Pharmacokinetic interaction between fimasartan and atorvastatin in healthy male volunteers

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Introduction: Major cardiovascular risk factors, including hypertension and dyslipidemia, are often comorbidities, frequently leading to concurrent prescription of angiotensin receptor blockers and 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins). The study’s objective was to evaluate the effect of coadministration of fimasartan and atorvastatin on their pharmacokinetics (PKs).

Subjects and methods: In a randomized, open-label, three-period, six-sequence, crossover, multiple-dose study, 36 healthy subjects received 120 mg fimasartan, 40 mg atorvastatin, or both (based on their assigned sequence) once daily for 7 days in each period, with a 7-day washout between periods. Blood samples for the PK analysis of fimasartan, atorvastatin, and the 2-hydroxy atorvastatin metabolite were collected up to 48 h after the last dose.

Results: The coadministration of fimasartan and atorvastatin was well tolerated and led to an increase in the peak concentration and area under the concentration–time curve at steady state of fimasartan by 2.18-fold (95% confidence interval [CI], 1.79–2.65) and 1.35-fold (95% CI, 1.26–1.43) and those of atorvastatin increased by 1.82-fold (95% CI, 1.51–2.18) and 1.12-fold (95% CI, 1.04–1.22), respectively.

Conclusion: Coadministration increased the systemic exposures of fimasartan and atorvastatin, but the clinical significance of this finding needs to be evaluated with respect to exposure responses and clinical outcomes.

Keywords: angiotensin receptor blocker, statin, HMG-CoA inhibitor, fixed dose combination, FDC
extrarenal pathways (ie, fecal elimination or biliary excretion), with the remainder metabolized by CYP3A4. In vitro studies have shown that fimasartan is also a substrate of OATP1B1, OATP2B1, and OATP1B3 and is transported by MDR1, MRP2, or BCRP. No significant drug interactions were observed when used in combination with hydrochlorothiazide, amlodipine, warfarin, or digoxin.

Statins, also known as HMG-CoA reductase inhibitors, are used in patients with hypercholesterolemia and mixed dyslipidemia for reducing total-cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, apolipoprotein B, and triglycerides, and for increasing high-density lipoprotein cholesterol (HDL-C). Statins lower the risk of cardiovascular disease in at-risk patients. Statins are usually prescribed in combination with other drugs, such as antihypertensive or antidiabetic drugs, to treat comorbidities and reduce overall cardiovascular risk. Atorvastatin is rapidly absorbed after oral administration, and its bioavailability is 14%, with an extensive first-pass effect. Atorvastatin is metabolized by CYP3A4 into the active metabolites, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin, and is subject to cellular membrane transport by OATP and P-glycoprotein. Alterations of atorvastatin pharmacokinetics (PKs) with inhibitors of these systems (eg, itraconazole, cyclosporine, and grapefruit) have been demonstrated. Atorvastatin is also known as a weak inhibitor of CYP3A4, OATP, and P-glycoprotein, affecting the PKs of other drugs.

Hypertension and dyslipidemia are major cardiovascular risk factors with high prevalence, which often exist as comorbidities. In clinics, antihypertensives and antihyperlipidemics are frequently prescribed to patients in combination. Potential drug–drug interactions (DDIs) should be considered important in ARB–statin combination therapy, because increased statin levels may be associated with statin-induced myopathy or rhabdomyolysis and increased ARB levels may cause hypotension and related symptoms. Therefore, the assessment of DDIs between these two agents is important to determine appropriate treatment regimens to maximize therapeutic efficacy and to minimize patient risks.

Because fimasartan and atorvastatin are frequently coadministered to patients, the assessment of DDIs of the two drugs was needed. The effect of fimasartan on the PKs of atorvastatin was investigated previously; however, the effect of atorvastatin on the PKs of fimasartan has been unknown. For these reasons, this study was designed to evaluate the effect of coadministration of fimasartan and atorvastatin on the PKs of each drug at steady state after multiple administrations.

Subjects and methods
Study population
Healthy Korean male subjects between the ages of 19 and 50, with body mass indexes (BMIs) of 19.0–28.0 kg·m⁻² were eligible for this study. Subjects who had significant hypersensitivity to fimasartan or atorvastatin, any significant disease or medical history, an HDL-C level of <35 mg·dL⁻¹, systolic blood pressure (SBP) >140 or <100 mmHg, and diastolic blood pressure (DBP) >90 or <65 mmHg were excluded. Subjects were prohibited from taking any medication without prior consent of the investigator, consuming beverages containing caffeine or alcohol, and smoking from 24 h prior to the first dose until the end of the study.

Study design
This study was designed as a randomized, open-label, three-period, six-sequence, crossover, multiple-dose study. Subjects were randomly assigned into six sequence groups and received 120 mg of fimasartan, 40 mg of atorvastatin, or both concomitantly, once daily for 7 days according to their treatment sequence (Figure 1). Blood samples for PK analysis were collected at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 48 h after the last dose of each period. After the last dose of the first and second period, subjects had a 7-day washout before starting the following period. The doses of fimasartan (120 mg) and atorvastatin (40 mg) in this study were determined based on common doses used in clinics, and were considered appropriate in terms of safety and therapeautic efficacy. Since the two drugs are prescribed for long-term use for chronic disease, the PKs and safety evaluation were conducted at steady state. The duration of drug administration needed to reach steady state was determined based on previous PK studies of fimasartan and atorvastatin.

This study protocol (ClinicalTrials.gov registry identifier: NCT02397590) was approved by the Institutional Review Board of Seoul National University Hospital (IRB no 06-2015-0730). All subjects provided written informed consent prior to enrollment.

Quantification of plasma levels of fimasartan, atorvastatin, and 2-hydroxy atorvastatin
The plasma concentration of fimasartan was measured using a validated high-performance liquid chromatography (HPLC; Agilent 1260 series; Agilent Technologies, Santa Clara, CA, USA) coupled with tandem mass spectrometry (MS/MS; API 4000 Qtrap, AB SCIEX; SCIEX, Framingham, MA, USA). The sample preparation for plasma involved a simple protein
precipitation with acetonitrile. Fifty microliters of plasma was thoroughly mixed with 450 μL of internal standard (IS; BR-A563 2.5 ng·mL\(^{-1}\) in 100% acetonitrile) and vortexed for 1 min. This mixture was injected onto the LC–MS/MS. The plasma samples were separated under gradient conditions using a mobile phase that consisted of 0.05% formic acid and 100% acetonitrile, and the samples were run at a flow rate of 0.35 mL·min\(^{-1}\). Fimasartan and IS were separated on an Poroshell 120 C18 column (3.0 × 50 mm, 2.7 μm; Agilent Technologies) and detected in a positive turbospray ionization mode. The plasma concentrations were extrapolated from the standard curve by comparing the ratio of the peak area of compound with that of IS. The method was validated over the range of 0.5–500 ng·mL\(^{-1}\). Precisions and accuracies of back-calculated concentrations were 4.662% and 95.87%–103.5%, respectively.

Plasma concentrations of atorvastatin and 2-hydroxy atorvastatin were also determined using an HPLC (Agilent 1260 series) coupled with MS/MS (Agilent 6490 Quadrupole). The sample preparation for plasma involved a simple protein precipitation with methanol. A mixture of 50 μL of deproteinized plasma and 200 μL of IS (atorvastatin-d5, 0.5 ng·mL\(^{-1}\) in methanol containing 0.1% formic acid) were vortexed for 1 min and separated under gradient conditions using a mobile phase that consisted of 5 mM ammonium formate and 100% acetonitrile, at a flow rate of 0.3 mL·min\(^{-1}\). Atorvastatin, 2-hydroxy atorvastatin, and IS were separated on an Xbridge C18 column (2.1 × 50 mm, 3.5 μm; Waters Corporation, Milford, MA, USA) and detected in the positive electrospray ionization mode with multiple reaction monitoring. The plasma concentrations were extrapolated from the standard curve by comparing the ratio of the peak area of compound with that of IS. The method was validated over the range of 0.1–150 ng·mL\(^{-1}\), and precisions and accuracies of back-calculated concentrations were <2.746% and 93.67%–103.8%, respectively.

**PK and statistical analysis**

Individual PK parameters of fimasartan, atorvastatin, and 2-hydroxy atorvastatin were analyzed using a non-compartmental analysis method with WinNonlin (Version 6.4; Certara, Princeton, NJ, USA). The area under the concentration–time curve for dose interval at steady state (AUC\(_{\text{τ,ss}}\)), maximum plasma concentration at steady state (C\(_{\text{max,ss}}\)), time to reach C\(_{\text{max}}\) at steady state (T\(_{\text{max,ss}}\)), terminal half-life (t\(_{1/2}\)), and other PK parameters were calculated.

Statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics for data

<table>
<thead>
<tr>
<th>Screening</th>
<th>Day –21 to Day –1</th>
<th>Day 1 to Day 7</th>
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</thead>
<tbody>
<tr>
<td>Day 29 to Day 35</td>
<td>Drug administration</td>
<td>Washout</td>
</tr>
<tr>
<td>PK sampling (Day 7 to Day 9)</td>
<td>Drug administration</td>
<td>Washout</td>
</tr>
<tr>
<td>Period 1</td>
<td>Period 2</td>
<td>Period 3</td>
</tr>
<tr>
<td>Sequence A</td>
<td>Fimasartan</td>
<td>Atorvastatin</td>
</tr>
<tr>
<td>Sequence B</td>
<td>Fimasartan</td>
<td>Fimasartan + atorvastatin</td>
</tr>
<tr>
<td>Sequence C</td>
<td>Atorvastatin</td>
<td>Fimasartan + atorvastatin</td>
</tr>
<tr>
<td>Sequence D</td>
<td>Atorvastatin</td>
<td>Fimasartan</td>
</tr>
<tr>
<td>Sequence E</td>
<td>Fimasartan + atorvastatin</td>
<td>Fimasartan</td>
</tr>
<tr>
<td>Sequence F</td>
<td>Fimasartan + atorvastatin</td>
<td>Atorvastatin</td>
</tr>
</tbody>
</table>

Figure 1 Study design. Subjects were randomly assigned to one of the indicated crossover treatment sequences (A–F), and fimasartan 120 mg and/or atorvastatin 40 mg were administered for 7 days in each period.

Abbreviation: PK, pharmacokinetic.
were calculated. Log-transformed \( C_{\text{\text{max,ss}}} \) and \( \text{AUC}_{\text{\text{\tau,ss}}} \) of each drug and its metabolite, if applicable, are presented as the ratio of the geometric means of coadministration of fimasartan and atorvastatin to fimasartan or atorvastatin alone. The log-transformed parameters were analyzed and compared by treatment using a mixed-effect model analysis of variance with the period, sequence, and treatment as fixed effects.

**Safety assessment**

Adverse events (AEs) were monitored throughout the study by the investigators’ questionnaire. The course, severity, outcomes, and relationships to the investigational drugs were evaluated by the investigator. Laboratory tests, 12-lead electrocardiograms (ECGs), and physical examinations were also assessed during the study. Vital signs, including SBP and DBP, were measured in the sitting position at 0 h (pre-dose) on Days 1 and 3 in each period, and at 0 (pre-dose), 2, 4, 12, 24, and 48 h after the last dose in each period.

**Results**

**Subjects**

A total of 38 subjects, aged 31.0 ± 6.5 years, weighing 67.9 ± 6.9 kg with a BMI of 22.67 ± 2.02 kg⋅m\(^{-2}\) were randomized into six groups. Each group had its own sequence of drug administration, and demographic characteristics were similar across the groups \((P = 0.4932, 0.6108, \text{ and } 0.5700 \text{ for age, weight, and BMI, respectively})\). Among the 38 subjects, two subjects withdrew consent prior to the first dose, and 36 subjects were administered the investigational drugs at least once and were included in the safety analysis. One subject withdrew consent after the second period so that 35 subjects completed the drug administrations and PK samplings. The PK analysis was conducted in these 35 subjects who completed the study.

**Pharmacokinetics**

After 7-day multiple administrations of 120 mg to reach steady state, fimasartan was rapidly absorbed and the plasma concentration reached a maximum at 0.5 h at median. Secondary peaks were observed within 4–8 h in most subjects. The \( C_{\text{\text{max,ss}}} \) and \( \text{AUC}_{\text{\text{\tau,ss}}} \) of fimasartan increased by 2.18- and 1.35-fold, respectively, when coadministered with atorvastatin, compared to those of fimasartan alone. The \( T_{\text{\text{max,ss}}} \) and \( t_{\text{1/2}} \) of fimasartan were not significantly changed by coadministration with atorvastatin (Figure 2, Table 1).

Atorvastatin and its 2-hydroxy metabolite reached their maximum concentrations at 1.0 and 2.0 h at median, respectively. The \( C_{\text{\text{max,ss}}} \) and \( \text{AUC}_{\text{\text{\tau,ss}}} \) of atorvastatin increased by 1.82- and 1.12-fold, respectively, when the two drugs were coadministered, compared to those of atorvastatin alone.

![Figure 2 Changes in mean plasma concentrations of fimasartan over time. Groups include 120 mg fimasartan alone (solid circles) or with 40 mg atorvastatin (open circles). The inset shows the data on a semilogarithmic scale (N=35).](image)
Effect of coadministration of fimasartan and atorvastatin

For 2-hydroxy atorvastatin, the $C_{\text{max,ss}}$ and $AUC_{\tau,ss}$ increased by 2.68- and 1.35-fold, respectively, after coadministration. Fimasartan coadministration did not affect the $T_{\text{max,ss}}$ and $t_{1/2}$ of atorvastatin and 2-hydroxy atorvastatin in terms of clinical significance. The ratio of the $AUC_{\tau,ss}$ of 2-hydroxy atorvastatin to the $AUC_{\tau,ss}$ of atorvastatin increased 1.20-fold after the coadministration of fimasartan (Figure 3, Table 2).

Safety and tolerability

Seven-day multiple coadministrations of fimasartan and atorvastatin were well tolerated, as well as single-drug administration of either fimasartan or atorvastatin in healthy subjects. A total of 15 AEs were considered to be related to the investigational drugs. Eight events, including dizziness, orthostatic hypotension, and blurred vision, occurred in four subjects with fimasartan monotherapy, whereas five events, including dizziness, were reported in three subjects with cotreatment. Two events, including chest discomfort and headache, occurred with atorvastatin treatment (Table 3). No serious AE was reported, and no participant discontinued the study due to an AE. All of the events were considered mild, and the subjects recovered without sequelae. There was no clinically significant change in vital signs, ECGs, clinical laboratory tests, or physical examinations during the study.

Discussion

This study was designed to evaluate the PK DDI between fimasartan and atorvastatin. Several studies have been conducted to evaluate drug interactions of other statins and ARB agents. Kang et al conducted a drug interaction study between fimasartan and rosuvastatin in healthy subjects. In that study, the $C_{\text{max,ss}}$ and $AUC_{\tau,ss}$ of fimasartan were slightly increased by 1.109- and 1.159-fold, respectively, and the $C_{\text{max,ss}}$ and $AUC_{\tau,ss}$ of rosuvastatin changed by

### Table 1 Pharmacokinetic parameters of fimasartan after 120-mg multiple oral doses of fimasartan with and without 40 mg of atorvastatin

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fimasartan + atorvastatin (N=35)</th>
<th>Fimasartan (N=35)</th>
<th>Geometric mean ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max,ss}}$ (ng·mL$^{-1}$)</td>
<td>630.57 ± 346.96</td>
<td>307.22 ± 220.81</td>
<td>2.18 (1.79–2.65)</td>
</tr>
<tr>
<td>$C_{\text{trough,ss}}$ (ng·mL$^{-1}$)</td>
<td>2.44 ± 1.13</td>
<td>3.35 ± 1.23</td>
<td></td>
</tr>
<tr>
<td>$AUC_{\tau,ss}$ (ng·h·mL$^{-1}$)</td>
<td>1,221.79 ± 421.12</td>
<td>904.17 ± 310.26</td>
<td>1.35 (1.26–1.43)</td>
</tr>
<tr>
<td>$T_{\text{max,ss}}$ (h)</td>
<td>0.75 (0.25–3.00)</td>
<td>0.50 (0.25–6.00)</td>
<td></td>
</tr>
<tr>
<td>$CL/F$ (L·h$^{-1}$)</td>
<td>105.06 ± 33.75</td>
<td>136.97 ± 40.52</td>
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</tr>
<tr>
<td>Half-life (h)</td>
<td>7.01 ± 2.25</td>
<td>7.92 ± 1.85</td>
<td></td>
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</tbody>
</table>

Note: Data presented as arithmetic mean ± standard deviation or median (minimum–maximum).

Abbreviations: $C_{\text{max,ss}}$, maximum plasma concentration at steady state; $C_{\text{trough,ss}}$, minimum plasma concentration at steady state; $AUC_{\tau,ss}$, area under the plasma concentration–time curve over the dosing interval at steady state; $T_{\text{max,ss}}$, time to reach maximum concentration at steady state; $CL/F$, apparent clearance at steady state; CI, confidence interval.

![Figure 3](https://www.dovepress.com/files/2305-figure3.png) Changes in mean plasma concentrations of (A) atorvastatin and (B) 2-hydroxy-atorvastatin over time. Groups include 40 mg atorvastatin alone (solid circles) or with 120 mg fimasartan (open circles). The insets show the data on a semilogarithmic scale (N=35).
Table 2 Pharmacokinetic parameters of atorvastatin and 2-hydroxy atorvastatin after 40-mg multiple oral doses of atorvastatin with or without 120 mg of fimasartan

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fimasartan + atorvastatin (N=35)</th>
<th>Atorvastatin (N=36)</th>
<th>Geometric mean ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max,ss} (ng·mL^{-1})</td>
<td>55.93 ± 32.96</td>
<td>29.95 ± 15.56</td>
<td>1.82 (1.51–2.18)</td>
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<tr>
<td>C_{trough,ss} (ng·mL^{-1})</td>
<td>0.32 ± 0.16</td>
<td>0.67 ± 0.35</td>
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<tr>
<td>AUC_{CI,ss} (ng·h·mL^{-1})</td>
<td>137.38 ± 78.24</td>
<td>125.48 ± 70.89</td>
<td>1.12 (1.04–1.22)</td>
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<tr>
<td>T_{max,ss} (h)</td>
<td>1.0 (0.5–4.0)</td>
<td>1.0 (0.5–4.0)</td>
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</tr>
<tr>
<td>CL/F</td>
<td>321.56 ± 112.19</td>
<td>355.3 ± 145.88</td>
<td></td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>7.09 ± 2.15</td>
<td>8.8 ± 2.06</td>
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<tr>
<td>2-Hydroxy atorvastatin</td>
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<tr>
<td>C_{max,ss} (ng·mL^{-1})</td>
<td>58.15 ± 27.49</td>
<td>22.69 ± 14.26</td>
<td>2.68 (2.27–3.17)</td>
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<td>C_{trough,ss} (ng·mL^{-1})</td>
<td>0.76 ± 0.32</td>
<td>1.24 ± 0.66</td>
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<tr>
<td>AUC_{CI,ss} (ng·h·mL^{-1})</td>
<td>213.14 ± 86.48</td>
<td>162.24 ± 73.51</td>
<td>1.35 (1.23–1.48)</td>
</tr>
<tr>
<td>T_{max,ss} (h)</td>
<td>1.5 (1.0–4.0)</td>
<td>2.0 (0.5–6.0)</td>
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<tr>
<td>Half-life (h)</td>
<td>8.45 ± 1.61</td>
<td>9.16 ± 1.62</td>
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<tr>
<td>AUC_{2-hydroxy-atorvastat} / AUC_{atorvastatin}</td>
<td>1.65 ± 0.43</td>
<td>1.37 ± 0.32</td>
<td>1.20 (1.13–1.28)</td>
</tr>
</tbody>
</table>

Note: Data presented as arithmetic mean ± standard deviation or median (minimum–maximum).
Abbreviations: C_{max,ss}, maximum plasma concentration at steady state; C_{trough,ss}, minimum plasma concentration at steady state; AUC_{CI,ss}, area under the plasma concentration–time curve over the dosing interval at steady state; T_{max,ss}, time to reach maximum concentration at steady state; CL/F, apparent clearance at steady state; CI, confidence interval.

1.090- and 0.870-fold, respectively. Son et al investigated drug interactions between telmisartan and rosuvastatin, and observed 1.1783- and 2.0128-fold increases in the AUC_{CI,ss} and C_{max,ss}, respectively, for rosuvastatin, and 1.1717- and 1.3501-fold increases in the AUC_{CI,ss} and C_{max,ss}, respectively, for telmisartan. In other studies, drug interactions between statin agents (ie, rosuvastatin, atorvastatin, or simvastatin) and ARBs (ie, olmesartan, valsartan, and losartan) were investigated, but no significant drug interactions were reported. Regarding fimasartan and atorvastatin, the effect of fimasartan on the PKs of atorvastatin was assessed in a previous study, which indicated that fimasartan increased the exposure of atorvastatin by 1.42- to 2.45-fold. However, the effect of atorvastatin on fimasartan exposure has not been investigated. To the best of our knowledge, the current study is the first to evaluate the effect of atorvastatin on the PKs of fimasartan. In addition, the effect of fimasartan on atorvastatin PK was confirmed in the current study.

Fimasartan is known to be a substrate of CYP3A4 and UGT1A3 enzymes and to be transported by OAT1, OATP1B1, OATP1B3, and BCRP (Figure 4). Fimasartan also inhibits the activity of the OATP1B1 transporter. Atorvastatin is a substrate and an inhibitor of CYP3A4, a substrate of UGT1A1 and UGT1A3 enzymes, and also a substrate of P-glycoprotein, OATP1B1, OATP1B3, and BCRP transporters.

When atorvastatin is administered with fimasartan, it is expected that the activity of CYP3A4 would be weakly inhibited and the first-pass effect of fimasartan would be reduced, thus increasing systemic exposure to fimasartan. As the inhibitory effect of atorvastatin is weak (defined by the US Food and Drug Administration guidelines as increasing the

Table 3 ADRs by treatment and SOC

<table>
<thead>
<tr>
<th>SOC</th>
<th>Fimasartan (n=35)</th>
<th>Atorvastatin (n=36)</th>
<th>Fimasartan + atorvastatin (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects reporting at least one event</td>
<td>4 (11.43) [8]</td>
<td>2 (5.56) [2]</td>
<td>3 (8.33) [5]</td>
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<tr>
<td>General disorders and administration-site conditions</td>
<td>1 (2.86) [1]</td>
<td>1 (2.86) [1]</td>
<td>1 (2.86) [1]</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>1 (2.86) [2]</td>
<td>1 (2.78) [1]</td>
<td>1 (2.78) [1]</td>
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<tr>
<td>Nervous system disorders</td>
<td>3 (8.57) [3]</td>
<td>1 (2.78) [1]</td>
<td>1 (2.78) [1]</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>1 (2.86) [1]</td>
<td>1 (2.86) [1]</td>
<td>1 (2.86) [1]</td>
</tr>
</tbody>
</table>

Notes: Data presented as number of subjects (% of subjects) [number of events]. Percentages are based on the subjects within each treatment group.
Abbreviations: ADR, adverse drug reaction; SOC, system organ class.
AUC of sensitive index substrates from >1.25- to <2-fold),\textsuperscript{32} the extent of drug interaction with fimasartan was also expected to be weak. We were able to confirm this in our study, whereby the AUC$_{\text{ss}}$ of fimasartan increased by only 1.35-fold after the coadministration with atorvastatin.

Fimasartan and atorvastatin are both substrates of OATP1B1 and OATP1B3 transporters, and the activities of OATP1B1 and OATP1B3 are supposedly inhibited by competition during the coadministration of the two compounds. Thus, the hepatic uptake of fimasartan should be decreased, and its systemic exposure after the coadministration with atorvastatin should be increased due to the competitive inhibition of the transporters, especially at high concentrations near the T$_{\text{max}}$. Because of this and the fact that the T$_{\text{max}}$ of both drugs are similar, we believe that the C$_{\text{max,ss}}$ of fimasartan increased to a greater extent than AUC$_{\text{ss}}$ did (2.18- and 1.35-fold, respectively).

Atorvastatin is metabolized to 2-hydroxy atorvastatin by CYP3A4. In a previous in vitro study using human hepatic microsomal CYP isoenzymes, the IC$_{50}$ value for the inhibition of CYP3A4 by fimasartan was found to be 283–494 μM.\textsuperscript{33} The average C$_{\text{max,ss}}$ of fimasartan following co-treatment in our study was 630.57 ng·mL$^{-1}$ (~1.3 μM). Because the IC$_{50}$ values were at least 218-fold greater than the C$_{\text{max,ss}}$ values, it is less likely that the activity of CYP3A4 is inhibited by fimasartan with typical dosages.

Instead of occurring via CYP inhibition, the increased C$_{\text{max,ss}}$ of atorvastatin and its metabolite may be explained by the competitive inhibition of OATP1B1 and OATP1B3, as mentioned above. In the concentration–time profile of atorvastatin, it was observed that the rate of concentration decrease after C$_{\text{max,ss}}$ was more rapid with a steeper slope after coadministration than after the administration with atorvastatin alone (Figure 2). The rapid fall of atorvastatin concentration can be explained by the short T$_{\text{max}}$ of fimasartan (0.75 h, median). Fimasartan may inhibit the transportation of atorvastatin into hepatocytes in a concentration-dependent manner. However, fimasartan is eliminated rapidly after the T$_{\text{max}}$. As the fimasartan concentration declines, the competitive inhibition of OATP1B1 and OATP1B3 would be attenuated, and atorvastatin would be transported into hepatocytes rapidly, quickly decreasing atorvastatin concentrations after the increased C$_{\text{max,ss}}$.

Nonetheless, the aforementioned drug interaction may be less meaningful in clinical settings. Considering the wide therapeutic range and highly variable PK parameters of fimasartan (CV% of 71.88 at maximum), the extent of increase in exposures due to drug interactions is less than the interindividual variability in the PK parameters when the drugs are administered alone. In addition, the relationship between exposure and response (ie, BP-lowering effect) was not significant when the AUC$_{\text{ss}}$ ranged from 500 to 2,500 ng·h·mL$^{-1}$. In addition, the incidences of fimasartan-related AEs were similar between fimasartan treatment and fimasartan–atorvastatin co-treatment, although the exposure of fimasartan differed by 1.35- to 2.18-fold between the two cohorts. Thus, the increases in exposures to both drugs seem to be less significant in terms of tolerability in our study, although safety and tolerability should be confirmed in relevant patient populations in future studies. Assessments of clinical endpoints would be helpful for the evaluation of the clinical significance of drug interactions between fimasartan and atorvastatin.

In conclusion, the systemic exposures of fimasartan and atorvastatin were increased by the coadministration of the drugs. The concurrent use of fimasartan and atorvastatin for 7 days

Figure 4 Proposed pathway of fimasartan metabolism.
was well tolerated in healthy male subjects. Clinical significance needs to be evaluated further in the context of exposure response and through future studies with clinical outcomes.

Acknowledgments
The authors deeply appreciate all of the support of the staff at the Clinical Trial Center, Seoul National University Hospital, during this study. This work was supported by Boryung Pharmaceutical, Co, Ltd, Seoul, Republic of Korea.

Disclosure
The authors report no conflicts of interest in this work.

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