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Pharmacokinetics and Tolerability of KM-023 in Healthy Subjects

건강한 자원자에서 KM-023 의 약동학 및 내약성에 대한 연구

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차 유 정

Pharmacokinetics and Tolerability of KM-023 in Healthy Subjects

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ABSTRACT

Introduction: KM-023 is a new second-generation non-nucleoside reverse transcriptase inhibitor that is under development for the treatment of human immunodeficiency virus (HIV) type-1 infection. This study determined KM-023 pharmacokinetic characteristics and tolerability in healthy subjects.

Methods: A randomized, double-blinded, placebo-controlled, dose-escalation study was conducted in 80 healthy Korean male volunteers. The subjects were allocated to single- or multiple-dose (once daily for 7 days) study that received 75, 150, 300, or 600 mg drug or placebo in a 4:1 ratio. The plasma and urine concentrations were quantified using liquid chromatography -tandem mass spectrometry. Plasma concentration-time data of KM-023 was analyzed by using non-compartmental methods. Adverse events were reported and tolerability monitoring was conducted.

Results: The average maximum concentration (C_{max}) and area under the concentration-time curve from time 0 to infinity (AUC_{inf}) values of KM-023 for the 75-600 mg doses in the single-dose study ranged from 440.2 ng/mL to 1245.4 ng/mL and 11142.4 ng·h/mL to 33705.6 ng·h/mL, respectively. The mean C_{max} at steady-state ($C_{max,ss}$) and area under the concentration-time curve within a dosing interval ($AUC_{\tau,ss}$) values ranged from 385.1 ng/mL to 1096.7 ng/mL and 3698.9 ng·h/mL to 10232.6 ng·h/mL, respectively, following 75-600 mg doses in the multiple-dose study. Dose proportionality was not observed for KM-023. KM-023 showed a 0.6-fold accumulation after multiple doses in the 600-mg dose group. KM-023 was generally well tolerated.

Conclusions: KM-023 demonstrated dose- and time-dependent nonlinear pharmacokinetic characteristics after single or multiple doses over a dose range (75-600 mg) in healthy subjects. KM-023 showed favorable tolerability in this study.

Keywords: ***KM-023, pharmacokinetics, tolerability***

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LIST OF ABBREVIATION

AE	Adverse event
AI	Accumulation index
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
AUC_{last}	AUC from drug administration to the last quantifiable
AUC_{inf}	AUC from drug administration to time infinity
AUC_{τ}	AUC from the dosing to time point of next dosing
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CL/F	Apparent clearance
PK	Pharmacokinetic
T_{max}	Observed time of maximum plasma concentration
$t_{1/2}$	Terminal elimination half-life

INTRODUCTION

Current practice guidelines recommend a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI), such as efavirenz or a ritonavir-boosted protease inhibitor, as a first-line therapy for the treatment of human immunodeficiency virus (HIV) type-1 infection (1, 2), which has reduced the mortality and morbidity of HIV-1-infected patients (3, 4). Among these drugs, the use of efavirenz with two NRTIs as an initial therapy regimen resulted in higher overall virological efficacy compared with lopinavir-ritonavir plus two NRTIs in phase III clinical trials (1, 5).

Despite its advantages, the use of efavirenz has been limited by the emergence of both central nervous system toxicities and viral resistance (6-9). Second-generation NNRTIs, such as rilpivirine and etravirine, were developed to overcome these shortcomings. These drugs showed improved viral resistance profiles with better efficacy and less toxicity compared with first-generation NNRTIs (9, 10).

KM-023 (3-[3-ethyl-5-isopropyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidine-4-carbonyl]-5-methyl benzonitrile) has been under development as a novel second-generation NNRTI (Kainos Medicine USA Inc., Morrisville, NC, USA) (Figure 1). KM-023 has displayed favorable safety profiles and pharmacological characteristics in preclinical studies. KM-023 exhibited antiviral activity in the low nanomolar range against laboratory strains and

clinical HIV-1 isolates, and it showed activity against K103N (unpublished data), which is the major efavirenz-resistant mutation (11). There were no significant findings in *in vivo* safety pharmacology studies conducted in mice and dogs. The oral bioavailability and terminal elimination half-life ($t_{1/2}$) of KM-023 were 64–69% and 5.09–5.75 h in preclinical studies in dogs and monkeys, respectively. KM-023 moderately induced cytochrome P450 (CYP) 3A4 in *in vitro* studies using human hepatocytes (unpublished data). This study assessed the tolerability and pharmacokinetic characteristics of KM-023 following single or multiple oral doses in healthy subjects.

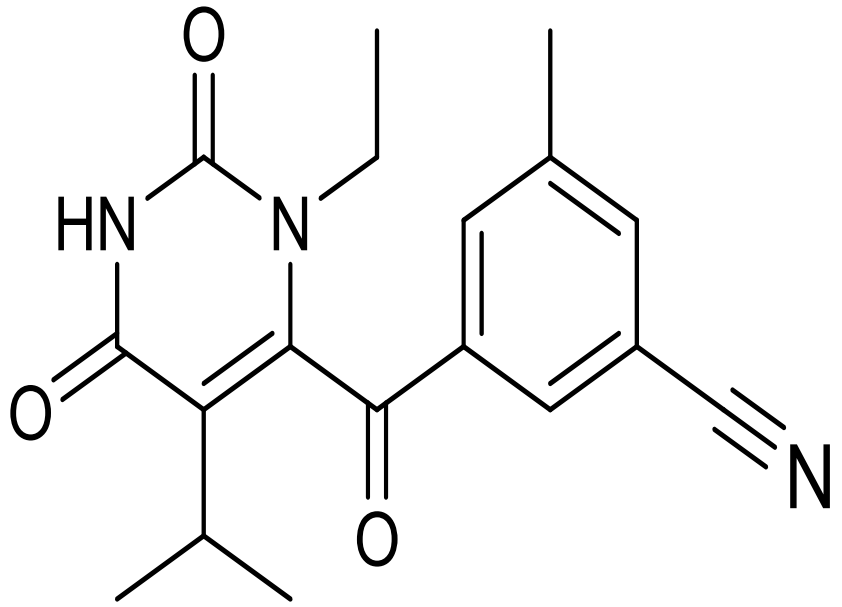

Figure 1. Chemical structure of KM-023

MATERIALS AND METHODS

Subjects

Eligibility criteria included adults aged 20-45 years with a body mass index of 18.5 to 25 kg/m^2 who had no clinically significant abnormalities upon clinical laboratory evaluation or physical examination. Volunteers who had clinically significant medical conditions or clinical laboratory test abnormalities, history of drug addiction or alcoholism, or positive serological tests (e.g., hepatitis B surface antigen, hepatitis C antibodies, and HIV) were excluded. Written informed consent was obtained from each subject prior to participation. Subjects who discontinued prior to completing the study were replaced.

The Seoul National University Hospital Institutional Review Board approved the study protocol. This study was performed according to the principles described in the Declaration of Helsinki and Good Clinical Practice (ClinicalTrials.gov identifier: NCT01348516) (12).

Study design

This study was conducted as a first-in-human, randomized, double-blind, placebo-controlled, single or multiple doses, dose-escalation clinical trial.

Eligible subjects in the single-dose study were randomly allocated into one of the following KM-023 dose groups: 75 mg, 150 mg, 300 mg, or 600 mg (each n=10). These subjects also randomly received a single oral dose of KM-023 or placebo at a ratio of 4:1.

Subjects in the multiple-dose study were also randomly assigned to one of four dose groups, which were the same as the single-dose study in doses and number of subjects. Subjects received KM-023 or placebo once daily for 7 days.

Determining KM-023 concentration

Blood and urine samples were collected to determine the pharmacokinetic characteristics of KM-023.

Blood samples (5 mL) in the single-dose study were collected into heparinized tubes pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 h after dosing to determine the KM-023 concentrations. Urine samples (20 mL) were collected at 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 72 h after dosing.

Blood samples (5 mL) in the multiple-dose study were collected into heparinized tubes pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 h after dosing on days 1 and 7. Samples for trough KM-023 concentration were obtained before dosing on days 2 to 6. Additional samples were collected at 0 h on days 8, 9, and 10. Urine samples were collected over the following time intervals of 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h after dosing on days 1 and 7.

Blood samples were centrifuged at 2,000 g for 10 min at 4°C. Separated plasma samples were stored at -70°C prior to analysis. Urine volume was measured, and 20-mL urine samples were stored at -70°C before analysis. KM-023 concentrations in plasma and urine were quantified using a validated liquid chromatography-tandem mass spectrometry method (LC-MS/MS). The internal standard was GS-9503 (3-[3-butyl-5-isopropyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidine-4-carbonyl]-5-methyl benzonitrile). Mass spectrometric detection was conducted using multiple reaction monitoring transition at mass-to-charge ratios 326.3->298.2 for KM-023 and 354.3->298.3 for GS-

9503 in both plasma and urine sample analyses. The assays were validated over a range of 0.5-500 ng/mL (plasma) and 5-5,000 ng/mL (urine). The assay accuracy and precision ranged from 94.2 to 97.1% and ≤ 7.5% in plasma and 88.6 to 97.0% and ≤ 3.6% in urine, respectively.

Pharmacokinetic analysis

Individual pharmacokinetic parameters were assessed using non-compartmental analysis using Phoenix® software (ver. 1.0, Certara, St. Louis, MO, USA). Maximal plasma concentrations (C_{max}) and time to C_{max} (T_{max}) were obtained from the observed values. The area under the time versus concentration curve (AUC) from time 0 to the last available measurement (AUC_{last}) and the AUC within a dosing interval (AUC_{τ}) were calculated using the linear up/log down method. The AUC from time 0 to infinity (AUC_{inf}) was the sum of AUC_{last} and C_t/λ_z, where C_t is the last measurable plasma concentration and λ_z is the elimination rate constant, as determined by linear regression analysis associated with the terminal (log-linear) portion of the plasma concentration-time curve. The half-life ($t_{1/2}$) was determined as $\ln 2/\lambda_z$. The apparent oral clearance (CL/F) was calculated as dose/AUC_{inf}. The fraction of unchanged drug excreted in the urine (f_e) was estimated as the amount of unchanged drug excreted in the urine (A_e) over the dose. The accumulation index was estimated by calculating $AUC_{144\text{-}168h}/AUC_{0\text{-}24h}$.

Tolerability assessments

Tolerability was evaluated by monitoring adverse events (AEs) throughout the study. Physical examination, vital sign measurements, 12-lead electrocardiogram (ECG), computerized impedance cardiography (CIC), and clinical laboratory tests were performed periodically before and after dosing during the study period.

Statistical analysis

Statistical analysis was performed using SPSS® software (version 17.0; SPSS, Inc., Chicago, IL, USA). All safety data and pharmacokinetic parameters were summarized as treatment and dose using descriptive statistics. Dose proportionality was assessed using linear regression on the log transformed C_{max} and AUC values. Dose proportionality was also evaluated concerning whether the 95% confidence interval (CI) for the log transformed C_{max} and AUC values included 1.0 in the power model. Repeated measures analysis of variance (RM-ANOVA) were used to investigate differences in the plasma trough concentrations in each treatment group to identify whether steady-state conditions were achieved by day 7. A P-value < 0.05 was considered statistically significant.

RESULTS

Study population

A total of 41 subjects were enrolled in the single-dose study**.** One subject who received 75 mg KM-023 discontinued the study because of a withdrawal of informed consent. A total of 41 subjects were enrolled in the multiple dose study. Of these subjects, one subject in the placebo group discontinued due to an influenza infection. No significant differences were observed in the demographic characteristics between the treatment groups (Table 1).

Table 1. Participants demography

Single dose	**Placebo n=8**	**75 mg n=9**	**150 mg n=8**	**300 mg n=8**	**600 mg n=8**	**Total n=41**	**P-value***
age (years)	27.1 ± 7.2	25.6 ± 4.1	28.1 ± 7.3	25.6 ± 3.5	27.8 ± 3.0	26.8 ± 5.2	0.629
body weight (kg)	66.2 ± 7.3	68.3 ± 6.1	67.4 ± 5.0	64.3 ± 10.4	66.4 ± 6.7	66.6 ± 7.1	0.728
height (cm)	172.4 ± 4.4	173.4 ± 4.4	174.0 ± 6.6	173.3 ± 6.2	174.8 ± 5.4	173.6 ± 5.2	0.806
BMI (kg/m^2)	22.3 ± 1.6	22.7 ± 1.1	22.3 ± 1.9	21.4 ± 2.4	21.8 ± 2.0	22.1 ± 1.8	0.658
Multiple doses	**Placebo n=9**	**75 mg n=8**	**150 mg n=8**	**300 mg n=8**	**600 mg n=8**	**Total n=41**	**P-value***
age (years)	25.4 ± 3.0	25.6 ± 2.2	25.3 ± 2.4	26.4 ± 2.3	27.0 ± 2.7	25.9 ± 2.5	0.695
body weight (kg)	64.5 ± 7.1	67.8 ± 7.9	64.6 ± 4.1	65.4 ± 8.2	67.5 ± 7.0	65.6 ± 6.9	0.827
height (cm)	172.0 ± 4.6	173.0 ± 5.5	172.8 ± 4.7	172.6 ± 4.1	174.1 ± 3.5	172.8 ± 4.3	0.940
BMI (kg/m^2)	21.8 ± 2.5	22.6 ± 1.9	21.6 ± 0.9	21.9 ± 2.2	22.2 ± 2.0	22.0 ± 2.0	0.845

The data are represented as the mean ± standard deviation.

BMI, body mass index

* The Kruskal-Wallis test was employed.

Pharmacokinetics

The average KM-023 plasma concentration-time profiles for each treatment group after single or multiple doses are illustrated in Figure 2. The predose concentrations were compared in the multiple-dose study using RM-ANOVA depending on the KM-023 dose, and steady state was attained after day 4 (75 mg) or day 6 (150-600 mg).

Following single or multiple doses of KM-023, the T_{max} values were ranged 0.5-6.0 h and the mean terminal elimination $t_{1/2}$ values were ranged 20.7-31.2 h. In the single dose study, the mean KM-023 C_{max} and AUC_{inf} values ranged from 440.2 to 1245.4 ng/mL and 11142.4 to 33705.6 ng·h/mL, respectively. In the multiple dose study, the mean KM-023 $C_{max,ss}$ and $AUC_{\tau,ss}$ values ranged from 385.1 to 1096.7 ng/mL and 3698.9 to 10232.6 ng·h/mL, respectively (Table 2). The C_{max} and AUC values increased as the dose escalated, but neither C_{max} nor AUC showed dose proportionality (Figure 2 and Table 3). After multiple doses of KM-023, the accumulation index ranged from 0.6 to 1.1. Notably, the accumulation index was 0.6 in the 600-mg dose group. The f_e values accounted for less than 1% at all dose levels. Therefore, renal clearance was not evaluated (Table 2).

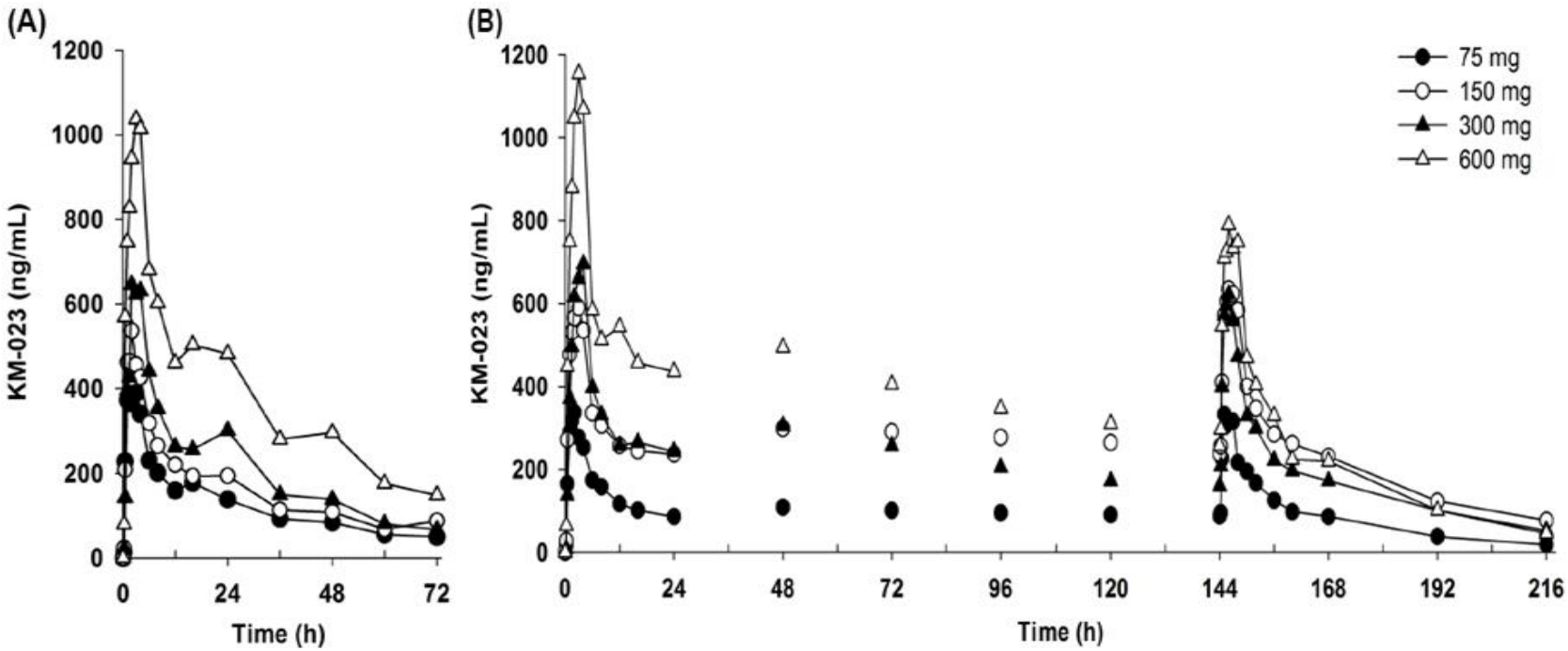

Figure 2. Mean plasma KM-023 concentration-time profiles after oral administration. (A, single dose; B, multiple doses)

Table 2. Pharmacokinetic parameters following single or multiple doses of KM-023

Single dose	**75 mg n=8**	**150 mg n=8**	**300 mg n=8**	**600 mg n=8**
$t_{1/2}$ (h)	29.3 ± 12.5	29.5 ± 11.9	31.2 ± 21.1	29.7 ± 15.6
T_{max} (h)	2.0 (1.0 - 4.0)	2.0 (1.0 - 6.0)	2.0 (1.0 - 4.0)	3.0 (0.5 - 4.0)
C_{max} (ng/mL)	440.2 ± 68.3	621.2 ± 104.9	832.4 ± 200.9	1245.4 ± 394.4
C_{max}/dose (ng/mL/mg)	5.9 ± 0.9	4.1 ± 0.7	2.8 ± 0.7	2.1 ± 0.7
AUC_{last} (ng·h /mL)	8738.2 ± 2882.1	11152.7 ± 3019.8	14663.0 ± 6414.5	26757.2 ± 14278.9
AUC_{inf} (ng·h /mL)	11142.4 ± 4808.3	14143.2 ± 5736.5	18122.4 ± 9157.8	33705.6 ± 18646.3
AUC_{inf}/dose (ng·h mL/mg)	148.6 ± 64.1	94.3 ± 38.2	60.4 ± 30.5	56.2 ± 31.1
CL/F (L/h)	16.2 ± 3.9	24.8 ± 5.6	40.3 ± 12.4	50.0 ± 21.9
f_e (%)	0.94 ± 0.64	0.65 ± 0.34	0.52 ± 0.41	0.25 ± 0.17
Multiple doses	**75 mg n=8**	**150 mg n=8**	**300 mg n=8**	**600 mg n=8**
$t_{1/2,ss}$ (h)	22.1 ± 5.4	25.9 ± 13.1	28.2 ± 19.4	20.7 ± 3.7
$T_{max,ss}$ (h)	1.3 (0.5 - 3.0)	1.3 (0.5 - 3.0)	1.5 (1.0 - 3.0)	2.0 (1.0 - 4.0)

$C_{max,ss}$ (ng/mL)	385.1 ± 126.3	740.0 ± 248.1	706.4 ± 192.5	1096.7 ± 489.1
$C_{max,ss}$/dose (ng/mL/mg)	5.1 ± 1.7	4.9 ± 1.7	2.4 ± 0.6	1.8 ± 0.8
$AUC_{\tau,ss}$(ng·h /mL)	3698.9 ± 1006.4	8252.3 ± 4060.7	6813.0 ± 1880.0	10232.6 ± 5710.2
$AUC_{\tau,ss}$/dose (ng·h mL/mg)	49.3 ± 13.4	55.0 ± 27.1	22.7 ± 6.3	17.1 ± 9.5
CL/F (L/h)	21.5 ± 5.4	22.3 ± 10.2	48.0 ± 17.6	71.9 ± 28.1
f_e (%)	0.52 ± 0.40	0.75 ± 0.52	0.28 ± 0.15	0.18 ± 0.12
Accumulation index	1.1 ± 0.2	1.1 ± 0.5	0.9 ± 0.2	0.6 ± 0.1

The data are represented as the mean ± standard deviation except for T_{max}, for which the median (range) is shown.
$t_{1/2}$, terminal elimination half-life; T_{max}, time to the maximum plasma concentration; C_{max}, maximum plasma concentration; AUC_{inf}, area under the plasma concentration-time curve extrapolated to infinity; CL/F, apparent oral clearance; f_e, percent of the amount excreted unchanged in urine; $C_{max,ss,}$ maximum plasma concentration at steady-state; $AUC_{\tau,ss}$, area under the plasma concentration-time curve within a dosing interval at steady-state.

Table 3. Assessment of KM-023 dose-proportionality

Single dose			
		C_{max}	AUC_{inf}
Power model			
Regression Line Intercept		4.00	7.02
Regression Line Slope		0.48	0.50
	(95% CI)	(0.38, 0.58)	(0.30, 0.70)
Multiple doses			
		$C_{max,ss}$	$AUC_{\tau,ss}$
Power model			
Regression Line Intercept		4.12	7.17
Regression Line Slope		0.44	0.38
	(95% CI)	(0.27, 0.61)	(0.14, 0.62)

Power model: Ln Y = a + b·ln(Dose), Y: parameter (C_{max}, AUC_{inf}, $C_{max,ss,}$ and $AUC_{\tau,ss}$)

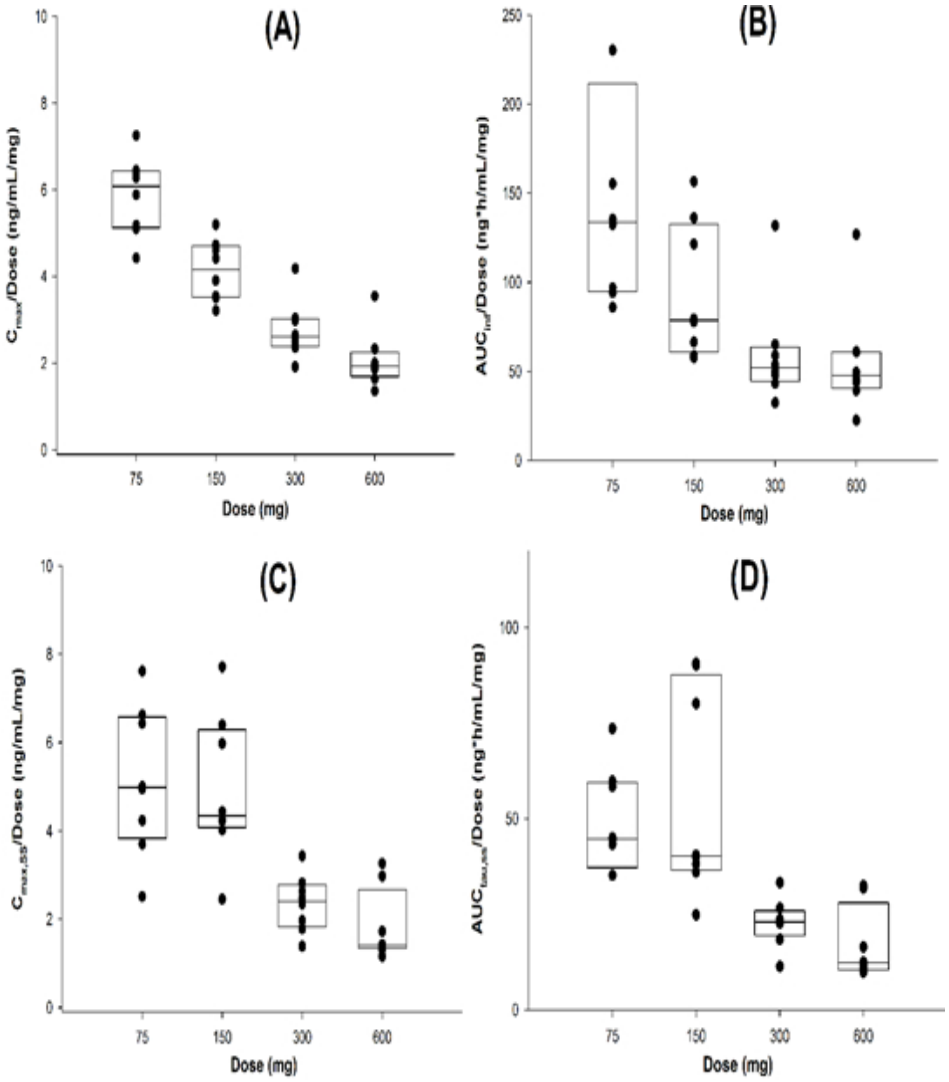

Figure 3. Comparisons of C_{max}/Dose (A), AUC_{inf}/Dose (B),$C_{max,ss}$/Dose (C), and $AUC_{\tau,ss}$/Dose (D) with respect to KM-023 doses. (A and B, single dose; C and D, multiple dose)

Tolerability

Fifteen subjects in the single dose study experienced a total of 17 AEs throughout the study. Nine AEs that occurred in 7 subjects were drug-related. Twenty-two subjects in the multiple-dose study experienced a total of 24 AEs during the study period. Seventeen AEs that occurred in 16 subjects were drug-related. Epistaxis (7 occurrences; 2 in one subject (single-dose study), 5 in four subjects (multiple-dose study)) was the most frequently reported AE. All 7 occurrences were deemed to be drug-related AEs by the investigators. No serious AEs occurred in this study (Table 4). There were no clinically meaningful changes from baseline in clinical laboratory test results, vital signs, ECGs, CICs, or physical examinations.

Table 4. Adverse events (AEs) per system organ class after single or multiple KM-023 doses

System Organ Class/AEs	Single dose		Multiple doses	
	All AEs	Drug-related AEs	All AEs	Drug-related AEs
General disorder				
Feeling hot	1 (1)			
Pruritus	1 (1)	1 (1)		
Oropharyngeal, respiratory, thoracic and mediastinal disorders				
Oropharyngeal pain	1 (1)		1 (1)	
Cough	1 (1)			
Rhinorrhea	1 (1)		1 (1)	1 (1)
Normal sputum	1 (1)			
Epistaxis	2 (1)	2 (1)	5 (4)	5 (4)
Nasal dryness			1 (1)	
Allergic rhinitis			1 (1)	
Oral mucosa erosion			1 (1)	1 (1)
Gingival pain			1 (1)	1 (1)

Toothache	1 (1)			
Chest discomfort			1 (1)	1 (1)
Influenza A			1 (1)	
Ophthalmologic disorders				
Corneal erosion Lt.	1 (1)			
Nervous system disorders				
Paresthesia	1 (1)	1 (1)	1 (1)	1 (1)
Dizziness	1 (1)			
Somnolence	2 (2)	2 (2)		
Neuralgia			1 (1)	1 (1)
Headache			2 (2)	2 (2)
Musculoskeletal disorders				
Back pain	2 (1)	2 (1)		
Gastrointestinal disorders				
Upper abdominal pain			1 (1)	1 (1)
Dyspepsia			2 (2)	2 (2)
Genitourinary disorders				
Dysuria	1 (1)	1 (1)		

Skin and subcutaneous tissue disorders				
Chapped lips			1 (1)	1 (1)
Eczema			2 (1)	
Contact dermatitis			1 (1)	
Total	17 (15)	9 (7)	24 (22)	17 (16)

The data are represented as the number of events (number of subjects)

DISCUSSION

The primary objective of this phase I clinical study was to investigate the pharmacokinetic characteristics of KM-023, a newly developed second-generation NNRTI, and evaluate its tolerability in healthy volunteers. KM-023 showed dose- and time-dependent nonlinear pharmacokinetics. In addition, there was no laboratory or clinical evidence of clinically significant AEs to KM-023. The present study provides initial information on the tolerability and pharmacokinetic characteristics of KM-023 in humans.

We could not calculate the renal CL because the mean f_e values were less than 1% in all dose groups. Our findings suggest that non-renal pathways primarily eliminated KM-023. These results are consistent with other NNRTIs, which show negligible renal excretion and extensive hepatic metabolism (13). However, the detailed metabolites and metabolic pathways of KM-023 have not been characterized. Therefore, an evaluation of the metabolic pathways and a measurement of metabolite concentrations and KM-023 potency are needed.

KM-023 showed less than dose-proportional nonlinear pharmacokinetics over the 75 to 600 mg dose range. This pattern was also observed in first-generation NNRTIs. After a single oral administration of efavirenz (100 to 1600 mg) and nevirapine (2.5 to 400 mg) in healthy subjects, the C_{max} or AUC increased less than dose-proportionally, which suggests diminished absorption or enhanced CL at higher doses (14, 15). The reduced absorption may be due

to the saturation of influx transporters, and the enhanced CL may result from induced enzymes involved in hepatic/intestinal metabolism (16). Further studies are needed to investigate the mechanism of the less than dose-proportional nonlinear pharmacokinetics of KM-023.

The accumulation index was 0.6-1.1 over the range of the 75-600 mg doses. Interestingly, the average accumulation index decreased to 0.6 in the 600-mg dose group. These findings indicate that the metabolic enzymes related to KM-023 metabolism were induced by multiple KM-023 administrations. A similar auto-induction phenomenon was also observed in efavirenz, nevirapine (13). KM-023 exhibited a moderate potential for pregnane X receptor (PXR) and CYP3A4 messenger RNA (mRNA) activation in primary human hepatocytes (unpublished data). The markedly increased CL/F values after multiple doses of 600 mg, which could be partially explained by an auto-induction of CYP3A4 enzymes due to a sustained relatively high exposure of KM-023, might be the reason for the apparently low accumulation. Therefore, it is anticipated that the exposure of KM-023 will be decreased when using high doses of KM-023 (particularly more than 600 mg) for clinical use.

The most frequent AE after KM-023 administration in the present study was epistaxis; however, there were no statistically significant changes in the occurrence rates between placebo and treatment groups, and the rate was not dose-dependent. Among widely used first-generation NNRTIs, efavirenz demonstrated CNS toxicity, while nevirapine and delavirdine demonstrated hepatotoxicity or hypersensitivity reactions such as a rash (8). We compared

the AEs that occurred after multiple doses of KM-023 in healthy subjects with the results obtained from first generation NNRTIs. Nervous system symptoms, headache (2 occurrences), paresthesia (1 occurrence), and neuralgia (1 occurrence) were reported after multiple doses of KM-023; however, these symptoms were not severe and transient. There were also no reported AEs or clinically significant laboratory abnormalities associated with hypersensitivity reactions and liver function.

In conclusion, the pharmacokinetics of KM-023 showed dose- and time-dependent nonlinear pharmacokinetic profiles. Single or multiple doses of KM-023 at 75-600 mg was well tolerated in healthy subjects. Further clinical trials evaluating the efficacy and safety of KM-023 in HIV-1 positive patients are warranted.

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국문 초록

서론: KM-023 은 인간 면역 결핍 바이러스 감염의 치료를 목적으로 새롭게 개발된 2 세대 비뉴클레오사이드 역전사 효소 억제제이다. 본 연구에서는 건강한 자원자에서 KM-023 의 약동학적 특성 및 내약성을 탐색하고자 하였다.

방법: 본 연구는 무작위 배정, 이중맹검, 위약 대조, 용량 증량 형태로 설계 되었으며, 80 명의 건강한 성인 남성이 연구에 참여 하였다. 자원자들은 KM-023 75, 150, 300, 600 mg 또는 위약을 단회 또는 반복 (1 일 1 회씩, 7 일 동안) 투여 받았다. 혈중 및 소변 약물 농도 측정에는 liquid chromatography-tandem mass spectrometry 를 이용하였다. 약동학 분석은 비구획 방법 (noncompartmental methods)을 이용하여 분석하였다. 임상시험 기간 동안 이상반응을 수집 하였으며, 내약성을 평가하였다.

결과: KM-023 75-600 mg 용량을 단회 투여시, 평균 최고혈중농도 (C_{max}) 및 체내노출 (area under the concentration-time curve from time 0 to infinity, AUC_{inf}) 값의 범위는 각각 440.2-1245.4 ng/mL 및 11142.4-33705.6 ng · h/mL 이었다. KM-023 75-600 mg 용량을 반복 투여시, 항정상태에서의 평균 최고혈중농도 ($C_{max,ss}$) 및 체내노출 (area under the concentration-time curve within a dosing interval, $AUC_{\tau,ss}$) 값의 범위는 각각

385.1−1096.7 ng/mL and 3698.9−10232.6 ng · h/mL 이었다. 용량−비례성은 관찰되지 않았다. KM−023 반복 투여시, 600 mg 용량군에서 축적 지수(accumulation index)가 0.6 으로 관찰 되었다. 또한 KM−023 75 mg 에서 600 mg 용량 범위에서 내약성이 양호함을 확인하였다.

결론: 건강한 자원자에서 KM−023 75−600 mg 을 단회 또는 반복 투여시 용량− 및 시간−의존적 비선형적 약동학적 특성을 보였다. KM−023 약물은 내약성이 양호한 안전한 약물이 될 수 있을 것으로 기대 된다.

주요어 : *KM−023, 약동학, 내약성*

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