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CLINICAL TRIAL REPORT

Clinical CYP2D6-Mediated Pharmacokinetic Drug-Drug Interactions of DA-8010 with Paroxetine or Mirabegron in Healthy Korean Participants

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Background and Objective: DA-8010 is a selective M3 muscarinic receptor antagonist under development for overactive bladder (OAB). This study examined potential CYP2D6-mediated pharmacokinetic interactions between DA-8010 and paroxetine or mirabegron.

Methods: An open-label, single-sequence, 2-part clinical study was conducted in healthy volunteers. In Part 1, the effect of paroxetine on the PK of DA-8010 was evaluated. Single-dose administration of DA-8010 5 mg was performed in both periods, with paroxetine 20 mg given once daily for 11 days in the second period. For PK characterization of DA-8010, plasma samples were obtained over a 48-hour period following dosing. Part 2 was designed to characterize reciprocal PK interactions between DA-8010 and mirabegron under multiple-dose conditions. Participants received DA-8010 at a 5 mg dose for five days during the initial phase. Subsequently, mirabegron 50 mg was administered alone for 10 days, after which coadministration with DA-8010 was continued for an additional five days. PK sampling for both DA-8010 and mirabegron was performed over 24 hours after dosing. PK parameters including maximum plasma concentration (C_{max}) and area under the curve (AUC) were estimated using non-compartmental analysis. CYP2D6 genotyping was performed for all participants.

Results: Eighteen participants completed Part 1, while seventeen completed Part 2. Exposure to DA-8010 increased following concomitant administration with paroxetine, with increases of 22.3% in C_{max} and 55.4% in AUC_{last}. When administered with mirabegron, $C_{max,ss}$ and $AUC_{tau,ss}$ of DA-8010 increased by 42.1% and 45.2%. In contrast, coadministration with DA-8010 produced little change in the $C_{max,ss}$, although a 20.1% increase in $AUC_{tau,ss}$ was observed. All participants were classified as CYP2D6 extensive or intermediate metabolizers, and the magnitude of PK interactions varied according to CYP2D6 phenotype.

Conclusion: Systemic exposure to DA-8010 increased mildly with paroxetine or mirabegron, while the pharmacokinetics of mirabegron were largely unaffected. The magnitude of interaction was within the mild range and varied according to CYP2D6 metabolic activity.

Keywords: drug interactions, cytochrome P450, pharmacogenomics, pharmacokinetics, genetic polymorphism

Introduction

Overactive bladder represents a symptom-based condition in which urinary urgency is the key feature, often occurring alongside increased urinary frequency, nocturia, and, in some cases, urge incontinence.[1] Epidemiologic studies indicate that overactive bladder affects approximately 11.8–22.0% of the adult population in Europe and the United States.[1–5] The condition becomes more common with advancing age, with prevalence estimates reaching nearly 30% among individuals older than 65 years.[4] Given its high prevalence and impact on quality of life, effective pharmacologic management remains a clinical priority.

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Current clinical guidelines recommend both antimuscarinic agents (e.g. oxybutynin, solifenacin, darifenacin, tolterodine, trospium, and fesoterodine) and beta-3 adrenoceptor agonists (eg, mirabegron, vibegron) as first-line pharmacotherapy options for OAB.[6] Among them, mirabegron is frequently prescribed either as monotherapy or in combination with antimuscarinics, particularly in patients who experience suboptimal response or intolerance to anticholinergic side effects.[7] Although mirabegron is primarily metabolized by CYP3A4, its metabolism also involves CYP2D6, and it has been reported to inhibit CYP2D6 to a moderate degree in clinical studies.[8] This raises the potential for pharmacokinetic (PK) drug-drug interactions (DDIs) when coadministered with CYP2D6 substrates. This consideration is particularly relevant in patients with OAB, who are frequently older adults and commonly receive multiple concomitant medications for comorbid conditions. In such settings, the risk of CYP2D6-mediated DDIs may be increased, and resulting changes in systemic exposure could have greater clinical implications in elderly populations.

DA-8010 is a muscarinic receptor antagonist designed to preferentially target the M3 subtype in the management of overactive bladder. Because bladder contraction is primarily mediated by M3 muscarinic receptor subtype, selective targeting of M3 receptors has been proposed as a strategy to maintain therapeutic efficacy while potentially reducing off-target anticholinergic adverse effects associated with less selective antimuscarinic agents.[9–11] Recent developments for OAB treatment have therefore focused on improving receptor selectivity or introducing alternative mechanisms of action, such as β3-adrenoceptor agonists, to enhance tolerability and treatment persistence.[2,12] Nonclinical data indicates that DA-8010 is predominantly metabolized by CYP2D6, suggesting that inhibition of CYP2D6 by concomitant medications may lead to an increase in systemic exposure. In addition, although DA-8010 itself is primarily a CYP2D6 victim drug, its potential to act as a perpetrator of CYP2D6-mediated DDIs in clinical settings also warrants evaluation.

Given the CYP2D6-dependent clearance of DA-8010, regulatory guidelines recommend evaluating the effect of a strong CYP2D6 inhibitor. Paroxetine, the index strong inhibitor of CYP2D6, is therefore an appropriate agent to assess the maximal inhibitory effect on DA-8010 metabolism. Meanwhile, mirabegron – a moderate CYP2D6 inhibitor that is frequently co-prescribed with antimuscarinics in OAB management – represents a clinically relevant scenario in which DA-8010 may be coadministered with a drug capable of altering its CYP2D6-mediated metabolism.

To comprehensively assess the CYP2D6-mediated DDI potential of DA-8010, a two-part clinical study was conducted. Part 1 investigated the impact of paroxetine, a strong CYP2D6 index inhibitor, on the PK of DA-8010, to evaluate the maximum inhibitory effect. Part 2 examined reciprocal PK interactions between DA-8010 and mirabegron under conditions representative of their potential concomitant use in the treatment of OAB. Furthermore, the influence of CYP2D6 phenotype on the magnitude of DDI was evaluated.

Methods

Ethics Statement

The study received ethical approval from the Institutional Review Board of Seoul National University Hospital and the Korean Ministry of Food and Drug Safety, covering both the protocol and informed consent materials (ClinicalTrials.gov identifier: NCT05992428). The study was performed in accordance with the ethical principles of the Declaration of Helsinki and in compliance with Korean Good Clinical Practice guidelines. Informed consent was obtained from all participants before any study-related procedure.

Study Participants

Healthy Korean participants aged 19–50 years, with a body mass index (BMI) ranging from 18.0 to 28.0 kg/m^2 were included in the study. Enrolled participants had no clinically significant abnormalities based on medical history, vital signs, clinical laboratory tests, 12-lead electrocardiograms, physical examinations, and Columbia Suicide Severity Rating Scale (C-SSRS, part 1 only).

Study Design

This study was a 2-part, open-label, single-sequence clinical trial (Figure S1). A fixed-sequence design was adopted to evaluate the pharmacokinetic drug–drug interaction potential, allowing each participant to receive both treatments and serve as their own control. Given the exploratory nature of the study, the objective was to characterize the magnitude of pharmacokinetic changes rather than to formally test a statistical hypothesis; therefore, a sample size of approximately 18 participants per part was considered sufficient based on the expected variability of DA-8010 pharmacokinetics.

In Part 1, participants received a single oral dose of DA-8010 5 mg in each study period, administered on Days 1 and 15. During the second period, paroxetine 20 mg was administered once daily for 11 consecutive days, from Day 6 through Day 16, to ensure attainment of steady state and maintain maximal inhibitory effect on CYP2D6 during the PK evaluation of DA-8010 in the second phase. Serial blood samples for PK assessment of DA-8010 were collected at 0 (pre-dose), 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 12, 24, and 48 hours post-dose on Day 1 and Day 15.

In Part 2, participants received DA-8010 5 mg once daily for five consecutive days during the first period. In the second period, mirabegron 50 mg was administered for 10 days to ensure steady state for reaching maximal CYP2D6 inhibition based on its elimination half-life of approximately 50 hours. After that, concomitant administration with DA-8010 was continued for an additional five days. A 4-day washout period was also included between the two periods. Serial blood samples for PK assessment were collected at 0 (pre-dose), 1, 2, 3, 3.5, 4, 4.5, 5. 5.5, 6, 6.5, 7, 8, 12, and 24 hours post-dose on Day 5, Day 19, and Day 24, and additionally at 0 hour (pre-dose) on Day 3, Day 4, Day 17, Day 18, Day 22, and Day 23, to confirm the attainment of steady state.

Bioanalytical Methods

Quantification of DA-8010 and mirabegron in plasma was performed using a validated LC–MS/MS assay. The bioanalytical method was fully validated according to regulatory guidance for bioanalytical method validation, including assessments of selectivity, linearity, accuracy, precision, recovery, matrix effects, and stability. Protein precipitation was applied as the sample preparation procedure for both compounds.[13]

For DA-8010, plasma samples were processed using protein precipitation with 100 µL of plasma and acetonitrile containing the internal standard (DA-8010-d3). After vortex-mixing and centrifugation at 13,000 rpm for 3 minutes at room temperature, the supernatant was diluted with 0.1% ammonium formate solution and analyzed by LC-MS/MS. The mobile phases consisted of 0.1% ammonium formate in distilled water (mobile phase A) and acetonitrile (mobile phase B). Chromatographic separation was achieved on a Waters ACQUITY UPLC® BEH C18 column (1.7 µm, 2.1 mm × 50 mm), and mass spectrometric detection was performed on a Waters Xevo TQ-XS MS using multiple reaction monitoring (MRM) with electrospray ionization in positive mode (ESI+). The MRM transitions were m/z 363.30 to 98.20 for DA-8010 and m/z 366.30 to 101.22 for the internal standard (DA-8010-d3). The calibration curves were linear over the concentration range of 0.005–5.00 ug/L, with accuracy and precision within acceptable limits.

For mirabegron, plasma samples (100 µL) were prepared by protein precipitation with acetonitrile containing the internal standard (rac-mirabegron-d_5). The samples were vortexed and centrifuged at 13,000 rpm for 3 minutes, and the resulting supernatant was diluted with distilled water prior to analysis. The mobile phases consisted of 0.1% ammonium formate and 0.5% ammonia solution in distilled water (mobile phase A) and methanol (mobile phase B). LC-MS/MS analysis was performed on a Waters Xevo TQ MS under positive electrospray ionization (ESI+) in MRM mode. The MRM transitions were m/z 397.32 to 260.21 for mirabegron and m/z 402.41 to 260.21 for the internal standard (rac-mirabegron-d_5). The calibration curves were linear within the range of 0.200–200 ug/L, demonstrating accuracy and precision within acceptable limits.

Pharmacogenetic Analysis

A retrospective pharmacogenetic analysis of CYP2D6 was conducted to explore the potential influence of CYP2D6 phenotype on the pharmacokinetics of DA-8010. Blood samples for CYP2D6 genotyping were collected from all participants prior to the first administration of the study drug. Genomic DNA was isolated from whole blood samples using the QIAamp DNA Mini Kit. CYP2D6 allelic variants were identified by single-base extension analysis performed with the SNaPshot multiplex system. The genotyping included prespecified common CYP2D6 alleles

observed in East Asian populations, including *1, *2, *5, *10, and *41. Phenotype classification was based on the CYP2D6 activity score system according to the CPIC guideline: individuals with a score > 2.25 were classified as ultrarapid metabolizers (UM; eg, *1×N or *2×N), 1.25–2.25 as extensive metabolizers (EM; eg, *1/*1 or *1/*2), 0–1.25 as intermediate metabolizers (IM; eg, *1/*10, *10/*10, or *1/*41), and 0 as poor metabolizers (PM; eg, *5/*5).[14]

Pharmacokinetic Assessment

A noncompartmental approach implemented in WinNonlin (version 8.3, Certara USA, Princeton, New Jersey) was used to analyze individual pharmacokinetic data for DA-8010 and mirabegron. In part 1, the primary PK parameters included the maximum plasma concentration (C_{max}), and the area under the curve from time zero to last measurable concentration (AUC_{last}) of DA-8010. In part 2, the primary PK parameters included the maximum plasma concentration at steady state ($C_{max,ss}$), and the area under the curve during the dosing interval ($AUC_{tau,ss}$). The AUC was derived using linear trapezoidal integration for the ascending phase and logarithmic trapezoidal integration for the terminal phase. Other PK parameters including the time to achieve C_{max} (T_{max}), terminal half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution on terminal phase (V_z/F) were also evaluated. The PK parameters of DA-8010 and mirabegron were stratified by CYP2D6 phenotype, and the magnitude of PK DDI following the co-administration was assessed within each phenotype.

Safety Assessment

Safety was evaluated throughout the study by monitoring treatment-emergent adverse events (TEAEs), vital signs, physical examinations, 12-lead electrocardiograms, and clinical laboratory tests.

Statistical Analysis

Statistical evaluations were performed with SAS (Version 9.4; SAS Institute, Cary, NC, USA). Pharmacokinetic parameters were logarithmically transformed and analyzed using a linear mixed-effects model. In the model, treatment was included as a fixed effect and participant as a random effect. Due to the fixed-sequence study design, period was not included as a separate factor. Based on the model results, geometric mean ratios (GMRs) and corresponding 90% confidence intervals (CIs) were calculated to compare pharmacokinetic parameters between monotherapy and combination therapy. The use of 90% CIs is consistent with standard practice in pharmacokinetic studies evaluating relative exposure and drug–drug interactions.

Within each CYP2D6 phenotype group, paired comparisons between monotherapy and combination therapy were additionally performed using the Wilcoxon signed-rank test to assess the statistical significance of exposure changes following co-administration. These subgroup analyses were exploratory in nature and were performed without adjustment for multiplicity. All statistical tests were two-sided, and a nominal significance level of 0.05 was applied.

Results

Subjects Disposition and Demographics

A total of 37 healthy Korean adults were included in the enrolled set. In Part 1, all 18 participants in the enrolled set completed the study, and 17 participants were included in the PK analysis set due to unevaluable PK data in one participant. In Part 2, 19 participants were included in the enrolled set, of whom 17 completed the study and were included in the PK analysis set.

CYP2D6 genotyping was performed in all participants who completed the study (18 in Part 1 and 17 in Part 2). In Part 1, 12 participants (66.7%) were classified as EM and 6 participants (33.3%) as IM, while in Part 2, 12 participants (70.6%) were EM and 5 participants (29.4%) were IM (Table 1).

Table 1 Demographic Characteristics of Participants Enrolled in Part 1 and Part 2

Characteristics	Part 1 (N=18)	Part 2 (N=19)
Age (yr)*	32.17 (6.91)	27.84 (5.23)
Height (cm)*	171.93 (7.62)	170.29 (7.63)
Body weight (kg)*	68.07 (10.74)	66.33 (10.40)
Sex[#]		
Male	15 (83.3)	14 (73.7)
Female	3 (16.7)	5 (26.3)
CYP2D6 phenotype[+#]		
Extensive metabolizer	12 (66.7)	12 (70.6)
Intermediate metabolizer	6 (33.3)	5 (29.4)

Notes: [+]Percentages based on the exploratory genetic analysis set, 18 in part 1 and 17 in part 2. *Values are shown as mean (standard deviation). [#]Values are shown as n (%).

Pharmacokinetic Results

In part 1, the overall exposure of DA-8010 was increased by the coadministration of paroxetine (Figure 1). The median T_{max} remained comparable while the terminal half-life ($t_{1/2}$) was prolonged from 6.54 to 7.53 hours, after the coadministration. Coadministration with paroxetine increased the C_{max} and AUC_{last} of DA-8010 by 22% and 55%. In EMs, coadministration with paroxetine increased the C_{max} and AUC_{last} of DA-8010 by 51% and 81%, respectively. In contrast, in IMs, C_{max} decreased by 17% and AUC_{last} increased by 17% (Table 2 and Figure 2).

In part 2, the overall exposure of DA-8010 was increased after the coadministration with mirabegron (Figure 3). The median $T_{max,ss}$ and $t_{1/2,ss}$ were comparable among the two treatments. When DA-8010 was administered in combination with mirabegron, Cmax,ss and $AUC_{tau,ss}$ were increased by 42% and 45%, respectively. In EMs, coadministration of mirabegron led to a 44% increase in $C_{max,ss}$ and a 60% increase in $AUC_{tau,ss}$ of DA-8010. In IMs, $C_{max,ss}$ and $AUC_{tau,ss}$ increased by 37% and 15%, respectively (Table 3 and Figure 4).

The overall PK profile of mirabegron was slightly changed after the coadministration with DA-8010 (Figure 3). The range of $T_{max,ss}$ and $t_{1/2,ss}$ for mirabegron remained comparable. The $C_{max,ss}$ remained comparable between treatments, whereas $AUC_{tau,ss}$ was increased by 20% (Table 4). In EMs, $C_{max,ss}$ decreased by 14% and $AUC_{tau,ss}$ increased by 12%, whereas in IMs, both parameters increased by 45% and 43%, respectively (Table 4 and Figure 4).

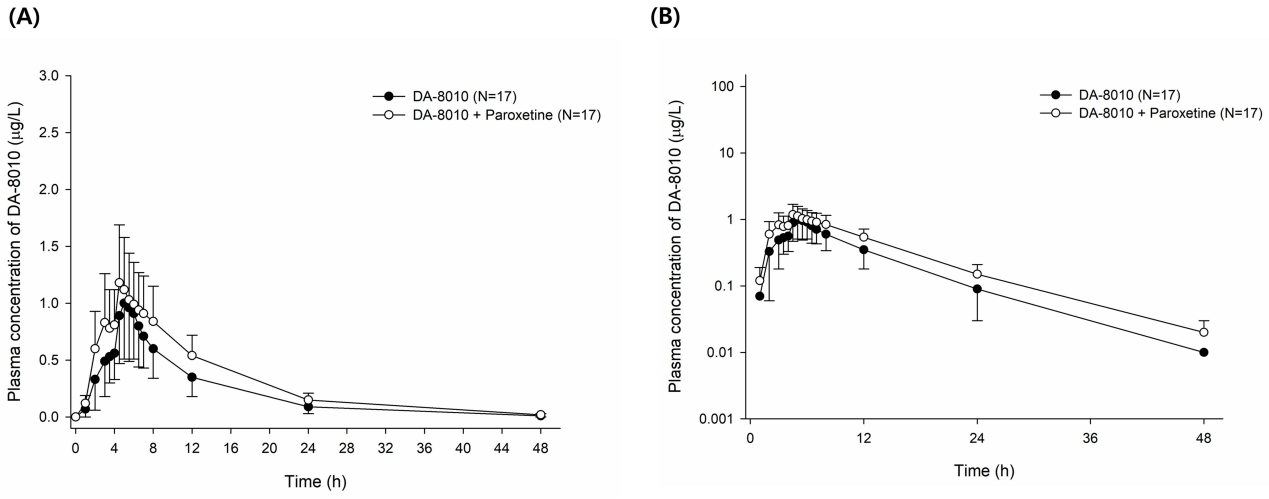

Figure 1 Mean plasma concentration-time profile of DA-8010 after a single administration of DA-8010 5 mg alone or co-administration with paroxetine 20 mg. Bars represent standard deviations ((**A**) linear scale, (**B**) log-linear scale).

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Table 2 Pharmacokinetic Parameters of DA-8010 After a Single Administration of DA-8010 5 mg Alone or Co-Administration with Paroxetine 20 mg (Part 1)

CYP2D6 Phenotype	PK Parameters	DA-8010 (n=17)	DA-8010 + Paroxetine (n=17)	GMR[b] (90% CIs)
All (N=17)	T_{max} (h)[a]	5.00 [4.50–6.00]	5.00 [3.00–8.00]	
	C_{max} (μg/L)	1.09 ± 0.53	1.28 ± 0.54	1.2226 (1.0035–1.4896)
	AUC_{last} (h·μg/L)	9.30 ± 4.12	13.63 ± 3.63	1.5535 (1.3500–1.7877)
	AUC_{inf} (h·μg/L)	9.49 ± 4.13	13.86 ± 3.66	
	$t_{1/2}$ (h)	6.54 ± 1.10	7.53 ± 1.19	
	CL/F (L/h)	627.94 ± 274.56	384.77 ± 105.51	
	V_z/F (L)	6039.89 ± 3214.01	4227.27 ± 1491.00	
EM (N=11)	T_{max} (h)[a]	5.00 [4.50–6.00]	5.00 [3.00–8.00]	
	C_{max} (μg/L)	0.94 ± 0.51	1.33 ± 0.54	1.5096 (1.2023–1.8955)
	AUC_{last} (h·μg/L)	7.66 ± 3.13	13.27 ± 3.13	1.8138 (1.5489–2.1241)
	AUC_{inf} (h·μg/L)	7.88 ± 3.15	13.47 ± 3.15	
	$t_{1/2}$ (h)	6.40 ± 1.27	7.35 ± 1.38	
	CL/F (L/h)	731.00 ± 280.10	393.81 ± 113.31	
	V_z/F (L)	6978.25 ± 3551.93	4229.58 ± 1609.11	
IM (N=6)	T_{max} (h)[a]	4.99 [4.50–5.50]	4.75 [4.00–6.00]	
	C_{max} (μg/L)	1.37 ± 0.49	1.18 ± 0.56	0.8306 (0.6662–1.0357)
	AUC_{last} (h·μg/L)	12.31 ± 4.24	14.30 ± 4.66	1.1694 (1.0018–1.3650)
	AUC_{inf} (h·μg/L)	12.44 ± 4.31	14.58 ± 4.70	
	$t_{1/2}$ (h)	6.80 ± 0.71	7.84 ± 0.71	
	CL/F (L/h)	439.01 ± 134.60	368.21 ± 97.15	
	V_z/F (L)	4319.58 ± 1527.94	4223.05 ± 1391.16	

Notes: Values are presented as arithmetic mean ± standard deviation, [a]Values are presented as the median [minimum – maximum]. [b]Geometric mean ratio of co-administration of DA-8010 5 mg PO and paroxetine 20 mg PO to DA-8010 5 mg PO.

Abbreviations: AUC_{last}, area under the plasma concentration-time curve from time zero to the last quantifiable concentration time; AUC_{inf}, area under the plasma concentration-time curve from time to infinite; C_{max}, maximum plasma concentration; CIs, confidence intervals; CL/F, apparent clearance; EM, Extensive metabolizer; GMR, geometric mean ratio; IM, intermediate metabolizer; $t_{1/2}$, terminal elimination half-life; V_z, apparent volume of distribution on terminal phase.

Safety Results

In Part 1, 6 TEAEs occurred in 3 participants following administration of DA-8010 alone, whereas 35 TEAEs occurred in 10 participants after coadministration of DA-8010 and paroxetine (Table S1). In Part 2, 11 TEAEs were reported in 7 participants receiving DA-8010 alone, 6 TEAEs in 5 participants receiving mirabegron alone, and 6 TEAEs in 2 participants receiving the combination treatment (Table S2). All TEAEs were mild in severity, and all events resolved without sequelae. No clinically significant abnormalities or changes were observed in vital signs, physical examinations, 12-lead electrocardiograms, or clinical laboratory tests.

Discussion

The present analysis examined potential pharmacokinetic interactions mediated by CYP2D6 in association with DA-8010, a selective M3 muscarinic receptor antagonist being developed for OAB. Regulatory guidelines recommend conducting a clinical DDI study with a strong CYP2D6 inhibitor when a drug is predominantly metabolized by a polymorphic enzyme such as CYP2D6, in order to assess the risk of altered systemic exposure.[14,15] In nonclinical studies, the fraction metabolized (F_m) via CYP2D6 for DA-8010 was estimated to be approximately 0.84 (in-house data), indicating that CYP2D6 is the primary metabolic pathway. Although CYP3A4 represents the major metabolic pathway for mirabegron, clinical data demonstrate that the drug can moderately inhibit CYP2D6, as evidenced by interaction studies with sensitive substrates.[8] Accordingly, two parts of the DDI study were designed to evaluate the DDI potential of DA-8010 – first with paroxetine, a strong CYP2D6 inhibitor, and second with mirabegron, a beta-3 adrenergic receptor agonist frequently coadministered in OAB therapy and known to exhibit moderate CYP2D6 inhibition.

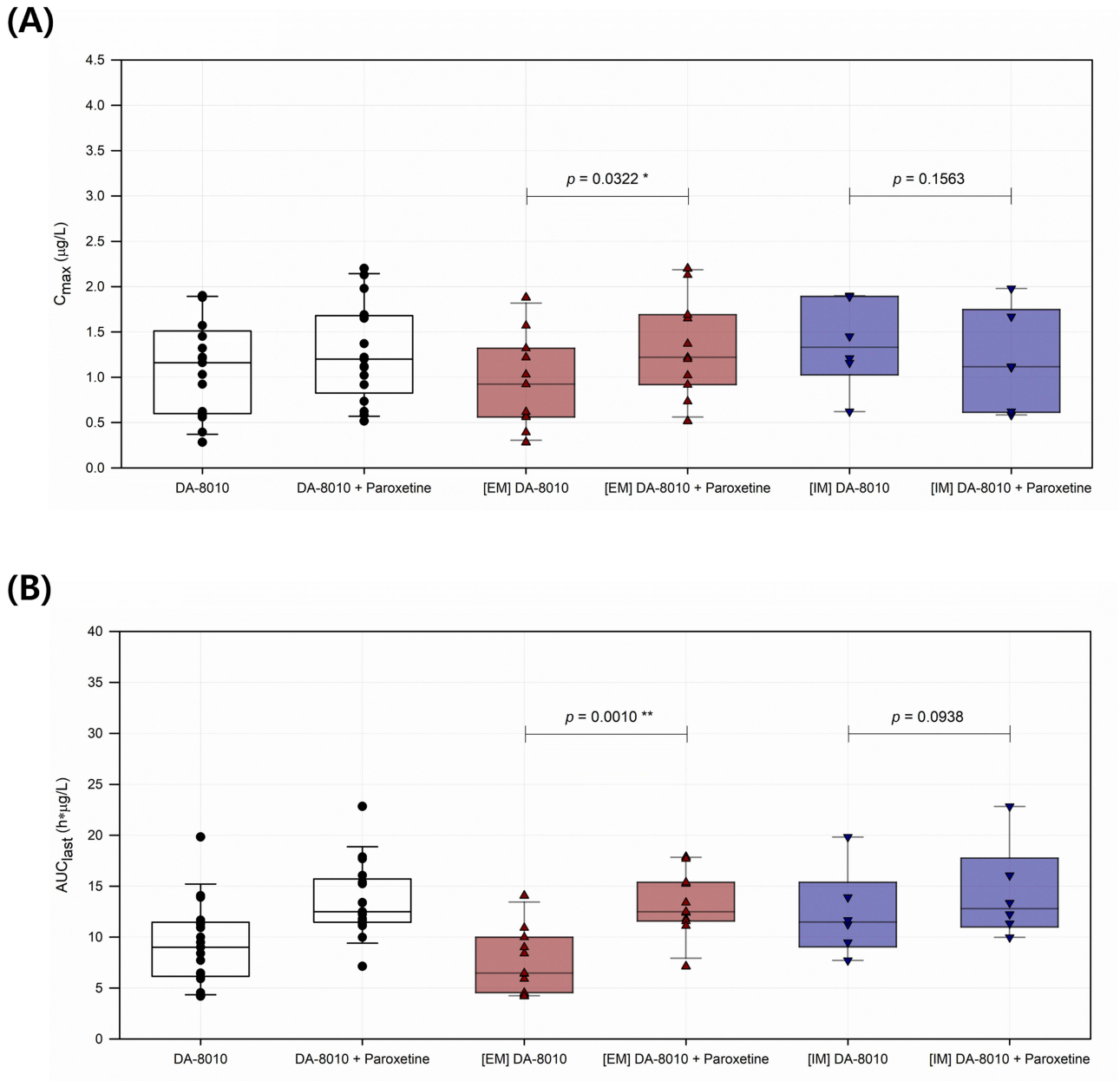

Figure 2 Comparison of (**A**) C_{max} and (**B**) AUC_{last} of DA-8010 after a single administration of DA-8010 5 mg alone or co-administration with paroxetine 20 mg by CYP2D6 phenotype.
Notes: P-values were derived from the Wilcoxon signed-rank test for paired comparisons between monotherapy and combination therapy within each CYP2D6 phenotype group. *p < 0.05, **p < 0.01 compared with DA-8010 alone.
Abbreviations: EM, CYP2D6 extensive metabolizer; IM, CYP2D6 intermediate metabolizer.

In the present study, the DDI evaluation was conducted at the clinically relevant dose of 5 mg. Given the previous evidence suggesting approximately dose-proportional PKs of DA-8010, the relative magnitude of interaction may be expected to be generally consistent within the therapeutic dose range of 2.5–5 mg.[16] However, as only a single dose level was investigated, extrapolation beyond this dose range remains uncertain.

In part 1, coadministration with paroxetine increased the C_{max} and AUC_{last} of DA-8010 by 22% and 55%, respectively. According to regulatory guidance, an increase in AUC of more than 25% but less than two-fold (1.25–2.0 fold) is generally considered to represent a mild pharmacokinetic interaction. Given the high F_m via CYP2D6 observed in preclinical studies, a larger magnitude of interaction might have been expected. The relatively

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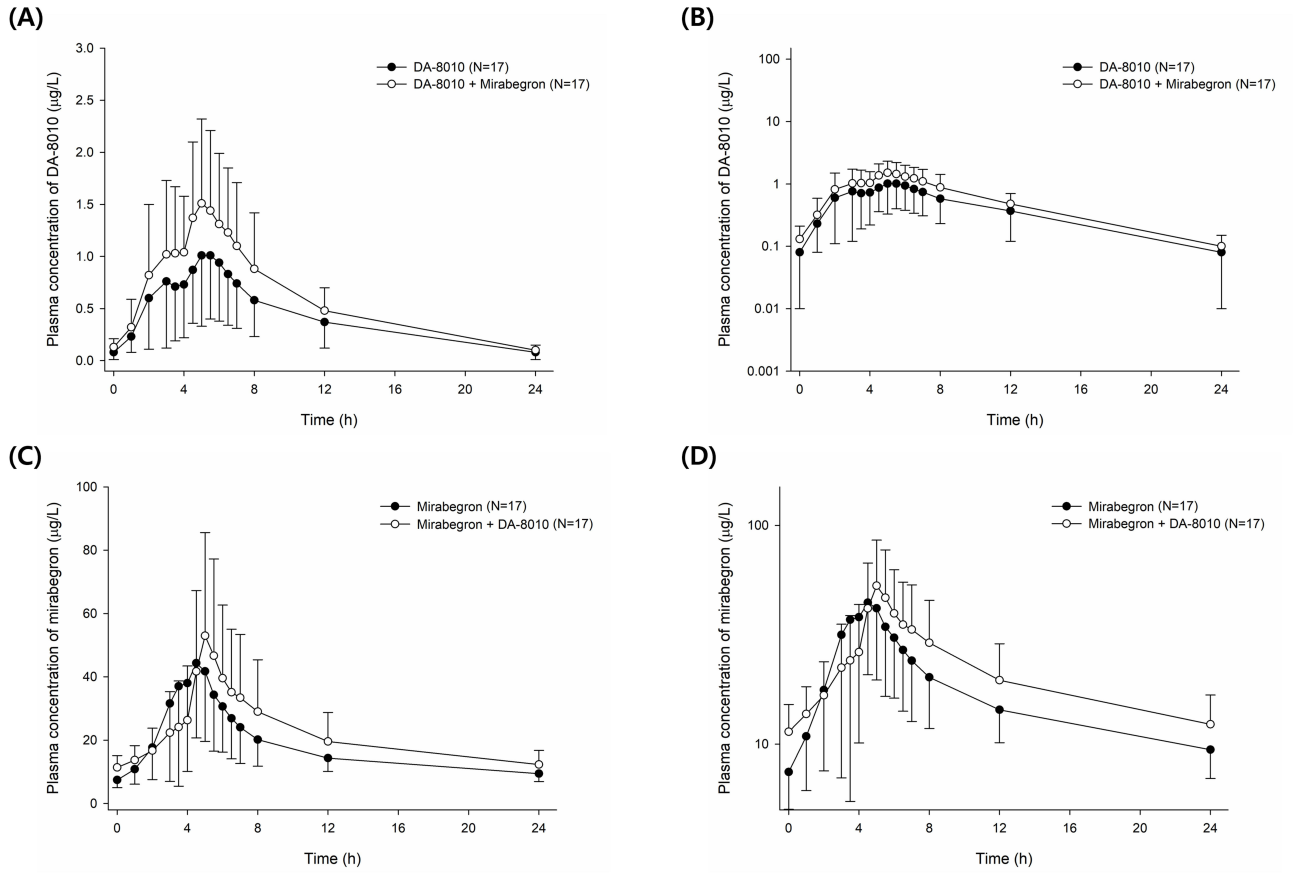

Figure 3 Mean plasma concentration-time profiles of DA-8010 and mirabegron at steady state following multiple oral administrations of DA-8010 5 mg and mirabegron 50 mg, alone and in combination. Panels show DA-8010 in (**A**) linear and (**B**) log-linear scales, and mirabegron in (**C**) linear and (**D**) log-linear scales. Error bars represent standard deviations.

modest change observed in humans may be attributed to the predominant expression of CYP2D6 in the liver rather than the intestine, along with compensatory metabolism by alternative CYP isoforms or other metabolic pathways following hepatic CYP2D6 inhibition.

Table 3 Pharmacokinetic Parameters of DA-8010 After Multiple Administrations of DA-8010 5 mg Alone or Co-Administration with Mirabegron 50 mg (Part 2)

CYP2D6 Phenotype	PK Parameters	DA-8010 (n=17)	DA-8010 + Mirabegron (n=17)	GMR[b] (90% CIs)
All (N=17)	$T_{max,ss}$ (h)[a]	5.00 [2.00–6.50]	5.00 [2.00–6.50]	
	$C_{max,ss}$ (μg/L)	1.11 ± 0.65	1.57 ± 0.79	1.4207 (1.1764–1.7157)
	$AUC_{tau,ss}$ (h·μg/L)	9.39 ± 5.75	13.25 ± 6.79	1.4524 (1.2755–1.6538)
	$t_{1/2,ss}$ (h)	5.33 ± 1.19	5.73 ± 2.00	
	CL_{ss}/F (L/h)	676.63 ± 311.38	455.34 ± 180.79	
	V_z/F (L)	5037.26 ± 2162.42	4109.79 ± 3199.03	
EM (N=12)	$T_{max,ss}$ (h)[a]	5.00 [2.00–6.50]	5.00 [2.00–6.50]	
	$C_{max,ss}$ (μg/L)	1.06 ± 0.55	1.52 ± 0.68	1.4416 (1.1149–1.8642)
	$AUC_{tau,ss}$ (h·μg/L)	7.82 ± 3.30	12.58 ± 5.44	1.6034 (1.3896–1.8501)
	$t_{1/2,ss}$ (h)	4.89 ± 1.12	5.81 ± 2.38	
	CL_{ss}/F (L/h)	753.13 ± 314.70	470.04 ± 193.12	
	V_z/F (L)	5216.98 ± 2135.06	4394.71 ± 3707.49	

(*Continued*)

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Table 3 (Continued).

CYP2D6 Phenotype	PK Parameters	DA-8010 (n=17)	DA-8010 + Mirabegron (n=17)	GMR[b] (90% CIs)
IM (N=5)	$T_{max,ss}$ (h)[a]	5.50 [3.50–5.50]	5.00 [3.00–5.50]	
	$C_{max,ss}$ (μg/L)	1.25 ± 0.91	1.67 ± 1.09	1.3717 (0.9910–1.8985)
	$AUC_{tau,ss}$ (h·μg/L)	13.14 ± 8.79	14.85 ± 9.93	1.1455 (0.8949–1.4663)
	$t_{1/2,ss}$ (h)	6.38 ± 0.47	5.53 ± 0.68	
	CL_{ss}/F (L/h)	493.03 ± 236.23	420.04 ± 161.17	
	V_z/F (L)	4605.93 ± 2416.39	3425.97 ± 1518.88	

Notes: Values are presented as arithmetic mean ± standard deviation. [a]Values are presented as the median [minimum – maximum]. [b]Geometric mean ratio of co-administration of DA-8010 5 mg PO and mirabegron 50 mg PO to DA-8010 5 mg PO.

Abbreviations: $AUC_{tau,ss}$, area under the plasma concentration-time curve during the dosing interval at steady state; CIs, confidence intervals; CL_{ss}/F, apparent clearance at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; EM, extensive metabolizer; IM, intermediate metabolizer; $T_{max,ss}$, time to reach maximum concentration at steady state; $t_{1/2,ss}$, terminal elimination half-life; V_z/F, apparent volume of distribution on terminal phase.

In part 2, coadministration with mirabegron resulted in a 42% increase in $C_{max,ss}$ and a 45% increase in $AUC_{tau,ss}$ of DA-8010. These findings align with the known CYP2D6 inhibitory effect of mirabegron, suggesting partial inhibition of CYP2D6-mediated metabolism. As with paroxetine, the magnitude of the DDI remained within the mild range, and the extent of exposure increase was within the established safety margin reported in previous clinical studies.[16] Overall, the observed interaction was consistent with a mild increase in systemic exposure of DA-8010 when coadministered with mirabegron, with no notable changes observed in safety findings in this study.

Overall, the incidence of adverse events was low, and most events were mild in severity and resolved without sequelae. No apparent relationship between systemic exposure and the occurrence of adverse events was observed across the study.

Exploratory pharmacogenomic analyses provided further insight. Among EMs, paroxetine increased the C_{max} and AUC_{last} of DA-8010 by 51% and 81%, respectively, whereas in IMs, C_{max} decreased by 17% and AUC_{last} increased by

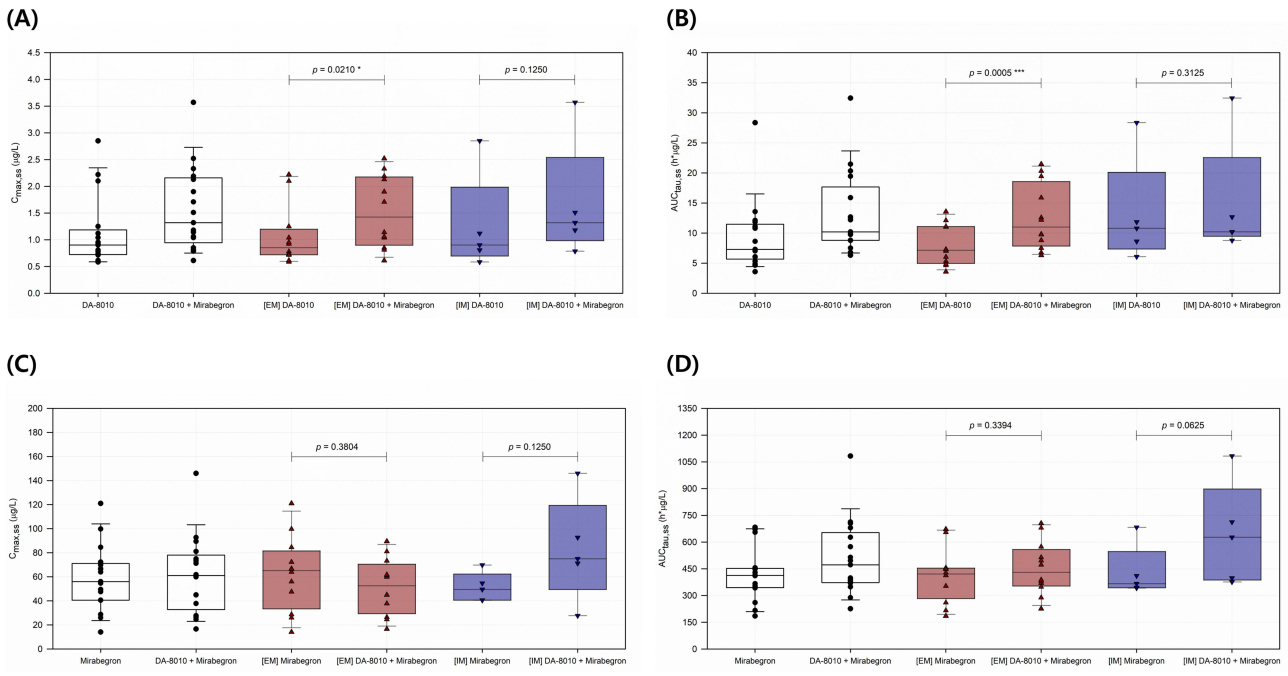

Figure 4 Comparison of steady-state pharmacokinetic parameters of DA-8010 and mirabegron after multiple administrations of DA-8010 5 mg and mirabegron 50 mg, alone or in combination, stratified by CYP2D6 phenotype ((**A**) DA-8010 $C_{max,ss}$; (**B**) DA-8010 $AUC_{tau,ss}$; (**C**) Mirabegron $C_{max,ss}$; (**D**) Mirabegron $AUC_{tau,ss}$).

Notes: P-values were derived from the Wilcoxon signed-rank test for paired comparisons between monotherapy and combination therapy within each CYP2D6 phenotype group. *p < 0.05, ***p < 0.001 compared with DA-8010 alone.

Abbreviations: EM, CYP2D6 extensive metabolizer; IM, CYP2D6 intermediate metabolizer.

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Table 4 Pharmacokinetic Parameters of Mirabegron After Multiple Administrations of Mirabegron 50 mg Alone or Co-Administration with DA-8010 5 mg (Part 2)

CYP2D6 Phenotype	PK Parameters	Mirabegron (n=17)	DA-8010 + Mirabegron (n=17)	GMR[b] (90% CIs)
All (N=17)	$T_{max,ss}$ (h)[a]	4.00 [2.00–6.50]	5.00 [3.00–12.00]	
	$C_{max,ss}$ (μg/L)	58.96 ± 26.87	60.86 ± 32.16	1.0051 (0.7820–1.2918)
	$AUC_{tau,ss}$ (h·μg/L)	417.58 ± 144.06	508.24 ± 208.13	1.2009 (1.0437–1.3818)
	$t_{1/2,ss}$ (h)	16.00 ± 4.28	15.15 ± 5.09	
	CL_{ss}/F (L/h)	135.20 ± 52.71	113.14 ± 43.13	
	V_z/F (L)	3247.88 ± 1661.63	2619.44 ± 1309.13	
EM (N=12)	$T_{max,ss}$ (h)[a]	3.75 [2.00–6.50]	5.25 [3.00–12.00]	
	$C_{max,ss}$ (μg/L)	62.28 ± 30.92	51.84 ± 23.17	0.8624 (0.6351–1.1710)
	$AUC_{tau,ss}$ (h·μg/L)	412.54 ± 150.07	453.56 ± 148.22	1.1169 (0.9384–1.3294)
	$t_{1/2,ss}$ (h)	14.85 ± 3.68	15.88 ± 5.25	
	CL_{ss}/F (L/h)	139.69 ± 60.28	122.42 ± 43.42	
	V_z/F (L)	3132.37 ± 1780.86	2918.59 ± 1231.80	
IM (N=5)	$T_{max,ss}$ (h)[a]	4.50 [3.00–5.00]	5.00 [4.50–6.50]	
	$C_{max,ss}$ (μg/L)	51.02 ± 12.12	82.52 ± 42.79	1.4515 (0.9390–2.2436)
	$AUC_{tau,ss}$ (h·μg/L)	429.69 ± 144.27	639.48 ± 287.00	1.4291 (1.1001–1.8565)
	$t_{1/2,ss}$ (h)	18.75 ± 4.75	13.54 ± 4.85	
	CL_{ss}/F (L/h)	124.41 ± 30.23	90.89 ± 37.13	
	V_z/F (L)	3525.10 ± 1478.66	1961.30 ± 1358.65	

Notes: Values are presented as arithmetic mean ± standard deviation. [a]Values are presented as the median [minimum – maximum]. [b]Geometric mean ratio of co-administration of DA-8010 5 mg PO and Mirabegron 50 mg PO to Mirabegron 50 mg PO.

Abbreviations: $AUC_{tau,ss}$, area under the plasma concentration-time curve during the dosing interval at steady state; CIs, confidence intervals; CL_{ss}/F, apparent clearance at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; EM, extensive metabolizer; IM, intermediate metabolizer; $T_{max,ss}$, time to reach maximum concentration at steady state; $t_{1/2,ss}$, terminal elimination half-life; V_z/F, apparent volume of distribution on terminal phase.

17%; the latter changes were not statistically significant. Considering the known variability of DA-8010 PKs, the mixed pattern of small increases and decreases observed in the IM subgroup likely reflects normal intrasubject PK variability rather than a mechanistically meaningful interaction. Similarly, in part 2, mirabegron coadministrations significantly increased $C_{max,ss}$ and $AUC_{tau,ss}$ by 44% and 60%, respectively, in EMs. In contrast, in IMs, the corresponding increases of 37% and 15% were not statistically significant. These results indicate that the DDI effect was primarily driven by EMs, likely due to higher baseline CYP2D6 activity and thus greater susceptibility to inhibition. In contrast, individuals with the IM phenotype already have reduced CYP2D6 activity at baseline, which may limit the additional inhibitory effect of CYP2D6 inhibitors. Taken together, these findings support that CYP2D6 plays a significant role in the metabolism of DA-8010 and are consistent with the understanding that the extent of CYP2D6-mediated DDIs can differ depending on metabolic phenotype.

For mirabegron itself, coadministration with DA-8010 resulted in an approximately 20% increase in $AUC_{tau,ss}$, while $C_{max,ss}$ remained unchanged, indicating that the extent of DDI was minimal. When stratified by CYP2D6 phenotypes, numerical changes in mirabegron exposure were observed. However, these changes are not considered clinically meaningful, as CYP2D6 is not a major metabolic pathway for mirabegron, and the limited sample size may have contributed to the observed variability. The relatively large numerical increases observed in the IM subgroup may therefore reflect interindividual variability rather than a genotype-dependent pharmacokinetic interaction.

All participants underwent CYP2D6 genotyping and were classified as either EMs or IMs, consistent with the expected phenotype distribution in East Asian populations.[17] While the study population comprised only EMs and IMs, which may limit extrapolation to other CYP2D6 phenotypes, inclusion of a broader genotype spectrum through prospective recruitment could have improved generalizability and enabled a more detailed evaluation of a genotype-dependent DDI effect. Furthermore, the limited number of participants within each CYP2D6 phenotype subgroup constrains the interpretation of subgroup-specific findings. In addition, the study did not assess the potential influence

of genetic variability in other metabolic pathways such as CYP3A4/5, which may also contribute to interindividual differences in drug metabolism. Nonetheless, the current findings remain highly representative of the Korean population and support the internal validity for the pharmacogenomic analysis within this genetically consistent cohort.

Conclusion

DA-8010 exposure increased following coadministration with paroxetine or mirabegron, whereas coadministration with DA-8010 had minimal effect on the pharmacokinetics of mirabegron. The magnitude of exposure increase was within the range of a mild interaction for both coadministered drugs. The increase in exposure was more pronounced and consistently observed in CYP2D6 extensive metabolizers, whereas changes in intermediate metabolizers were smaller and less consistent across pharmacokinetic parameters.

Data Sharing Statement

De-identified individual participant data that support the finding of this study from the corresponding author (leejh413@snu.ac.kr) upon reasonable request and with appropriate approvals, at any time after publication.

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Disclosure

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