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Original Article

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Comparison of pharmacokinetics of a fixed-dose combination of atorvastatin/ezetimibe 5 mg/10 mg versus separate tablets in healthy subjects

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- Authors: Nothing to declare

ABSTRACT

The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors are well-established treatment options for dyslipidemia. For patients not meeting low-density lipoprotein cholesterol targets with monotherapy, combination therapy with another lipid-lowering agent including ezetimibe, is recommended. This study compared the pharmacokinetics (PKs) and safety of a fixed-dose combination (FDC) of atorvastatin/ezetimibe 5 mg/10 mg with the individual components in healthy Korean subjects. A randomized, open-label, single-dose, 2-treatment, 2-sequence, crossover study was conducted in 60 healthy subjects. An FDC of atorvastatin/ezetimibe 5 mg/10 mg or the corresponding individual components was administered in the first period, and the alternative in the second period after a 14-day washout. Serial blood samples were collected up to 72 hours post-dose to calculate PK parameters such as maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve to the last measurable concentration (AUC_{last}). The geometric mean ratios (GMRs) and 90% confidence intervals (CIs) of the C_{max} and AUC_{last} for the atorvastatin and total ezetimibe were estimated compared to the individual components. Adverse events (AEs) and other safety variables were monitored to evaluate safety and tolerability profile. Sixty subjects were enrolled and 58 subjects completed the study. For atorvastatin, the GMRs (90% CIs) for C_{max} and AUC_{last} were 1.18 (1.04–1.33) and 1.04 (1.00–1.08), respectively, and the corresponding values were 1.37 (1.26–1.50) and 0.98 (0.93–1.03) for total ezetimibe. No clinically significant treatment-emergent AEs were observed with either formulations. The FDC of atorvastatin/ezetimibe 5 mg/10 mg was safe and showed similar exposure to those of the individual components.

Trial Registration: ClinicalTrials.gov Identifier: NCT05202405

Keywords: Dyslipidemia; Pharmacokinetics; Atorvastatin; Ezetimibe; Drug Combinations

INTRODUCTION

Dyslipidemia is characterized by elevated triglyceride and low-density lipoprotein cholesterol (LDL-C) with decreased high-density lipoprotein cholesterol levels. According to a 2022

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report from the Korean Society of Lipid and Atherosclerosis, 45.4% of Korean adults are diagnosed with dyslipidemia [1]. Dyslipidemia is a well-known risk factor for cardiovascular diseases. Many guidelines have reported a correlation between LDL-C levels and the risk of atherosclerotic coronary heart disease events. Therefore, lipid-lowering therapy is recommended for patients with dyslipidemia [2,3].

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase mediates the first and rate-limiting step of cholesterol biosynthesis by converting HMG-CoA to mevalonate. HMG-CoA reductase inhibitors, commonly referred to as statins, competitively inhibit the activity of enzymes that reduce intracellular cholesterol synthesis [4]. In a meta-analysis of real-world data, statins significantly decreased the risks of all-cause mortality and cardiovascular disease events [5]. Therefore, guidelines recommend statins as first-line lipid-lowering medications. According to the guidelines, the recommended starting dose of atorvastatin is 10 mg once daily, with subsequent escalation up to 80 mg once daily based on the patient's LDL-C level [6,7].

Ezetimibe is usually administered in combination with statins or alone and is recommended at 10 mg once daily [8]. Ezetimibe is converted to ezetimibe-glucuronide during first-pass metabolism, which accounts for 80–90% of the total drug in the plasma [9]. Both ezetimibe and ezetimibe-glucuronide lower lipid levels by locally inhibiting cholesterol absorption at the brush border of the small intestine. This reduced the amount of cholesterol delivered to the liver, decreasing hepatic cholesterol storage [8]. Because the glucuronide conjugate of ezetimibe has a higher affinity for the Niemann-Pick C1-Like 1 protein, which is responsible for cholesterol absorption, its cholesterol-lowering effect is thought to be more active than that of the parent compound [10].

In clinical trials involving hypercholesterolemia patients, the combination therapy of atorvastatin 5 mg and ezetimibe 5 mg resulted in a more significant reduction in the apolipoprotein B/A1 ratio compared to atorvastatin 20 mg alone [11]. Additionally, the combination of 5 mg with ezetimibe 10 mg led to a more substantial decrease in LDL-C levels than either atorvastatin 5 mg, 10 mg monotherapy, or ezetimibe 10 mg monotherapy [12]. The Food and Drug Administration (FDA) label also shows consistent LDL-C reduction with ezetimibe across all statins, and studies have confirmed that ezetimibe plus statin therapy is superior to statin monotherapy for lipid reduction [8].

Fixed-dose combinations (FDCs) have been reported to improve medication compliance in patients with chronic diseases. Therefore, the FDC for atorvastatin/ezetimibe was developed to improve patient compliance, thereby enhancing clinical outcomes. The present study compared the pharmacokinetic (PK) characteristics and safety of the FDC of atorvastatin/ezetimibe 5 mg/10 mg with corresponding individual components.

METHODS

The study protocol and informed consent form were reviewed and approved by the Korean Ministry of Food and Drug Safety and the Institutional Review Board of H plus Yangji Hospital (HYJ 2021-12-013-001). This study followed the Korean Good Clinical Practice guidelines and the tenets of the Declaration of Helsinki. All participants provided written informed consent before undergoing any procedures related to this study.

Subjects

Healthy males and non-pregnant females over 18 years with a body mass index (BMI) of 18.0–30.0 kg/m^2 were eligible. The major exclusion criteria were a history of active liver disease, myopathy, a serum aminotransferase level 3-fold higher than the upper reference limit, and persistent unexplained elevation of serum aminotransferase levels.

Study design

The study was a randomized, open-label, single-dose, 2-treatment, 2-sequence, crossover trial (ClinicalTrials.gov identifier: NCT05202405). The subjects were randomized to one of 2 sequences: Sequence A: administered individual components first, followed by the FDC; Sequence B: administered FDC first, followed by individual components. An FDC of atorvastatin/ezetimibe 5 mg/10 mg (test formulation) or the corresponding individual components (reference formulation) was administered under a fasted state with 150 mL of water in the first period, and the alternative was administered in the second period after 14-day washout.

Based on previous studies, the maximum intra-subject coefficient of variations (CVs) for the PK parameters (maximum plasma concentration [C_{max}]) were assumed to be 31.86% and 20.24% for atorvastatin and ezetimibe, respectively [13,14]. Conservatively assuming 32% for intra-subject CVs and setting the test to reference ratio as 0.95, the minimum sample size required to detect a 20% difference in PK parameters between the 2 formulations with 80% statistical power at a 5% significance level was calculated to be 44 subjects. Considering the anticipated withdrawal rate of 25%, a sample size of 60 subjects was selected for this study.

PK assessment

Blood samples for the PK assessment of atorvastatin were collected pre-dose (0 hour) and 0.17, 0.33, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours after dosing. For total and free ezetimibe, samples were collected before pre-dose (0 hour) and at 0.33, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours after dosing. About 10 mL of blood was collected in ethylenediaminetetraacetic acid tubes for each sampling point and centrifuged at 3,000 rpm for 10 minutes at 4°C. Five aliquots of the supernatant were stored at –70°C until analysis.

Bioanalytic methods used for PK assessment were based on validated analytical procedures adopted by the Guideline on Bioanalytical Method Validation (European Medicines Agency [EMA]) [15]. Plasma concentrations of atorvastatin, total ezetimibe and free ezetimibe were measured by liquid chromatography-mass spectrometry (LC-MS/MS) using Waters ACQUITY system (Waters Corporation, Milford, MA, USA) and Xevo™ TQ-XS MS (Waters Corporation), retrospectively. The 10 μL of internal standard (atorvastatin-d5, 10 ng/mL in 50% methanol) was added to 100 μL of plasma. After vortex-mixing at 1,500 rpm for 3 minutes and centrifuging at 4,000 rpm for 1 minutes, 10 μL of supernatant was injected into the LC-MS/MS. An analytical column (Waters ACQUITY UPLC® BEH C18, 1.7 μm, 2.1 × 50 mm) was used as the stationary phase, and the mobile phase consisted of 0.1% formic acid in distilled water and acetonitrile with a ratio of 55:45 under a gradient condition with a flow rate of 0.6 mL/min. The concentrations of atorvastatin were determined by computing the peak-area ratios of atorvastatin to atorvastatin-d_5, and the mass-to-charge (m/z) transitions were 559.25 > 440.25 for atorvastatin, and 564.30 > 445.30 for atorvastatin-d_5. The calibration curve was 0.02 to 40 ng/mL.

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For total ezetimibe, 100 μL plasma samples along with 10 μL of internal standard (ezetimibe-d_4, 20 ng/mL in 50% methanol) were vortex-mixed at 1,500 rpm for 3 minutes and centrifuged at 4,000 rpm for 1 minutes. The 20 μL of the supernatant was injected into the LC-MS/MS. An analytical column (Waters ACQUITY PREMIER BEH C18, 1.7 μm, 2.1 × 50 mm) was used as the stationary phase, and the mobile phase consisted of 0.05% acetic acid in distilled water and acetonitrile with a ratio of 65:35 under a gradient condition with a flow rate of 0.7 mL/min. The concentrations of ezetimibe were determined by computing the peak-area ratios of ezetimibe to ezetimibe-d_4, and the m/z transitions were 408.30 > 271.20 for ezetimibe, and 412.30 > 271.20 for ezetimibe-d_4. The calibration curve was 0.05 to 20 ng/mL.

For free ezetimibe, 100 μL plasma samples along with 10 μL of internal standard (ezetimibe-d_4, 20 ng/mL in 50% methanol) were vortex-mixed at 1,500 rpm for 3 minutes and centrifuged at 4,000 rpm for 1 minutes. The 10 μL of the beta-glucuronidase in distilled water was injected to each sample and mixed at 1,400 rpm in 37°C thermomixer for 60 minutes and centrifuged at 4,000 rpm for 1 minutes. The 2 μL of the supernatant was injected into the LC-MS/MS. The stationary and the mobile phase were set in the same manner of total ezetimibe. The calibration curve was 0.5 to 200 ng/mL.

PK analysis

The PK analysis was conducted on participants who completed the study with quantifiable concentrations of atorvastatin and ezetimibe. PK parameters of atorvastatin, total ezetimibe, free ezetimibe were estimated from observed data by noncompartmental methods using Pheonix WinNonlin Version 8.0 (Certara, Princeton, NJ, USA): the C_{max}, time to reach maximum plasma concentration (T_{max}), the area under the concentration-time curve from zero to last measurable time (AUC_{last}), and from time zero to infinity (AUC_{inf}), terminal elimination half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V_z/F).

Safety assessment

Safety and tolerability were evaluated in subjects who had received treatment at least once, based on adverse events (AEs), clinical laboratory tests (hematology, clinical chemistry, coagulation, and urinalysis), vital signs, physical examination, and 12-lead electrocardiogram throughout the study. The investigators determined the clinical significance and relationship with the treatment of all findings.

Statistical analysis

SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. Descriptive statistics were presented for continuous data, and frequencies and percentages for each category were presented for categorical data. To compare the AUC_{last} and C_{max} after a single oral dose of the test and reference formulations, the geometric mean ratios (GMRs) and 90% confidence intervals (CIs) were calculated using a generalized linear model. When the GMRs (90% CIs) for these parameters were within the range of 0.8–1.25, the FDC and the corresponding individual components were determined to be bioequivalent.

RESULTS

Study population

Sixty participants were enrolled, and 58 completed the study as 2 subjects dropped out due to AEs. The 2 sequences had no significant differences in age, height, weight, or BMI (**Table 1**).

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Table 1. Demographic characteristics of subjects in each sequence

Characteristic	Sequence A* (n = 30)	Sequence B* (n = 30)	*p*-value
Sex			1.000†
Male	23 (76.7)	23 (76.7)	
Female	7 (23.3)	7 (23.3)	
Age (yr)	28.47 ± 6.24	27.47 ± 5.66	0.518‡
Height (cm)	173.27 ± 6.86	171.10 ± 6.30	0.222§
Weight (kg)	72.31 ± 11.62	72.06 ± 11.02	0.831§
BMI (kg/m^2)	24.00 ± 2.98	24.54 ± 2.99	0.513§

Data presented as number (%) or mean ± standard deviation.
BMI, body mass index; FDC, fixed-dose combination.
*Sequence A, administered individual components (co-administration of atorvastatin 5 mg and ezetimibe 10 mg) first, followed by the FDC (atorvastatin/ezetimibe 5 mg/10 mg); Sequence B, administered FDC first, followed by individual components.
The *p*-values were calculated by using an †Fisher's exact test, ‡*t*-test, §Mann-Whitney *U* test.

PKs

A total of 58 subjects were included in the PK analysis set. The median T_{max} value of atorvastatin was 0.50 hours for both the FDC and the corresponding individual components. The C_{max} and AUC_{last} of atorvastatin were 2.04 ± 1.01 ng/mL and 9.75 ± 3.83 h*ng/mL for the FDC, and 1.79 ± 0.96 ng/mL and 9.49 ± 4.00 h*ng/mL for the corresponding individual components.

The median T_{max} value of total ezetimibe was 1.0 hours for both the FDC and the corresponding individual components. The C_{max} and AUC_{last} of total ezetimibe were 98.81 ± 47.52 ng/mL and 561.90 ± 232.24 h*ng/mL for the FDC, and 74.41 ± 41.90 ng/mL and 582.78 ± 265.77 h*ng/mL for the corresponding individual components.

For free ezetimibe, the median T_{max} value was 1.0 hours for both FDC and the corresponding individual components. The C_{max} and AUC_{last} of free ezetimibe were 6.20 ± 3.86 ng/mL and 74.35 ± 30.39 h*ng/mL for the FDC, and 4.70 ± 2.66 ng/mL and 77.91 ± 31.95 h*ng/mL for the corresponding individual components

The GMRs (90% CIs) of the test to reference formulation for C_{max} and AUC_{last} were 1.18 (1.04–1.33) and 1.04 (1.00–1.08) for atorvastatin and the corresponding values were 1.37 (1.26–1.50) and 0.98 (0.93–1.03) for total ezetimibe. The systemic exposure of all FDC components were similar to those of the corresponding individual components; however, the C_{max} was slightly higher for FDC than for the corresponding individual components (**Table 2**, **Figs. 1-3**).

Safety and tolerability

Two subjects withdrew from the study after receiving the reference formulation due to adverse drug reactions (ADRs): one reported dyspepsia and vomiting, while the other reported a headache. As a result, 58 subjects completed treatment with the test formulation, and 60 subjects completed treatment with the reference formulation. Four ADRs were reported in 2 subjects after the administration of the FDC, all assessed as probably not related to the investigational product. Six ADRs were reported in 5 subjects after the administration of the corresponding individual components. Among them, 2 ADRs (headache) reported in 2 subjects were considered possibly related, whereas 4 ADRs reported in 3 subjects were assessed as probably not related to the investigational product (**Table 3**). All ADRs were recovered without clinically significant sequelae. There were no clinically significant changes in vital signs, physical examination, or 12-lead electrocardiogram during the study.

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Table 2. Pharmacokinetic parameters after a single oral administration of FDC formulation of atorvastatin/ezetimibe 5 mg/10 mg or concomitant administration of individual components of atorvastatin 5 mg and ezetimibe 10 mg

Parameters	FDC formulation (n = 58)	Atorvastatin 5 mg + Ezetimibe 10 mg (n = 58)	GMRs (90% CI)
C_{max} (ng/mL)	2.04 ± 1.01	1.79 ± 0.96	1.18 (1.04–1.33)
T_{max} (h)	0.50 (0.33–6.00)	0.50 (0.33–6.00)	
AUC_{last} (h*ng/mL)	9.75 ± 3.83	9.49 ± 4.00	1.04 (1.00–1.08)
AUC_{inf} (h*ng/mL)	10.56 ± 4.12	10.46 ± 4.33	
$T_{1/2}$ (h)	10.01 ± 3.25	10.21 ± 5.66	
CL/F (L/h)	0.54 ± 0.18	0.56 ± 0.22	
V_z/F (L)	7.52 ± 2.93	7.79 ± 3.20	
C_{max} (ng/mL)	98.81 ± 47.52	74.41 ± 41.90	1.37 (1.26–1.50)
T_{max} (h)	1.00 (0.50–3.00)	1.00 (0.50–6.00)	
AUC_{last} (h*ng/mL)	561.90 ± 232.24	582.78 ± 265.77	0.98 (0.93–1.03)
AUC_{inf} (h*ng/mL)	627.17 ± 267.34	632.46 ± 285.76	
$T_{1/2}$ (h)	19.56 ± 13.06	19.15 ± 11.11	
CL/F (L/h)	0.02 ± 0.01	0.02 ± 0.01	
V_z/F (L)	0.48 ± 0.26	0.50 ± 0.36	
C_{max} (ng/mL)	6.20 ± 3.86	4.70 ± 2.66	
T_{max} (h)	1.00 (0.33–12.00)	1.00 (0.33–24.00)	
AUC_{last} (h*ng/mL)	74.35 ± 30.39	77.91 ± 31.95	
AUC_{inf} (h*ng/mL)	85.66 ± 37.26	96.04 ± 73.10	
$T_{1/2}$ (h)	20.72 ± 15.16	25.56 ± 32.49	

Data are presented as mean ± standard deviation, except for T_{max} presented as median (minimum–maximum). The geometric mean ratios and their 90% CIs are the ratios of the FDC to the individual components.
FDC, fixed-dose combination; GMR, geometric mean ratio; CI, confidence interval; C_{max}, maximum concentration; T_{max}, time to maximum concentration; AUC_{last}, area under the serum concentration versus time curve versus time from zero to the time of last measured serum concentration; AUC_{inf}, area under the serum concentration versus time curve extrapolated to infinity; $T_{1/2}$, half-life; CL/F, apparent clearance; V_z/F, apparent volume of distribution.

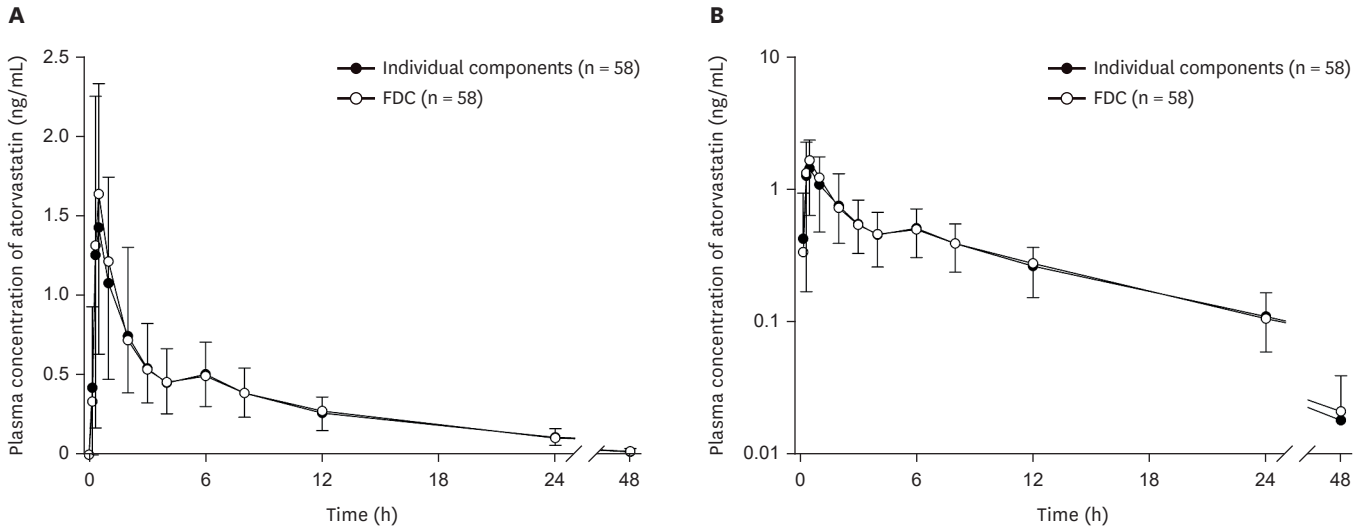

Figure 1. Mean plasma concentration-time profiles of atorvastatin after a single oral administration of FDC formulation of atorvastatin/ezetimibe 5 mg/10 mg or concomitant administration of individual components of atorvastatin 5 mg and ezetimibe 10 mg in (A) linear scale and (B) log scale.
FDC, fixed-dose combination.

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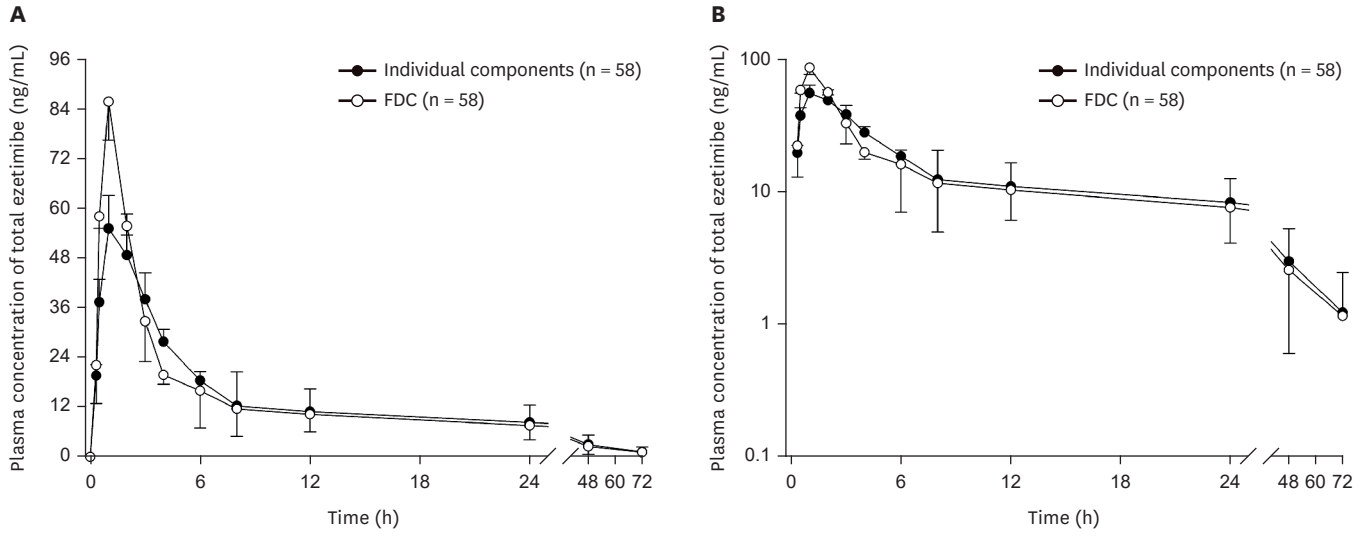

Figure 2. Mean plasma concentration-time profiles of total ezetimibe after a single oral administration of FDC formulation of atorvastatin/ezetimibe 5 mg/10 mg or concomitant administration of individual components of atorvastatin 5 mg and ezetimibe 10 mg in (A) linear scale and (B) log scale.
FDC, fixed-dose combination.

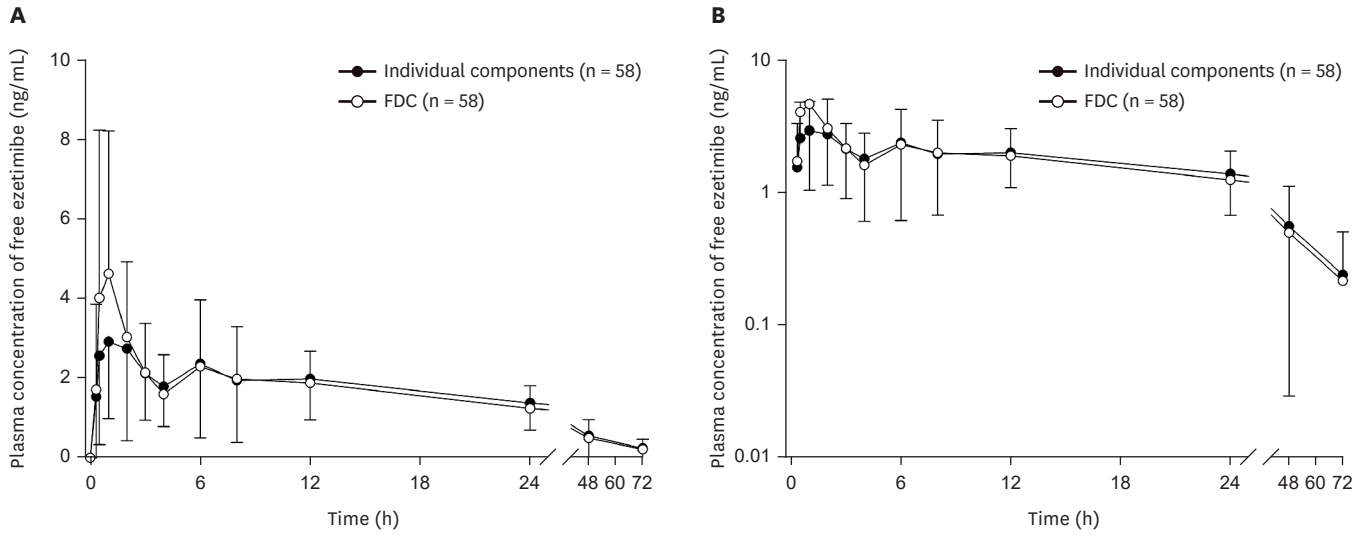

Figure 3. Mean plasma concentration-time profiles of free ezetimibe after a single oral administration of FDC formulation of atorvastatin/ezetimibe 5 mg/10 mg or concomitant administration of individual components of atorvastatin 5 mg and ezetimibe 10 mg in (A) linear scale and (B) log scale.
FDC, fixed-dose combination.

Table 3. Treatment-emergent adverse events occurring in subjects after a single oral administration of FDC formulation of atorvastatin/ezetimibe 5 mg/10 mg or concomitant administration of individual components of atorvastatin 5 mg and ezetimibe 10 mg

Signs and symptoms	FDC (n = 58)	Atorvastatin 5 mg + Ezetimibe 10 mg (n = 60)
Neutrophil count decreased	1 (1.7), [1]	1 (1.7), [1]
Amylase increased	1 (1.7), [1]	0 (0.0), [0]
Haemoglobin decreased	0 (0.0), [0]	1 (1.7), [1]
Lipase increased	1 (1.7), [1]	0 (0.0), [0]
Lymphocyte count increased	1 (1.7), [1]	0 (0.0), [0]
Headache	0 (0.0), [0]	2 (3.3), [2]
Dyspepsia	0 (0.0), [0]	1 (1.7), [1]
Vomiting	0 (0.0), [0]	1 (1.7), [1]

Data are displayed as the number of subjects (percentage), [number of events].
FDC, fixed-dose combination.

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DISCUSSION

In this study, the GMRs and 90% CIs for the AUC_{last} of atorvastatin and total ezetimibe in the test and reference formulations were within the bioequivalence range. According to the EMA guidelines and numerous studies, the AUC has been used as a reliable indicator of drug exposure [16,17]. The GMRs and 90% CIs of the corresponding values for the C_{max} of atorvastatin and ezetimibe slightly exceeded the bioequivalence range in this study. However, this difference is suspected to be originated from intraindividual variability of atorvastatin and ezetimibe based on the results of the dissolution study (in house). Considering that high doses of atorvastatin and ezetimibe were both well tolerated in previous studies [18-20], the slight difference of the C_{max} in the FDC is not expected to have a clinically significant impact on the safety. Indeed, in the phase 3 study involving patients with primary hypercholesterolemia (NCT05131997), the FDC with the same composition as in this study showed a greater reduction in LDL-C compared to monotherapy of atorvastatin 5 mg or ezetimibe 10 mg without significant safety issues.

After oral administration, ezetimibe is rapidly absorbed and undergoes first-pass metabolism in the intestinal wall and the liver to form ezetimibe-glucuronide, an active metabolite. Ezetimibe-glucuronide is secreted through the gallbladder into the intestinal lumen, where it undergoes hydrolysis of the conjugate by β-glucuronidase and is reconverted to the parent drug [21]. As the parent drug is reabsorbed into the systemic circulation, free ezetimibe and ezetimibe-glucuronide exhibit multiple peaks in their plasma concentration-time profiles. Multiple peaks in the plasma concentrations of free ezetimibe were observed in this study following the administration of both the reference and test formulations, with the second peak occurring at approximately 6 hours post-dose. In this study, the GMR of total ezetimibe for the FDC and individual components was estimated in accordance with the bioequivalence guidelines for ezetimibe recommended by the Ministry of Food and Drug Safety, which suggest assessing the bioequivalence of either total or free ezetimibe [22].

According to EMA and FDA guidelines for investigation of bioequivalence, a replicated crossover design is recommended to assess bioequivalence of the highly variable drugs [19,23]. However, this study was conducted using a conventional 2 × 2 crossover design, considering the higher dropout risk of the replicative design owing to the longer study duration. The intra-subject CVs of all components of this study were calculated from the analysis of log-transformed PK parameters (C_{max}, AUC_{last}) using a linear mixed model. The highest intra-subject CV, observed for the C_{max} of atorvastatin, was 40%. The T/R ratio was assumed to be 1.0 based on the GMRs of AUC_{last} obtained from the results of this study, which were 1.04 for atorvastatin and 0.98 for total ezetimibe. Considering the highest intra CV, approximately 54 subjects would have been needed for the conventional crossover study to detect a 20% difference between the 2 formulations with 80% statistical power at a 5% level of significance. Therefore, the number of subjects was adequate to evaluate the pharmacokinetic differences between the FDC and the corresponding individual components.

This study compared the PK profile and safety of a newly developed FDC tablet of atorvastatin/ezetimibe 5 mg/10 mg with the corresponding individual components. Based on this study's results, the systemic exposure of the FDC was similar to the corresponding individual components, and both formulations were tolerable in healthy subjects. These results support the use of the FDC of atorvastatin/ezetimibe 5 mg/10 mg in patients with hyperlipidemia.

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The FDC of atorvastatin/ezetimibe 5 mg/10 mg was safe and showed similar exposures to those of the individual components.

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