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ORIGINAL RESEARCH

Pharmacokinetic and bioequivalence study comparing a fimasartan/rosuvastatin fixed-dose combination with the concomitant administration of fimasartan and rosuvastatin in healthy subjects

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Purpose: A new fixed-dose combination (FDC) formulation of 120 mg fimasartan and 20 mg rosuvastatin was developed to increase therapeutic convenience and improve treatment compliance.

Methods: A randomized, open-label, single-dose, two-treatment, two-way crossover study with a 7-day washout period was conducted to compare the pharmacokinetic (PK) characteristics and bioequivalence between an FDC of fimasartan/rosuvastatin and the separate co-administration of fimasartan and rosuvastatin in healthy Korean volunteers. The plasma concentrations of fimasartan and rosuvastatin were analyzed by a validated liquid chromatography-tandem mass spectrometry method, for which serial blood samples were collected for up to 48 hours post-administration of fimasartan and 72 hours post-administration of rosuvastatin, in each period. The PK parameters were calculated using a non-compartmental method.

Results: A total of 78 subjects completed the study. All the 90% CIs of the geometric mean ratios (GMRs) fell within the predetermined acceptance range. The GMR and 90% CI for the area under the plasma concentration-time curve from time 0 to the last measurement (AUC_{0-t}) and the maximum plasma concentration (C_{max}) for fimasartan were 0.9999 (0.9391–1.0646) and 1.0399 (0.8665–1.2479), respectively. The GMR and 90% CI for the AUC_{0-t} and C_{max} for rosuvastatin were 1.0075 (0.9468–1.0722) and 1.0856 (0.9944–1.1852), respectively. Treatment with fimasartan and rosuvastatin was generally well tolerated without serious adverse events.

Conclusion: The new FDC formulation of 120 mg fimasartan and 20 mg rosuvastatin can be substituted for the separate co-administration of fimasartan and rosuvastatin, for the advantage of better compliance with convenient therapeutic administration.

Keywords: fixed-dose combination, pharmacokinetics, bioequivalence, fimasartan, rosuvastatin

Introduction

The coexistence of high blood pressure (BP) and elevated cholesterol, the two major risk factors for cardiovascular disease, is a prevalent health concern, and the risk of coronary heart disease (CHD) synergistically increases in patients with both hypertension and dyslipidemia.[1] The risk of CHD can be reduced by more than 50% by the effective and concurrent treatment of hypertension and hypercholesterolemia.[2]

Fimasartan (Kanarb®, Boryung Pharmaceutical Co. Ltd., Seoul, Republic of Korea), an angiotensin II type 1 receptor blocker (ARB), was approved in 2010 by the Korean Food and Drug Administration for the management of mild to moderate hypertension.[3,4] Following the oral administration of fimasartan in healthy volunteers, the maximum

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plasma concentration (C_{max}) achieved was 0.5–3.0 hours after dosing, with a terminal half-life ($t_{1/2}$) of 5–16 hours.[5,6] According to the investigator's brochure, >90% of the fimasartan moiety in human plasma comprises the parent drug, with the proportion of the major active metabolite of fimasartan, M4, being <7.2%.[7] The findings from several in vitro and in vivo studies indicate that fimasartan is primarily excreted into the bile either in the parent form or as a glucuronide conjugate (20%).[8] OATP1B1, OATP2B1, OATP1B3, MDR1, and BCRP have important roles in the hepatobiliary uptake and excretion of fimasartan.[8–10]

Rosuvastatin, a synthetic inhibitor of HMG-CoA reductase, can significantly reduce the levels of low-density lipoprotein cholesterol in hyperlipidemic patients when administered at doses of 10–40 mg, with the reduction being higher than those induced by atorvastatin, pravastatin, or simvastatin.[11] When orally administered at doses of 10–80 mg in healthy volunteers, the C_{max} of rosuvastatin is observed at 3–5 hours after dosing, with a $t_{1/2}$ of 13–20 hours.[11,12] In total, 72% of the orally administered rosuvastatin is eliminated via the bile, and 28% via urinary excretion.[13] The main transporters involved in the hepatic uptake and efflux of rosuvastatin are OATP1B1 and BCRP.[14,15]

Fixed-dose combination (FDC) tablets, comprising two or more therapeutic agents, are beneficial for increasing therapeutic convenience and improving treatment compliance. An FDC tablet of fimasartan and rosuvastatin 120 mg/20 mg has been developed by Boryung Pharmaceutical Co. Ltd. The objective of this study was to compare the pharmacokinetic (PK) characteristics and bioequivalence between the FDC tablet of fimasartan/rosuvastatin 120 mg/20 mg and the two drugs when separately co-administered, as well as the safety profiles of fimasartan and rosuvastatin in combination therapy (ClinicalTrials.gov: NCT02205190).

Methods

Study subjects

This study was conducted at the Clinical Trial Center, Kyungpook National University Hospital (KNUH, Daegu, Republic of Korea), in accordance with the ethical principles of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice Guideline, and local laws and regulations. The protocol was approved by the Institutional Review Board of KNUH. Written informed consent was obtained from all the subjects prior to their participation in this study.

Healthy Korean male volunteers, aged between 19 and 55 years of age, weighing ≥50 kg, and within ±20% of their ideal body weights, were selected for this study. It was essential that none of the subjects had clinically significant abnormalities as judged by a detailed medical history, physical examination, routine clinical laboratory tests (hematology, biochemistry, and urinalysis), serology tests (performed using hepatitis B surface antigens, anti-hepatitis C virus antibody, anti-human immunodeficiency virus antibody, and the Venereal Disease Research Laboratory test), and 12-lead electrocardiography, performed within 3 weeks prior to administration of the drugs in this study.

The subjects were excluded if they had any of the following: a history of hypersensitivity to any drug including fimasartan and rosuvastatin; history or evidence of cardiovascular, hepatobiliary, renal, endocrine, hematological, respiratory, gastrointestinal, central nervous system, psychiatric, or neuromuscular disorders, or malignant disease; systolic BP of ≥140 or ≤100 mmHg, or diastolic BP of ≥90 or ≤65 mmHg; history of alcohol abuse (>21 units/week), or excessive smoking (>10 cigarettes/day); use of any prescription medication or herbal remedies within 2 weeks prior to the commencement of the study, or use of any over-the-counter remedies within 1 week prior to the first administration of the study drug; use of any other investigational drug within 3 months prior to the first administration of the drugs in this study; donation of whole blood within 2 months or any blood products within 1 month prior to the first administration of the drugs in this study; intake of abnormal diets that could affect absorption, distribution, metabolism, and excretion of a given drug within 7 days prior to the administration of the drugs in this study; positive serologic tests; or ineligibility to participate in this study at the discretion of the study investigator.

Study design and procedure

A randomized, open-label, single-dose, two-period, two-way crossover study was conducted at the KNUH Clinical Trial Center. Eighty healthy Korean male subjects were enrolled and randomized to one of the two treatment sequences in a 1:1 ratio, in which the treatments consisted of a single oral dose of fimasartan/rosuvastatin 120 mg/20 mg FDC (Boryung Pharm. Co. Ltd.) as the test treatment, or the co-administration of fimasartan 120 mg (Kanarb® tablet 120 mg; Boryung Pharm. Co. Ltd.) and rosuvastatin 20 mg (Crestor® tablet 20 mg; AstraZeneca Korea, Seoul, Republic of Korea) as separate agents, as the reference treatment. The washout period was 7 days, which was five-fold longer than the $t_{1/2}$s of both fimasartan and rosuvastatin as reported in previous PK studies.[5,6,11,12]

The subjects were admitted to the study center at 8 pm, a day prior to dosing. Each study drug was orally administered under fasting conditions along with 240 mL of water. The subjects fasted for 10 hours prior to dosing and the fasting was continued until 4 hours after dosing. Standard meals were provided at 4 and 10 hours after dosing. No additional water intake was allowed for 2 hours before and after dosing during each administration.

For PK analysis of fimasartan, blood samples were collected at 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 48 hours post-administration of the drug. For PK analysis of rosuvastatin, blood samples were collected at 0, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 8, 12, 24, 48, and 72 hours post-administration of the drug. An indwelling intravenous catheter was placed in either the forearm or dorsum of the hand of each subject. After discarding 1 mL of blood from the catheter, 9 mL of blood was collected into a tube containing sodium heparin and was centrifuged at 3,000 rpm for 10 minutes at 4°C, to separate the plasma. Following centrifugation, the plasma samples were transferred to four different tubes and stored at −70°C until analysis by Kyung Hee Drug Analysis Center of Kyung Hee University (Seoul, Republic of Korea).

Analysis of the plasma concentrations of fimasartan and rosuvastatin

The plasma concentrations of fimasartan were determined by an Agilent 1200 series high-performance liquid chromatography (HPLC) system (Agilent Technologies, Santa Clara, CA, USA) coupled to an MDS SCIEX API-4000 triple quadrupole mass spectrometer (Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA), with some modifications of a validated method.[16] Chromatographic separation was performed on a Luna HILIC column (2.1×50 mm internal diameter, 2.6 µm particle size; Phenomenex, Torrance, CA, USA), at a flow rate of 200 µL/min. The mobile phase consisted of a 20:80 (v/v) mixture of 0.05% formic acid in distilled water, and 0.05% formic acid in acetonitrile. Multiple reaction monitoring transitions were performed at mass-to-charge (m/z) ratios of 502.42 → 207.10 and 526.48 → 207.20 for fimasartan and BR-A-563 (the internal standard), respectively. The frozen plasma was thawed at room temperature and vortexed for 10 seconds. Following the addition of 20 µL of BR-A-563 (1,000 ng/mL) to 50 µL of plasma in a polypropylene tube, 50 µL of 1% formic acid and 1 mL of organic solvent (ethyl acetate: hexane =8:2) was added and vortexed for 10 minutes. After the mixture had been centrifuged at 4,000 rpm for 10 minutes at 4°C, 800 µL of the upper layer was transferred to a polypropylene vial and dried with a stream of nitrogen gas at 50°C. The residue was reconstituted with 2 mL of 90% acetonitrile solution (0.05% formic acid in distilled water: 0.05% formic acid in acetonitrile in the ratio 9:1 [v/v]). After vortexing for 5 minutes, the tube was centrifuged at 4,000 rpm for 10 minutes at 4°C. A 3 µL aliquot of this solution was injected into the liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) system for analysis.

The plasma concentrations of rosuvastatin were determined by an Agilent 1200 series HPLC system coupled to an API-4000 triple quadrupole mass spectrometer with some modifications of a validated method.[17] Chromatographic separations were performed on a Halo-C18 column (2.1×100 mm internal diameter, 2.7 µm particle size), at a flow rate of 200 µL/min. The mobile phase consisted of a 20:80 (v/v) mixture of 0.1% formic acid in distilled water, and 0.1% formic acid in methanol. Multiple reaction monitoring transitions were performed at m/z ratios of 482.37 → 258.30 and 488.35 → 264.30 for rosuvastatin and rosuvastatin-d_6 (the internal standard), respectively. The frozen plasma was thawed at room temperature and vortexed for 10 seconds. After adding 20 µL of rosuvastatin-d_6 (250 ng/mL) to 200 µL of plasma in a polypropylene tube, 20 µL of 1% HCl and 1.5 mL of methyl tert-butyl ether were added and vortexed for 10 minutes. After the mixture had been centrifuged at 14,000 rpm for 10 minutes at 4°C, 1.4 mL of the upper layer was transferred to a polypropylene vial, and dried with a stream of nitrogen gas at 50°C. The residue was reconstituted with 200 µL of 50% methanol, and vortexed for 5 minutes. The tube was centrifuged at 14,000 rpm for 10 minutes at 4°C, and the upper layer was transferred to a clean vial, and a 10 µL aliquot of this solution was injected into the LC-MS/MS system for analysis.

The linear calibration curves ranged between 2 and 1,500 ng/mL for fimasartan ($r \geq 0.9990$), and between 0.1 and 80 ng/mL for rosuvastatin ($r \geq 0.9993$). The overall intra-day accuracy ranged from 94.2% to 117.3% at concentrations of 2, 6, 200, and 1,500 ng/mL for fimasartan, and from 96.6% to 109.0% at concentrations of 0.1, 0.3, 25, and 80 ng/mL for rosuvastatin. The overall inter-day accuracy ranged from 95.8% to 113.5% for fimasartan, and from 97.3% to 103.5% for rosuvastatin. The intra-day precision (% coefficient of variation, CV) ranged from 0.4% to 15.7% for fimasartan, and from 0.7% to 8.7% for rosuvastatin. The inter-day precision (%CV) ranged from 1.8% to 10.3% for fimasartan, and from 1.0% to 8.3% for rosuvastatin. The lower limit of quantification was 2 ng/mL for fimasartan and 0.1 ng/mL for rosuvastatin.

PK analysis

The following PK parameters were calculated for fimasartan and rosuvastatin by non-compartmental methods using the Phoenix WinNonlin software, version 6.4 (Pharsight, Sunnyvale, CA, USA). The C_{max} and the time to reach C_{max} (t_{max}) were obtained directly from the observed plasma concentration-time data. The area under the plasma concentration-time curve from time 0 to the last measurement (AUC_{0-t}) was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. The AUC from time 0 to infinity ($AUC_{0-\infty}$) was calculated using the following formula: $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$, where, C_t is the last measurable concentration, and λ_z is the terminal elimination rate constant estimated from a linear regression line of the log-transformed plasma concentrations vs time over the terminal log-linear portion (at least three final data points). The $t_{1/2}$ was calculated to be $0.693/\lambda_z$.

Statistical analyses

The sample size for this study was calculated based on the intra-subject variability of the fimasartan C_{max} (42%), the highest value among AUC_{0-t} values, and C_{max} values of fimasartan and rosuvastatin in earlier PK studies.[18] In each group, 29 subjects were required for detecting a difference of 20% or more in the log-transformed PK parameters between the two different treatments (FDC vs the co-administration of the individual tablets) with 80% power and at a 5% level of significance. Therefore, a total of 80 subjects were to be enrolled, assuming an estimated attrition rate of 25%.

The baseline demographics, safety data, and PK parameters were summarized using descriptive statistics. The results were represented as the mean ± SD, except for the t_{max} values, which were expressed as the median, maximum, and minimum values. The differences in baseline demographics between the two groups were determined by the Mann–Whitney *U* test or independent *t*-test for the age, height, and body weight of the individuals; and the chi-squared test for smoking and drinking parameters, using the SPSS software for Windows OS (version 18.0; SPSS Korea, Seoul, Republic of Korea). The differences in the PK parameters between the two treatment strategies were compared using a mixed-effects model ANOVA model, with subject-within-sequence as a random effect, and sequence, period, and treatment as fixed effects. A *P*-value below 0.05 indicated statistical significance.

To assess the bioequivalence between the test and the reference treatment, the C_{max} and AUC_{0-t} of fimasartan and rosuvastatin were considered the primary PK parameters after natural logarithm (ln) transformation. The fimasartan/rosuvastatin (120 mg/20 mg) FDC formulation was considered bioequivalent to single agents concomitantly administered if the 90% CI of the geometric mean ratios (GMRs) (FDC/single agents) for those parameters fell within the predetermined standard range of 0.800–1.250, used by the Korea Ministry of Food and Drug Safety (MFDS).[19] All statistical analyses for GMRs with 90% CIs were performed using the SAS software (version 9.2.; SAS Institute Inc., Cary, NC, USA).

Assessment of safety and tolerability

Safety and tolerability assessments were conducted for all the subjects who received at least one dose of the study drugs throughout the study period, based on clinical adverse events (AEs) or AEs identified in the laboratory, which were observed after dosing, and included all subjective symptoms reported by the subjects and objective signs observed by the investigators. Vital signs (BP, heart rate) of the participants were monitored at screening, on days 1 and 8 (pre-dose and at 2, 4, 6, 12, and 24 hours after dosing), and at the follow-up visit. Body temperature was assessed at screening and at the follow-up visit. Physical examination was performed at screening, before dosing in each period (days 1 and 8), before discharge in each period (days 2 and 9), and at the follow-up visit. Electrocardiograms and routine laboratory tests (hematology, urinalysis, and serum chemistry) were conducted at screening, before dosing in period II (days 5–7), and at the follow-up visit. The AEs were monitored and recorded using the Medical Dictionary for Regulatory Activities (version 16.0), and categorized per system organ class and preferred term, and summarized according to the number of events, number of subjects, severity, seriousness, and causality. All the laboratory tests were performed at the Department of Laboratory Medicine, KNUH.

Results

Demographic characteristics

A total of 80 healthy male subjects were enrolled in this study and randomly assigned to one of two different groups in a 1:1 ratio. However, one subject who withdrew consent prior to the initiation of period I was replaced by another subject from the waiting list. During period II, two subjects in group 1 withdrew consent. In total, 78 subjects (group 1, n=38; group 2, n=40) who completed the study were considered for the PK analyses of fimasartan. However, only 75 subjects were considered for the PK analyses of rosuvastatin,

Table 1 Demographic characteristics of study subjects according to groups

Demographic variables	Overall (n=80)	Group 1 (n=40)	Group 2 (n=40)	*P*-value[a]
Age (years)				0.7168[b]
Mean ± SD	25.6±4.5	26.1±5.2	25.2±3.8	
Range	(19–42)	(19–39)	(20–42)	
Height (cm)				0.0648[c]
Mean ± SD	173.9±6.3	175.2±6.1	172.6±6.3	
Range	(161.7–187.4)	(163.7–185.4)	(161.7–187.4)	
Weight (kg)				0.1668[c]
Mean ± SD	68.9±7.2	70.1±7.1	67.8±7.2	
Range	(52.6–82.0)	(56.4–82.0)	(52.6–81.8)	
Smoking (%)				1.0000[d]
No	54 (67.5)	27 (67.5)	27 (67.5)	
Yes	26 (32.5)	13 (32.5)	13 (32.5)	
Drinking (%)				0.6481[d]
No	32 (40.0)	17 (42.5)	15 (37.5)	
Yes	48 (60.0)	23 (57.5)	25 (62.5)	

Notes: Data are given as the mean ± SD (range) for age, height, and weight, and number of subjects (%) for smoking and drinking. [a]Compared between two groups by Mann–Whitney *U* test[b], independent *t*-test[c], and chi-squared test[d]. Group 1 = RT; group 2 = TR; R = co-administration of fimasartan 120 mg and rosuvastatin 20 mg; T = fixed-dose combination formulation of fimasartan 120 mg and rosuvastatin 20 mg.

because the plasma concentrations of rosuvastatin administered concomitantly with fimasartan were not detectable for three subjects during period I. It was concluded that the three subjects had intentionally avoided taking the study medication, even though all the medicines were administered under supervision. All the 80 subjects receiving fimasartan and/or rosuvastatin at least once were included for the safety assessment.

The means ± SD (ranges) for the age, height, and weight of the subjects were 25.6±4.5 years (19.0–42.0 years), 173.9±6.3 cm (161.7–187.4 cm), and 68.9±7.2 kg (52.6–82.0 kg), respectively. The baseline demographics showed no statistical difference between the two groups (Table 1).

PK data

Figure 1 illustrates the mean (SD) plasma concentration vs time profiles of fimasartan and rosuvastatin following a single oral administration of an FDC formulation and the co-administration of fimasartan and rosuvastatin as separate tablets. The descriptive statistics for the PK parameters of fimasartan and rosuvastatin between an FDC formulation and the co-administration of fimasartan and rosuvastatin are summarized in Table 2. The intra-subject variability (%CV) values for AUC_{0-t} and C_{max} of fimasartan following the administration of the FDC or the co-administration of individual tablets in our study ranged from 24.1% to 27.0%, and from 48.1% to 48.6%, respectively. The CV% for AUC_{0-t}

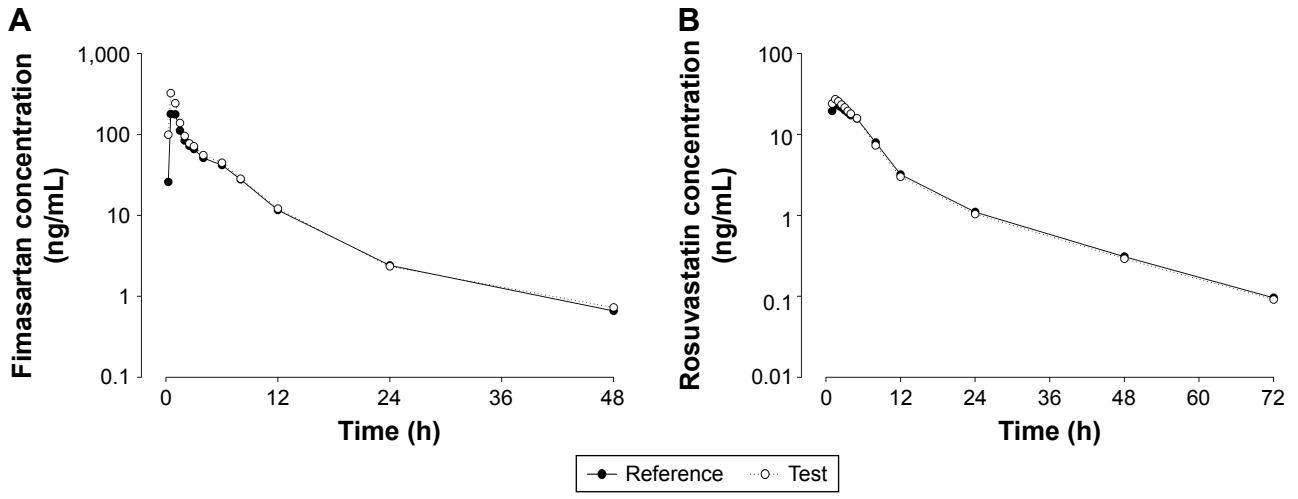

Figure 1 Mean plasma concentration-time profiles for (**A**) fimasartan (n=78), and (**B**) rosuvastatin (n=75), following administration of a single dose of fimasartan/rosuvastatin 120 mg/20 mg FDC tablet (○), and single doses of 120 mg fimasartan and 20 mg rosuvastatin individually co-administered (•) in healthy subjects.
Abbreviation: FDC, fixed-dose combination.

Table 2 Pharmacokinetic parameters of fimasartan and rosuvastatin following administration of fimasartan 120 mg and rosuvastatin 20 mg as a fixed-dose combination vs separate tablets under fasting conditions in healthy male subjects

	Pharmacokinetic parameter	FDC	Separate tablets	ANOVA *P*-value[a]
Fimasartan (n=78)	AUC_{0-t}, ng × h/mL	815.8±281.4 (24.1)	826.7±318.8 (27.0)	0.9907
	$AUC_{0-\infty}$, ng × h/mL	843.7±279.1 (23.2)	855.0±315.8 (25.9)	0.9430
	C_{max}, ng/mL	360.3±247.4 (48.1)	353.1±245.3 (48.6)	0.7414
	$t_{1/2}$, h	4.2±1.0 (17.1)	4.3±1.0 (16.8)	0.3914
	t_{max}, h[b]	0.50 (0.50–6.00)	0.75 (0.25–6.00)	0.1286
Rosuvastatin (n=75)	AUC_{0-t}, ng × h/mL	227.1±111.6 (34.4)	228.4±122.0 (37.4)	0.8233
	$AUC_{0-\infty}$, ng × h/mL	231.0±112.0 (33.9)	232.5±121.8 (36.7)	0.8859
	C_{max}, ng/mL	37.6±21.6 (57.5)	37.0±27.3 (51.8)	0.1165
	$t_{1/2}$, h	12.6±4.9 (27.1)	12.3±5.8 (33.1)	0.6911
	t_{max}, h[b]	1.50 (1.00–5.00)	1.50 (1.00–5.00)	0.2492

Notes: [a]Compared between two groups by ANOVA. Data are presented as arithmetic means ± SD (intra-subject coefficient of variation, %), except for t_{max} values as median (range)[b].

Abbreviations: AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the last measurement; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, maximum plasma concentration; $t_{1/2}$, terminal half-life; t_{max}, time to reach C_{max}; FDC, fixed-dose combination.

and C_{max} of rosuvastatin ranged from 34.4% to 37.4%, and from 40.2% to 51.8%, respectively. All 90% CIs for the ratio (FDC/co-administration) of the geometric means for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ fell within the predetermined acceptance range (Table 3).

Safety and tolerability assessments

Single oral doses of 120 mg of fimasartan and 20 mg of rosuvastatin, as an FDC tablet or as individual agents, were generally well tolerated in the healthy adult subjects selected in this study. In total, 13 subjects (16.25% of the 80 subjects) experienced at least one of the 14 reported AEs after the administration of the FDC. Of all the 14 AEs, seven were determined to be possibly related to the study drugs (five instances of increased CPK, and one instance each of increased ALT and dyspepsia) (Table 4). A total of 17 subjects (21.25% of 80 subjects) experienced at least one of the 20 reported AEs after the concurrent administration of the individual tablets. Of all the 20 AEs, 13 were determined to be possibly related to the study drugs (five instances of increased CPK, two instances of total bilirubin increased, two instances of headache, and one instance each of increased urinary protein, diarrhea, myalgia, and dizziness). There was no statistically significant difference in the incidence of AEs or study drug-related adverse drug reactions between treatment groups (Table 4). All the AEs were transient and resolved spontaneously without any specific treatment, and there were no instances of severe or serious AEs, with the exception of one where the CPK had increased severely. No subjects withdrew from the study because of the AEs.

Table 3 Geometric mean ratios and 90% CIs for the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ following administration of fimasartan 120 mg and rosuvastatin 20 mg as a fixed-dose combination vs separate tablets in healthy volunteers

Pharmacokinetic parameter	Geometric mean ratio (90% CI)	
	Fimasartan (n=78)	Rosuvastatin (n=75)
AUC_{0-t}	0.9999 (0.9391–1.0646)	1.0075 (0.9468–1.0722)
$AUC_{0-\infty}$	0.9978 (0.9390–1.0601)	1.0045 (0.9452–1.0676)
C_{max}	1.0399 (0.8665–1.2479)	1.0856 (0.9944–1.1852)

Abbreviations: AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the last measurement; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, maximum plasma concentration.

Discussion

This study indicates that the PK and tolerability profiles of an FDC tablet comprised of fimasartan and rosuvastatin were comparable to those of individual tablets co-administered to healthy subjects. The GMR and its 90% CI of the FDC and individual tablets for each individual drug fell entirely within the conventional bioequivalence range of 0.80–1.25 for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} (Table 3). Both the FDC and individual tablets were well tolerated in this study.

The intra-subject variability (%CV) values obtained in our study were comparable to those reported by other studies (Table 2).[20,21] The power of this study, calculated from the intra-subject %CV values of AUC_{0-t} and C_{max} for fimasartan and rosuvastatin, ranged from 44.8% to 99.9%. Although most of the intra-subject %CVs for AUC_{0-t} and C_{max} were

Table 4 Adverse drug reactions (ADRs) that were reported following a single oral administration of 120 mg of fimasartan and/or 20 mg of rosuvastatin as a fixed-dose combination vs separate tablets in healthy volunteers

System organ class/preferred term	FDC (n=80)			Separate tablets (n=80)			*P*-value[a]
Number of subjects with AEs	13 (14)			17 (20)			0.544
Number of subjects with ADRs	7 (7)			11 (13)			0.454
Severity of ADRs	Mild	Moderate	Severe	Mild	Moderate	Severe	
Number of subjects with ADRs (number of events)	4 (4)	2 (2)	1 (1)	8 (9)	4 (4)		
Investigations							
CPK increased	2 (2)	2 (2)	1 (1)	3 (3)	2 (2)		
Bilirubin total increased					2 (2)		
ALT increased	1 (1)						
Urinary protein increased				1 (1)			
Nervous system disorders							
Headache				2 (2)			
Dizziness				1 (1)			
Gastrointestinal disorders							
Diarrhea				1 (1)			
Dyspepsia	1 (1)						
Musculoskeletal and connective tissue disorder							
Myalgia				1 (1)			

Note: [a]Fisher's exact test.
Abbreviations: AEs, adverse events; FDC, fixed-dose combination.

higher than 30%, all the 90% CI values for the AUC_{0-t} and C_{max} were within the predetermined range of 0.8–1.25, according to the guidelines for FDC.[19,22]

As recommended by the guidelines for bioavailability and bioequivalence studies, blood samples were collected for up to 48 hours post-administration of fimasartan and 72 hours post-administration of rosuvastatin (at least three or more times the terminal $t_{1/2}$s of fimasartan and rosuvastatin, which are 5–16 and 13–20 hours, respectively), in order to capture 90% of the relevant AUCs.[22] The $AUC_{0-t}/AUC_{0-\infty}$ ratio was greater than 90% for fimasartan and rosuvastatin in all the 78 and 75 subjects, respectively, and the mean $AUC_{0-t}/AUC_{0-\infty}$ ratios for fimasartan and rosuvastatin ranged from 96.1% to 98.0% in our study, indicating that the sampling schedule was appropriate for providing a reliable estimate of the extent of exposure. The washout period of 7 days in this study was based on the longer $t_{1/2}$ of rosuvastatin (13–20 hours) obtained from earlier PK studies, and was adequate for ensuring the complete elimination of the study medications from the blood after period I, as fimasartan and rosuvastatin were not detectable in the pre-dose plasma samples in period II.

The FDC formulations and the individual tablets of fimasartan and rosuvastatin were both well tolerated in this study. During the study, a total of 34 AEs were reported by 30 subjects. The most common AE was elevation of serum CPK, which is one of the most commonly described features of statin-induced AEs.[23] One instance of severe CPK elevation occurred in one subject after the administration of the FDC formulation; however, the AE was transient and resolved spontaneously without any specific treatment.

The present study has several limitations that need to be considered. First, the study was conducted in healthy young male volunteers, who are not representative of the target patients. According to the investigator's brochure and the report by Lee et al, systemic exposure of fimasartan increased by 69% in elderly subjects, with no significant difference in efficacy by age or sex.[5] No apparent clinically relevant differences in rosuvastatin PKs according to age and sex have been reported.[11] Second, only a single dose was administered in this study. The third limitation of this study would be the relatively small sample size used. A long-term investigation involving a larger patient population is therefore necessary in the future for generalizing these results to other populations.

In conclusion, the FDC tablets comprised of fimasartan 120 mg/rosuvastatin 20 mg were bioequivalent to the individual drugs co-administered in healthy subjects under

fasting conditions. There was no significant difference in the safety profiles between the two treatment strategies.

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Data sharing statement

We, all the authors, intend to share individual de-identified participant data. However, there must be a limit in our data sharing, because this study was sponsored by a pharmaceutical company.

Disclosure

The authors report no conflicts of interest in this work.

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