TCP Transl Clin Pharmacol
2019;27(4):134-140
https://doi.org/10.12793/tcp.2019.27.4.134

Pharmacokinetic comparison between fixed-dose combination of fimasartan/amlodipine 60/10 mg and the corresponding loose combination through partial replicated crossover study in healthy subjects

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ORIGINAL ARTICLE

Check for updates

Received 8 Oct 2019
Revised 29 Nov 2019
Accepted 1 Dec 2019

Keywords
Amlodipine,
Fimasartan,
Fixed-dose combination,
Scaled bioequivalence,
Partial replicated crossover

pISSN: 2289-0882
eISSN: 2383-5427

Combination therapies of antihypertensive drugs are recommended in cases where hypertension is not controlled by monotherapy. This study aimed to compare the pharmacokinetics (PKs) between fixed-dose combination (FDC) of fimasartan/amlodipine 60/10 mg and the corresponding loose combination. Because of the high intra-subject variability for maximum plasma concentration (C_{max}) of fimasartan, a randomized, open-label, 3×3 partial replicated crossover design was adopted. Subjects received a single dose of FDC of fimasartan/amlodipine 60/10 mg or the corresponding loose combination in each period. Blood samples for PK analysis were collected up to 48 hours for fimasartan and 144 hours for amlodipine, respectively. Geometric mean ratios (GMRs) and its 90% confidence intervals (CIs) of the FDC to the loose combination for C_{max} and area under the concentration-time curve from time 0 to the last quantifiable time point (AUC_{last}) were calculated. Sixty healthy subjects were randomized, and 57 subjects completed the study. The concentration-time profiles of fimasartan and amlodipine were similar between the FDC and loose combination. The GMRs (90% CIs) of the FDC to the loose combination for C_{max} and AUC_{last} were 1.0440 (0.9202–1.1844) and 1.0412 (0.9775–1.1090) for fimasartan, and 1.0430 (1.0156–1.0711) and 1.0339 (1.0055–1.0631) for amlodipine, respectively. The GMRs and its 90% CIs for C_{max} and AUC_{last} of fimasartan and amlodipine were included not only in the scaled bioequivalence criteria but also in the conventional bioequivalence criteria. In conclusion, FDC of fimasartan/amlodipine 60/10 mg showed comparable PK profiles with the corresponding loose combination, which suggests their bioequivalence.

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Reviewer
This article was reviewed by peer experts who are not TCP editors.

Introduction

Hypertension is a major risk factor for cardiovascular diseases, so blood pressure (BP) control is important in preventing relevant complications.[1] According to the hypertension management guideline of the Korean Society of Hypertension, if the systolic blood pressure (SBP)/diastolic blood pressure (DBP) exceeds 160/100 mmHg, or is 20/10 mmHg higher than the tar-

get BP, combination therapy with two antihypertensive agents of different classes is recommended.[2] Especially, it is well known that the concomitant use of a calcium channel blocker (CCB) with an angiotensin II receptor blocker (ARB) is more effective than doubling the dose of one single drug.[3-6]

Fimasartan, an ARB, is rapidly absorbed, reaching its maximum plasma concentration (C_{max}) in 0.5–3.0 hours, and has a terminal elimination half-life of 9.0–16.0 hours. More than 90% of fimasartan in the plasma presents as the parent drug, and its relatively very small portion undergoes metabolism, mainly by CYP3A4.[7] Additionally, fimasartan is known as a highly variable drug (HVD), in that its intra-subject variability for C_{max} is larger than 30%.[8-10] Amlodipine, a CCB, reaches at C_{max} within 6.0–8.0 hours and has a terminal elimination half-life of 40–60 hours,[11] and it is extensively metabolized by CYP3A4.[12] In a previous drug-drug interaction study, there was no clinically relevant pharmacokinetic (PK) interaction between fimasartan and amlodipine.[7]

Fixed-dose combination (FDC) is known to improve patients' compliance and reduce medical costs, and it may be more effective in controlling BP in some patients.[13-16] Referring to these points, an FDC tablet of fimasartan/amlodipine 60/10 mg was developed by Boryung Pharmaceutical Co., Ltd. (Seoul, Republic of Korea).

According to the bioequivalence study guidelines of the regulatory agencies, including the Korea Ministry of Food and Drug Safety (MFDS), a replicated crossover design can be used for bioequivalence studies of an HVD, and a widened bioequivalence range can be accepted.[17-19] Since fimasartan is an HVD, a full or partial replicated crossover design can be selected for the bioequivalence study between FDC of fimasartan/amlodipine 60/10 mg and the corresponding loose combination.

The aim of this study was to compare the PK characteristics and evaluate the bioequivalence between FDC of fimasartan/amlodipine 60/10 mg and the corresponding loose combination in healthy male subjects.

Methods

Subjects and study design

The study protocol was approved by the institutional review board of Seoul National University Hospital (Seoul, Republic of Korea) and MFDS (NCT02920047). All the procedures were performed in compliance with the Korean Good Clinical Practice guidelines and tenets of the Declaration of Helsinki. All the subjects provided written informed consent prior to any procedures related to the study.

This study included healthy male subjects between 19 and 50 years of age, weighing ≥ 55 kg and with a body mass index ranging from 18.0 to 27.0 kg/m^2. All subjects had no clinically significant abnormalities based on their medical histories, vital signs, physical examination, clinical laboratory tests, and 12-lead electrocardiogram (ECG). Subjects with any hypersensitivity to drugs such as fimasartan and amlodipine were excluded from the study. Additionally, subjects having SBP ≤ 100 mmHg or ≥ 140 mmHg, or DBP ≤ 65 mmHg or ≥ 90 mmHg were excluded from the study at the screening.

This study was designed as a randomized, open-label, two-treatment, three-period, three-sequence, partial replicated crossover study with 14-days washout between periods. The enrolled subjects were randomly assigned to one of the three sequences, and received a single oral dose of an FDC tablet of fimasartan/amlodipine 60/10 mg (Boryung Pharmaceutical Co., Ltd., Seoul, Republic of Korea) as the test drug, or a loose combination of fimasartan 60 mg (Kanarb® tablet 60 mg, Boryung Pharmaceutical Co., Ltd.) and amlodipine 10 mg (Norvasc® tablet 10 mg, Pfizer Inc., Seoul, Republic of Korea) as the reference drug in each period. Each sequence consisted of a single oral administration of the test drug in one period and the reference drug in the other two periods (Sequence A: Reference → Reference → Test; Sequence B: Reference → Test → Reference; Sequence C: Test → Reference → Reference).

Blood samples for PK analysis of fimasartan were collected at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 12, 24, and 48 h post-dose. For amlodipine, blood samples were collected at 0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, and 144 h post-dose. Approximately 5 or 8 mL of the blood sample was collected in a heparinized tube for each blood sampling point and subsequently centrifuged at 3,000 rpm for 10 minutes at 4°C. The supernatants were then transferred to three Eppendorf tubes and stored at –70°C until analysis.

Determination of plasma fimasartan and amlodipine concentrations

Plasma concentrations of fimasartan and amlodipine were analyzed at Kyung Hee Drug Analysis Center of Kyung Hee University (Seoul, Republic of Korea).

Plasma concentrations of fimasartan were determined by a validated high-performance liquid chromatography (HPLC, Agilent 1200 series, Agilent Technologies, USA) coupled with tandem mass spectrometry method (MS/MS, The Applied Biosystems MDS SCIEX API 4000 triple quadrupole mass spectrometer, Applied Biosystems, Canada). In the HPLC system, a Luna C18 column (50 × 2.0 mm, 3.0 μm, Phenomenex, USA) was used for the chromatographic separation of fimasartan and BR-A-563 (Internal standard; IS) under gradient conditions. The MS/MS system was operated in the ionization mode using positive ion electrospray and the multiple reaction monitoring (MRM) mode. The MRM mode was monitored based on an m/z transition of 502.4 → 207.1 for fimasartan and 526.5 → 207.2 for BR-A-563 (IS).

Plasma concentrations of amlodipine were determined by a validated HPLC (Agilent 1100 series, Agilent Technologies, USA) coupled with MS/MS method (The Applied Biosystems MDS SCIEX API 2000 triple quadrupole mass spectrometer,

Applied Biosystems, Canada). A Luna C18 column (50 × 2.0 mm, 3.0 μm, Phenomenex, USA) was used for the chromatographic separation of amlodipine and amlodipine-d-4 (IS) under gradient conditions. The MS/MS system was operated in the ionization mode using positive ion electrospray and the MRM mode. The MRM mode was monitored based on an m/z transition of 409.0 → 238.0 for amlodipine and 413.1 → 238.0 for amlodipine-d-4 (IS).

The calibration curves were linear in the range of 1–1000 ng/mL for fimasartan and 0.2–20 ng/mL for amlodipine ($r^2 \geq 0.9955$ for fimasartan and ≥ 0.9983 for amlodipine). The intra- and inter-batch accuracy ranges were 90.2–106.3% and 99.8–100.6% for fimasartan, and 93.1–105.3% and 99.2–100.0% for amlodipine, respectively. The intra- and inter-batch precision coefficient of variation (CV)% were < 10.0% and < 5.2% for fimasartan, and < 5.5% and < 4.3% for amlodipine, respectively.

PK analysis

The following PK parameters were calculated by non-compartmental methods using WinNonlin® software, version 7.1 (Pharsight, Mountain View, CA, USA). C_{max} and time to reach C_{max} (T_{max}) were determined from the observed plasma concentration-time profiles. The area under the concentration-time curve from 0 to last measurable time point (AUC_{last}) was calculated using the linear trapezoidal rule for the ascending concentrations and log trapezoidal rule for the descending concentrations. The area under the concentration-time curve from 0 to infinity (AUCinf) was calculated using the following formula: $AUC_{inf} = AUC_{last} + C_{last}/\lambda_z$, where C_{last} is the last measurable concentration, and λ_z is the terminal elimination rate constant. The terminal elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$.

Statistical analysis

A minimum sample size of 45 subjects was estimated to achieve the widened bioequivalence range of the HVD with 80% statistical power at a 5% level of significance, assuming that the highest intra-subject variability of fimasartan was 62%.[17,19] After considering the dropout rate, the total number of 60 subjects were chosen to enroll in this study.

The statistical analyses were performed using SAS® software version 9.4 (SAS Institute, Cary, NC, USA). Analysis of variance (ANOVA) was performed to compare the treatments, considering period, sequence, and the group as fixed effects, and subject nested within the sequence as a random effect. Geometric mean ratios (GMRs) and its 90% confidence intervals (CIs) for C_{max} and AUC_{last} variables were estimated. The scaled bioequivalence criteria for the C_{max} of fimasartan was calculated using exp [±0.760*(SWR)], where S_{WR} is the intra-subject standard deviation of the log-transformed values of C_{max} of the reference drug estimated by this study results.[17,19] The bioequivalence between the two treatments was assessed by using the scaled bioequivalence criteria for the C_{max} of fimasartan and the conventional bioequivalence criteria for the other PK variables of fimasartan and amlodipine. We used Cochran's Q test to evaluate whether the incidence of adverse events (AEs) is different between the treatments.

Blood pressure monitoring

SBP and DBP were measured at 0 (pre-dose), 4, 8, 12, 24, 48, 72, 96, and 144 h post-dose in each period.

Safety and tolerability assessments

Safety and tolerability were evaluated by AE monitoring, clinical laboratory tests, 12-lead ECG, physical examination, and vital signs. All the AEs were coded according to the Medical Dictionary for Regulatory Activities ver.19.1 and summarized by treatment, severity, and relationships with treatments.

Results

Demographic characteristics

A total of 60 healthy Korean male subjects were enrolled and randomized, and 57 subjects completed the study since three subjects withdrew their consent before the second period. Age, height, weight, and body mass index of the enrolled subjects were 30.6 ± 6.6 (mean ± standard deviation) years, 173.1 ± 5.5 cm, 70.4 ± 7.6 kg, and 23.5 ± 2.0 kg/m^2, respectively. There was no significant difference among the sequences in demographic characteristics. Safety and tolerability were assessed in all the enrolled subjects, and the PK characteristics were analyzed in 56 subjects who had completed the study without major deviation; one subject was excluded from the PK evaluation due to inclusion criteria violation, whose weight was 54 kg at the screening.

Pharmacokinetics

The mean plasma concentration-time profiles and PK characteristics of fimasartan were similar between the FDC and loose combination (Fig. 1A, Table 1). For fimasartan, the majority of the subjects exhibited double-peak plasma concentration-time profiles. Unlike the individual AUC_{last} values of fimasartan, the individual C_{max} values of fimasartan were highly variable between two treatments (Fig. 2A, 2B). The GMRs (90% CIs) of the FDC to the loose combination for C_{max} and AUC_{last} of fimasartan were 1.0440 (0.9202–1.1844) and 1.0412 (0.9775–1.1090), respectively. Since the intra-subject CV% for the C_{max} of fimasartan was 48.51%, the expanded bioequivalence range for the C_{max} of fimasartan was 0.7051–1.4182.[17,19] The GMR and its 90% CI for C_{max} of fimasartan fell not only within the expended bioequivalence range but also within the conventional bioequivalence criteria of 0.80–1.25. The corresponding values for the AUC_{last} of fimasartan were also included in the conventional bioequivalence criteria (Table 2).

The mean plasma concentration-time profiles and PK parameters of amlodipine were comparable between the FDC and loose combination (Fig. 1B, Table 1). The individual values of

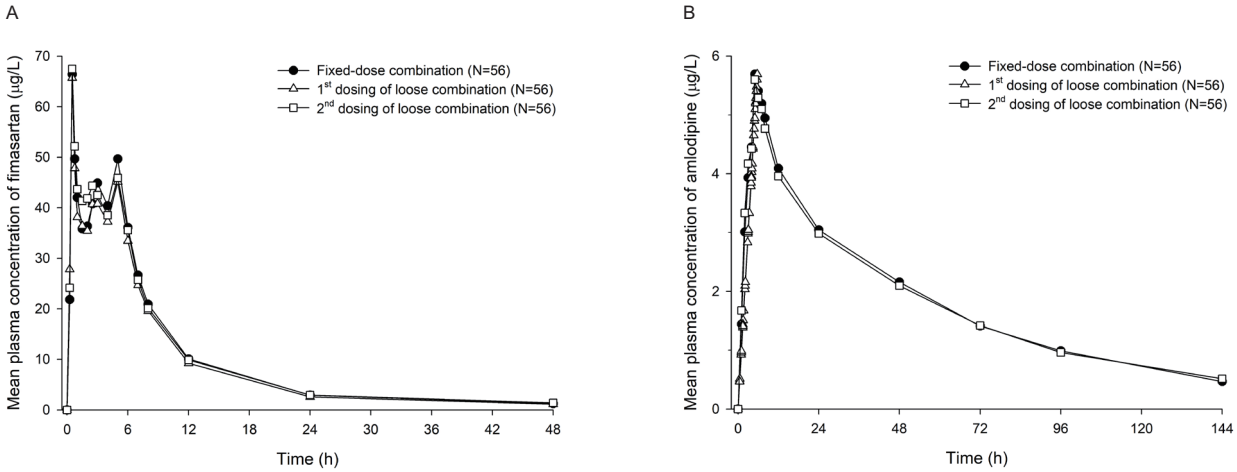


Figure 1. Mean plasma concentration-time profiles of (A) fimasartan and (B) amlodipine following a single administration of fixed-dose combination (FDC) of fimasartan/amlodipine 60/10 mg or the corresponding loose combination with a linear scale.

Table 1. Pharmacokinetic parameters of fimasartan and amlodipine following a single administration of fixed-dose combination (FDC) of fimasartan/amlodipine 60/10 mg or the corresponding loose combination

Parameter	Fixed-dose combination (N = 56)	1st dosing of loose combination (N = 56)	2nd dosing of loose combination (N = 56)	Intra-subject CV%[a]
Fimasartan				
T_{max} (h)	2.75 [0.25–6.00]	2.50 [0.25–6.00]	1.25 [0.48–6.00]	-
C_{max} (μg/L)	96.74 ± 73.90 [31.45–380.21]	89.94 ± 70.59 [11.92–366.43]	91.78 ± 57.21 [21.54–285.90]	48.51
AUC_{last} (h*μg/L)	433.56 ± 169.28 [192.91–975.86]	405.25 ± 169.08 [103.48–905.72]	431.24 ± 162.70 [195.35–1047.62]	23.18
AUC_{inf} (h*μg/L)	456.52 ± 173.97	424.91 ± 172.25	456.04 ± 167.39	-
$t_{1/2}$ (h)	5.83 ± 1.41	5.62 ± 1.08	6.03 ± 1.47	-
Amlodipine				
T_{max} (h)	5.00 [3.00–8.00]	5.00 [2.00–8.03]	5.00 [3.00–12.00]	-
C_{max} (μg/L)	5.97 ± 1.23 [2.47–9.07]	5.68 ± 1.23 [3.11–8.78]	5.77 ± 1.20 [2.85–8.64]	9.71
AUC_{last} (h*μg/L)	256.89 ± 64.06 [122.50–390.77]	243.27 ± 61.59 [120.95–401.00]	254.20 ± 64.93 [127.86–454.20]	9.92
AUC_{inf} (h*μg/L)	287.02 ± 76.06	274.07 ± 75.02	290.75 ± 100.6	-
$t_{1/2}$ (h)	42.83 ± 7.34	43.04 ± 8.14	43.88 ± 9.45	-

Data are expressed as mean ± SD, except for T_{max}, which are expressed as median [minimum-maximum], and C_{max} and AUC_{last}, which are expressed as mean ± SD [minimum-maximum].
CV, coefficient of variation; C_{max}, maximum plasma concentration; AUC_{last}, area under the concentration-time curve (AUC) from 0 to last measurable time point; AUC_{inf}, AUC from 0 to infinity; $t_{1/2}$, half-life; T_{max}, time to reach C_{max}; SD, standard deviation.
[a]Intra-subject CV% was calculated from PK data of the loose combination.

C_{max} and AUC_{last} of amlodipine showed no significant variations between the two treatments (Fig. 2C, 2D). The GMRs (90% CIs) of the FDC to the loose combination for C_{max} and AUC_{last} of amlodipine were 1.0430 (1.0156–1.0711) and 1.0339 (1.0055–1.0631), respectively. All the GMRs and their 90% CIs for C_{max} and AUC_{last} of amlodipine were within the conventional bioequivalence criteria of 0.80–1.25 (Table 2).

Effect on blood pressure

The reductions in SBP and DBP were similar between the FDC and loose combination (Fig. 3); In the FDC and loose combination groups, the lowest mean ± standard deviation values of SBP were 101.7 ± 8.9 mmHg and 101.4 ± 8.8 mmHg, respectively, and the corresponding values of DBP were 56.8 ± 5.9 mmHg and 57.1 ± 6.0 mmHg, respectively.

Safety and tolerability assessments

No clinically significant changes were observed in clinical laboratory tests, 12-lead ECG, physical examination, and vital signs. During the study, a total of 44 treatment-emergent AEs (TEAEs) were reported in 24 subjects. Among them, 15 TEAEs occurred in 11 subjects who received the FDC, and 29 TEAEs

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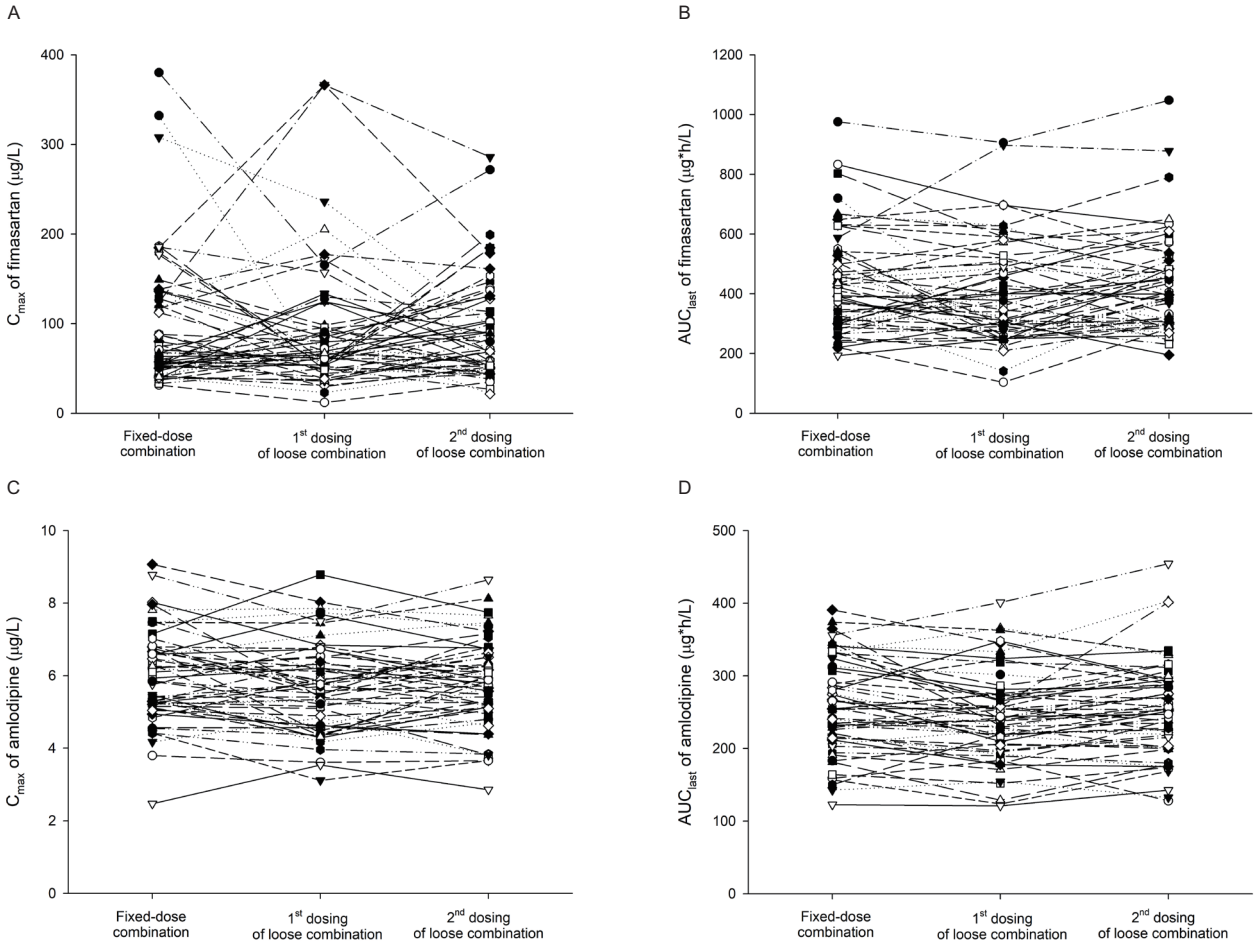


Figure 2. Individual comparison of (A) C_{max} and (B) AUC_{last} of fimasartan, and (C) C_{max} and (D) AUC_{last} of amlodipine following a single administration of fixed-dose combination (FDC) of fimasartan/amlodipine 60/10 mg or the corresponding loose combination.

Table 2. Comparison of pharmacokinetic parameters of fimasartan and amlodipine between fixed dose-combination (FDC) of fimasartan/amlodipine 60/10 mg and the corresponding loose combination

Drug	PK Parameter	Geometric mean		Geometric Mean Ratio[b] (90% CI)	Scaled BE criteria
		FDC	Loose combination[a]		
Fimasartan	C_{max} (μg/L)	83.66	80.14	1.0440 (0.9202–1.1844)	0.7051–1.4182
	AUC_{last} (h*μg/L)	437.73	420.40	1.0412 (0.9775–1.1090)	-
Amlodipine	C_{max} (μg/L)	5.84	5.59	1.0430 (1.0156–1.0711)	-
	AUC_{last} (h*μg/L)	255.85	247.47	1.0339 (1.0055–1.0631)	-

PK, pharmacokinetic; CI, confidence interval; BE, bioequivalence; C_{max}, maximum plasma concentration; AUC_{last}, area under the concentration-time curve from 0 to last measurable time point.
[a]Data from 1st and 2nd dosing of loose combination of fimasartan 60 mg tablet and amlodipine 10 mg tablet in 56 subjects were used.
[b]Geometric mean ratio is the ratio of the FDC to the loose combination.

occurred in 18 subjects who received the loose combination. There was no significant difference in the TEAEs between the two treatments (p-value = 0.8338).

Discussion

This study compared the PK properties and evaluated the bioequivalence between FDC of fimasartan/amlodipine 60/10 mg and the corresponding loose combination. The FDC and loose combination showed similar PK characteristics in healthy male subjects. The GMR and its 90% CI for C_{max} of fimasartan were included in the scaled bioequivalence criteria, which was 0.7051-1.4182. Also, the GMRs and their 90% CIs for the other

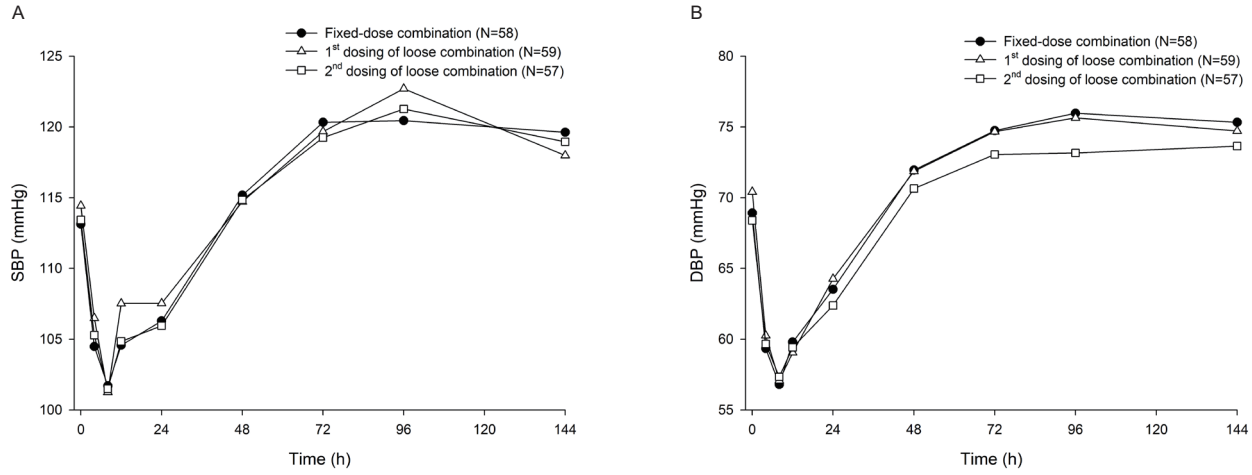


Figure 3. Mean (A) systolic blood pressure (SBP) and (B) diastolic blood pressure (DBP) following a single administration of fixed-dose combination (FDC) of fimasartan/amlodipine 60/10 mg or the corresponding loose combination.

PK variables of drugs were within the conventional bioequivalence criteria of 0.80–1.25. These results indicated that the FDC was bioequivalent to the loose combination when administered to healthy male subjects.

Conventional 2 × 2 crossover bioequivalence studies with HVDs have the disadvantage of requiring large sample sizes for attaining sufficient statistical power. According to the guidelines of the regulatory agencies, a replicated crossover design can be used for bioequivalence studies with HVDs,[17-19] and it is helpful for reducing the number of subjects needed to demonstrate bioequivalence by up to about 50%.[20] Based on the highest observed intra-subject CV% for the C_{max} of fimasartan (62%), approximately 114 subjects would be required for detecting a 20% difference between the two treatments with 80% statistical power at a 5% level of significance under the conventional 2 × 2 crossover design, while this study could reduce the number of subjects by up to 60 subjects through the partial replicated crossover design by widening the bioequivalence range. Using the intra-subject CV% for the C_{max} of fimasartan calculated in this study (48.51%), about 57 subjects are enough to achieve the conventional bioequivalence criteria with 80% statistical power at a 5% level of significance under partial replicated design. Therefore, a sample size of 60 subjects chosen in this study was sufficient to assess the conventional bioequivalence as well as the scaled bioequivalence through partial replicated design between the FDC of fimasartan/amlodipine 60/10 mg and the corresponding loose combination.

Although the subjects had normal BP, BP was monitored as a safety assessment. After a single administration of the FDC or the loose combination, the maximal decreases in SBP/DBP were 11.41/12.12 mmHg and 12.56/12.21 mmHg, respectively. Although BP evaluation was not the primary aim of this study, these results suggest that FDC of fimasartan/amlodipine 60/10 mg will show similar BP-lowering effects compared to the corresponding loose combination.

In conclusion, FDC of fimasartan/amlodipine 60/10 mg showed similar PK profiles with the corresponding loose combination. The GMRs and their 90% CIs for C_{max} and AUC_{last} of fimasartan and amlodipine fell not only within the scaled bioequivalence criteria but also within the conventional bioequivalence criteria, indicating the bioequivalence between the FDC and loose combination.

Acknowledgments

This study was sponsored by Boryung Pharmaceutical Co., Ltd., Seoul, Republic of Korea.

Conflict of interest

- Authors: Heechan Lee is currently employed by Hanall BioPharma Co., Ltd., Seoul, Republic of Korea. His contribution to the manuscript was based on his prior employment, and the current manuscript does not reflect any position of Hanall BioPharma Co., Ltd.. All the other authors have no competing interests to declare.
- Reviewers: Nothing to declare
- Editors: Nothing to declare

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