

# Pharmacokinetics, Tolerability and Pharmacogenetics of DA-8031 After Multiple Ascending Doses in Healthy Male Subjects

Sejung Hwang <sup>1</sup>  
Dae Young Lee<sup>2</sup>  
Joo-Youn Cho <sup>1,3</sup>  
Jae-Yong Chung<sup>4</sup>  
In-Jin Jang <sup>1</sup>  
Kyung-Sang Yu <sup>1,3</sup>  
SeungHwan Lee <sup>1</sup>

<sup>1</sup>Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea; <sup>2</sup>Drug Metabolism and Pharmacokinetics (DMPK), Drug Evaluation, Dong-A ST Research Institute, Gyeonggi-do, Republic of Korea; <sup>3</sup>Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Republic of Korea; <sup>4</sup>Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Bundang Hospital, Seongnam, Republic of Korea

Correspondence: SeungHwan Lee  
Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, 101 Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea  
Tel +82-2-2072-2343  
Fax +82-2-2072-0720  
Email leejh413@snu.ac.kr

**Purpose:** DA-8031 is a novel selective serotonin reuptake inhibitor for the treatment of premature ejaculation. This study investigated the pharmacokinetics, safety and tolerability of multiple oral doses of DA-8031. In addition, a genetic analysis was explored to evaluate the effect of genetic polymorphisms on the pharmacokinetics of DA-8031.

**Subjects and Methods:** A dose block-randomized, double-blind, placebo-controlled study was conducted in 3 dose groups with 20, 30 and 40 mg of DA-8031. Healthy male subjects were randomized to DA-8031 or placebo at a 4:1 ratio in each dose group of 10 subjects by oral administration once daily for 7 consecutive days. Serial blood and urine samples were collected for the pharmacokinetic evaluation, and the pharmacokinetic-related genes were analyzed by DMET™ plus. A safety evaluation was conducted including adverse events (AEs) monitoring and 12-lead electrocardiogram (ECG).

**Results:** The plasma DA-8031 concentration reached the maximum concentration ( $C_{max}$ ) in 2.2 to 3.0 h and was eliminated with a mean half-life of 25.5 to 26.7 h at steady state. The accumulation index of DA-8031 ranged 2.3 to 2.8. The systemic exposure of DA-8031 of the CYP2D6 intermediate metabolizer (IM) was significantly higher compared to the CYP2D6 poor metabolizer (PM). There were no clinically significant QTc interval changes, and all the adverse events were mild.

**Conclusion:** After multiple oral doses of DA-8031 20, 30, and 40 mg in this study, the systemic exposure of DA-8031 increased in a more than dose-proportional manner with the increasing doses, and DA-8031 was generally well tolerated. In addition, the genetic polymorphisms of CYP2D6 have an impact on the pharmacokinetics of DA-8031.

**Keywords:** selective serotonin reuptake inhibitors, clinical pharmacology, phase 1 study, pharmacogenomics

## Introduction

Premature ejaculation (PE) is one of the common male sexual dysfunctions, and its prevalence rate is globally 20–30% and 11–33% in Korea.<sup>1,2</sup> Although the etiologies of PE are not fully understood, psychological factors such as the anxiety for rapid ejaculation<sup>1</sup> or neurobiological factors associated with the hyposensitivity of 5-hydroxytryptamine (5-HT) 2C and the hypersensitivity of 5-HT<sub>1A</sub> receptors are thought to contribute to the pathophysiology of PE.<sup>1,3,4</sup>

So far, there are two approaches in the treatment of PE based on the etiologies: One is behavioral/psychotherapy, and the other is pharmacotherapy.<sup>1</sup> Off-label and on-demand selective serotonin reuptake inhibitors (SSRIs) and tricyclic

antidepressants (TCAs) are commonly used for PE.<sup>1</sup> SSRIs and TCAs are approved by and commonly used for the treatment of mood disorders and anxiety.<sup>5,6</sup> SSRIs including fluoxetine, paroxetine and sertraline are used as an off-label drug for the treatment of PE, and SSRIs are thought to increase the latency by inhibiting serotonin transporters that reabsorb 5-HT from the nerve terminal.<sup>7</sup> Recently, dapoxetine (Johnson & Johnson, Priligy, New Brunswick, NJ, USA) got marketing approval in some countries including Europe for the treatment of PE as a short-acting SSRI used in an on-demand manner.<sup>8,9</sup> However, dapoxetine showed a high prevalence of discontinuation in a clinical trial,<sup>10</sup> and on-demand SSRIs might be an inappropriate approach for lifelong PE and have limited effects compared to daily SSRIs.<sup>11,12</sup> On the other hand, the daily SSRI treatments currently used increase the risk of adverse effects such as headache, nausea, diarrhea and sexual dysfunctions (reduced libido and erectile dysfunctions)<sup>4,7,9,11,13</sup> due to the potential drug-drug interactions and another serotonin sub-receptor and neurotransmitter receptor selectivity.<sup>4,11,14</sup> Thus, a novel SSRI is needed to overcome these current defects of on-demand and daily SSRIs.

DA-8031 is a novel SSRI for the treatment of PE.<sup>15,16</sup> In a preclinical study in rats, DA-8031 delayed the latency to ejaculation.<sup>15</sup> In a first-in-human single ascending dose clinical study, DA-8031 was rapidly absorbed at a median time of 2–3 h and eliminated with a mean terminal  $t_{1/2}$  of 17.9–28.7 h with a dose range of 5–120 mg. Although QT prolongation was observed after a single dose of 120 mg, DA-8031 was well tolerated after single doses of 80 mg or less.<sup>16</sup>

With regards to the chemical structure and metabolites of DA-8031, the previous *in vitro* study revealed that the chemical structure of DA-8031 and DA-8031 metabolized to M2, M4 and M1, and then M4 and M1 metabolized to M5.<sup>16</sup> In addition, the *in-vitro* study also revealed that five cytochrome-P450 enzymes (CYPs) (CYP2C19, CYP2C8, CYP2D6, CYP3A4 and CYP3A5) were involved in the metabolism pathway of DA-8031. In the first-in-human single ascending dose clinical study, the metabolic ratios of M4 and M5 were higher than those of M1 and M2. This previous study also showed that the exposure of DA-8031 and the metabolic ratios of the metabolites (M1, M4, and M5) were different according to the genetic polymorphism of CYP2D6, extensive and intermediate metabolizer. This result suggested that CYP2D6 is involved in the pathway for the formation of M1, M4 and M5. Otherwise, the

genetic variability of CYP2C19 had a limited effect on the metabolism of M1.<sup>16</sup>

The aim of this study was to investigate the pharmacokinetics, safety, and tolerability after multiple ascending oral doses of DA-8031. In addition, it evaluated the effect of genetic polymorphisms of drug metabolizing enzymes on the pharmacokinetics of DA-8031.

## Methods

The clinical trial was approved by the Institutional Review Board (IRB) at Seoul National University Hospital and conducted in accordance with the Declaration of Helsinki and Korean Good Clinical Practice (KGCP) (ClinicalTrials.gov identifier: NCT01104948, IRB number: 1002–068-310). Written informed consents were obtained from all subjects prior to clinical study related procedures.

## Study Population

Healthy Korean male subjects aged 20–45 years with a body weight ranging from 60 to 90 kg, and a body mass index (BMI) ranging from 18.5 to 25 kg/m<sup>2</sup> were eligible to participate in this study. Subjects who had received tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) or monoamine oxidase (MAO) inhibitors and whose 12-lead electrocardiogram indicated a QTc interval > 430 ms, PR interval > 200 ms or QRS interval > 120 ms were excluded considering the QT prolongations observed during the single ascending dose study of DA-8031.<sup>16</sup>

## Study Design and Procedures

This study was a dose block-randomized, double-blind, placebo-controlled, multiple ascending dose study with 3 dose groups: 20, 30 and 40 mg of DA-8031. The subjects were randomized to DA-8031 or placebo in a 4:1 ratio in each dose group of 10 subjects and orally administered once daily for 7 days. The dose escalation was determined after assessing the safety and pharmacokinetic data of the previous dose group. Pharmacokinetic blood samples were collected at 0 (before dosing), 1, 2, 3, 4, 5, 6, 8, 12 and 24 hours after the first dose (Day 1), at pre-dose during multiple doses (Day 2 to Day 6), and 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96 and 120 hours at steady state after the last dose (Day 7). For each blood sampling, 6 mL of blood were collected in heparin and centrifuged at 1981 g for 10 min at 4°C, and three aliquots of supernatant were stored at –20°C until analysis. Plasma

concentrations of DA-8031 and its metabolites (M1, M2, M4 and M5) were analyzed separately using a validated high-performance liquid chromatography (HPLC)–tandem mass spectrometry (MS/MS) system in the positive ionization mode.<sup>16</sup>

## Pharmacokinetic Analysis

The PK analysis was conducted in subjects who completed the study with quantifiable concentrations of DA-8031 and metabolites. The PK parameters were estimated by non-compartmental methods using WinNonlin<sup>®</sup> (Pharsight Co, Mountain View, CA, USA) and included maximum plasma concentration ( $C_{max}$ ), time to reach  $C_{max}$  ( $T_{max}$ ), area under the concentration-time curve (AUC) calculated by the linear-up/log-down trapezoidal method, half-life ( $T_{1/2}$ ), clearance (CL), accumulation index as the AUC during the dosing interval at steady state divided by the AUC during the dosing interval after the first dose ( $AUC_{0-24h,ss}/AUC_{0-24h}$ ), and metabolic ratio (MR) determined by  $AUC_{metabolite}/AUC_{DA-8031}$ . These parameters were obtained both after a single dose and at the steady state after multiple doses.

## Genetic Analysis

DMET<sup>™</sup> plus (Affymetrix, Santa Clara, CA, USA) at DNA Link. Co. Ltd. (Seoul, Korea) was used to conduct the analysis of genes associated with the PK of DA-8031. In total, 225 genes were analyzed which were associated with the enzymes and transporters related to the pharmacokinetics. In this study, five cytochrome-P450 (CYP) enzymes (CYP2C19, CYP2C8, CYP2D6, CYP3A4 and CYP3A5) were selected which are known to be involved in the metabolism of DA-8031 reported in the in vitro study. Based on the genotypes, subjects were classified as follows: for CYP2C19, ultra-rapid metabolizer (UM) (\*17/\*17, \*1/\*17), extensive metabolizer (EM) (\*1/\*1), intermediate metabolizer (IM) (\*1/\*2, \*1/\*3) or poor metabolizer (PM) (\*2/\*2, \*2/\*3, \*3/\*3),<sup>17</sup> and for CYP2D6, ultra-metabolizer (UM) (\*1/\*1xN, \*1/\*2xN, \*2/\*2xN), extensive metabolizer (EM) (\*1/\*1, \*2/\*2, \*1/\*2, \*1/\*10, \*2/\*10), intermediate metabolizer (IM) (\*10/\*10, \*10/\*41) or poor metabolizer (PM) (\*3/\*4, \*4/\*4, \*5/\*5, \*5/\*6),<sup>17</sup> and for CYP3A4, extensive metabolizer (EM) (\*1/\*1) or intermediate metabolizer (IM) (\*1/\*16, \*1/\*22),<sup>18,19</sup> and for CYP3A5, extensive metabolizer (EM) (\*1/\*1), intermediate metabolizer (IM) (\*1/\*3) or poor metabolizer (PM) (\*3/\*3).<sup>20</sup>

## Safety and Tolerability Assessments

The safety and tolerability were evaluated by monitoring adverse events (AEs) by self-reporting and investigators' questionnaire, physical examinations, vital signs, 12-lead electrocardiogram (12-lead ECGs), clinical laboratory test and computerized impedance cardiography (CIC). Twelve-lead ECGs were conducted at 0, 1, 2, 3, 4, 6 and 8 hours one day before the first dose (Day -1) as baseline, pre-dose (0), 1, 2, 3, 4, 6 and 8 hours after the first dose (Day 1), pre-dose and 2 hours post-dose during the multiple doses (Day 2 to Day 6), and pre-dose, 1, 2, 3, 4, 6, 8, 24 and 72 hours after the last dose (Day 7). ECG recordings were analyzed for the ventricular rate, PR interval, QT interval and QRS duration, and the heart-rate corrected QT intervals (QTc) were calculated by Bazett's formula ( $QTcB = QT/[RR \text{ interval}]^{1/2}$ ) and Fridericia's formula ( $QTcF = QT/[RR \text{ interval}]^{1/3}$ ).

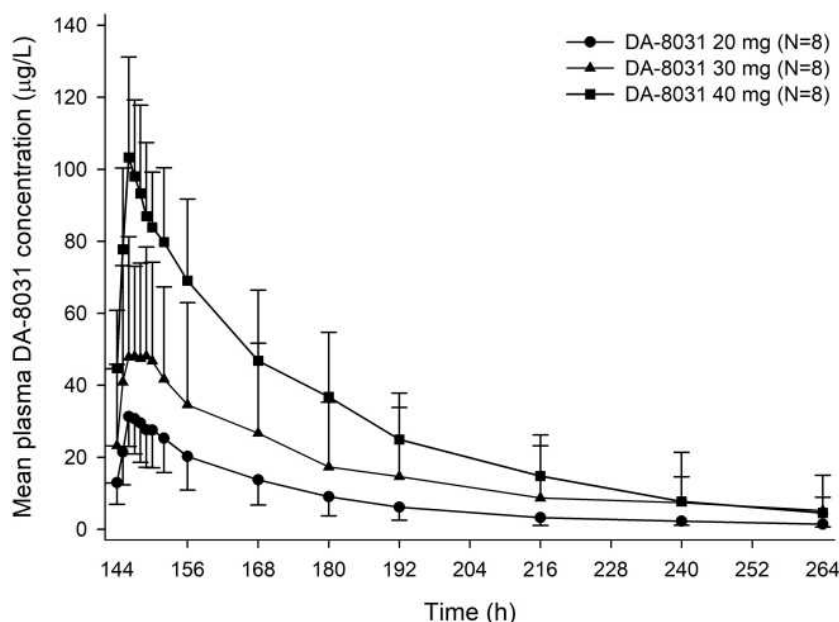
## Statistical Analysis

SAS<sup>®</sup> software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analysis. Analysis of variance (ANOVA) and a power model were performed to evaluate the dose proportionality for the AUC and  $C_{max}$ . To assess the effect of the genetic polymorphisms on PK, dose-normalized  $C_{max}$  at steady state ( $C_{max,ss}/D$ ) and dose-normalized AUC during the dosing interval at steady state ( $AUC_{0-24h,ss}/D$ ) were assumed to have a log-normal distribution. The parameters were evaluated using the generalized linear model with the dose as the covariates, and the geometric mean ratio (GMR) and 90% confidence interval (90% CI) were calculated to assess the difference in the PK parameters between the genotypes. The changes in the maximum QTcB and QTcF intervals from the baseline of each dosage group were compared with the placebo group using ANOVA with Dunnett's *t*-test. Moreover, statistical significance was defined as a *p*-value < 0.05.

## Results

### Study Population

A total of 32 healthy Korean male subjects were enrolled, and 30 subjects completed the study; Two subjects (each subject in 20 mg and 30 mg) withdrew their consents after several doses of DA-8031. The PK analysis was conducted in 24 subjects who received DA-8031, and the safety analysis was conducted in 32 subjects who received DA-8031 at least once. The age, weight, height, and body mass



**Figure 1** Mean plasma DA-8031 concentration-time profiles at steady state after multiple oral doses of DA-8031 20, 30 or 40 mg. Bars represent standard deviations.

index (BMI) of the 32 enrolled subjects were  $26.3 \pm 4.1$  (mean  $\pm$  standard deviation) years,  $68.9 \pm 4.6$  kg,  $173.8 \pm 4.7$  cm, and  $22.8 \pm 1.6$  kg/m<sup>2</sup>, respectively.

## Pharmacokinetics

DA-8031 was rapidly absorbed and reached the maximum concentration with a median time of 2–3 hours at steady

**Table 1** Pharmacokinetic Parameters of DA-8031 After a Single or Multiple Oral Doses

Day	Parameters	Treatment		
		20 mg (N=8)	30 mg (N=8)	40 mg (N=8)
Single dose (Day 1)	$T_{max}$ (h) <sup>a</sup>	2.5 (1.0–6.0)	2.0 (2.0–4.0)	2.0 (2.0–6.0)
	$C_{max}$ (µg/L)	18.5 $\pm$ 3.6	29.2 $\pm$ 12.1	49.9 $\pm$ 14.1
	$AUC_{0-24h}$ (µg h/L)	219.5 $\pm$ 75.3	353.7 $\pm$ 214.6	608.1 $\pm$ 168.5
	$AUC_{inf}$ (µg h/L)	339.3 $\pm$ 142.2	646.4 $\pm$ 728.0	1119.6 $\pm$ 74.9*
	$T_{1/2}$ (h)	14.6 $\pm$ 4.0	15.5 $\pm$ 9.7	19.0 $\pm$ 11.5*
	CL/F (L/h)	70.9 $\pm$ 36.2	75.8 $\pm$ 38.7	47.3 $\pm$ 21.3*
Multiple doses (Day 7)	$T_{max,ss}$ (h) <sup>a</sup>	2.5 (2.0–5.0)	2.5 (1.0–6.0)	3.0 (2.0–5.0)
	$C_{max,ss}$ (µg/L)	33.7 $\pm$ 9.8	55.5 $\pm$ 30.7	104.9 $\pm$ 26.8
	$AUC_{0-24h,ss}$ (µg h/L)	504.7 $\pm$ 207.1	872.5 $\pm$ 648.6	1668.9 $\pm$ 493.1
	$T_{1/2,ss}$ (h)	26.7 $\pm$ 7.2	26.1 $\pm$ 13.6	25.5 $\pm$ 4.4
	CL <sub>ss</sub> /F (L/h)	46.9 $\pm$ 22.4	45.0 $\pm$ 19.8	25.8 $\pm$ 7.7
	Accumulation index	2.3 $\pm$ 0.3	2.4 $\pm$ 0.3	2.8 $\pm$ 0.3

**Notes:** Values are presented as the mean  $\pm$  standard deviation. Accumulation index is calculated as  $AUC_{0-24h,ss}/AUC_{0-24h}$ ; <sup>a</sup>Values are presented as the median (minimum-maximum); \*N=7, Terminal elimination constants of one subject of the 40 mg dose group were not estimated.

**Abbreviations:**  $AUC_{0-24h}$ , area under the curve from 0 hours to 24 hours;  $AUC_{0-24h,ss}$ , area under the curve from 0 hours to 24 hours at steady state;  $AUC_{inf}$ , area under the curve from 0 hours to infinity; CL/F, total clearance; CL<sub>ss</sub>/F, total clearance at steady state;  $C_{max}$ , maximum concentration;  $C_{max,ss}$ , maximum concentration at steady state;  $T_{1/2}$ , half-life;  $T_{1/2,ss}$ , half-life at steady state;  $T_{max}$ , time of  $C_{max}$ ;  $T_{max,ss}$ , time of  $C_{max}$  at steady state.

state after multiple oral doses (Figure 1). The mean  $T_{1/2}$  ranged from 25.5 to 26.7 hours. The mean apparent clearance of DA-8031 at steady state was 46.9 and 45.0 L/h after multiple oral doses of 20 and 30 mg, respectively, but decreased to 25.8 L/h after multiple doses of 40 mg. The mean accumulation indexes were 2.3, 2.4 and 2.8 after multiple oral doses of 20, 30, or 40 mg of DA-8031, respectively (Table 1).

Regarding the analysis of dose proportionality, there were no statistical differences in the dose-normalized  $C_{max,ss}$  and  $AUC_{0-24h,ss}$  among the 20, 30 and 40 mg dose groups of DA-8031 assessed by ANOVA ( $C_{max,ss}$ ,  $p = 0.05$ ;  $AUC_{0-24h,ss}$ ,  $p = 0.11$ ). However, the 95% CIs of the slope of  $C_{max,ss}$  and  $AUC_{0-24h,ss}$  in the power model were 1.10–2.13 and 1.08–2.41, respectively.

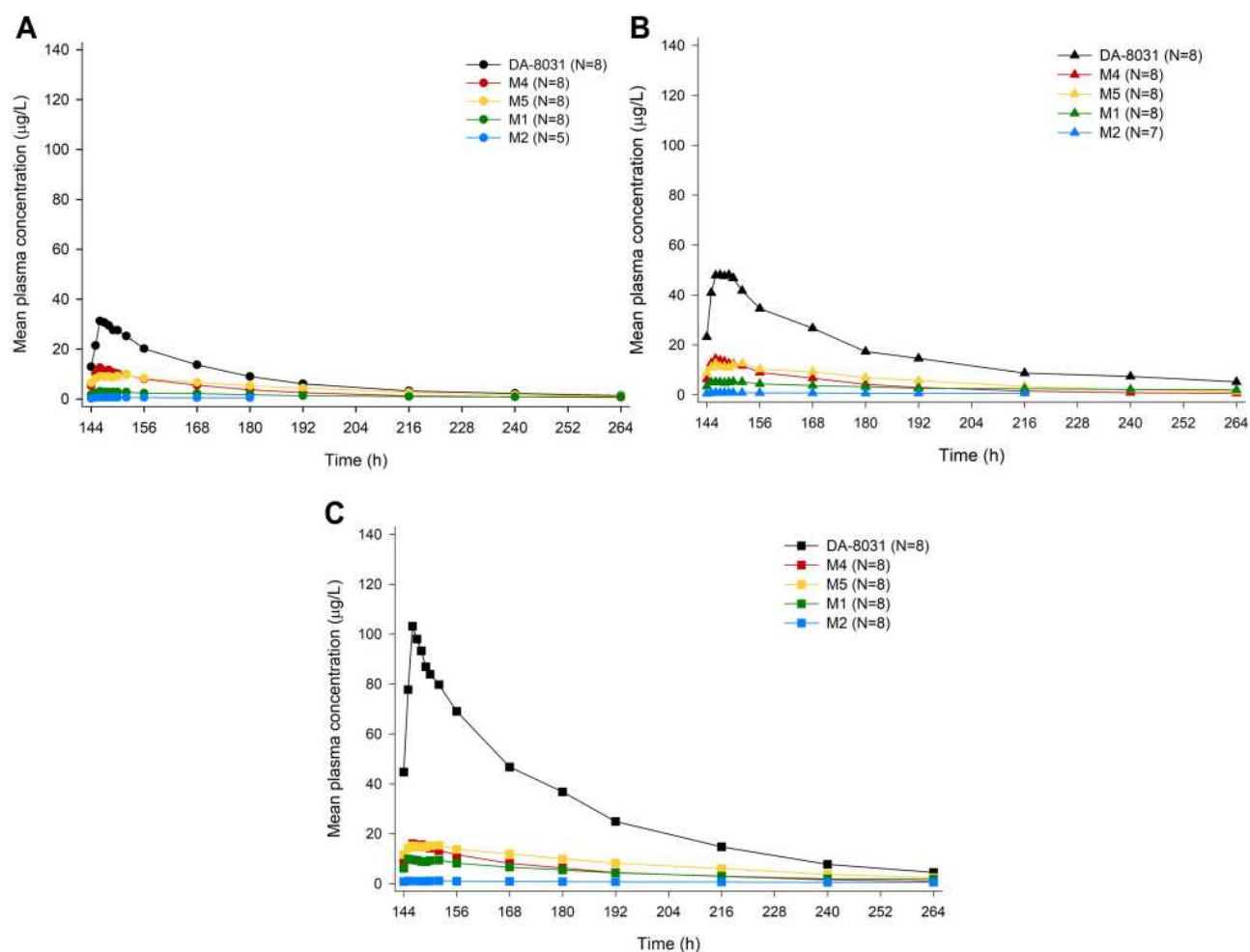
M4 and M5 were the major metabolites of DA-8031 with a metabolic ratio of 0.19–0.48 and 0.22–0.46,

respectively (Figure 2A–C). The MR of M4 and M5 at steady state decreased in the 40 mg dose group compared to the 20 or 30 mg dose group (Supplementary Table 1).

## Effect of the Genetic Polymorphism on PK

In this study, there were 16 subjects with CYP2D6 EM, 8 subjects with CYP2D6 IM, and no subjects with CYP2D6 UM or PM. Regarding CYP2C19, there were 11 subjects with EM, 7 subjects with IM, 6 subjects with PM and no subjects with UM (Table 2). The frequency distributions of CYP2D6 and CYP2C19 in this study were similar to those previously known in Koreans from previous reports.<sup>21,22</sup>

The dose-normalized  $C_{max,ss}$  of DA-8031 was 1.6-fold higher, and the dose-normalized  $AUC_{0-24h,ss}$  of DA-8031 was 1.9-fold higher in subjects with CYP2D6 EM than in



**Figure 2** Mean plasma concentration-time profiles of DA-8031 and M4, M5, M1, M2 at steady state after multiple oral doses of DA-8031 20, 30 or 40 mg. ((A) DA-8031 20 mg, (B) DA-8031 30 mg, (C) DA-8031 40 mg).

**Table 2** Dose-Normalized Pharmacokinetic Parameters of DA-8031 at Steady State After Multiple Oral Doses According to the CYP2D6 and CYP2C19 Phenotype

Parameters	CYP2D6				CYP2C19					
	EM	IM	GMR for IM to EM (90% CI)	P- value	EM	IM	GMR for IM to EM (90% CI)	PM	GMR for PM to EM (90% CI)	P-value
	(N=16)	(N=8)			(N=11)	(N=7)		(N=6)		
Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD				
$C_{max,ss}/Dose$	1.66 ± 0.48	2.84 ± 0.87	1.65 (1.38–1.98)	<0.0001	2.05 ± 0.57	2.26 ± 1.28	1.02 (0.72–1.45)	1.81 ± 0.71	1.00 (0.67–1.47)	0.9917
$AUC_{0-24h,ss}/Dose$	23.94 ± 8.29	48.16 ± 17.39	1.94 (1.54–2.44)	<0.0001	31.57 ± 9.12	36.61 ± 26.23	1.00 (0.63–1.58)	27.47 ± 14.45	0.96 (0.57–1.60)	0.9827
MR of M4	0.46 ± 0.26	0.15 ± 0.08	0.33 (0.21–0.51)	0.0004	0.26 ± 0.11	0.35 ± 0.27	0.87 (0.39–1.95)	0.55 ± 0.35	1.51 (0.61–3.71)	0.5035
MR of M5	0.46 ± 0.20	0.18 ± 0.11	0.33 (0.20–0.56)	0.0016	0.34 ± 0.16	0.39 ± 0.32	0.66 (0.27–1.59)	0.39 ± 0.21	0.85 (0.32–2.27)	0.6286
MR of M1	0.11 ± 0.02	0.13 ± 0.02	1.13 (0.95–1.34)	0.2236	0.13 ± 0.02	0.12 ± 0.01	0.98 (0.82–1.17)	0.09 ± 0.02	0.69 (0.57–0.85)	0.0032
MR of M2	0.026 ± 0.009	0.015 ± 0.006	0.59 (0.46–0.77)	0.0024	0.022 ± 0.010	0.024 ± 0.013	0.96 (0.61–1.52)	0.023 ± 0.006	0.91 (0.55–1.52)	0.9281

**Note:** Values are represented as the mean ± standard deviations.

**Abbreviations:**  $AUC_{0-24h,ss}$ , area under the curve from 0 hours to 24 hours at steady state; CI, confidence interval;  $C_{max,ss}$ , maximum concentration at steady state; EM, extensive metabolizer; GMR, geometric mean ratio; IM, intermediate metabolizer; MR, metabolic ratio; PM, poor metabolizer.

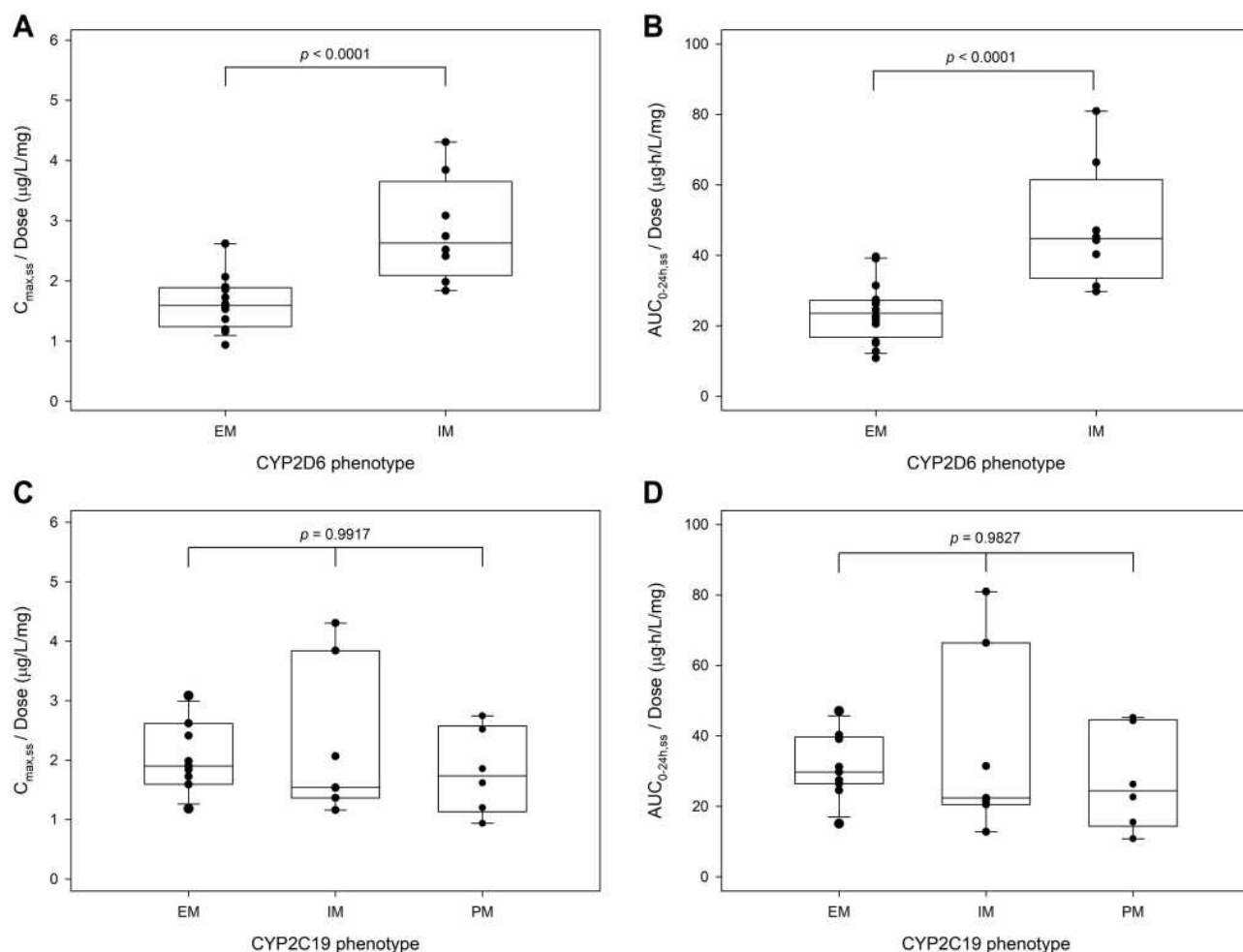
those with CYP2D6 IM (Figure 3A and B and Table 2). The MRs of M4, M5 and M2 showed significant differences according to the CYP2D6 phenotype (Table 2). On the other hand, the PK of DA-8031 did not significantly differ according to the CYP2C19 phenotype (Figure 3C and D), and the polymorphisms of CYP3A4 and CYP3A5 did not have any effect on the PK of DA-8031 (data not shown). All the subjects had the same genotype for CYP2C8; thus, the analysis of CYP2C8 was not conducted.

## Safety and Tolerability

A total of 32 AEs was reported in 15 (46.9%) of the 32 subjects (Table 3). Seven AEs occurred in 6 placebo subjects, and 25 AEs occurred in 26 DA-8031 subjects (Table 3). Among the 25 AEs, 18 AEs in 9 subjects were assessed to be related to DA-8031. The most frequently reported AEs related to DA-8031 was nausea (4 cases) followed by electrocardiogram QT prolongation (3 cases). There were no serious AEs, and all AEs were mild. All subjects recovered without sequelae, and there were no significant trends in the frequency of the AEs with the ascending doses.

The mean QTcB and QTcF interval did not over 450 msec (Figure 4A and B). The prolongation of QTcB interval over 450 msec was observed in 1 subject in the 20 mg dose group, 2 subjects in the 30 mg dose

group and 1 subject in the 40 mg dose group and not in the placebo. The QTcB interval prolongation of the subject in 20 mg dose group was observed at 2 hours after 3 multiple doses (Day 3) and was evaluated to not be associated with DA-8031 because of a lack of rest before recording the 12-lead ECGs and immediately disappearing. Two subjects in the 30 mg dose group and 1 subject in the 40 mg dose group were observed at 0–4 hours after 5–7 multiple doses (Day 5–7). Their QTcB interval decreased below 450 msec at least 2 hours after the prolongation. In the case of using Fridericia's formula, the prolongation of the QTcF intervals over 450 msec was observed in 2 subjects in the 30 mg dose group at 2–4 hours after the last dose of the multiple doses (Day 7) and decreased below 450 msec at 6 hours post-dose. The maximum changes in the QTcB and QTcF intervals after multiple doses from baseline were significantly different between the 30 mg and 40 mg dose groups and placebo (QTcB interval:  $p = 0.004$ ,  $p < 0.001$ ; QTcF interval:  $p = 0.003$ ,  $p = 0.001$ ). However, no clinical symptoms related to the prolongation of the QTc interval were observed. No clinically significant changes were reported in the physical examination, computerized impedance cardiography (CIC), and clinical laboratory test.



**Figure 3** Dose-normalized  $C_{max}$  and  $AUC_{last}$  of DA-8031 at steady state after multiple oral doses according to the CYP2D6 and CYP2C19 phenotype. (Dose-normalized (A)  $C_{max}$ , (B)  $AUC_{0-24h}$ , (C)  $C_{max,ss}$ , (D)  $AUC_{0-24h,ss}$ ).

## Discussions

The pharmacokinetics of DA-8031 after multiple doses were similar to those after a single dose, and the systemic exposure showed non-linearity with the increasing doses. The accumulation index ranged from 2.3 to 2.8 which were similar to the expected values based on the PK after a single ascending dose.<sup>16</sup>

About the dose proportionality, at steady state, although the dose-normalized  $C_{max,ss}$  and  $AUC_{0-24h,ss}$  were not significantly different between the dose groups, the 95% CIs of the slope of the PK parameters in the power model did not include 1. Overall, the systemic exposure increased more than dose-proportionally with the increasing doses after multiple oral administrations with a dose range of 20–40 mg. Likewise, the apparent clearance of DA-8031 and the MR of the metabolites at steady state decreased in the 40 mg dose group, but not  $T_{1/2}$ . This phenomenon might

be caused by the saturation of first-pass metabolism which was also observed in other SSRIs such as paroxetine and/or by the saturation of the P-glycoprotein (P-gp) transporter in the gastrointestinal track associated with the absorption of DA-8031.<sup>23–25</sup>

The genetic polymorphism of CYP2D6 and CYP2C19 can influence the metabolism of SSRIs, affecting interindividual differences in PK parameters and eventually affecting the drug efficacy and safety.<sup>17</sup> These polymorphisms also had an impact on the metabolism of DA-8031. The systemic exposure of DA-8031 was significantly lower in subjects with CYP2D6 EM than in those with CYP2D6 IM after multiple oral doses of DA-8031. The metabolic ratio of M4, M5 and M2 were significantly higher in subjects with CYP2D6 EM than in those with CYP2D6 IM. However, the effect of genetic polymorphism on the metabolism to M1 and M2 were not obvious

**Table 3** Summary of Adverse Events (AEs) After Multiple Oral Doses of DA-8031

	Treatment			
	Placebo	20 mg	30 mg	40 mg
	(N=6)	(N=9)	(N=9)	(N=8)
<b>Total Events</b>	<b>4 (66.7) [7]</b>	<b>2 (22.2) [2]</b>	<b>5 (55.6) [11]</b>	<b>5 (62.5) [12]</b>
Related	3 (50.0) [3]	0 (0.0) [0]	5 (55.6) [11]	4 (50.0) [7]
Not Related	1 (16.7) [4]	2 (22.2) [2]	0 (0.0) [0]	1 (12.5) [5]
<b>Eye disorders</b>				
Vision blurred			1 (11.1) [1]	
<b>Gastrointestinal disorders</b>				
Constipation			1 (11.1) [1]	
Diarrhoea			1 (11.1) [1]	1 (12.5) [1]
Epigastric discomfort			1 (11.1) [2]	
Gingival pain		1 (11.1) [1]		
Lip blister		1 (11.1) [1]		
Nausea			1 (11.1) [2]	3 (37.5) [3]
<b>General disorders and administration site conditions</b>				
Pyrexia	1 (16.7) [1]			
<b>Investigations</b>				
Electrocardiogram QT prolonged			2 (22.2) [2]	1 (12.5) [1]
Blood pressure orthostatic decreased	3 (50.0) [3]			2 (25.0) [2]
<b>Nervous system disorders</b>				
Dizziness				1 (12.5) [2]
Headache	1 (16.7) [1]		1 (11.1) [1]	1 (12.5) [1]
Insomnia			1 (11.1) [1]	
Syncope				1 (12.5) [1]
<b>Respiratory, thoracic and mediastinal disorders</b>				
Cough	1 (16.7) [1]			
Sputum purulent	1 (16.7) [1]			
<b>Skin and subcutaneous tissue disorders</b>				
Pruritus				1 (12.5) [1]

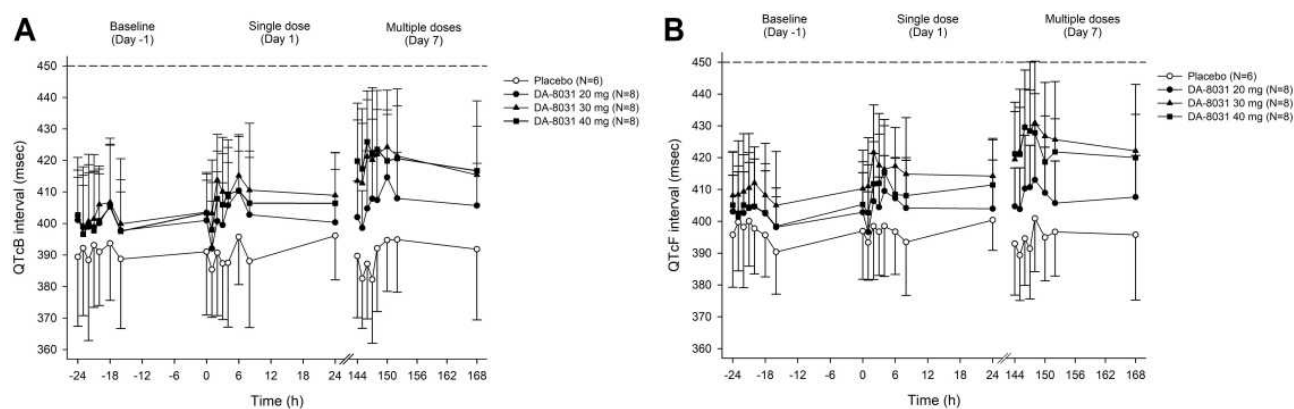
**Notes:** AEs are categorized by systemic organ class (SOC) and preferred term (PT); Values are presented as number of subjects (percentage of subjects) [number of events].

because of the low concentration and MR. In summary, the results of a previous and this study support that DA-8031 is metabolized to M4 and sequentially to M5 by CYP2D6 and to M2 and M1 by CYP2D6 or CYP2C19 with a limited proportion, also observed in the nonclinical study. However, there were no CYP2D6 UM and PM in this study. Therefore, additional pharmacogenetic assessments may be considered in a larger number of subjects.

Based on the assessments of safety and tolerability, the most commonly observed AEs were consistent with the previously reported AEs of SSRIs.<sup>13</sup> The risk of QT prolongation with SSRIs has recently become an

important consideration for the selection of SSRIs.<sup>26–29</sup> Moreover, in the case of DA-8031, the preclinical and first-in-human single ascending dose study showed that DA-8031 induced *hERG* current inhibition and QT prolongation.<sup>16</sup> In the single ascending dose study, 6 of the 8 subjects receiving a 120 mg dose showed QTc intervals longer than 450 msec.<sup>16</sup> In this multiple ascending dose study, the QT intervals increased after multiple doses of 30 and 40 mg of DA-8031 compared to those of the placebo. In addition, the QT prolongation grade 1 referring to CTCAE version 5.0 was observed in all dose groups.<sup>30</sup> However, the prolongation of the QTcB





**Figure 4** Mean (A) QTcB and (B) QTcF interval-time profiles before and after a single or multiple oral doses of placebo or DA-8031 20, 30 or 40 mg. Bars represent standard deviations.

interval of 1 subject in the 20 mg dose group seems to be not associated with DA-8031. And despite the QT prolongation, the prolongations were not over 500 msec and disappeared 2 hours after the observation, and none of the subjects showed any clinical symptoms. Consequently, although there is little concern about QT prolongation within the dose range of 20–40 mg, further assessment of cardiac safety including the QT prolongation of DA-8031 needs to be considered in patients with PE.

## Conclusion

DA-8031 showed more than the dose-proportional increase of systemic exposure, and the systemic exposure of DA-8031 was affected by the genetic polymorphisms of CYP2D6. DA-8031 was well tolerated in the dose range of 20–40 mg after multiple doses over 7 days despite the mild QT prolongations observed.

## Data Sharing Statement

The individual de-identified participant data that supporting the results in this study are available from the corresponding author (leejh413@snu.ac.kr) or sponsor on a reasonable request.

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## Disclosure

All authors report no conflicts of interest regarding the publication of this manuscript.

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