinetic parameters, statistical analysis, and the individual subject plots. If two or more NQ values occur in succession between measurable concentrations, the profile will be deemed to have terminated at the last measurable concentration prior to these NQs. For the purpose of individual subject plots, these NQs will be set to 0, and the subsequent measurable concentrations will be retained. For the derivation of pharmacokinetic parameters, these NQs and any subsequent measurable concentrations will be omitted (set to missing).
- PK parameters following single and repeat dose will be estimated according to the following guidelines:

- C_{max} will be obtained directly from the concentration-time data.
- t_{max} is the time at which C_{max} is observed.
- λ_Z will be estimated at terminal phase by linear regression after log-transformation of the concentrations:
  - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.

- A minimum number of three data points in the terminal phase will be used in calculating λ_z with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope) and including C_{last}.
- The duration of time over which λz is estimated should generally be at least twice the subsequently estimated terminal phase half-life (t ½); exceptions to this duration made at the discretions of the PK scientist
- The adjusted correlation coefficient (R^2 adjusted) in general should be greater than 0.90. Any value less than 0.90 may be used at the PK Scientist's best knowledge and judgment.
- An appropriate number of decimal places should be used for λ_z to enable the reported value of $t_{½}$ to be calculated.

- $t_{1/2}$ will be calculated as $\ln 2/\lambda_Z$.
- AUC is calculated as follows:
  - The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.
  - $AUC_{(0\text{-}t)} = \int_0^t C(t)dt$. (AUCtau for repeat dose)
  - $AUC_{(0\text{-}inf)} = \int_0^t C(t)dt + \int_t^\infty C(t)dt = AUC_{(0\text{-}t)} + C_t/\lambda_z$. (single dose only)
  - C_t is last observed quantifiable concentration.
- $\%AUC_{ex}$ will be calculated as $(1 - [AUC_{(0\text{-}t)}/AUC_{(0\text{-}inf)}]) \times 100$.
- CL/F will be calculated as dose/$AUC_{(0\text{-}inf)}$, parent drug only.
- V_z/F will be calculated as $CL/F/\lambda_Z$, parent drug only.

The following PK parameters will also be derived using SAS

(version 9.2) or WinNonlin (WNL) Professional (Version 6.3 or higher) as deemed appropriate.

- R_{ac} Accumulation ratio calculated as:
  C_{max} (last dose interval)/ C_{max} (first dose interval).
  $AUC_{(0\text{-}\tau)}$ (last dose interval)/ $AUC_{(0\text{-}\tau)}$ (first dose interval).

6.1.4 Pharmacodynamic Variables

The pharmacodynamic parameters will be recorded at the time points mentioned in the table of assessments in the CSP section 7.

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)

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

Profile of Mood States (POMS):

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".

Korean Wechsler Adult Intelligence Scale-IV (K-WAIS-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.

Columbia Suicide Severity Rating Scale (C-SSRS):

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

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

- alpha synuclein oligomer
- total Tau
- phospho-Tau and
- ratio of CSF concentration/Plasma Cmax

6.1.5 Efficacy Variables

Efficacy will not be tested in this study.

6.2 Analysis Populations

6.2.1 Safety Population

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.

6.2.2 Pharmacokinetic Population

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.

Data may/will be excluded (depending on the protocol and compound under study) from PK analysis (concentrations listed only) if any of the following criteria are fulfilled:

– Concomitant medication, which could render the plasma concentration-time profile unreliable

- The pre-dose concentration is greater than 5% of the corresponding C_{max} in any given treatment period (single dose cohort only).
- Subject vomits within 2 x the reported median Tmax for the analyte (oral studies only).
- Subject has moderate or severe diarrhea within 2 x the reported median t_{max} for the analyte (oral studies only).

Any data excluded will be discussed in the CSR. Subjects who receive placebo will not be part of the PK analysis set.

6.2.3 Pharmacodynamic Population

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.

6.3 Statistical Analysis Methods

6.3.1 Listings and Descriptive Statistics

All original and derived parameters as well as population characteristics 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 and maximum) will be calculated for each quantitative variable (unless otherwise stated). All listings will include repeated and unscheduled measurements.

Study Part A and Part B will be analyzed separately. For each part Tables, listings and figures will be generated separately.

The following rules will apply to any repeated measurements:

- 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).

All descriptive statistics will be presented by cohorts (dose). Subjects receiving placebo within each cohort will be presented as pooled treatment group.

All descriptive statistics will be presented by cohorts for measurements obtained during each treatment period. Descriptive statistics for all data obtained at Screening and follow-up will be presented.

6.3.2 Statistical Significance Level

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

6.3.3 Software

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.2 or later. The PK analysis will be performed using WinNonlin Professional Software Version 6.3.

6.3.4 Missing Data

Any AEs with unknown severity or causality will be considered as ‘severe’ and ‘related’ respectively, for the tabulations. The unknown severity or causality without imputation will be presented in listings.

AEs with missing dates/times will be handled as described below. The incomplete dates/times without imputation will be presented in listings.

Concomitant medications (CMs) with missing times will be handled as described below. The incomplete times without imputation will be presented in listings.

All other data will be analyzed and reported as observed. No imputation schemes for other missing values will be applied.

Handling of AEs with Missing Dates/Times

Any AEs with incomplete start and or end dates/times will be handled as described below for the classification as treatment-emergent, assignment to treatment periods and calculation of duration.

- Adverse events with unknown start times, but with start date known, will be imputed with a time of 00:00 hours, unless the start date corresponds to any given dosing date, in this case the start time will be imputed with the time of dosing. If this results in a start date/time after end date/time of the AE then the start time will also be imputed with 00:00 hours.
- Adverse events with completely unknown start dates will be imputed with the date and time of first IMP administration, unless the end date is known and prior to first administration of IMP, then the start date will be imputed as the date of screening and a time of 00:00 hours.
- Adverse events with completely unknown end times, will be imputed with an end time of 23:59 hours;
- Adverse events with completely unknown end dates will be imputed with the date of final FU (or date of discontinuation in the case of withdrawals).

Adverse events with partially known start dates will be treated as follows:

- If only the day is missing, then the day will be imputed with the first day of the month, unless the month and year in which the AE started is a month and year in which IMP was administered, then the day will be imputed with the first day on which IMP was administered in that month. If this results in a start date after end date then the day will be imputed with the first day of the month.
- If both the day and month is missing and the year is a year in which IMP was administered then the day and month will be imputed with the day and month of first IMP administration. If this results in a start date after end date then the day and month will be imputed with 01JAN. If the year is not a year in which IMP was administered then the day and month will also be imputed with 01JAN.
- If only the year is missing then the year will be imputed with the year of first IMP administration.

Adverse events with partially known end dates will be treated as follows:

- If only the day is missing, then the day will be imputed with the last day of the month, or date of final FU/early discontinuation if this is earlier.
- If the day and month is missing then the end date will be imputed as 31 December, or date of final FU/early discontinuation if this is earlier.

Handling of CMs with Missing Dates/Times

Any CMs with incomplete start and or end dates/times will be handled as described below for the classification as concomitant medication, assignment to treatment periods and calculation of duration.

- Concomitant medications with unknown start times, but with start date known, will be imputed with a time of 00:00 hours, unless the start date corresponds to any given dosing date, in this case the start time will be imputed with the time of dosing. If this results in a start date/time after end date/time of the CM then the start time will also be imputed with 00:00 hours.
- Concomitant medications with completely unknown start dates will be imputed with the date and time of first IMP administration, unless the end date is known and prior to first administration of IMP, then the start date will be imputed as the date of screening and a time of 00:00 hours.
- Concomitant medications with completely unknown end times will be imputed with an end time of 23:59 hours.
- Concomitant medications with completely unknown end dates will be imputed with the date of final FU (or date of discontinuation in the case of withdrawals).

Concomitant medications with partially known start dates will be treated as follows:

- If only the day is missing, then the day will be imputed with the first day of the month, unless the month and year in which the CM started is a month and year in which IMP was administered, then the day will be imputed with the first day on which IMP was administered in that month. If this results in a start date after end date then the day will be imputed with the first day of the month.

- If both the day and month is missing and the year is a year in which IMP was administered then the day and month will be imputed with the day and month of first IMP administration. If this results in a start date after end date then the day and month will be imputed with 01JAN. If the year is not a year in which IMP was administered then the day and month will also be imputed with 01JAN.
- If only the year is missing then the year will be imputed with the year of first IMP administration.

Concomitant medications with partially known end dates will be treated as follows:

- If only the day is missing, then the day will be imputed with the last day of the month, or date of final FU/early discontinuation if this is earlier.
- If the day and month is missing then the end date will be imputed as 31 December, or date of final FU/early discontinuation if this is earlier.

6.3.5 Interim Analysis

No formal interim analysis is planned.

6.3.6 Protocol Deviations

Major protocol deviations will be defined at the data review meeting (DRM). Subjects with major protocol deviations might be excluded from the Pharmacokinetic population.

All protocol deviations will be recorded by the Investigator and will be listed by subject with each study part, by cohort. All protocol deviations will be discussed between PAREXEL and the Sponsor during the data review meeting before database lock in order to determine whether these may warrant exclusion of a subject from the statistical analyses.

Protocol deviations will be presented using the safety population.

All protocol deviations will be listed [Listing 16.2.2.1 (Part A) and Listing 16.2.2.2 (Part B)] by study part and cohort will include, the subject number, actual study day (if applicable), visit, time point, date/time, and a description of the deviation and classification (major or minor).

Protocol deviations will be summarized [Table 14.1.3.1 (Part A) and Table 14.1.3.2 (Part B)] by treatment period for each study part for the subjects in the safety population.

Major protocol deviations will include the following:

- Deviation from the inclusion and exclusion criteria
- Deviation from study medication compliance in terms of medical conditions and/or AEs that may have interfered with drug absorption or with respect to factors likely to affect the primary endpoints
- Deviation from study procedure compliance; Non-compliance to study procedures or deviations from study procedures likely to affect the primary endpoints.

Time window deviations for PK blood sampling and safety or exploratory assessments will also be listed as protocol deviations. Tolerance windows for safety, PK blood sampling and exploratory assessments (when applicable) are provided in the final Windows Allowance Agreement (WAA).

6.3.7 Demographic Data

All demographic data will be listed and summarized using the safety population.

Demographic characteristics will be tabulated [Table 14.1.2.1 (Part A) and Table 14.1.2.2 (Part B)] within each study part, and by cohort (n, mean, standard deviation, minimum and maximum for age, height, weight and BMI; and frequency counts and percentages for sex, race and ethnicity).

Demographic characteristics will be listed [Listing 16.2.4.1.1 (Part A) and Listing 16.2.4.1.2 (Part B)] by subject within each study part, and by cohort and will include subject number, age (years), gender, race, ethnicity, height (cm), weight (kg) and BMI (kg/m^2).

Informed consent [Listing 16.2.1.2.1 (Part A) and Listing 16.2.1.2.2 (Part B)], study visits [Listing 16.2.1.3.1 (Part A) and Listing 16.2.1.3.1 (Part B)], Failed Inclusion and exclusion criteria will be listed [Listing 16.2.1.4.1 (Part A) Listing 16.2.1.4.2 (Part B)] and Assignment to Analysis Populations [Listing 16.2.3.1 (Part A) and Listing 16.2.3.2 (Part A)].

6.3.8 Subject Disposition

Subject disposition will be tabulated [Table 14.1.1.1 (Part A) and Table 14.1.1.2 (Part B)] within each study part, and by cohort including number and percentage of dosed, withdrawn and completed subjects and primary reason for discontinuation.

Subject disposition will be listed [16.2.1.1.1 (Part A) and Listing 16.2.1.1.2 (Part B)] within each study part, and by cohort and will include the following information: Subject Number, Primary Reason for Withdrawal, AE number, Date of Last Drug Administration, Date of Completion/Early termination, Date of Final Contact with subject, Subject status at the time of completion, Blind Broken (Yes/No), Date/Time of Blind and Reason Broken Blind.

Subject disposition will be summarized for each treatment and overall including the number of subjects randomised, number and percentage of subjects dosed, number and percentage of discontinued subjects and primary reason for discontinuation* [Table 14.1.1.1 (Part A) and Table 14.1.1.2 (Part B)]. This will be done for subjects in the safety population.

*The primary reason for discontinuation will be documented as one of the following:

- 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 CSSRS)
- Liver Safety monitoring
- After enrollment, the subject is found to violate the inclusion/or exclusion criteria
- Adverse event
- Subject lost to follow-up
- Major protocol violation
- Use of prohibited medications
- Any serious safety concern
- Premature termination of the study

- Death
- Other

6.3.9 Medical History

Medical history will be coded using Version 19.1 of the Medical Dictionary for Regulatory Activities (MedDRA).

Medical history will be summarized [Table 14.1.4.1 (Part A) and Table 14.1.4.2 (Part B)] by overall within study part by cohort using safety population.

Medical history will be listed [Listing 16.2.4.2.1 (Part A) and Listing 16.2.4.2.2 (Part B)] by study part, and will include subject Number, Medical History Number, Description of Disease/Procedure, MedDRA Preferred Term, MedDRA System Organ Class, Start Date/Study day, Stop Date, Status, Medication Taken, and Concomitant medication number.

6.3.10 Concomitant Medication

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.

Summary tables will be provided for prior medications and significant nondrug therapies significant nondrug therapies within each study part, and by cohort [Table 14.1.5.1 (Part A) and Table 14.1.5.2 (Part B)] for the safety population. Summary tables will be provided for concomitant medications and significant nondrug therapies within each study part, and by cohort [Table 14.1.6.1 (Part A) and Table 14.1.6.2 (Part B)] for the safety population.

Prior and concomitant medication will be listed [Listing 16.2.4.3.1 (Part A) and Listing 16.2.4.3.2 (Part B)] by subject within each study part, by cohort, and will include, at least, the following information: Product/s (study drug), medication/generic name (trade name), dose (and dose units), frequency, route of administration, start date/study day, end date/end date, duration, indication and origin (medical history or AE). Duration of concomitant medication will be calculated and included in the listing. The duration of prior or concomitant medications will be calculated based on the start and end dates. Duration of medication administration will not be calculated for concomitant medications with start date and/ or end date missed.

6.3.11 Exposure to the Investigational Medicinal Product

Exposure to study drug will be listed [Listing 16.2.5.1.1 (Part A) and Listing 16.2.5.1.2 (Part B)] by subject within each study part and will include: Subject Number, Time Point, Treatment Received, Date/Time of Administration, Dose (unit), Partial Dose Taken and Comments.

6.3.12 Pharmacokinetic Concentrations and Variables

The analysis of the PK data will be based on the Pharmacokinetic Population (see section 6.2.3).

Concentrations below the (LLOQ) will be indicated by BLQ in the listings.

Pharmacokinetic concentration data will be listed [Listing 16.2.6.1.1 (Part A) and Listing 16.2.6.1.2 (Part B)] by subject including actual sampling times relative to dosing. Plasma concentrations will be summarized [Table 14.2.1.1 (Part A) and Table 14.2.1.2 (Part B)] within each part, by cohorts and nominal time point The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: n, arithmetic mean, SD, 95% CI of Arithmetic mean, coefficient of variation (CV%), geometric mean, 95% CI of Geometric mean, geometric SD, SD on log scale (SD(log)), geometric CV% (calculated as: gCV% =SQRT(e^{s^2}-1)*100; where s is the standard deviation of the log-transformed values), median, minimum and maximum values.

Pharmacokinetic parameters will be listed [Listing 16.2.6.2.1 (Part A) and Listing 16.2.6.2.2 (Part B)] by subject and summarized [Table 14.2.2.1 (Part A) and Table 14.2.2.2 (Part B)] within each study part, and by cohorts, nominal timepoint. Descriptive statistics for calculated PK parameters will include: n, arithmetic mean, SD, 95% CI of Arithmetic mean, coefficient of variation (CV%), geometric mean, 95% CI of Geometric mean geometric SD, SD on log scale (SD (log)), geometric CV%. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

Individual plasma concentration versus actual times will be plotted by cohorts of SAD [Figure 14.2.1.1.1 (Part A) and Figure 14.2.1.2.1 (Part A)] and MAD [Figure 14.2.1.1.2 (Part B) and Figure 14.2.1.2.2 (Part B)] parts including elderly male or post-menopausal females cohort for KM-819 in linear and semi-logarithmic scale.

Arithmetic (+/-SD) mean and geometric mean plasma concentrations versus nominal times will also be presented in linear-linear scale of SAD [Figure 14.2.2.1.1 (Part A) and Figure 14.2.3.1.1 (Part A)], MAD [Figure 14.2.2.1.2 (Part B) and Figure 14.2.3.1.2 (Part B)] and young vs. elderly male or post-

menopausal females cohorts [Figure 14.2.2.2.1(Part A), Figure 14.2.2.2.2 (Part B) and Figure 14.2.3.2.1 (Part A), Figure 14.2.3.2.2 (Part B)]).

Median plasma concentrations versus nominal times will also be presented in linear-linear scale (single ascending dose [Figure 14.2.4.1.1 (Part A)], multiple ascending dose [Figure 14.2.4.1.2 (Part B)] and young vs. elderly male or post-menopausal females cohorts [Figure 14.2.4.2.1 (Part A) , Figure 14.2.4.2.2 (Part B)].

All Single dose cohorts will be overlaid on the same plot. Similar plots will be generated for multiple dosing and young vs. elderly male or and post-menopausal females cohorts.

Individual urine concentration for SAD will be presented by cohort and subject [Listing 16.2.6.4 (Part A)].

6.3.12.1 Presentation of PK Data, Descriptive Statistics and PK Assessment

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of concentration data:

- The individual concentrations will be reported to the same precision as the source data (for example, if the source data is presented to five significant digits, the individual values will be presented to five significant digits).
- The arithmetic mean, median, standard deviation (SD), geometric mean, geometric SD will be tabulated to one more significant digit compared to the source data, but with a maximum of four significant digits.
- Minimum and maximum values will be tabulated to the same precision as the source data, but with a maximum of four significant digits.
- 95% CI of Arithmetic mean and 95% CI of Geometric mean will be presented to two decimal places.
- Coefficient of variation (CV%) and geometric CV% will be presented to one decimal place.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of PK parameters:

- Individual PK parameters will be presented to four significant digits, with the exception of tmax, which will be presented to two decimal places. In addition, parameters directly derived from source data (e.g. Cmax,) shall be reported with the same precision as the source data (if this is not four significant digits).
- The arithmetic mean, median, standard deviation (SD), geometric mean, geometric SD will be reported to four significant digits, all other descriptive statistics will be reported to three significant digits except, coefficient of variation (CV%) and geometric CV% which will be presented to one decimal place.
- For tmax the minimum and maximum will be presented to two decimals places and the rest of the descriptive statistics to three decimal places.
- P-values will be presented to four decimal places.
- Estimates and confidence intervals (95% CI of Arithmetic mean and 95% CI of Geometric mean) in the form of percentages will be presented to two decimal places.
- Source data shall be used in all derived PK parameter calculations without prior rounding.

6.3.12.2 Handling of Values Below the Limit of Quantification (BLQ) in Concentration Summaries and Listings

Graphical presentation:

For graphs of arithmetic means all BLQ mean concentrations will be substituted by zeros. Graphs of geometric means include only time points with minimum concentration greater than zero. Any arithmetic mean that is BLQ will be excluded from log/linear presentation of arithmetic means. Any BLQ values prior to the last quantifiable concentration will be plotted at zero for individual linear/linear graphs and excluded from log/linear graphs. All BLQ values after the last quantifiable concentration will be excluded from individual linear/linear and log/linear graphs.

Handling of values below the limit of quantification (BLQ) in listings and for the calculation of descriptive statistics at each time point:

All concentrations below the limit of quantification (BLQ) or missing data will be labeled as such in the concentration data listings. Missing samples will be reported as no sample ("NS") and excluded from analysis. Values that are BLQ will be substituted with zero for the calculation of descriptive

statistics of concentration by time point and will be displayed as "not calculable" or NC for the calculation of statistical summaries.

6.3.12.3 Assessment of Dose Proportionality

For Part A, dose proportionality [Table 14.2.3.1 (Part A)] will be assessed for parameters C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ and for Part B [Table 14.2.3.2 (Part B)] for paramters AUC_{tau} and C_{max} on Day 1 and Day 7 using the pharmacokinetic population via the power model.

Individual concentration values will be used to perform a least-squares linear regression analysis, using the formula log_pkvar = β0 × log_dose + β1, where 'log_pkvar' represents the natural log transformed C_{max}, AUC_{last} or $AUC_{(0-inf)}$ and 'log_dose' represents the natural log transformed dose. An estimate of the slope of the regression line and corresponding 95% confidence interval (CI) will be obtained.

The following SAS code will be used:

```
PROC REG DATA=pkparam alpha=0.05;
        MODEL log_pkvar = log_dose / CLB;
RUN;
```

For each of the parameters C_{max}, AUClast, $AUC_{(0-inf)}$ of part A and C_{max}, AUC_{tau} of part B a plot of the log-transformed concentration against the log-transformed dose will be constructed including the fitted line from the linear regression and the line of unity.

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 [Figure 14.3.1.1 (Part A) and Figure 14.3.1.2 (Part B)]. Plots of dose-normalized parameters versus dose [Figure 14.3.2.1 (Part A) and Figure 14.3.2.2 (Part B)] will also be provided.

Additionally, an analysis of variance (ANOVA) [Table 14.2.4] of the natural log-transformed dose-normalized PK parameters AUCinf/dose and Cmax/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.

```
Proc Mixed Data = data;
        By parameter;
```

```
    Class Subject;
    Model log (pk Parameter) = log (dose)/ ddfm = kr outp=pred;
    Random subject;
    Estimate 'Mean Log Slope' lgdose 1 /cl alpha=0.05;
Run;
```

6.3.12.4 Time Invariance (Part B Only)

If data permits, the time invariance ratio will be calculated as the ratio of AUC(0-τ) on Day 7 to AUC(0-∞) on Day 1 (If have reliable AUC(0-∞) on Day 1) for each subject in each cohort. An ANOVA with terms for subject as a random effect and day as a fixed effect will be performed by dose on the loge-transformed AUC. Day will be treated as a class variable in the model. The time invariance of KM-819 will be assessed by calculating the ratio of the geometric least square means of AUC(0-τ) to AUC(0-∞) and the corresponding 90% CI for each dose. AUC(0-∞) on Day 1 will be considered as the reference phase in the analysis [Table 14.2.5].

An example of SAS code is included here.

```
ODS output solutionf=stat;
Proc Mixed;
   by dose;
   class subject day;
   model logAUC = day / ddfm=kr;
   random subject;
   lsmeans day;
   estimate 'test vs ref' day -1 1/cl alpha=0.1;
run;
```

The time invariance ratio will also be listed and summarized along with other PK parameters.

6.3.12.5 Steady State Assessment (Part B Only)

To evaluate whether steady state was achieved, statistical analysis of Cτ levels will be performed before Day 7, after a log-e transformation of the data from all active treatment doses. Only pre-dose concentration on days 1-7 for the 7 day analysis will be included in the analysis. A mixed effect model

will be fitted separately with day as a continuous covariate and subject as a random effect. The coefficient of the slope of the day effect on the log-e scale for each treatment dose will be used to assess whether steady state was achieved on Day 7. Using the estimate of variance, the 90% confidence intervals for the slopes will be calculated. If the 90% limits for the slope is including one then steady-state is statistically confirmed.[Table 14.2.6].

An example of SAS code to assess achievement of steady-state is included here.

```
ODS output solutionf=stat;
Proc Mixed;
   by dose;
   where (Day in (1,2,3,4,5,6,7));
   class subject;
   model logCtau = Day/cl alpha=0.1 solution;
   random intercept/subject=subject type=un;
run;
```

6.3.13 Pharmacodynamic Variables

The analysis of the pharmacodynamic (PD) data will be based on the pharmacodynamic population.

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) [Table 14.2.8.1 (Part A) and Table 14.2.8.2 (Part B)]
- Profile of Mood States (POMS) [Table 14.2.9.1 (Part A) and Table 14.2.9.2 (Part B)]
- Korean Wechsler Adult Intelligence Scale-IV (K-WAIS-IV) [Table 14.2.10.1 (Part A) and Table 14.2.10.2 (Part B)]
- C-SSRS

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

- alpha synuclein oligomer [Table 14.2.11]
- total Tau [Table 14.2.12]

- phospho-Tau [Table 14.2.13]
- Ratio of CSF concentration/Plasma Cmax. [Table 14.2.14]

For Part A and Part B, the PD parameters (Bond and Lader Visual Analogue Scale (VAS) [Listing 16.2.9.4.1 (Part A) and Listing 16.2.9.4.2 (Part B)], Profile of Mood States (POMS) [Listing 16.2.9.5.1 (Part A) and Listing 16.2.9.5.2 (Part B)], Korean Wechsler Adult Intelligence Scale-IV (K-WAIS-IV) [Listing 16.2.9.6.1 (Part A) and Listing 16.2.9.6.2 (Part B)], C-SSRS [Listing 16.2.9.7.1 (Part A) and Listing 16.2.9.7.2 (Part B)],

In Part B only, PD parameters in plasma and CSF including: alpha synuclein oligomer [Listing 16.2.9.8], total Tau [Listing 16.2.9.9], phospho-Tau [Listing 16.2.9.10], Ratio of CSF concentration/Plasma Cmax. [Listing 16.2.9.11]) will be listed within each study part and by cohort and time point and will include both absolute values and changes from baseline. Listing of CSF Concentration of KM-819 will be presented [Listing 16.2.6.3 (Part B)].

The baseline for each of Bond and Lader Visual Analogue Scale (VAS), Profile of Mood States (POMS), Korean Wechsler Adult Intelligence Scale-IV (K-WAIS-IV), alpha synuclein oligomer, total Tau and phospho-Tau parameters will be the Day 1.

Pharmacodynamic data will be summarized using descriptive statistics (n, mean, SD, minimum, median and maximum).

6.3.13.1 Statistical Analysis (Pharmcodynamic Analysis)

No formal statistical analysis is planned for the study.

6.3.14 Pharmacokinetic/Pharmacodynamic Analysis

No formal PK/PD statistical analysis will be performed for the study. Relationship between Pharmacokinetics and Pharmacodynamics parameters are assessed graphically.

PD parameters (Part A and Part B): Bond and Lader Visual Analogue Scale (VAS), Profile of Mood States (POMS) Korean Wechsler Adult Intelligence Scale-IV (K-WAIS-IV); Part B only: alpha synuclein oligomer, total Tau phospho-Tau) will be plotted vs PK parameters (AUCinf, AUClast and Cmax) [Figure 14.4.1.1 (Part A), Figure 14.4.1.2(Part B) , Figure 14.4.2.1 (Part A), Figure 14.4.2.2(Part B), Figure 14.4.3.1 (Part A), Figure 14.4.3.2(Part B), Figure 14.4.4 (Part B), Figure 14.4.5 (Part B), 14.4.6 (Part B)] with in each study part, by cohorts and nominal time point.

6.3.15 Safety Analysis

The analysis of the safety variables will be based on the safety population.

Safety will be assessed based on reported AEs, clinical laboratory assessments, vital signs measurements, 12-lead ECGs, and abnormal findings from physical examination.

Safety data will be summarized using descriptive statistics (n, mean, SD, minimum, median and maximum) will be reported within each study part and by cohort and time point and will include both absolute values and changes from baseline.

Categorical data will be summarized using frequencies and percentages will be reported within each study part, and by cohort.

6.3.15.1 Adverse Events

The following listings will be produced:

- All AEs. [Listing 16.2.7.1 (Part A) and Listing 16.2.7.2 (Part B)]:
- Withdrawals due to AEs [Listing 14.3.2.2.1 (Part A) and Listing 14.3.2.2.2 (Part B)]
- SAEs. [Listing 14.3.2.3.1 (Part A) and Listing 14.3.2.3.2 (Part B)]

A treatment-emergent AE (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.

The following information will be included in the AE listing [Listing 16.2.7.1 (Part A) and Listing 16.2.7.2 (Part B)]: Verbatim, MedDRA lower level term (LLT), preferred term (PT), system organ class (SOC), AE onset date (and time) and study day, AE end date (and time) and duration (days), Concomitant Medication Administered, Related to Medical history condition, relationship to IMP, AE outcome, severity, AE ongoing and SAE indicator flag.

A table of summary of Treatment Emergent Adverse Events [Table 14.3.1.1.1 (Part A) and Table 14.3.1.1.2 (Part B)]; A table of number and percentage of subjects with AEs summarized by SOC, PT [Table 14.3.1.2.1 (Part A) and Table 14.3.1.2.2 (Part B)]; SOC, PT and severity [Table 14.3.1.4.1 (Part A) and Table 14.3.1.4.2 (Part B)]; SOC, PT and maximum severity [Table 14.3.1.5.1 (Part A) and Table 14.3.1.5.2 (Part B)] will be presented for each study part and also the number (percentage) of subjects with AEs summarized by SOC, PT, and relationship [Table 14.3.1.3.1 (Part A) and Table

14.3.1.3.2 (Part B)] to IMP. In the case of multiple occurrences of the same AEs (at the same preferred term level) in an individual patient, the AE with the greatest severity will be reported.

Serious AE, if any occur, will be summarized.

6.3.15.2 Clinical Safety Laboratory Tests (hematology, biochemistry and urinalysis)

Laboratory values (hematology [Listing 16.2.8.2.1 (Part A) and Listing 16.2.8.2.2 (Part B)], biochemistry [Listing 16.2.8.1.1 (Part A) and Listing 16.2.8.1.2 (Part B)] and urinalysis [Listing 16.2.8.3.1 (Part A) and Listing 16.2.8.3.2 (Part B)]) will be listed for each study part by subject and study time point including changes from baseline (with the exception of urinalysis). The baseline for the laboratory values will be the results obtained on Day -1.

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings. The Investigator will assess whether the values outside the clinical reference range are clinically significant and these will be reported as abnormal not clinically significant (NCS) or abnormal clinically significant (CS). Clinically significant laboratory values will be recorded by the Investigator as AEs. Shift from baseline of laboratory finding for hematology and clinical chemistry (Normal, Low NCS, Low CS, High NCS and High CS) will be summarized, using frequencies and percentages, for each laboratory test by cohort group and nominal time point within each study.

Screening serology [Listing 16.2.8.4.1 (Part A) and Listing 16.2.8.4.2 (Part B)], drug screen test [Listing 16.2.8.5.1 (Part A) and Listing 16.2.8.5.2 (Part B)], pregnancy test [Listing 16.2.8.6.1 (Part A) and Listing 16.2.8.6.2 (Part B)] , Alcohol breath test [Listing 16.2.8.7.1 (Part A) and Listing 16.2.8.7.2 (Part B)]results will be listed.

Any laboratory parameters that are given as '<xx' or '>xx' in the database will be imputed with the absolute value of the number without the sign (e.g., <2.2 will be imputed as 2.2) for the calculation of the changes from baseline and for the descriptive statistics.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for non-categorical data including hematology [Table 14.3.5.2.1 (Part A) Table 14.3.5.2.2 (Part B)] and biochemistry [Table 14.3.5.1.1 (Part A) and Table 14.3.5.1.2 (Part B)] and any quantitative urinalysis [Table 14.3.5.3.1 (Part A) and Table 14.3.5.3.2 (Part B)] will be presented for each study part, by cohort and time point for both

observed values and changes from baseline. Urinalysis results (normal or abnormal) will also be tabulated.

Abnormal laboratory values will be listed using conventional and standard units [Listing 14.3.4.1.1 (Part A), Listing 14.3.4.1.2 (Part B), Listing 14.3.4.2.1 (Part A), Listing 14.3.4.2.2 (Part B), Listing 14.3.4.3.1 (Part A) and Listing 14.3.4.3.2 (Part B)]. Shift tables for hematology [Table 14.3.5.5.1 (Part A), Table 14.3.5.5.2 (Part B)] and biochemistry [Table 14.3.5.4.1 (Part A) and Table 14.3.5.4.2 (Part B)] will be constructed that show the change in quantitative laboratory values from baseline with each study part, and by cohort and nominal time point.

No change from baseline will be calculated for screening visits.

6.3.15.3 Vital Signs

Vital signs data will be listed [Listing 16.2.9.1.1 (Part A) , Listing 16.2.9.1.2 (Part B)] by subject for each study part by subject including subject number, time point, changes from baseline for supine measurements, flags for measurements outside the reference ranges and the corresponding Investigator assessment (CS or NCS)and repeat/unscheduled measurements. 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. The baseline for each measurement will be the mean of the triplicate assessments obtained on Day -1.

Vital signs data will be summarized [Table 14.3.6.1.1 (Part A) and Table 14.3.6.1.2 (Part B)], descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and changes from baseline will be presented by for each study part, by cohort and time point for both observed values and changes from baseline.

No change from baseline will be calculated for screening visits.

6.3.15.4 Twelve-Lead Electrocardiogram

All ECG parameters obtained from the ECG measurement will be listed [Listing 16.2.9.2.1 (Part A) and Listing 16.2.9.2.2 (Part B)] by subject for each study part by subject and time point including changes from baseline and repeat/unscheduled measurements. 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. The baseline for each measurement will be the mean of the triplicate assessments obtained on Day -1.

All ECG parameters will be summarized [Table 14.3.6.2.1 (Part A) and Table 14.3.6.2.2 (Part B)], descriptive statistics (n, mean, SD, median, minimum, maximum) will be presented within each study part, and by cohort and time point for both observed values and changes from baseline.

No change from baseline will be calculated for screening visits.

6.3.15.5 Physical Examination

Abnormal physical examination results will be listed [Listing 16.2.9.3.1 (Part A) and Listing 16.2.9.3.2 (Part B)] by subject within each study part, by cohort and time point. Listing of spinal X-ray will be provided (if appropriate).

7. REFERENCES

1. SAS® Version 9.2 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
2. WinNonlin Professional Software Version 6.3. http://www.pharsight.com
3. Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST. Confidence interval criteria for assessment of dose proportionality. Pharm Res. 2000 Oct; 17(10): 1278-83.
4. CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, Guideline on the investigation of bioequivalence, London, 20 January 2010.

8. TABLES AND LISTINGS TO BE INCLUDED IN SECTION 14 OF THE CLINICAL STUDY REPORT

Subject Disposition

Table 14.1.1.1 Summary of Subject Disposition (Safety Population) (Part A)

Table 14.1.1.2 Summary of Subject Disposition (Safety Population) (Part B)

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Table 14.1.4.1 Summary of Medical History (Safety Population) (Part A)

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Table 14.1.5.1 Summary of Prior Medications and Significant Non-Drug Therapies (Safety Population) (Part A)

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Table 14.2.3.1 Statistical Analysis To Assess Dose Proportionality of KM-819 Pharmacokinetic Parameters (Power Model) (Pharmacokinetic Population) (Part A)

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Table 14.2.9.1 Summary of Profile of Mood States (Pharmacodynamic Population) (Part A)

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Table 14.2.10.1 Summary of Observed and Change From Baseline of Korean Wechsler Adult

Table 14.3.1.4.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity (Safety Population) (Part B)

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Listing 14.3.4.3.1 Abnormal Urinalysis Values (Safety Population) (Part A)

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Table 14.3.5.1.1 Summary of Biochemistry (Safety Population) (Part A)

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Table 14.3.5.2.2 Summary of Hematology (Safety Population) (Part B)

Table 14.3.5.3.1 Summary of Urinalysis (Safety Population) (Part A)

9. FIGURES

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10. LISTINGS TO BE INCLUDED IN SECTION 16 OF THE CLINICAL STUDY REPORT

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Listing 16.2.1.4.1 Failed Inclusion and Exclusion Criteria (Part A)

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11. DOCUMENTATION OF STATISTICAL METHODS

- Appendix 16.1.9.1.1: Raw SAS Output of Table 14.2.3.1 Statistical Analysis To Assess Dose Proportionality Analysis of KM-819 Pharmacokinetic Parameters (Power Model) (Pharmacokinetic Population) (Part A)
- Appendix 16.1.9.1.2: Raw SAS Output of Table 14.2.3.2 Statistical Analysis To Assess Dose Proportionality Analysis of KM-819 Pharmacokinetic Parameters (Power Model) (Pharmacokinetic Population) (Part B)
- Appendix 16.1.9.2: Raw SAS Output of Table 14.2.4 Statistical Analysis To Assess dose-normalized parameters KM-819 Pharmacokinetic Parameters (ANOVA Model) (Pharmacokinetic Population) (Part A)
- Appendix 16.1.9.3: Raw SAS Output of Table 14.2.5 Statistical Analysis of Time Invariance of KM-819 Pharmacokinetic Parameters (ANOVA Model) (Pharmacokinetic Population) (Part B)
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