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ORIGINAL RESEARCH

A first-in-human study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of KM-819 (FAS-associated factor 1 inhibitor), a drug for Parkinson's disease, in healthy volunteers

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Background: KM-819 is a novel FAS-associated factor 1 (FAF1) inhibitor, and a neuroprotective agent, under clinical development for the treatment of Parkinson's disease as a disease-modifying drug.

Methods: This first-in-human, single and multiple ascending dose study investigated the safety, tolerability, pharmacokinetics, and pharmacodynamics of KM-819 in healthy volunteers. Additionally, the effect of age on safety and pharmacokinetics were assessed. The starting dose was determined considering the no observed adverse effect level based on preclinical studies, and the dose escalations in subsequent cohorts were decided based on safety, tolerability, and pharmacokinetic data from previous dose cohorts.

Results: After a single dose, the KM-819 plasma exposure showed a less than dose-proportional increase across a dose range of 10–400 mg. After repeated dosing, KM-819 plasma exposure increased in an approximately dose-proportional manner across the evaluated dose range (30–400 mg once daily for 7 days). The mean elimination half-life was 1.8 to 4.8 h with the lower KM-819 doses (≤30 mg), which increased to around 9 h with the higher doses (100–400 mg). When administered to the elderly population, KM-819 plasma exposure increased to 102% after a 200 mg once-daily dosing for 7 days. No clear treatment-related effects on the estimated pharmacodynamic variables were observed. Single or multiple doses of KM-819 were generally well tolerated.

Conclusion: The data from this study can be used to guide rational drug dosing and choose therapeutic regimens in subsequent clinical studies.

Keywords: first-in-human, KM-819, pharmacokinetics, pharmacodynamics, safety

Introduction

Parkinson's disease is a progressive neurodegenerative disease caused by the loss of dopaminergic neurons in the substantia nigra in the midbrain. The symptoms include bradykinesia, resting tremor, rigidity, unstable posture, and postural reflex impairment.[1] The available drugs for the development and progression of Parkinson's disease are limited and not sufficient to cater for the existing medical needs. Although the mechanism for the neuronal loss is unknown, the movement control ability can be temporally improved by the dopamine precursor L-3,4-dihydroxyphenylalanine. The currently available drugs for the treatment of Parkinson's disease can be classified largely into 4 classes (dopamine replacement, dopamine catechol-O-methyl transferase inhibitors,

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dopamine agonists, and monoamine oxidase type B inhibitors).[2] Although these drugs help to supplement dopamine or aid in relieving symptoms, there is no remedy for the development of the disease, such as inhibiting the death of the dopaminergic neuronal cells. Further, the presently used drugs require increasing dose over time and have serious side effects, such as impulse control disorders, movement impairment, and hallucinations.[3–5]

FAS-associated factor 1 (FAF1) is a protein related to Fas-mediated apoptosis.[6] It has been reported that the expression of FAF1 is increased in the brain in Parkinson's disease.[7] A significant increase in FAF1 expression in the midbrain has been confirmed by animal models of Parkinson's disease. The cells and animal models of Parkinson's disease have also demonstrated an inhibition of cell death when FAF1 expression is reduced.[8] Therefore, FAF1 is validated as a potential novel target for new drug discovery for Parkinson's disease.

KM-819 is an innovative new drug that protects the neuronal cells from death through inhibition of FAF1. KM-819 inhibits Parkinson's disease progression by inhibiting the Fas-mediated cell death pathway.[9,10] According to an in vitro study, KM-819 was found to protect the dopaminergic neurons treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in a dose-dependent manner. In an MPTP-treated mice model, KM-819 protected the dopaminergic neuronal cells both in the substantia nigra and striatum, as well as improved the behavioral impairments. This suggested that KM-819 has a potential capability of delaying or stopping the progression of Parkinson's disease. Therefore, if successful, KM-819 can be considered as a disease-modifying drug (unpublished data). In a subacute toxicity study, KM-819 did not show adverse effects after repeated administration for 4 weeks in Sprague Dawley rats (up to 500 mg/kg/day) and for 2 weeks in beagle dogs (up to 1,000 mg/kg/day).[11] Based on these data, a first-in-human trial was performed to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of KM-819 in healthy young male subjects and healthy elderly subjects.

Material and methods

Subjects

Male subjects aged 19–45 years old (for the young cohorts) or over 60 years old (for the elderly cohorts) with a body mass index (BMI) of 18.5–30.0 kg/m^2 were eligible to participate in this study. All the subjects were deemed healthy by a physical examination, medical history, vital signs, clinical laboratory tests (hematology, blood chemistry, and urinalysis), and 12-lead electrocardiogram (ECG) performed up to 4 weeks prior to the first administration of the study drug. The subjects with a history of hepatic, renal, psychiatric, or cardiovascular disorders, those with known hypersensitivity to KM-819 and any components of the formulation, those who reported use of other drugs that might interfere with the study results within 2 weeks of the study drug administration, and those with a history of drug abuse were excluded from the study. Female subjects were excluded because fertility and early embryonic development study was not completed. Specific inclusion and exclusion criteria are presented in Table S1.

Study design

This study was approved by the ethics review board of CHA Bundang Medical Center, Seongnam, Republic of Korea. All the subjects were given detailed written and oral information about the study and written informed consent were obtained before screening for eligibility. The study was conducted at the Clinical Trials Center of CHA Bundang Medical Center, Seongnam, Republic of Korea in compliance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice Guidelines of the International Conference on Harmonization, and local laws and regulations. This study was registered at ClinicalTrials.gov (https://ClinicalTrials.gov, identifier: NCT03022799).

This was a first-in-human, randomized, single and multiple-dose, placebo-controlled dose escalation study in healthy subjects. In the single ascending dose (SAD) study, 40 healthy young male subjects and 8 healthy elderly male subjects were enrolled and randomized to receive either KM-819 or placebo. Each of the 5 dose escalation cohorts consisted of 8 healthy young male subjects; 6 subjects received a single dose of 10, 30, 100, 200, or 400 mg KM-819 and 2 subjects received placebo. After completion of the 5 dose escalation cohorts, 8 elderly male subjects were enrolled into an additional cohort, in which 6 subjects received 200 mg KM-819 and 2 subjects received placebo. In each of the 6 single-dose cohorts, there were 2 sentinel subjects for each dose escalation cohort. Two subjects were dosed on the first day (1 subject received KM-819 and 1 subject received placebo) and the remaining 6 subjects were dosed at least 24 hours after the first 2 subjects. All the subjects underwent a 3-day confinement period during which they were hospitalized for study-related activities (day −1 to day 3). The subjects were required to return for outpatient visits on day 4, day 7, and for a follow-up visit on day 14 (Figure 1A).

In the multiple ascending dose (MAD) study, 32 healthy young male subjects and 8 healthy elderly male subjects were enrolled and randomized to receive either KM-819 or

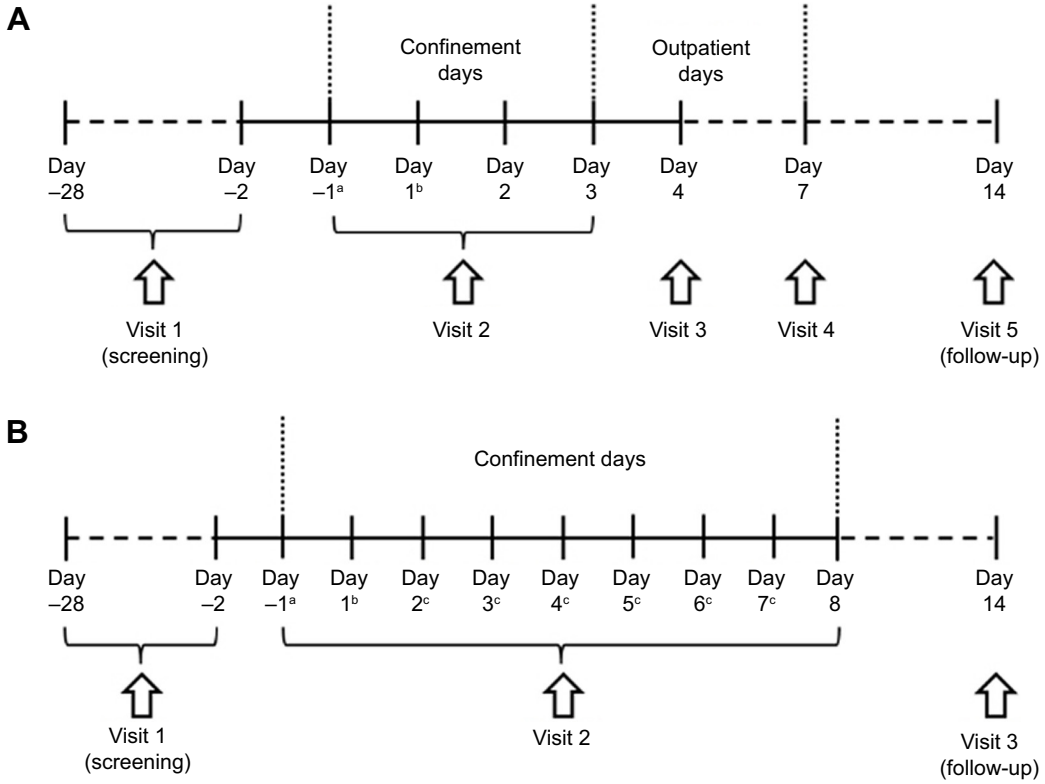

Figure 1 Study Design of the single ascending dose (SAD) study (**A**), and multiple ascending dose (MAD) study (**B**).
Notes: [a]Baseline; [b]Randomization and study drug administration; [c]Study drug administration.

placebo. Each of the 4 dose escalation cohorts consisted of 8 healthy young male subjects; 6 subjects received 30, 100, 200 or 400 mg of KM-819 once daily (QD) for 7 days and 2 subjects received placebo. The cohorts were dosed sequentially with escalating doses. After completion of the 4 dose escalation cohorts, 8 elderly male subjects were enrolled into an additional cohort, in which 6 subjects received 200 mg KM-819 QD for 7 days and 2 subjects received placebo. All the subjects underwent an 8-day confinement period during which they were hospitalized for study-related activities (day −1 to day 8). The subjects were required to return for a follow-up visit on day 14 (Figure 1B).

An escalation to the next dose level was decided only after the safety and tolerability data for all subjects in the cohort and available plasma PKs from the previously administered dose cohort were reviewed. The results of exploratory PD assessments and the central nervous system scales were not included in the review for dose escalation decisions.

Rationale for dose selection

The United States Food and Drug Administration (US FDA) guidance document for estimating the safe starting dose in clinical trials for therapeutics in adult healthy volunteers[12] and allometric scaling modeling and simulation was used for the initial calculation of the starting human dose. Based on the US FDA guidance document and no observed adverse effect level (NOAEL) of 500 mg/kg/day obtained from the 4-week rat toxicology study,[11] the human equivalent dose (HED) was estimated to be 5,600 mg for a human subject weighing 70 kg. A 10-fold safety factor was applied to the HED, resulting in an estimated maximum recommended starting dose (MRSD) of 560 mg per person for a 70 kg subject. In addition to the US FDA guidance document, an allometric scaling method was used to predict the human PKs. The human PK parameters were predicted as follows: apparent oral clearance (CL/F)=2.93 L/h, apparent volume of distribution (V_z/F)=39.2 L, and apparent terminal elimination half-life ($t_{1/2}$)=9.27 h. Using these predicted human PK parameters, a simulation was performed based on the assumption that the human PK behaves like a one-compartment model with first-order absorption and first-order elimination rate. The bioavailability (F) was assumed to be 35% (mean F from animal data). Based on a simulated human PK profile and animal efficacy data, a lower dose was selected as the starting dose. The study had an initial starting dose of 10 mg, which is 56-fold below the estimated MRSD derived from the rat NOAEL.

PK assessments

In the SAD study, blood samples (6 mL) for the PK study of KM-819 were obtained on day 1 predose and 0.25, 0.5,

1, 2, 4, 6, 8, 12, 24, 48, and 72 hours postdose. The urine samples for the possible analysis of KM-819 and qualitative analysis of any metabolites were collected at day 1 predose and from 0 to 24 hours postdose. In the MAD study, the blood samples for the PK study were collected on day 1 predose and 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hours postdose, on days 2, 3, 4, 5, and 6 predose, and on day 7 predose and 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose. The cerebrospinal fluid (CSF) samples for the PK analysis were collected on day 1 predose and on day 7 (at 1 hour after the last dosing). The CSF (approximately 2 mL) samples were collected by lumbar puncture between the third and fourth lumbar vertebrae.

The blood samples were centrifuged at 3,000 rpm for 10 min at 4°C, and the obtained plasma samples (0.8 mL) were transferred into 3 polypropylene tubes (1.5 mL). Similarly, the urine (1 mL) and CSF samples were (0.5 mL) were transferred into 3 polypropylene tubes (1.5 mL). All the tubes were immediately stored in a freezer at −70°C until analysis.

The KM-819 concentrations in plasma and urine were analyzed by an ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). The system comprised of a Waters ACQUITY UPLC™ (Waters Corporation, Milford, MA, USA) coupled with a Waters Xevo™ TQ MS (Waters Corporation, Milford, MA, USA). Briefly, a sample of either plasma or urine was mixed with dimethyl sulfoxide in the presence of an internal standard (KM-819-d_5) in a Master Block 96 well plate (Greiner Bio-One International GmbH, Kremsmünster, Austria). The mixture was then vortexed for 3 min and centrifuged for 1 min at 4,000 rpm. Subsequently, 0.400 mL of methanol was added, vortexed for 3 min, and centrifuged for 1 min at 4,000 rpm. After transferring 0.250 mL of the supernatant to another 96 well plate, 0.150 mL of 0.1% (w/v) ammonium acetate was added, vortexed for 3 min, and centrifuged for 1 min at 4,000 rpm. Then, a 2 µL of the aliquot was injected into the UPLC-MS/MS system for analysis. The quantification was performed using multiple reaction monitoring of the transitions m/z 460.1→214.2 and m/z 467.1→219.2 for KM-819 and KM-819-d_5, respectively. The calibration curves were linear over the range of 2–20,000 ng/mL for plasma and 0.5–1,000 ng/mL for urine. The limits of quantification for plasma and urine were 2 ng/mL and 0.5 ng/mL, respectively.

The PK parameters of KM-819 were estimated using non-compartmental methods in the Phoenix WinNonlin 6.3 software (Certara USA Inc., Princeton, NJ, USA). The maximum plasma concentration after a single dose (C_{max}), the maximum plasma concentration at steady-state ($C_{max,ss}$), time to C_{max} (T_{max}), and $C_{max,ss}$ ($T_{max,ss}$) were determined directly from the concentration-time curve. The terminal phase rate-constant (λ_z) was estimated by a linear regression of the data points included in the terminal phase of the log-linear plot of the concentration-time curve, and the elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$. The area under the plasma concentration-time curve (AUC) from time 0 to 24 hours postdose (AUC_{0-24}), the AUC from zero extrapolated to infinity (AUC_{inf}), the AUC from time 0 hour to the last quantifiable concentration (AUC_{last}), and the AUC over the dosing interval at steady-state (AUC_{tau}) were calculated using the linear trapezoidal rule. Any BLQ (below the limit of quantification) values occurring prior to C_{max} were assigned a value of zero; BLQ values after the last quantifiable concentration were treated as missing. The apparent oral clearance (CL/F) was calculated using the ratio of the dose to the AUC_{tau}, and the accumulation index was calculated as the ratio of the AUC_{tau} and $C_{max,ss}$ on day 7 to the AUC_{0-24} and C_{max} on day 1.

PD assessments

In the SAD study, Bond and Lader visual analog scale (VAS), profile of mood states (POMS), and Korean Wechsler Adult Intelligence Scale-IV (K-WAIS-IV) were used on day −1, day 1 predose and at 3, 6, 12, 24, 48, and 72 hours postdose.[13–15] The Columbia Suicide Severity Rating Scale (C-SSRS) was used at screening and on day 3. In the MAD study, Bond and Lader VAS, POMS and K-WAIS-IV were used on day −1, day 1 predose, day 7 predose, and at 3, 6, 12, and 24 hours postdose. The C-SSRS was used at screening, on day 3 and day 8. The samples for estimation of alpha-synuclein oligomer (blood and CSF), total tau (CSF), and phosphor-tau (CSF) were collected on day 1 predose and on day 7 (1 hour after the last dosing). Protein concentrations were estimated at the University of California at San Diego (ADCS Biomarker Core).

Safety assessments

Safety was assessed throughout the study based on vital signs, clinical laboratory tests, 12-lead ECGs, physical examinations, and adverse events (AEs) reported by the subjects or observed by the medical investigators. All adverse events were coded using MedDRA version 19.1.

Statistical analyses

All demographic data, PK parameters, PD parameters, and safety data were summarized using descriptive statistics for continuous variables and using the number and percentage of subjects for categorical variables. The dose proportionality was assessed for C_{max}, AUC_{last}, and AUC_{inf} in the SAD study and for C_{max}, AUC_{0-24} (on day 1), $C_{max,ss}$, $C_{min,ss}$, and AUC_{tau},

(on day 7) in the MAD study, using a power model with the following equation:

$$\ln(\text{PK parameter}) = \beta 0 + \beta 1 \times \ln(\text{Dose})$$

The estimate of the slope of the regression line (β1) and the corresponding 95% CI were calculated. All statistical analyses were performed in the SAS® version 9.3 software (SAS Institute Inc., Cary, NC, USA) and a *P*-value <0.05 was considered statistically significant.

Results

Subjects

A total of 88 subjects were enrolled, 66 subjects received KM-819 (36 in the SAD study and 30 in the MAD study), and 22 subjects received placebo (12 in the SAD study and 10 in the MAD study). Two subjects in the MAD study who received KM-819 dropped out before completion of the study by withdrawing consent, and the remaining 86 subjects completed the study as per protocol. The safety analysis included all the randomized subjects in the SAD (N=48) or MAD (N=40) studies. The PK analysis included 66 subjects who received KM-819 in the SAD (N=36) or MAD (N=30) studies, and the PD analysis included 64 subjects who received KM-819 in the SAD (N=36) or MAD (N=28) studies. The demographic characteristics of the enrolled subjects are enumerated in Table 1.

Pharmacokinetics

The mean plasma concentration-time profiles of KM-819 in the SAD and MAD studies are presented in Figure 2. In the SAD study, the KM-819 concentrations were quantifiable at less than 0.5 hour following administration of all doses including the elderly male cohort. The median T_{max} values were 1–4 hours following administration of all doses and a similar T_{max} was observed in the elderly cohort. The mean $t_{1/2}$ was 1.8–4.8 hours for KM-819 doses ≤30 mg and increased to around 9 hours for higher doses. There was a moderate degree of variability for the major PK parameters (AUC_{inf} and C_{max}), with a coefficient of variation (CV%) ranging up to 55%. After administering a single dose of 200 mg KM-819, C_{max} was found to be similar between the young and the elderly subjects. The elderly subjects, however, showed a 17% higher $t_{1/2}$ and a 49% higher AUC compared to the young subjects (Table 2). The concentrations of KM-819 in urine were very low, and 24-hour recovery of KM-819 in urine (percent of dose) was less than 1% for all subjects.

In the MAD study, the single dose PK was similar to that observed in the SAD study. The mean variability (CV%) for the major PK parameters (AUC_{tau} and $C_{max,ss}$) were moderate to high ranging up to 96%. The geometric mean accumulation ratio for KM-819 AUC and C_{max} ranged from 0.63–1.49 for all doses indicating no significant accumulation. After 200 mg QD dosing for 7 days, the day 7 KM-819 $C_{max,ss}$ and AUC_{tau} were increased to 191% and 102%, respectively in the elderly population (Table 3). Consistent with the estimated $t_{1/2}$ (around 9 hours in the SAD study), the steady-state trough concentrations were achieved after 5 days of repeated dose in each group (data not shown).

Based on the power model, KM-819 AUC and C_{max} showed a less than dose-proportional increase after a single dose administration of KM-819 in both the SAD and MAD

Table 1 Demographic characteristics of the study subjects

SAD study							
Parameter (unit)	**Placebo[a] (N=12)**	**KM-819**					
		10 mg (N=6)	**30 mg (N=6)**	**100 mg (N=6)**	**200 mg (N=6)**	**400 mg (N=6)**	**200 mg[b] (N=6)**
Age (years)	35.6 (19.8)	23.7 (6.3)	25.2 (7.6)	26.2 (5.0)	27.5 (6.4)	26.3 (4.1)	75.0 (5.8)
Height (cm)	172.0 (7.1)	175.5 (2.1)	175.2 (7.3)	175.3 (6.3)	176.8 (4.9)	177.2 (5.9)	167.5 (5.2)
Weight (kg)	69.5 (9.5)	70.5 (5.9)	68.3 (9.2)	70.8 (8.3)	77.1 (5.6)	71.4 (9.5)	70.6 (11.1)
BMI (kg/m^2)	23.6 (3.3)	22.9 (1.4)	22.3 (2.8)	23.0 (2.2)	24.7 (1.8)	22.7 (2.6)	25.1 (3.2)
MAD study							
Parameter (unit)	**Placebo[a] (N=10)**	**KM-819**					
		30 mg (N=6)	**100 mg (N=6)**	**200 mg (N=6)**	**400 mg (N=6)**	**200 mg[b] (N=6)**	
Age (years)	38.5 (19.7)	27.5 (7.6)	30.2 (6.9)	28.7 (5.7)	22.5 (1.4)	72.8 (6.6)	
Height (cm)	173.1 (7.6)	176.3 (2.3)	169.2 (10.9)	175.3 (5.3)	171.3 (3.9)	165.5 (4.8)	
Weight (kg)	72.6 (14.2)	74.0 (8.9)	66.6 (6.3)	71.9 (8.6)	69.3 (6.6)	64.5 (1.7)	
BMI (kg/m^2)	24.1 (3.5)	23.8 (3.2)	23.4 (2.8)	23.4 (2.7)	23.7 (2.9)	23.6 (1.7)	

Notes: Data are shown as mean (SD). [a]Subjects who received placebo within each cohort were pooled. [b]Elderly male subjects.
Abbreviations: SAD, single ascending dose; MAD, multiple ascending dose; BMI, body mass index.

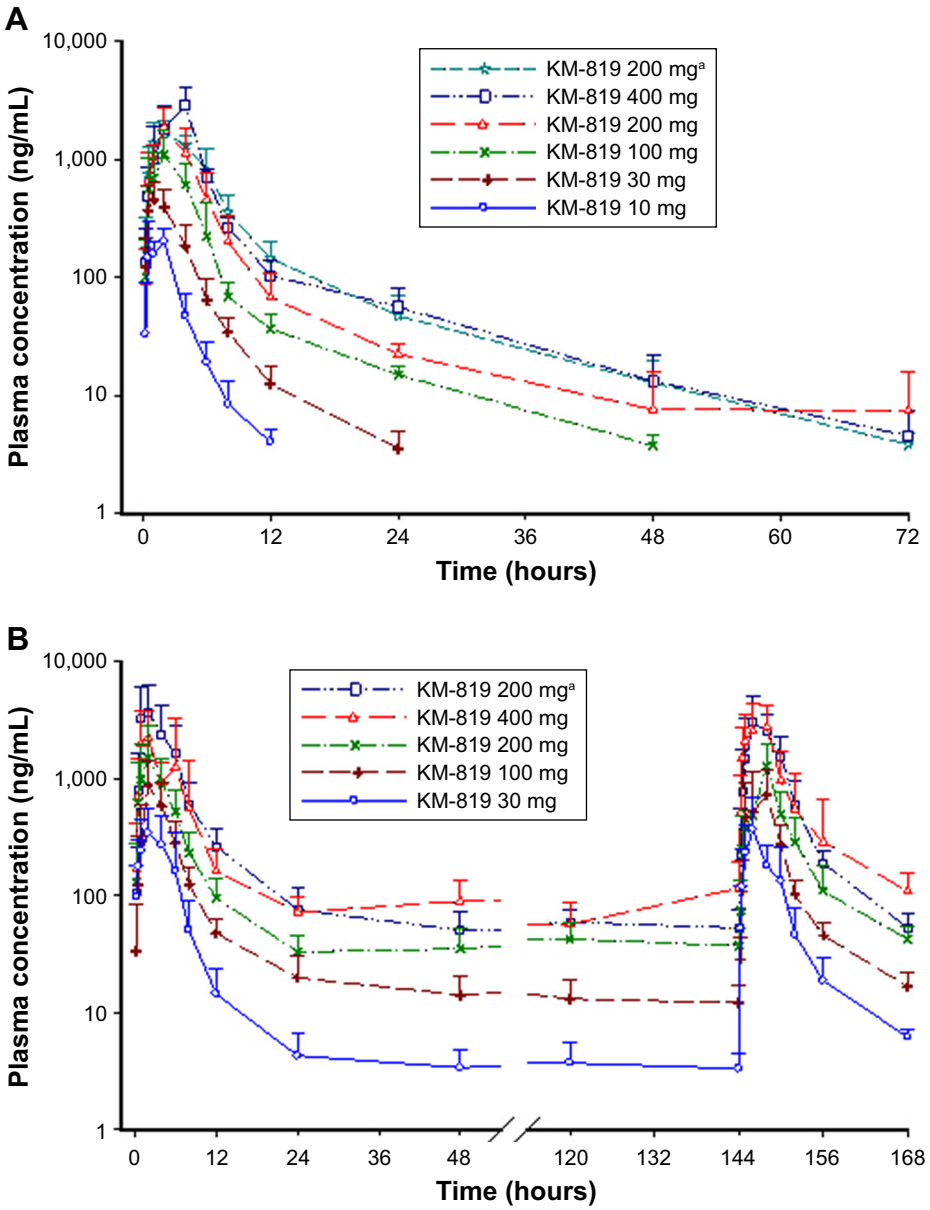

Figure 2 Mean plasma concentration-time profile of KM-819 in the single ascending dose (SAD) (**A**) and multiple ascending dose (MAD) (**B**) studies.
Note: [a]Elderly subjects cohort.

Table 2 Pharmacokinetic parameters of KM-819 in the SAD study

Parameter (unit)	KM-819 dose					
	10 mg (n=6)	30 mg (n=6)	100 mg (n=6)	200 mg (n=6)	400 mg (n=6)	200 mg[a] (n=6)
C_{max} (ng/mL)	244.1 (31.4)	503.6 (28.0)	1,152 (36.7)	1,879 (55.3)	2,767 (43.4)	1,766 (26.0)
T_{max} (h)	1.50 (0.50–2.00)	1.00 (0.50–2.00)	2.00 (1.00–4.00)	2.00 (1.00–4.00)	4.00 (2.00–4.00)	2.00 (1.0–4.00)
AUC_{last} (ng·h/mL)	583.4 (24.5)	1,705 (17.1)	4,306 (31.1)	7,637 (47.7)	12,210 (33.3)	10,840 (10.3)
AUC_{inf} (ng·h/mL)	594.2 (24.4)	1,731 (17.3)	4,872 (30.8)	7,338 (51.9)	12,640 (36.1)	10,970 (9.8)
$t_{1/2}$ (h)	1.786 (28.3)	4.791 (25.0)	9.159 (41.2)	9.010 (71.6)	8.527 (63.2)	10.55 (28.5)
t_{lag} (h)	0.00 (0.00–0.25)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.25)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
CL/F (mL/h)	16,830 (24.4)	17,340 (17.3)	20,530 (30.8)	27,260 (51.9)	31,650 (36.1)	18,230 (9.8)

Notes: Data are shown as geometric mean (coefficient of variation%), except T_{max} and t_{lag} which are as median (min–max). The terminal phase rate-constant (λ_z) related pharmacokinetics parameters such as $t_{1/2}$ and AUC_{inf} were not estimated for 2 subjects in the 100 mg cohort, 1 subject in the 200 mg cohort and 1 subject in the 400 mg cohort, due to either the duration of time over which λ_z was estimated being less than 1.5-fold the subsequently estimated $t_{1/2}$ and/or the adjusted regression coefficient (R^2 adjusted) being less than 0.8. [a]Elderly male subjects.
Abbreviations: SAD, single ascending dose; C_{max}, maximum plasma concentration; T_{max}, time to achieve C_{max}; AUC_{last}, area under the concentration-time curve (AUC) from time zero to the last quantifiable concentration; AUC_{inf}, AUC from time zero extrapolated to infinity; $t_{1/2}$, terminal elimination half-life; t_{lag}, lag time; CL/F, apparent oral clearance.

Table 3 Pharmacokinetic parameters of KM-819 in the MAD study

Parameter (unit)	KM-819 dose (QD for 7 days)				
	30 mg (N=6)	100 mg (N=6)	200 mg (N=6)	400 mg (N=6)	200 mg[a] (N=6)
Day 1					
C_{max} (ng/mL)	512.0 (30.9)	1,009 (33.0)	1,465 (77.2)	3,163 (50.7)	3,542 (76.4)
T_{max} (h)	2.00 (1.00–6.00)	2.00 (1.00–4.00)	3.00 (2.00–6.00)	2.00 (1.00–6.00)	2.00 (1.00–6.00)
AUC_{0-24} (ng·h/mL)	1,761 (21.3)	3,735 (38.5)	6,485 (62.2)	11,260 (37.1)	17,590 (53.3)
Day 7					
$C_{max,ss}$ (ng/mL)	418.5 (51.7)	1,012 (39.5)	1,111 (64.3)	3,172 (37.9)	3,231 (52.5)
$C_{min,ss}$ (ng/mL)	NC	9.983 (31.1)	32.44 (19.4)	75.14 (28.4)	44.82 (48.3)
$T_{max,ss}$ (h)	2.00 (1.00–6.00)	3.00 (1.00–4.00)	4.00 (4.00–4.00)	2.00 (0.50–4.00)	2.00 (1.00–4.00)
AUC_{tau} (ng·h/mL)	1,572 (24.8)	3,477 (17.9)	8,023 (7.7)	19,530 (96.4)	16,250 (34.1)
R_{ac} (AUC)	0.8923 (0.70–1.13)	0.9727 (0.69–1.37)	0.7568 (0.57–1.00)	1.485 (0.86–2.56)	0.9241 (0.67–1.28)
R_{ac} (C_{max})	0.8173 (0.53–1.26)	1.003 (0.73–1.39)	0.6227 (0.55–0.71)	1.117 (1.00–1.25)	0.9122 (0.53–1.58)

Notes: Data are shown as geometric mean (Coefficient of variation%), except T_{max} which is as median (min–max) and R_{ac} which is as geometric mean (95% confidence interval). The AUC_{tau} was not estimated for 1 subjects in the 100 mg cohort, 2 subject in the 200 mg cohort and 3 subject in the 400 mg cohort, due to either the duration of time over which terminal phase rate-constant (λ_z) being estimated was less than 1.5-fold the subsequently estimated $t_{1/2}$ and/or the adjusted regression coefficient (R^2 adjusted) being less than 0.8 and/or %AUCex (percentage of AUC_{inf} that is due to extrapolation beyond last sampling time point) was >40%. [a]Elderly male subjects.
Abbreviations: MAD, multiple ascending dose; C_{max}, maximum plasma concentration; T_{max}, time to achieve C_{max}; AUC_{0-24}, area under the concentration-time curve (AUC) from time zero to 24 hours postdose; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{min,ss}$, minimum plasma concentration at steady state; $T_{max,ss}$, time to achieve $C_{max,ss}$; AUC_{tau}, AUC over the dosing interval at steady state; R_{ac} (AUC), observed accumulation by AUC; R_{ac} (C_{max}), observed accumulation by C_{max}; QD, once daily; NC, not calculated.

studies, as the upper boundary of 95% CI of the slope was below 1.0. After repeat dosing of KM-819 for 7 days in the MAD study, KM-819 AUC on day 7, however, had a dose-proportional increase, but C_{max} showed a less than dose-proportional increase, and C_{min} had a slightly more than dose-proportional increase (Table 4).

In the MAD study, after repeat dose of KM-819 30 mg for 7 days in the 30 mg cohort, no CSF KM-819 concentrations were measurable at 1 hour postdose on day 7. In the higher dose cohorts (≥100 mg QD), KM-819 concentrations were, however, measurable in more than half of the CSF samples after repeat dose and the ratio of CSF/C_{max} was calculated for those subjects with measurable CSF KM-819 concentrations on day 7. The mean CSF/C_{max} ratios (%) were 0.067%, 0.074%, 0.049%, and 0.032% for 100 mg, 200 mg, 400 mg cohort, and 200 mg elderly cohort, respectively.

Pharmacodynamics

No signs of KM-819 treatment-related effects on the Bond and Lader VAS were observed. There were no apparent treatment or cohort differences in the POMS study results. There were no clear treatments differences in the K-WAIS-IV study results, but the day 7 values were slightly higher than the day 1 and baseline values, possibly pointing to a training effect. This effect was less pronounced in the placebo cohorts, and was less likely to be significantly different. Likewise, there were no apparent treatment or cohort differences in the C-SSRS study results.

No clear treatment- or dose-related changes from day 1 to day 7 were apparent in the alpha-synuclein oligomer, total tau, and phosphor tau estimations in the CSF or alpha-synuclein oligomer estimation in the plasma. The results of

Table 4 Assessment of dose proportionality of KM-819 pharmacokinetic parameters (power model)

Part	Day	Parameter	N	Estimated mean slope	95% CI
SAD	1	C_{max} (ng/mL)	30	0.667	0.5644–0.7697
		AUC_{last} (ng·h/mL)	30	0.8027	0.7166–0.8888
		AUC_{inf} (ng·h/mL)	26	0.8233	0.7307–0.9158
MAD	1	C_{max} (ng/mL)	24	0.6764	0.4702–0.8827
		AUC_{0-24} (ng·h/mL)	24	0.7157	0.5458–0.8856
	7	$C_{max,ss}$ (ng/mL)	22	0.7158	0.4918–0.9397
		$C_{min,ss}$ (ng/mL)	21	1.1852	1.0233–1.3471
		AUC_{tau} (ng·h/mL)	16	0.9124	0.7227–1.1021

Abbreviations: SAD, single ascending dose; MAD, multiple ascending dose; C_{max}, maximum plasma concentration; AUC_{last}, area under the concentration-time curve (AUC) from time zero to the last quantifiable concentration; AUC_{inf}, AUC from time zero extrapolated to infinity; AUC_{0-24}, AUC from time zero to 24 hours postdose; $C_{max,ss}$, maximum plasma concentration at steady state; $C_{min,ss}$, minimum plasma concentration at steady state; AUC_{tau}, AUC over the dosing interval at steady state.

these parameters were highly variable, without any discernable trend (Table S2).

Safety and tolerability

In total, 17 treatment-emergent adverse events (TEAEs) were reported from 12 of the 48 subjects in the SAD study (Table 5). Ten of these were considered to be related to the KM-819 by the investigator. No treatment- or dose-related trend in the incidence of TEAEs was observed. There were no serious adverse events (SAEs) reported, no subjects were withdrawn from the SAD study due to AEs, and there were no TEAEs leading to death.

The incidence of TEAEs was notably higher in the MAD study than in the SAD study. In total, 82 TEAEs were reported from 24 of the 40 subjects in the MAD study (Table 5). The lumbar puncture procedure performed in the MAD study was most probably attributable to the higher incidence of TEAEs. Sixty-eight out of the 82 reported TEAEs were considered by the investigator to be related to KM-819. No treatment-related trend in the incidence of TEAEs was

Table 5 Treatment emergent adverse events in the SAD and MAD studies

SAD study							
Parameter (unit)	**Placebo[a] (N=12)**	**KM-819**					
		10 mg (N=6)	**30 mg (N=6)**	**100 mg (N=6)**	**200 mg (N=6)**	**400 mg (N=6)**	**200 mg[b] (N=6)**
Subjects with any TEAEs	3 (25.0)	2 (33.3)	2 (33.3)	2 (33.3)	1 (16.7)	0	2 (33.3)
Eye swelling	1 (8.3)	0	0	0	0	0	0
Abdominal discomfort	0	0	0	0	1 (16.7)	0	0
Hyperbilirubinemia	0	2 (33.3)	0	1 (16.7)	0	0	0
Influenza	1 (8.3)	0	0	0	0	0	0
Face injury	0	0	0	0	0	0	1 (16.7)
Pain in extremity	0	0	1 (16.7)	0	0	0	0
Headache	1 (8.3)	0	0	0	0	0	2 (33.3)
Hypoesthesia	0	0	0	1 (16.7)	0	0	0
Syncope	0	0	1 (16.7)	0	0	0	0
Proteinuria	0	0	0	1 (16.7)	0	0	0
Cough	1 (8.3)	0	0	0	0	0	0
Hot flush	0	0	0	0	0	0	1 (16.7)

MAD study						
Parameter (unit)	**Placebo[a] (N=10)**	**KM-819**				
		30 mg (N=6)	**100 mg (N=6)**	**200 mg (N=6)**	**400 mg (N=6)**	**200 mg[b] (N=6)**
Subjects with any TEAEs	5 (50.0)	2 (33.3)	4 (66.7)	5 (83.3)	5 (83.3)	3 (50.0)
Erythema of eyelid	0	0	0	0	1 (16.7)	0
Abdominal discomfort	1 (10.0)	0	0	1 (16.7)	0	0
Abdominal pain	0	0	0	0	0	1 (16.7)
Diarrhea	1 (10.0)	0	0	0	0	1 (16.7)
Nausea	0	2 (33.3)	1 (16.7)	4 (66.7)	0	0
Vomiting	0	2 (33.3)	0	4 (66.7)	0	0
Hyperbilirubinemia	1 (10.0)	0	0	1 (16.7)	0	0
Back pain	3 (30.0)	0	2 (33.3)	1 (16.7)	1 (16.7)	2 (33.3)
Muscle hemorrhage	0	0	0	0	0	1 (16.7)
Musculoskeletal stiffness	0	0	0	1 (16.7)	1 (16.7)	0
Neck pain	0	0	0	0	0	1 (16.7)
Dizziness	2 (20.0)	1 (16.7)	1 (16.7)	2 (33.3)	0	0
Headache	2 (20.0)	2 (33.3)	1 (16.7)	5 (83.3)	4 (66.7)	1 (16.7)
Hypoesthesia	1 (10.0)	0	0	2 (33.3)	0	0
Anxiety	1 (10.0)	0	0	0	0	0
Insomnia	0	0	0	0	0	1 (16.7)
Epistaxis	0	0	0	0	1 (16.7)	0
Oropharyngeal pain	0	0	0	1 (16.7)	0	0
Erythema	1 (10.0)	0	0	0	0	0
Hyperhidrosis	1 (10.0)	0	0	0	1 (16.7)	0

Notes: Data are shown as number of subjects with adverse events (percentage calculated using the number of subjects in the safety population as denominator). [a]Subjects who received placebo within each cohort were pooled. [b]Elderly male subjects.

Abbreviations: SAD, single ascending dose; MAD, multiple ascending dose; TEAE, treatment-emergent adverse event.

detected, but the incidence of TEAEs in the 200 mg KM-819 treatment group where young males were dosed, was notably higher than that in the other treatment groups. There was 1 SAE reported (a headache which was considered unlikely to be related to KM-819, and probably related to the lumbar puncture procedure), and 2 subjects were withdrawn from the MAD study due to AEs (headache). There were no TEAEs leading to death.

In the SAD study for the first two dose cohorts (10 mg and 30 mg KM-819), an increasing trend of bilirubin levels was apparent on day 2, with bilirubin levels returning to normal on day 7. At higher doses, this effect was not observed. No other treatment- or dose-related or clinically relevant trends were observed for the clinical laboratory parameters, vital signs measurements, 12-lead ECG, or physical examination evaluations during the study. Overall, no remarkable or significant safety concerns were observed from the safety data in the study.

Discussion

The existing standard of care for Parkinson's disease is symptomatic treatment by dopamine replacement, dopamine agonists, or analogous mechanisms. A disease-modifying treatment is one of the major unmet medical needs for halting disease progression.[2] KM-819 is an orally active small molecule drug developed as an inhibitor for FAF1, a proapoptotic protein, involved in Parkinson's disease.[7,8]

This first-in-human study investigated the safety, tolerability, PKs, and PDs of single and multiple escalating doses of KM-819 in healthy volunteers. The effect of age on safety and PKs were also assessed. The KM-819 steady-state exposure increased in an approximately dose-proportional manner across the evaluated dose range (30–400 mg once daily for 7 days) with the maximum KM-819 concentrations occurring between 1 and 4 hours postdose. Consistent with the estimated $t_{1/2}$, the steady-state concentrations of KM-819 were achieved after 5 days of dosing. When administered to the elderly population, KM-819 C_{max} and AUC increased to 191% and 102% after 200 mg QD dosing for 7 days. The administration of KM-819 was safe and well tolerated and resulted in no SAEs or deaths.

The terminal phase $t_{1/2}$ was <5 hours for the lower doses (10 mg and 30 mg) and increased to 8.5–9.2 hours for the higher doses of KM-819. The dose-dependent nature of $t_{1/2}$ may be the result of unmasking the true $t_{1/2}$ values as the concentrations in the terminal phase increased with higher doses. Because KM-819 plasma concentrations declined in a bi-exponential manner, $t_{1/2}$ may be a good predictor of drug accumulation and fluctuation, and support once daily or twice daily dosing of KM-819.

This study showed that the exposure of the elderly subjects to KM-819 was generally higher than that observed in the young subjects. At steady state, C_{max} and AUC increased on average to 191% and 102% in the elderly subjects, whereas no differences in t_{lag} and T_{max} were observed between the young and the elderly subjects. It is believed that there is no difference in the absorption of KM-819 between these two populations (young and elderly), but the elimination of KM-819 might have been inhibited and resulted in increased $t_{1/2}$ and PK exposures in the elderly population. Considering that Parkinson's disease prevalence is increasing with age and Parkinson's disease affects about 1% of the population above 60 years,[16] these findings are ideal for a drug targeting Parkinson's disease in the elderly population.

The mean CSF/C_{max} ratios (%) of KM-819 were less than 0.1% in each cohort and no dose-dependent trend was observed. The CSF sample after administrated KM-819 was only obtained on day 7 at 1 hour after the last dosing in this study. Therefore, the estimated drug concentration in CSF could not reflect the maximum CSF concentration on day 7. The transport across the blood–brain barrier (BBB) requires time,[17,18] and the included subjects in this study were all healthy with an intact BBB, which limited the penetration of KM-819 in the CSF. BBB dysfunctions have been reported in Parkinson's disease,[19–21] the CSF concentrations of KM-819 in patients with Parkinson's disease are expected to be higher than observed in this study.

The AUC_{tau} was not estimated for 6 subjects in the MAD study, due to either the duration of time over which terminal phase rate-constant (λ_z) was estimated being less than 1.5-fold the subsequently estimated $t_{1/2}$ and/or the adjusted regression coefficient (R^2 adjusted) being less than 0.8 and/or %AUCex (percentage of AUC_{inf} that is due to extrapolation beyond last sampling time point) was $>40\%$. Therefore smaller sample size would affect the slope estimate of AUC_{tau} in power model at day 7 in the MAD study.

This study was performed in healthy young and elderly subjects who were not on any concomitant medication. In the real-life clinical settings, many elderly patients will likely be on a cocktail of medications. Therefore, the current data should be extrapolated with caution to the medicated elderly subjects on multiple medications.

Conclusion

KM-819, a FAF 1 inhibitor, exhibited favorable pharmacokinetic and safety profiles in this first-in-human study.

These results support dose selection and further clinical evaluation of KM-819 for a phase II study.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Data availability

The raw data of this study will not be shared because of confidentiality.

Disclosure

S Yoo, YT Chung, and JM Lee are the employees of Kainos Medicine Inc. J Hong, S Jhee and J Kim are the employees of PAREXEL, which performed work for this study under contract to Kainos Medicine Inc. The other authors report no conflicts of interest related to this work.

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Supplementary materials

Table S1 Inclusion and exclusion criteria for KM-819 first-in-human study

Inclusion 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 subjects should be between 19 and 45 years old (for young adult cohorts) or over 60 years old (for elderly cohorts).
3	Subject should have a body mass index (BMI) range of 18.5–30 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 subjects must not donate sperm starting at screening, throughout the study period and for at least 90 days after final study drug administration.
6	Female subjects with child bearing age were excluded.
7	Subject agrees not to participate in another investigational study while on study treatment.
Exclusion 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 $>1 \times$ ULN but $<1.5 \times$ 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 $>1.5 \times$ 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 rhinoconjunctivitis, 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 (noncutaneous) 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 SBP >140 mmHg; or mean 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, one additional triplicate measurement may be taken at screening and check-in.
9	Subject has a mean QTcF interval of >430 ms (for males) and >450 ms (for females) at screening or check-in. If the mean QTcF exceeds the limits above, one additional ECG can be taken. If this 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, eg, St John's Wort) in the 2 weeks before study drug administration. Acetaminophen up to 2,000 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 (eg, barbiturates, rifampin) in the 3 months prior to check-in.

(*Continued*)

Table S1 (*Continued*)

Exclusion criteria	
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.
21	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.
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).

Abbreviations: ULN, upper limit of normal; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; MAD, multiple ascending dose.

Table S2 Summary of change from baseline (day 1 predose) to day 7 for PD parameters

Parameter (unit)	Placebo[a] (N=10)	KM-819				
		30 mg (N=6)	100 mg (N=6)	200 mg (N=6)	400 mg (N=6)	200 mg[b] (N=6)
Alpha-synuclein oligomer, CSF (pg/mL)	20.30 (58.53)	49.94 (72.09)	−252.56 (643.49)	0.60 (18.22)	18.21 (103.83)	34.87 (51.42)
Alpha-synuclein oligomer, plasma (pg/mL)	−4,464.91 (15,002.05)	3,884.41 (30,559.28)	575.46 (18,379.46)	3,809.51 (14,003.04)	−64,843.29 (130,397.59)	−11,712.09 (17,679.68)
Total tau, CSF (pg/mL)	20.82 (29.73)	60.30 (64.42)	9.23 (15.82)	−3.16 (15.01)	27.86 (66.07)	29.30 (100.07)
Phosphor-tau, CSF (pg/mL)	5.31 (7.89)	6.41 (19.04)	0.21 (1.13)	4.47 (7.88)	6.70 (11.82)	5.16 (10.88)

Notes: Data are shown as mean SD. [a]Subjects who received placebo within each cohort were pooled. [b]Elderly male subjects.
Abbreviation: CSF, cerebrospinal fluid.