

Original Research**Pharmacokinetic Interaction of Telmisartan With S-Amlodipine: An Open-Label, Two-Period Crossover Study in Healthy Korean Male Volunteers**

Yook-Hwan Noh, MD¹; Hyeong-Seok Lim, MD, PhD^{1,2}; Mi Jo Kim, MD¹; Yo Han Kim, MD¹; Hee Youn Choi, MD¹; Hye Ryoung Sung, MD¹; Seok-Joon Jin, MD¹; Jonglae Lim³; and Kyun-Seop Bae, MD, PhD^{1,2}

¹Department of Clinical Pharmacology and Therapeutics, Asan Medical Center, Seoul, Korea; ²College of Medicine, University of Ulsan, Seoul, Korea; and ³Technical Research Center, CKD Research Institute, Yongin, Korea

ABSTRACT

Background: Telmisartan belongs to a class of orally active angiotensin II receptor blockers (ARBs), and S-amlodipine is an enantiomer of amlodipine. Amlodipine is a racemic mixture and the calcium channel blocking (CCB) effect is confined to S-amlodipine, whereas R-amlodipine has a 1000-fold lower activity and no racemization occurs in vivo in human plasma. Combination therapy of ARBs with CCBs provides advantages for blood pressure control and vascular protection over monotherapy.

Objective: To investigate the effects of coadministration of telmisartan and S-amlodipine on the steady-state pharmacokinetic properties of each drug as a drug–drug interaction study required before developing the fixed-dose combination agent.

Methods: This study comprised 2 separate parts, A and B; each was a multiple-dose, open-label, 2-sequence, 2-period, crossover study in healthy male Korean volunteers. In part A, volunteers were administered 80 mg of telmisartan, either alone or with 5 mg of S-amlodipine. In part B, volunteers were administered 5 mg of S-amlodipine, either alone or with 80 mg of telmisartan. Blood samples were taken on days 9 and 37, following the final dose of each treatment, and at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after administration in part A, and were taken at 0 (predose), 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, and 24 hours after administration in part B. Plasma concentrations were determined using LC-MS/MS. The pharmacokinetic properties of each drug after coadministration of telmisartan and S-amlodipine were compared with those of each drug administered alone. Tolerability was assessed using measurements of vital signs, clinical chemistry tests, and interviews.

Results: Fifty-six volunteers were enrolled (32 in part A and 24 in part B), and all completed except 4 volunteers (3 withdrawn in part A and 1 withdrawn in part B). The geometric mean ratios (GMRs) (90% CI) for the $C_{max,ss}$ and $AUC_{\tau,ss}$ of telmisartan (with or without S-amlodipine) were 1.039 (0.881–1.226) and 1.003 (0.926–1.087), respectively. The GMRs (90% CI) for $C_{max,ss}$ and $AUC_{\tau,ss}$ of S-amlodipine (with or without telmisartan) were 0.973 (0.880–1.076) and 0.987 (0.897–1.085). Total 11 adverse events (AEs) were reported in 7 volunteers (21.9%) in part A. A total of 9 AEs were reported in 6 volunteers (25.0%) in part B. Statistical analysis confirmed that the 90% CIs for these pharmacokinetic parameters were within the commonly accepted bioequivalence range of 0.8 to 1.25, indicating that the extent of bioavailability of S-amlodipine was not affected by telmisartan. The intensity of all AEs was considered to be mild, and there were no significant differences in the prevalences of AEs between the 2 formulations.

Conclusions: Following multiple-dose coadministration of high doses of telmisartan and S-amlodipine, the steady-state pharmacokinetic properties of telmisartan were not significantly affected, and telmisartan had no significant effect on the pharmacokinetic properties of S-amlodipine at steady state in these selected groups of healthy volunteers. Both formulations were generally well-tolerated. ClinicalTrials.gov identifiers: NCT01356017 and NCT01356043.

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Key words: *S*-amlodipine, drug–drug interaction, healthy volunteers, pharmacokinetics, telmisartan.

INTRODUCTION

Angiotensin II receptor blockers (ARBs), which antagonize angiotensin II type 1 (AT1) receptors, are among the most popular class of drugs used in the treatment of hypertension. ARBs are widely recognized because of their good tolerability, the possibility of convenient once-daily dosing and their efficient blood pressure (BP)-lowering properties.^{1–4} ARBs may cause renal insufficiency, hyperkalemia, and orthostatic hypotension.⁵ ARB should not be used in pregnancy because of the risk for congenital malformations.⁶ Telmisartan belongs to a class of orally active and highly selective ARBs and was approved and introduced to the European and US markets in the late 1990s for the treatment of hypertension.^{1,7–9} Moreover, telmisartan was the first ARB to receive approval from the US Food and Drug Administration (FDA) and the European Commission for the reduction of cardiovascular morbidity in angiotensin-converting enzyme (ACE) inhibitor–insensitive patients manifesting cardiovascular disease (history of congestive heart disease, stroke, and/or peripheral arterial disease) and/or type 2 diabetes mellitus with documented target organ damage.^{8,9}

Amlodipine is in the dihydropyridine class of calcium channel blockers (CCBs).¹⁰ Adverse events associated with the dihydropyridines include dizziness, flushing, headache, gingival hyperplasia, peripheral edema, mood changes, and various gastrointestinal complaints.⁵ Amlodipine is used therapeutically as a racemic mixture,¹¹ although its enantiomers have markedly different pharmacologic activities. Essentially, the CCB effect is confined to *S*-amlodipine,¹² whereas *R*-amlodipine has a 1000-fold lower CCB activity.¹³ Thus, the antihypertensive and antianginal effects of amlodipine by the CCB effect are attributed to *S*-amlodipine, whereas *R*-amlodipine is regarded as an impurity that might be inactive or have undesirable activities.¹⁴ An amlodipine formulation available at present contains *R*- and *S*-amlodipine in a 1:1 ratio, whereas only *S*-amlodipine possesses the desirable activity and no racemization occurs in vivo in human plasma after single enantiomer administration. This finding supports the need for the development of a successful amlodipine formulation composed of only *S*-amlodipine.^{15–17}

In clinical practice, ARBs are expected to be prescribed along with amlodipine, which is one of the most widely used CCBs. To reduce the rate of cardiovascular events in patients with hypertension, guidelines for the management of hypertension advise physicians to prescribe 2 or more agents from different classes of drugs in patients with a systolic BP (SBP) >20 mm Hg and/or a diastolic BP (DBP) >10 mm Hg above the recommended goal (SBP/DBP <140/<90 mm Hg).^{18,19} Furthermore, clinical evidence has repeatedly reported the advantages of combination therapy with ARBs with CCBs over monotherapy, in BP control and vascular protection.^{20–22}

Because a fixed-dose combination (FDC) formulation might increase adherence by decreasing the number of required daily doses and might help to improve patient compliance,^{21,23,24} an FDC formulation of telmisartan/*S*-amlodipine is being developed as an antihypertensive agent. The purpose of the present study was to determine whether there are any significant pharmacokinetic interactions between high doses of telmisartan and *S*-amlodipine when coadministered for 9 days in healthy volunteers, and to assess the tolerability of the regimen, for the purposes of application submission to regulatory authorities for the development and marketing of the FDC formulation.

SUBJECTS AND METHODS

The study was divided into 2 parts and was conducted from April 20, 2011, to August 23, 2011, at the Clinical Trial Center (CTC) of Asan Medical Center in Seoul, Korea. The protocol was approved by the institutional review board at Asan Medical Center. All procedures were performed in accordance with the Good Clinical Practice guidelines,²⁵ as well as the Declaration of Helsinki and its amendments.²⁶ All participants provided written informed consent before being screened for eligibility.

Study Population

Eligible volunteers were Korean men aged 20 to 50 years, with a weight >55 kg and a body mass index between 19 and 26 kg/m². All volunteers were healthy as confirmed on medical history, physical examination, vital sign measurements (resting BP, heart rate, and body temperature), 12-lead ECG, serology (hepatitis B surface antigen, anti–hepatitis C virus antibody, and anti-HIV antibody), urinary drug screen (amphetamine, barbiturates, cocaine, opioids, benzodiazepines, tetrahydrocannabinol, and methadone), and

routine clinical laboratory tests (including biochemistry, hematology, and urinalysis). All tests were performed at the Department of Laboratory Medicine, Asan Medical Center (accredited by the College of American Pathologists) within 4 weeks of the first administration of the study drug. Volunteers who had any medical history that might affect drug absorption, distribution, metabolism, and/or excretion, such as a history of gastrectomy or any disorder of the pancreas, liver, or kidney, were excluded. Volunteers were excluded if they showed a sitting SBP of ≥ 140 or < 100 mm Hg, DBP ≥ 90 or < 60 mm Hg, or a pulse rate of ≥ 95 or < 50 beats/min at screening. Volunteers were asked to abstain from alcohol-, grapefruit-, and caffeine-containing foods and beverages for 72 hours before the first administration until discharge. The use of over-the-counter or prescribed drugs was not allowed from 7 or 14 days before the study, respectively, until after the last follow-up visit.

Study Design

The volunteers were orally administered 80 mg of telmisartan alone for 9 days, 5 mg of *S*-amlodipine alone for 9 days, or 80 mg of telmisartan with 5 mg of *S*-amlodipine concomitantly for 9 days.

The doses of telmisartan and *S*-amlodipine used in this study were determined based on dosage regimens required for hypertensive patients (telmisartan: 40 or 80 mg once daily; *S*-amlodipine: 2.5 or 5 mg once daily). To maximize the possibility of finding drug–drug interactions, 80 mg of telmisartan and 5 mg of *S*-amlodipine were used, which are the maximum doses in terms of safety and therapeutic efficacy. Drug administration followed a 9-day dosing regimen to reach steady state, determined by the known pharmacokinetic characteristics of each agent.^{27,28}

This study was subdivided into 2 parts, A and B, to evaluate the pharmacokinetic changes caused by coadministration of telmisartan with *S*-amlodipine. Each part was a multiple-dose, open-label, 2-treatment, 2-sequence, 2-period, crossover study. All fasting volunteers visited the center every morning (8 AM) during the treatment period for a vital sign check followed by drug administration with 240 mL of water. They were admitted to the trial center 16 hours before the last dosing in each treatment period and were confined until 24 hours after dosing, for serial pharmacokinetic sampling. On the last dosing day, the study drugs were administered after an overnight fast, and food intake was restricted for a further 4 hours after drug admin-

istration. The volunteers' mouths were examined after drug ingestion to guarantee swallowing, which was then recorded in the written source documents. Volunteers received standardized meals 4 and 9 hours after the last dosing. After discharge, they visited the CTC for the assessment of tolerability and pharmacokinetic properties of the study drug, given a 19-day washout period (> 5 -fold half-life of telmisartan and *S*-amlodipine).^{27,28} The same procedure was repeated with the alternate drug until the last follow-up for safety profile assessment. All dietary, smoking, and drug/herbal product restrictions were maintained throughout the study period. After the last follow-up visit, all volunteers were financially compensated for their participation.

Part A Study: Effect of *S*-Amlodipine on the Pharmacokinetic Properties of Telmisartan

Part A of the study aimed to explore the effect, if any, of amlodipine on the pharmacokinetic properties of telmisartan at steady state. Volunteers enrolled in part A were randomly assigned to a sequence group for the 2 treatments, according to a randomization table. Each sequence group consisted of 16 volunteers who were administered 80 mg of telmisartan with or without 5 mg of *S*-amlodipine for 9 days in treatment period 1, followed by alternate treatments for 9 days in period 2.

Blood samples for the pharmacokinetic analysis of telmisartan were taken from an intravenous cannula on days 9 and 37, following the final dose of each treatment, and at 0 (before dosing), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after drug administration. The cannula was placed in the forearm. At least 8 mL of blood was collected using Vacutainer tubes (Becton Dickinson Korea, Seoul, Korea) at each sampling time. The first 1 mL of blood drawn at each sampling time was discarded. The cannula was flushed with 1.5 mL physiologic saline after blood sampling.

Part B Study: Effect of Telmisartan on the Pharmacokinetic Properties of *S*-Amlodipine

Part B of the study was performed to determine the effect of telmisartan on the pharmacokinetic properties of *S*-amlodipine at steady state. Volunteers enrolled in part B were randomly assigned to a sequence group for the 2 treatments according to a randomization table. Each sequence group consisted of 12 volunteers, who were administered 5 mg of *S*-amlodipine with or without 80 mg of telmisartan for 9 days in treatment period 1, followed by alternate treatments for 9 days in period 2.

Blood samples for the pharmacokinetic analysis of *S*-amlodipine were taken from an intravenous cannula on days 9 and 37, following the administration of final dose of each treatment, and at 0 (before dosing), 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, and 24 hours after drug administration. The cannula was placed in the forearm. At least 8 mL blood was collected using Vacutainer tubes at each sampling time. The first 1 mL of blood drawn at each sampling time was discarded. The cannula was flushed with 1.5 mL physiologic saline after blood sampling.

Assay of *S*-Amlodipine and Telmisartan Concentrations in Plasma

Next, 8-mL blood samples were collected in heparinized tubes and separated into plasma by centrifugation at 1800g for 8 minutes at 4°C. The plasma was immediately placed into polypropylene tubes at <−20°C and then transferred to a freezer at <−80°C until analysis, with randomized sample codes concealing the treatments during determination of plasma drug concentrations.

Plasma concentrations of telmisartan and *S*-amlodipine were measured separately by Seoul Pharma Laboratories, Inc, Seoul, Korea, which is certified by the Good Laboratory Practice of the Korean Food and Drug Administration (KFDA). The method used in Seoul Pharma Laboratories was validated according to standard operating procedures and KFDA guidelines on bioanalytical method validation.²⁹ Telmisartan, *S*-amlodipine, and the internal standards—valsartan for telmisartan and desmethyl sibutramine for *S*-amlodipine—were provided by Chong Kun Dang Pharmaceutical Corp., Seoul, Korea.

Determination of Plasma Telmisartan Concentrations

Plasma concentrations of telmisartan were quantitated by a validated method³⁰ using UPLC (Acquity UPLC system, Waters Corporation, Milford, Massachusetts) coupled with MS-MS (Quattro Premier XE mass spectrometry, Waters Corporation). Frozen human plasma samples were thawed at ambient temperature. A total of 50 μ L of plasma were added to 800 μ L of internal standard solution (valsartan, 500 ng/mL in acetonitrile), vortexed for 30 seconds, and centrifuged at 3000g for 5 minutes. Then, 5 μ L of supernatant was injected into the LC-MS/MS. A Kinetex 2.6 μ XB-C18 100-Å column (internal diameter, 2.1 \times 100 mm; particle size, 2.6 μ m; Phenomenex, Inc, Torrance, California) was used for chromatographic separation. The

tandem mass spectrometry system was operated in positive ion mode with electrospray ionization. Ion pairs from m/z 515.1 \rightarrow 276.3 for telmisartan and from m/z 436.3 \rightarrow 291.3 for the internal standard were selected for quantitation. For optimized mass conditions, ion spray capillary voltage was 3800 V, collision gas was argon, nebulizing gas was nitrogen, and the desolvation temperature was 400°C. The plasma concentration of telmisartan was determined from the standard curve by using the ratio between the peak area of telmisartan and that of the internal standard.

The lower limit of quantitation (LLoQ) was 2 ng/mL, with the calibration curve ranging from 2 to 2000 ng/mL ($r^2 > 0.999$). Intraday accuracy ranged from 102.3% to 104.6% and interday accuracy ranged from 102.8% to 104.5%. The intra- and interday precision, expressed as %CV, was <1.9%, validating the plasma concentration analysis method over the given quantification range. The analyte was stable in human plasma following three freeze–thaw cycles, in plasma after storage for 24 hours at room temperature, in stock solution after storage for 6 hours at room temperature, and in a UPLC autosampler after storage at 4°C for 24 hours.

Determination of Plasma *S*-Amlodipine Concentrations

Plasma concentrations of *S*-amlodipine were quantitated by a validated method³¹ using UPLC (Acquity) coupled with MS-MS (Zevo TQ MS, Waters Corporation). Frozen human plasma samples were thawed at ambient temperature. In brief, 150 μ L of 0.1-M sodium hydroxide and 20 μ L of internal standard solution (desmethyl sibutramine: 100 ng/mL in 50% acetonitrile) were added to 300 μ L of plasma, and vortexed for 30 seconds. Then, 3 mL of methyl *tert*-butyl ether/hexane (8:2 vol/vol) was added and vortexed for 10 minutes. The mixture was centrifuged at 1800g for 5 minutes. After the organic solvent was evaporated using Nitrogen evaporator EYELA MG-2200 (Tokyo Rikakikai Co, Tokyo, Japan), the residues were reconstituted with 150 μ L of 70% acetonitrile, and 5 μ L of reconstituted solution was injected into the LC-MS/MS. A Kinetex 2.6 μ C₈ column (internal diameter, 2.1 \times 100 mm; particle size, 2.6 μ m; Phenomenex) was used for chromatographic separation. The MS/MS system was operated in positive ion mode with electrospray ionization. Ion pairs from m/z 409.0 \rightarrow 237.9 for *S*-amlodipine and from m/z 266.3 \rightarrow 124.9 for the internal standard were selected for the

quantitation. For the optimized mass conditions, ion spray capillary voltage was 3000 V, collision gas was argon, nebulizing gas was nitrogen, and the desolvation temperature was 450°C. The plasma concentration of *S*-amlodipine was determined from the standard curve by using the ratio between the peak area of *S*-amlodipine and that of the internal standard.

The LLoQ was 0.05 ng/mL, with the calibration curve ranging from 0.05 to 10 ng/mL ($r^2 > 0.999$). The intra- and interday accuracy ranged from 97.6% to 103.8%, and the intra- and interday precision, expressed as the %CV, was <7.3%, validating the plasma concentration analysis method over the given quantification range. The analyte was stable in human plasma following 3 freeze-thaw cycles, in plasma after storage for 25 hours at room temperature, in stock solution after storage for 6 hours at room temperature, and in a UPLC autosampler after storage at 4°C for 24 hours.

Pharmacokinetic Analyses

Individual pharmacokinetic properties of telmisartan and *S*-amlodipine were analyzed using noncompartmental methods with Phoenix WinNonlin version 6.1 software (Pharsight Corporation, Mountain View, California).³² The actual blood sampling times were used in the pharmacokinetic analysis. $C_{\max,ss}$ and $T_{\max,ss}$ were obtained directly from the observed values. $AUC_{\tau,ss}$ was estimated using the log-linear trapezoidal rule.³³ The apparent clearance at steady state was calculated by dividing the dosage amount by $AUC_{\tau,ss}$.

Tolerability Assessment

Tolerability was assessed at predefined regular intervals throughout the study by physical examination, including vital sign measurements (SBP and DBP, heart rate, and tympanic temperature), ECG, and clinical laboratory testing (biochemistry, hematology, and urinalysis). The results were analyzed at the Department of Laboratory Medicine, Asan Medical Center (AMC), accredited by the College of American Pathologists. SBP and DBP were measured after a 3-minute rest; before each drug administration; and at 1, 2, 4, 8, 24 hours after the last dosing. BP and heart rate in the upper arm was measured using an automated oscillometric device (Welch Allyn 53NTP; Welch Allyn Inc, Skaneateles Falls, New York) while volunteers were in a sitting position by the attending nurses. The tympanic temperature was measured using an infrared ear thermometer (Braun

ThermoScan IRT 4520, Braun GmbH, Kronberg, Germany) by the attending nurses.

Adverse events (AEs) were monitored using spontaneous reporting and were elicited by asking volunteers general health-related questions throughout the study. The clinical importance of AEs and any abnormalities in physical examination findings, vital signs, or laboratory tests was determined by study investigators.

Statistical Analysis

Statistical analysis was performed using Phoenix WinNonlin version 6.1 and R version 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria).³⁴ Arithmetic means, SDs, median, maximum and minimum values for continuous data, and absolute and relative frequencies for categorical data were calculated. The sample size of this study was calculated based on the number estimated to provide $\geq 80\%$ power at a significance level of 0.05.³⁵

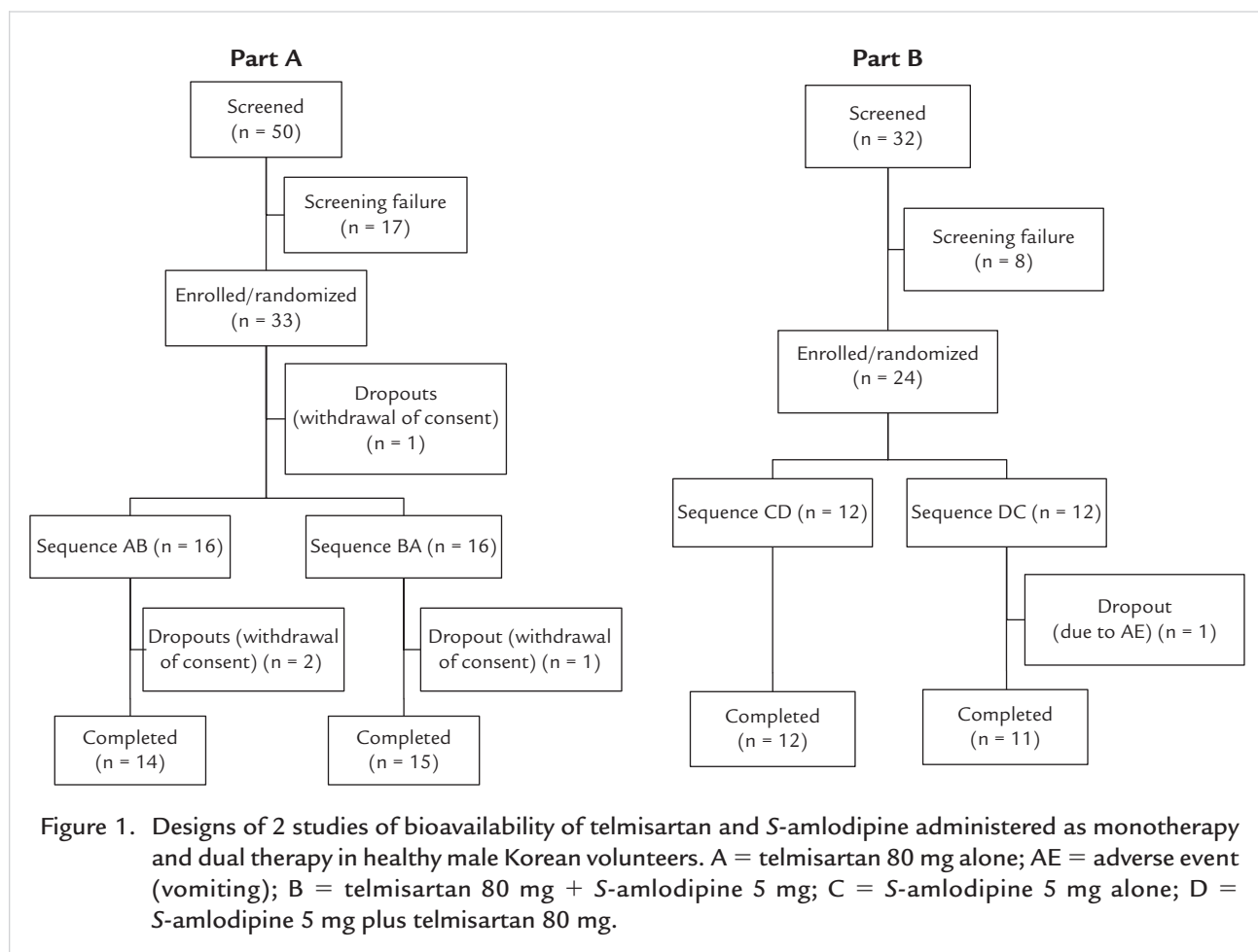
To compare the pharmacokinetic profiles of telmisartan and *S*-amlodipine, the log-transformed individual $C_{\max,ss}$ and $AUC_{\tau,ss}$ values were compared using a mixed-model ANOVA with sequence, period, and treatment as fixed effects, and subjects nested within the sequence as the random effect.³⁶ Treatment effects ($C_{\max,ss}$ and $AUC_{\tau,ss}$) were presented as ratios and 90% CIs of the geometric means for coadministration of telmisartan and *S*-amlodipine to telmisartan or *S*-amlodipine alone in part A or B, respectively. In pharmacokinetic drug–drug interactions analysis, no drug interaction following coadministration of the substrate and the interacting drug can be concluded at the 0.05 significance level if the corresponding 90% CI for log-transformed $C_{\max,ss}$ and $AUC_{\tau,ss}$ values is completely contained within the no-effect boundaries (-0.2231 to 0.2231).³⁴

RESULTS

Baseline Characteristics

In part A of the study, 32 healthy male volunteers (mean [SD] age, 25.7 [5.3] years; weight, 69.3 [7.0] kg; height, 174.8 [5.8] cm) were enrolled. Three volunteers withdrew their participation consent following the first period of drug administration (Figure 1). Safety profiles were assessed in all 32 volunteers who were administered the study drug. Pharmacokinetic characteristics were evaluated in the 29 volunteers who completed part A of the study.

In part B of the study, 24 healthy male volunteers (mean [SD] age, 28.1 [5.5] years; weight, 70.4 [7.2] kg;



height, 175.7 [6.1] cm) were enrolled. One volunteer dropped out due to vomiting of day 7 of study drug administration during the second period because it might have affected the steady-state pharmacokinetic properties of that volunteer. Safety profiles were assessed in all 24 volunteers who were administered the study drug. Pharmacokinetic characteristics were evaluated in the 23 volunteers who completed part B of the study.

The baseline characteristics of the 2 treatment groups were not significantly different in either study part.

Pharmacokinetic Characteristics

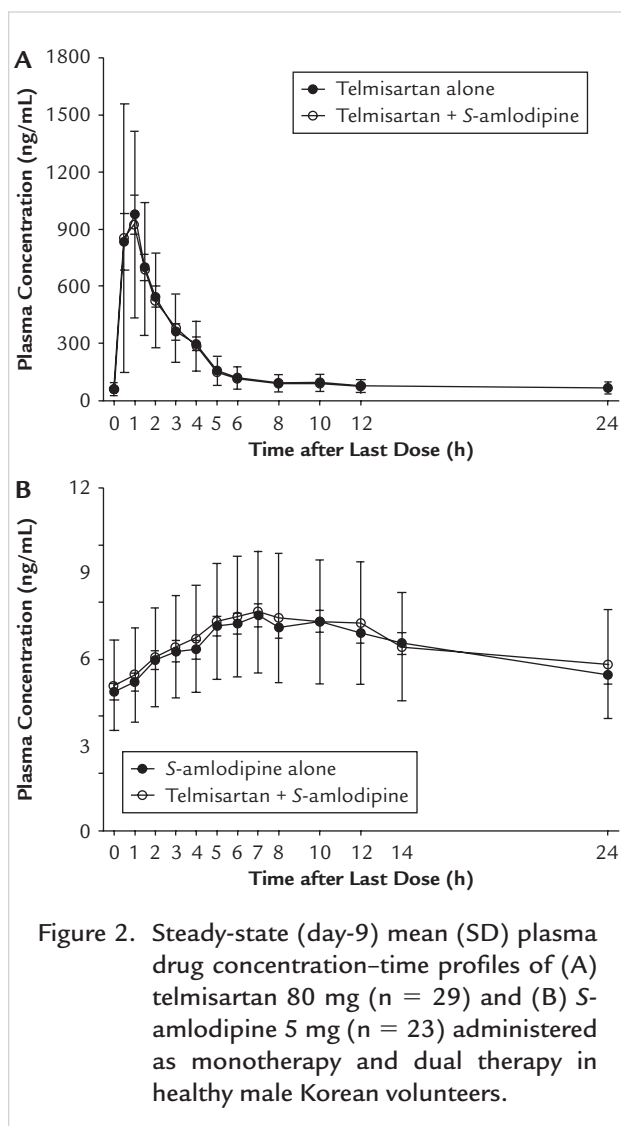
Effect of S-Amlodipine on the Pharmacokinetic Properties of Telmisartan

After 9-day multiple administration of 80 mg of telmisartan with or without 5 mg of *S*-amlodipine, the concentration–time profiles were similar between treatment groups; median $T_{\max,ss}$ was 1.0 hour, with plasma drug concentrations declining exponentially thereafter (Figure 2A). The mean (SD) telmisartan

$C_{\max,ss}$ values were 1151.75 (642.18) and 1188.38 (579.25) ng/mL after administration alone and with *S*-amlodipine, respectively (Table I). The geometric mean ratio (GMR) (90% CI) of the telmisartan $C_{\max,ss}$ was 1.039 (0.881–1.226), which suggests that $C_{\max,ss}$ was similar between the 2 treatments (Table II). After administration of telmisartan with and without *S*-amlodipine, the GMR (90% CI) of the telmisartan $AUC_{\tau,ss}$ was 1.003 (90% CI, 0.926–1.087), suggesting a similar $AUC_{\tau,ss}$ profile of telmisartan administered with or without *S*-amlodipine.

Effect of Telmisartan on the Pharmacokinetic Properties of S-Amlodipine

The concentration–time profiles of *S*-amlodipine was similar with 9-day multiple administrations of the drug with and without telmisartan (Figure 2B). The median (range) $T_{\max,ss}$ of *S*-amlodipine was 7.0 hours in both treatment groups (ranges: monotherapy, 3.1–14.1 hours; dual therapy, 5.0–14.0 hours) (Table I). The mean



$C_{\max,ss}$ after coadministration of *S*-amlodipine and telmisartan was similar to that of *S*-amlodipine administered alone. The GMR (90% CI) of the *S*-amlodipine $C_{\max,ss}$ was 0.973 (0.880–1.076) (Table II). The mean (SD) $AUC_{\tau,ss}$ values were 154.18 (39.57) and 157.89 (46.02) ng · h/mL after the administration of *S*-amlodipine with and without telmisartan, respectively (Table I). The GMR (90% CI) of *S*-amlodipine $AUC_{\tau,ss}$ was 0.987 (0.897–1.085), suggesting that the bioavailability of amlodipine was not affected by telmisartan (Table II).

Tolerability

During the study, a total of 20 AEs that were regarded as possibly related to study drug (11 AEs in part A; 9 in part B) were reported in 13 volunteers (7 vol-

unteers in part A; 6 in part B). In part A, these included increased total blood bilirubin levels (telmisartan monotherapy, 5 cases; telmisartan + *S*-amlodipine, 3 cases), abdominal discomfort (1 and 0 cases, respectively), dizziness (1 and 0), and headache (0 and 1). In part B, the study drug–related AEs were elevated total blood bilirubin (*S*-amlodipine monotherapy, 2 cases; telmisartan + *S*-amlodipine, 3 cases), headache (1 and 1), vomiting (1 and 0), and elevated blood alanine aminotransferase (ALT) (0 and 1). All of the events were described as being mild in intensity, and there were no significant differences in the prevalences of AEs between the 2 formulations. There were no serious AEs reported, and all of the AEs were resolved without sequelae.

There were no clinically significant findings on physical examination or ECG, and there were no clinically relevant changes in the routine laboratory parameters (clinical chemistry, hematology, and urinalysis).

In part A of the study, after 9-day multiple administration of telmisartan alone and with *S*-amlodipine, the greatest decreases in mean (SD) SBP were 8.7 (2.5) and 8.5 (2.7) mm Hg, respectively; DBP, 6.4 (2.9) and 7.6 (2.8) mm Hg. In part B of the study, after 9-day multiple administration of *S*-amlodipine alone or with telmisartan, the greatest decreases in SBP were 3.8 (2.9) and 8.8 (4.0) mm Hg, respectively; DBP, 4.9 (3.5) and 8.6 (3.7) mm Hg (Figure 3).

DISCUSSION

The findings from the present multiple-dose studies suggest that there was no evidence for any pharmacokinetic interaction between telmisartan 80 mg and *S*-amlodipine 5 mg when coadministered in these selected healthy male Korean volunteers. The $AUC_{\tau,ss}$ at day 9 for telmisartan differed by 0.3% when given together with *S*-amlodipine compared with alone. Similarly, the C_{\max} values varied by 3.9%. In the case of *S*-amlodipine, telmisartan $AUC_{\tau,ss}$ and C_{\max} values were reduced by 1.3% and 2.7% with coadministration and monotherapy, respectively. On statistical analysis, the 90% CIs for these pharmacokinetic parameters were within the commonly accepted bioequivalence criteria of 0.8 to 1.25, suggesting that the extent of the bioavailability of *S*-amlodipine was not affected by coadministration with telmisartan.³⁷

Both telmisartan and *S*-amlodipine were administered at high doses (80 and 5 mg, respectively). Despite these high doses, the tolerability of both agents was acceptable, whether given alone or in combination, for 9-day periods

Table I. Steady-state pharmacokinetic (PK) properties of telmisartan and *S*-amlodipine after multiple oral administrations of telmisartan 80 mg, *S*-amlodipine 5 mg, or both in healthy male Korean volunteers.*

PK Parameter	Telmisartan PK Properties (n = 29)		<i>S</i> -Amlodipine PK Properties (n = 23)	
	Telmisartan Monotherapy Administration	Telmisartan + <i>S</i> -Amlodipine Administration	<i>S</i> -Amlodipine Monotherapy Administration	Telmisartan + <i>S</i> -Amlodipine Administration
$T_{\max,ss}$, median (range), h	1.0 (0.3–2.0)	1.0 (0.5–3.0)	7.0 (3.1–14.1)	7.0 (5.0–14.0)
$C_{\max,ss}$, mean (SD), ng/mL	1151.75 (642.18)	1188.38 (579.25)	7.92 (1.83)	8.01 (2.18)
$AUC_{\tau,ss}$, mean (SD), ng · h/mL	4020.71 (2184.76)	3951.67 (1667.05)	154.18 (39.57)	157.89 (46.02)
CL_{ss}/F , mean (SD), L/h	25.65 (14.60)	25.99 (19.27)	35.16 (12.21)	40.71 (43.28)

CL_{ss}/F = apparent clearance at steady state.

*No significant between-group differences were found.

in this selected population. The AEs were predominantly mild in intensity, and no serious AEs were reported. The headache, dizziness, vomiting, elevated blood ALT, and elevated total blood bilirubin reported in the present study are frequently reported with ARBs and/or CCBs.^{28,38,39} The headaches and dizziness were likely due to the pharmacologic effects of lowering BP and/or depletion of sodium/volume in healthy volunteers.

No significant pharmacokinetic drug–drug interactions between ARBs and amlodipine have been reported in several previous studies in healthy volunteers.^{40,41} The findings from the present study support those, although *S*-amlodipine was used rather than amlodipine. In the present study, the authors suggest the

absence of pharmacologic drug interactions by presenting the pharmacokinetic properties of telmisartan and *S*-amlodipine in these healthy male Korean volunteers. Moreover, the findings provide important information for further drug development of an FDC of telmisartan + *S*-amlodipine.

Although the present study was conducted in normotensive volunteers, BP-lowering effects were observed following multiple administrations of telmisartan and/or *S*-amlodipine for 9 days. In all of the treatment groups, SBP and DBP were slightly decreased after the drugs were administered in multiple doses, and coadministration of telmisartan and *S*-amlodipine decreased both SBP and DBP more than administration of telmisartan or *S*-amlodipine alone. This finding is supported by those from previous studies of combination therapy with amlodipine and valsartan/telmisartan/olmesartan.^{20,42,43} The BP measured after 9-day treatment in these healthy volunteers may be somewhat different from that in hypertensive patients after long-term treatment. Therefore, further long-term studies in hypertensive patients are needed to evaluate the clinical efficacy of combination therapy with telmisartan and *S*-amlodipine.

CONCLUSIONS

From the findings of the present study, the authors conclude that following multiple-dose administration, the steady-state pharmacokinetic properties of telmisartan were not significantly affected when high-dose telmisartan co-administered with high-dose *S*-amlodipine, and that telmisartan had no significant effect on

Table II. Geometric mean ratios (90% CIs)* of steady-state pharmacokinetic (PK) properties of telmisartan and *S*-amlodipine after multiple oral administration of telmisartan 80 mg, *S*-amlodipine 5 mg, or both in healthy male Korean volunteers.

PK Parameter	Telmisartan (n = 29)	<i>S</i> -Amlodipine (n = 23)
$C_{\max,ss}$	1.039 (0.881–1.226)	0.973 (0.880–1.076)
$AUC_{\tau,ss}$	1.003 (0.926–1.087)	0.987 (0.897–1.085)

*Ratio of telmisartan or *S*-amlodipine alone to telmisartan with *S*-amlodipine using ANOVA of the mixed-effects model.

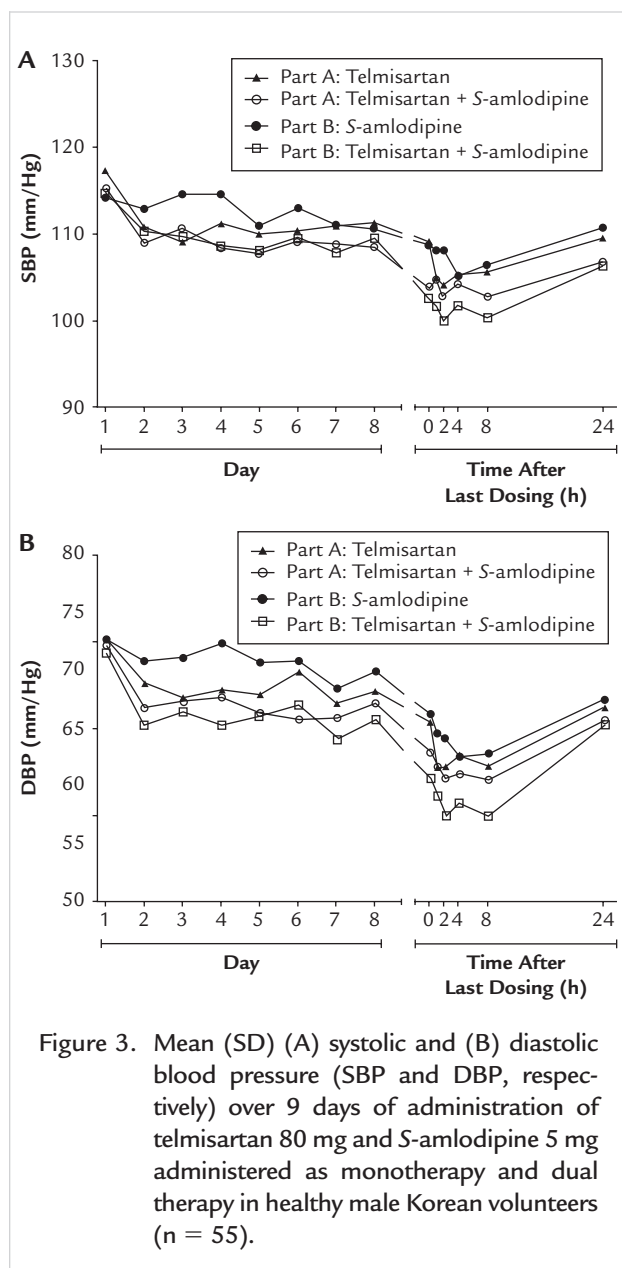


Figure 3. Mean (SD) (A) systolic and (B) diastolic blood pressure (SBP and DBP, respectively) over 9 days of administration of telmisartan 80 mg and S-amlodipine 5 mg administered as monotherapy and dual therapy in healthy male Korean volunteers (n = 55).

the pharmacokinetic properties of S-amlodipine at steady state in these selected healthy male Korean volunteer populations. The findings also suggest that concurrent once-daily administration of telmisartan and S-amlodipine was well-tolerated, without the need for adjustment of the dose of either agent, if a combination of agents is considered appropriate.

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All of the authors agreed on the contents of the manuscript, and the corresponding author made the final decision regarding its submission. Drs. Bae, H.S. Lim, Noh, Jin, M.J. Kim, Y.H. Kim, Sung, and Choi equally contributed to the study design, data interpretation, and data collection. Dr. Noh contributed to the data analyses, literature search, figure creation, and manuscript writing. Dr. J.L. Lim reviewed the manuscript.

CONFLICT OF INTEREST

These 2 studies were designed for the sponsor by the authors and then were contracted to the authors for completion. Dr. J.L. Lim is an employee of Chong Kun Dang Pharmaceutical Corp. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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Address correspondence to: Kyun-Seop Bae, MD, PhD, 88, Olympic-ro 43-gil, Songpa-gu, Seoul, Korea, 138-736. E-mail: ksbae@amc.seoul.kr