Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Pharmacokinetic Interactions Between the Fixed-Dose Combination of Ezetimibe/Rosuvastatin 10/20 Mg and the Fixed-Dose Combination of Telmisartan/Amlodipine 80/5 Mg in Healthy Subjects

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Background: Management of hypertension and hyperlipidemia, which are common comorbid risk factors for cardiovascular diseases, require multiple medications. The development of a fixed-dose combination (FDC) containing ezetimibe, rosuvastatin, telmisartan, and amlodipine aims to enhance patient adherence and persistence, but the potential interactions among the four medications have not been studied. This study aimed to evaluate the pharmacokinetic (PK) interactions between the FDC of ezetimibe/rosuvastatin 10/20 mg (ER) and the FDC of telmisartan/amlodipine 80/5 mg (TA).

Methods: An open-label, single-sequence, three-period, three-treatment crossover study was conducted in healthy male subjects. All subjects received ER for 7 days, TA for 9 days and ER combined with TA for 7 days during each treatment period. For PK analysis of total/free ezetimibe, rosuvastatin, telmisartan, and amlodipine, serial blood samples were collected for 24 hours at steady state. Safety profiles were assessed throughout the study.

Results: Thirty-eight subjects were enrolled, and 34 subjects completed the study. The systemic exposure to each active ingredient after coadministration of the two FDCs was similar to that after each FDC alone. The geometric mean ratios and 90% confidence intervals for the maximum plasma concentration (μg/L) and the area under the plasma concentration-time curve (h·μg/L) of the combination therapy to monotherapy, assessed at steady state, were as follows: total ezetimibe, 1.0264 (0.8765–1.2017) and 0.9359 (0.7847–1.1163); free ezetimibe, 1.5713 (1.2821–1.9257) and 0.9941 (0.8384–1.1788); rosuvastatin, 2.1673 (1.7807–2.6379) and 1.1714 (0.9992–1.3733); telmisartan, 1.0745 (0.8139–1.4186) and 1.1057 (0.8379–1.4591); and amlodipine, 0.9421 (0.8764–1.0126) and 0.9603 (0.8862–1.0405). Both combination therapy and monotherapy were well tolerated by the subjects.

Conclusion: The coadministration of ezetimibe/rosuvastatin 10/20 mg and ezetimibe/rosuvastatin 10/20 mg was well tolerated in healthy subjects, and the PK interaction between those two FDCs was not clinically significant.

Keywords: drug–drug interactions, pharmacokinetics, fixed-dose combination, ezetimibe, rosuvastatin, telmisartan, amlodipine

Introduction

The coadministration of multiple medications has become increasingly common, especially for managing complex medical conditions. Various cross-sectional investigations have revealed marked metabolic distinctions between individuals with hypertension and those with normal blood pressure, potentially linked to disrupted glucose metabolism, insulin resistance, lipid abnormalities, and hypertension.[1] Consequently, the management of complex cardiovascular disorders often involves the simultaneous administration of multiple medications to achieve optimal therapeutic outcomes.[2]

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For the prevention and management of cardiovascular diseases, common combinations of drugs for hypercholesterolemia include ezetimibe, a cholesterol absorption inhibitor, and rosuvastatin, a potent statin. This combination targets both dietary and endogenous sources of cholesterol, leading to a comprehensive reduction in low-density lipoprotein cholesterol levels. In the treatment of hypertension, telmisartan and amlodipine are frequently combined, and fixed-dose combinations (FDCs) of these two drugs have been developed.[3] Telmisartan is an angiotensin II receptor blocker, and amlodipine is a calcium channel blocker that works together effectively to control blood pressure.[4]

The utilization of FDCs of medications presents a promising opportunity to streamline drug administration procedures. These combinations aim to reduce the pill burden for patients, simplify medication regimens and improve patient adherence and persistence.[5–11] Furthermore, FDCs could lead to reduced treatment costs due to the incorporation of cost-effective generic medications.[6] Despite the benefits of FDCs, the combination of multiple components has potential for pharmacokinetic and pharmacodynamic interactions that can significantly impact the safety and efficacy of individual medications.[4,6] Therefore, it is crucial to thoroughly evaluate drug interactions before various medications are combined. Although drug–drug interactions (DDIs) between ezetimibe and rosuvastatin, as well as between telmisartan and amlodipine, have been studied individually, there is limited research on DDIs when all four components are used concurrently.[12–15] Because the components of FDCs cannot be titrated individually, the evaluation of DDIs between the individual drugs within the FDCs is crucial for generating clinically significant information for their development.

Ezetimibe, which is primarily metabolized in the liver by glucuronidation, undergoes limited oxidative metabolism.[16] Rosuvastatin is known to be metabolized in the liver via the cytochrome P450 (CYP450) system through the involvement of CYP2C9.[16] Telmisartan undergoes substantial hepatic metabolism, primarily via glucuronidation, and amlodipine is extensively metabolized by the liver through CYP3A enzymes.[17] The distinct metabolic pathways affected by these drugs raise questions about potential interactions when these drugs are administered together.

Based on these findings, this clinical study aimed to evaluate the pharmacokinetic interactions between the FDC of 20 mg of ezetimibe and 10 mg of rosuvastatin (Rosuvamibe tablet 10/20 mg; Yuhan Corporation, Seoul, Republic of Korea) and the FDC of 80 mg of telmisartan and 5 mg of amlodipine (Twynsta tablet 80/5 mg; Boehringer-Ingelheim Corporation, Ingelheim, Germany) in healthy subjects.

Method

Ethics Statement

The study protocol received approval from the Institutional Review Board of Seoul National University Hospital, and the study was conducted in strict adherence to the principles outlined in the Declaration of Helsinki and Korean Good Clinical Practice (KGCP) guidelines. The study was registered on ClinicalTrials.gov under the registration number NCT03632668. Informed consent was obtained from all subjects before any study-related procedures were performed.

Subjects

Healthy male Subjects aged between 19 and 50, with a body mass index (BMI) ranging from 18.0 to 27.0 kg/m^2 were recruited for this study. Subjects without clinically significant abnormalities based on medical interviews, physical examinations, vital signs, clinical laboratory tests, 12-lead electrocardiograms (ECGs) or previous major gastrointestinal surgeries were included in the study. Participants were also required to refrain from using any medications that could affect drug metabolism, such as barbiturates, for at least 30 days prior to their participation.

Study Design

This was an open-label, three-period, one-sequence, multiple dosing crossover study. The participants received 20 mg of ezetimibe and 10 mg of rosuvastatin (ER FDC) once daily for 7 days in period 1; 80 mg of telmisartan and 5 mg of amlodipine (TA FDC) once daily for 9 days in period 2; and the combination of these two FDC tablets once daily for 7 days in period 3. All investigational products were orally administered in a fasting state with 150 mL of pure water. There was a 7-day washout period between period 1 and 2, considering the elimination half-life ($t_{1/2}$) reported in the literature after the last administration of the ER FDC (Figure 1).[16]

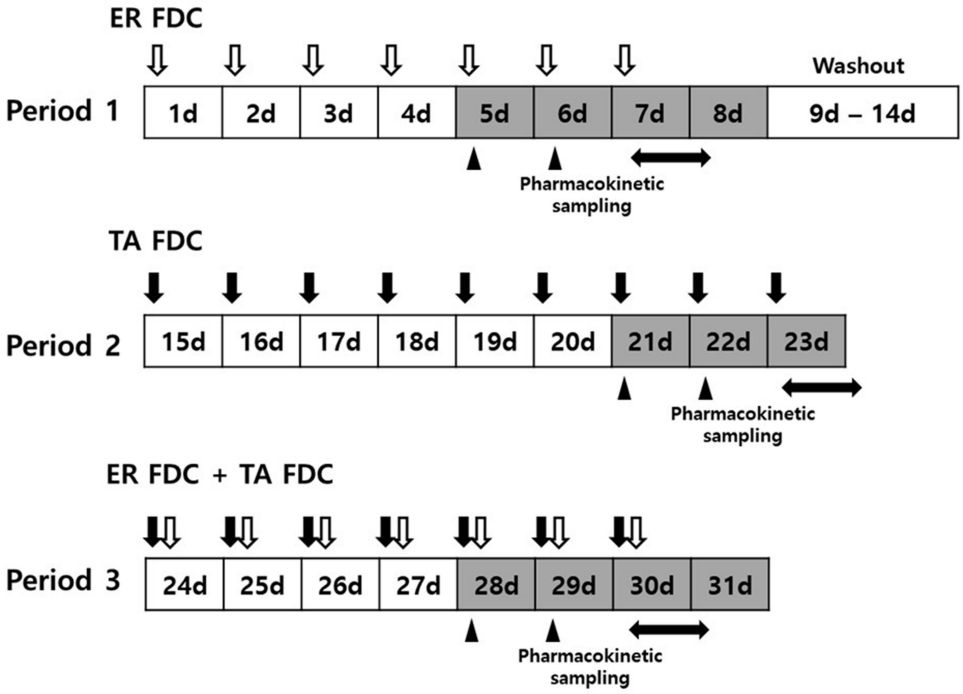

Figure 1 Study design.
Note: The gray box represents admission days.
Abbreviations: ER FDC, fixed-dose combination of 10 mg of ezetimibe and 20 mg of rosuvastatin; TA FDC, fixed-dose combination of 80 mg of telmisartan and 5 mg of amlodipine.

Blood samples for pharmacokinetic analysis were collected before administering treatment on days 5, 6, 7, 21, 22, 23, 28, 29, 30 and 0.25; 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, and 24 hours after administering treatment on Days 7, 23, and 30 for analysis of pharmacokinetics at steady-state (Figure 1). Blood samples were centrifuged at 3000 rpm and 4 °C for 10 minutes, after which the supernatant was separated and stored below −70 °C until the analysis.

Safety evaluation relied on various criteria, encompassing adverse events (AEs), vital signs, physical examinations, electrocardiograms, and clinical laboratory tests, including urinalysis.

Bioanalytical Methods

Plasma concentrations of ezetimibe and its unbound fraction, rosuvastatin, telmisartan, and amlodipine were determined using validated liquid chromatography coupled with tandem mass spectrometry. Sample preparation involved protein precipitation for total/free ezetimibe and telmisartan and liquid–liquid extraction for rosuvastatin and amlodipine. Different sample preparation Methods were employed to determine the concentrations of total and free ezetimibe. For free ezetimibe, samples were prepared with 80 uL of 0.2 M phosphate buffer and 500 uL of 100% acetonitrile. For total ezetimibe, an additional step involved adding 30 uL of beta-glucuronidase along with the phosphate buffer with one-hour incubation at 37°C.

The mobile phases used were 0.1% formic acid in distilled water (mobile phase A) and 100% acetonitrile (mobile phase B) for free/total ezetimibe and rosuvastatin; 0.1% formic acid in distilled water (mobile phase A) and 0.1% formic acid in 100% acetonitrile (mobile phase B) for telmisartan; and 0.1% formic acid in distilled water (mobile phase A) and 100% methanol (mobile phase B) for amlodipine. Internal standards, including ezetimibe-d4, rosuvastatin-d6, telmisartan-d3, and amlodipine-d4, were used to quantify total/free ezetimibe, rosuvastatin, telmisartan, and amlodipine, respectively. The specific instruments used were TQ5500 (AB Sciex) for total ezetimibe and free ezetimibe, API 4000 (AB Sciex) for rosuvastatin, Xevo-TQ (Waters Corporation) for telmisartan, and API4000 Qtrap (AB Sciex) for amlodipine. Chromatographic separations were carried out using different columns depending on the analyte: Hypersil Gold, ZORBAX Eclipse XDB-C18, Xbridge C18, and Synergi 4u Hydro-RP 80A. Mass

spectrometry was performed using multiple reaction monitoring with electrospray ionization (ESI) (-) for ezetimibe and ESI (+) for rosuvastatin, telmisartan, and amlodipine. The lower limit of quantification for the plasma assay varied for each analyte: 1 ng/mL for total/free ezetimibe, 0.4 ng/mL for rosuvastatin, 5 ng/mL for telmisartan, and 0.1 ng/mL for amlodipine. The calibration curves demonstrated linearity within specific concentration ranges for each analyte. The accuracy and precision of the calibration curves were within acceptable ranges for total/free ezetimibe, rosuvastatin, telmisartan, and amlodipine.

Pharmacokinetic Analysis

The pharmacokinetic (PK) parameters of the total ezetimibe, free ezetimibe, rosuvastatin, telmisartan, and amlodipine were calculated via the noncompartmental method using WinNonlin 7.0 (Certara USA, Princeton, New Jersey). The primary PK parameters included the maximum plasma concentration at steady state ($C_{max,ss}$) and the area under the time-concentration curve within a dosing interval at steady state ($AUC_{tau,ss}$) of each component. The $AUC_{tau,ss}$ was calculated using the linear trapezoidal method for the ascending concentrations and the log trapezoidal method for the descending concentrations. The time to achieve C_{max} ($T_{max,ss}$), $t_{1/2}$ at steady state ($t_{1/2,ss}$), apparent clearance at steady state (CL_{ss}/F), and apparent volume of distribution at steady state ($V_{d,ss}/F$) were also evaluated.

Statistical Analysis

The pharmacokinetic and safety data are summarized by appropriate descriptive statistics and presented for each treatment group. The geometric mean ratios (GMRs) and 90% confidence intervals (CIs) of combination therapy to monotherapy for $C_{max,ss}$ and $AUC_{tau,ss}$ of total ezetimibe, free ezetimibe, rosuvastatin, telmisartan and amlodipine were estimated using a linear mixed-effects model. All the statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

Subjects Disposition and Demographics

A total of 38 subjects were randomized, and 34 subjects completed the study. Among the randomized subjects, 35 received the study medication at least once and were included in the safety analysis. The 34 subjects who completed the study as planned were included in the pharmacokinetic analysis.

Pharmacokinetics

The overall exposure to ezetimibe and rosuvastatin was similar after the coadministration of two FDCs compared to that after the monotherapy of each FDC (Figure 2). Neither the $C_{max,ss}$ nor the $AUC_{tau,ss}$ of total ezetimibe significantly changed after combination therapy (Table 1 and Figure 3). The median time to reach the maximum plasma concentration at steady state also remained comparable. When the two FDCs were administered together, the $C_{max,ss}$ values of free ezetimibe and rosuvastatin were 1.57- and 2.17-fold greater, respectively, than those of monotherapy, but the $AUC_{tau,ss}$ values were similar (Table 1, Figures 2 and 3). The median $T_{max,ss}$ of free ezetimibe and rosuvastatin were shortened after combination therapy (Table 1). Other pharmacokinetic parameters, including CL_{ss} and $V_{d,ss,}$ exhibited no significant changes.

The overall exposure to telmisartan and amlodipine were also comparable after the coadministration of two FDCs compared to that after the monotherapy of each FDC (Figure 4). The $C_{max,ss}$ and the $AUC_{tau,ss}$ of telmisartan and amlodipine were similar between the treatment groups, and the median $T_{max,ss}$ was similar between the treatment groups (Table 2, Figures 4 and 5). Additional pharmacokinetic parameters, including CL_{ss} and $V_{d,ss,}$ were also comparable between the treatment groups.

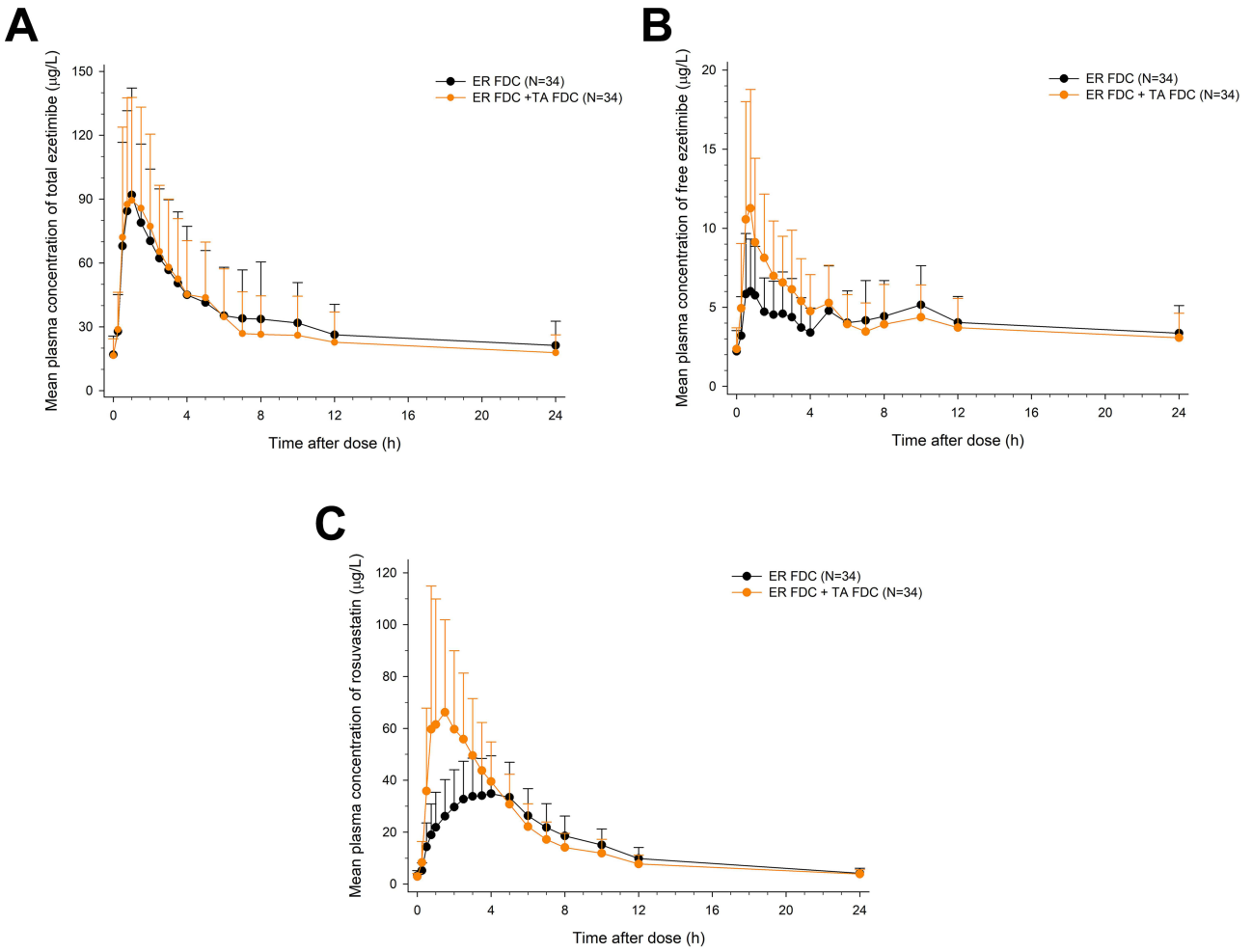

Figure 2 Mean plasma concentration–time profiles of the lipid-lowering agents (**A**) total ezetimibe, (**B**) free ezetimibe, and (**C**) rosuvastatin at steady state after multiple administrations of ER-FDC alone and with TA-FDC.
Note: Error bars represent the standard deviation.
Abbreviations: ER FDC, fixed-dose combination of 10 mg of ezetimibe and 20 mg of rosuvastatin; TA FDC, fixed-dose combination of 80 mg of telmisartan and 5 mg of amlodipine.

Safety and Tolerability

A total of 26 treatment emergent adverse events (TEAEs) occurred in 14 subjects who received the study medication at least once. All the TEAEs were mild in severity, and most of them were resolved without any medical intervention. A total of 19 adverse drug reactions (ADRs) were reported in 10 subjects (Table 3). The most common ADRs were dizziness and headache, and the incidence of ADRs was similar among the treatment groups (Table 3). There were no clinically significant abnormalities in the physical examination, vital signs, 12-lead ECG, or clinical laboratory test Results. Both the combination therapy of the two FDCs and the monotherapy of each FDC were well tolerated.

Discussion

This study aimed to evaluate the drug–drug interactions between two FDCs: an FDC of ezetimibe (20 mg) and rosuvastatin (10 mg) and an FDC of telmisartan (80 mg) and amlodipine (5 mg). After coadministering these FDCs, the pharmacokinetic parameters of ezetimibe, rosuvastatin, telmisartan, and amlodipine were comparable to those observed when each FDC was administered separately, with the exception of the $C_{max,ss}$ for free ezetimibe and rosuvastatin (Table 1 and Table 2). Furthermore, both the combination therapy and the monotherapy were well tolerated.

Table 1 Pharmacokinetic Parameters of Total Ezetimibe, Free Ezetimibe, and Rosuvastatin After Multiple Administrations of the Fixed-Dose Combination (FDC) of Ezetimibe (20 Mg) and Rosuvastatin (10 Mg), Both Alone and in Combination with the FDC of Telmisartan (80 Mg) and Amlodipine (5 Mg)

Pharmacokinetic Parameters	Monotherapy (N=34)	Combination Therapy (N=34)	GMR* (90% CIs)
Total ezetimibe			
$C_{max,ss}$ (μg/L)	118.37 ± 47.68	118.45 ± 44.74	1.0263 (0.8765–1.2017)
$AUC_{tau,ss}$ (h·μg/L)	805.13 ± 402.99	742.99 ± 367.89	0.9359 (0.7847–1.1163)
$T_{max,ss}$ (h)	1.00 [0.50–4.03]	1.00 [0.50–5.00]	
$t_{1/2,ss}$ (h)	16.09 ± 11.53	20.87 ± 21.56	
CL_{ss}/F (L/h)	15.08 ± 6.32	16.00 ± 6.68	
$V_{d,ss}/F$ (L)	330.44 ± 267.87	450.61 ± 489.46	
Free ezetimibe			
$C_{max,ss}$ (μg/L)	8.42 ± 3.31	14.49 ± 7.31	1.5713 (1.2821–1.9257)
$AUC_{tau,ss}$ (h·μg/L)	97.05 ± 38.21	100.17 ± 40.28	0.9941 (0.8384–1.1788)
$T_{max,ss}$ (h)	3.00 [0.50–12.00]	0.75 [0.25–3.50]	
$t_{1/2,ss}$ (h)	21.19 ± 15.86	18.88 ± 14.37	
CL_{ss}/F (L/h)	118.57 ± 49.53	117.03 ± 48.17	
$V_{d,ss}/F$ (L)	3092.44 ± 1654.50	2916.28 ± 2018.26	
Rosuvastatin			
$C_{max,ss}$ (μg/L)	37.61 ± 15.04	86.53 ± 50.96	2.1673 (1.7807–2.6379)
$AUC_{tau,ss}$ (h·μg/L)	349.76 ± 142.63	404.42 ± 160.65	1.1714 (0.9992–1.3733)
$T_{max,ss}$ (h)	4.00 [1.50–5.00]	1.00 [0.50–3.50]	
$t_{1/2,ss}$ (h)	8.13 ± 2.11	9.14 ± 2.52	
CL_{ss}/F (L/h)	66.49 ± 32.39	56.52 ± 21.68	
$V_{d,ss}/F$ (L)	783.99 ± 467.45	743.50 ± 343.66	

Notes: Values are presented as the mean ± standard deviation, except for $T_{max,ss}$, which is presented as the median [minimum–maximum]; *Geometric mean ratio of combination therapy to monotherapy.

Abbreviations: $AUC_{tau,ss}$, area under the plasma concentration-time curve during the dosing interval at steady state; CIs, confidence intervals; CL_{ss}/F, apparent clearance at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; GMR, geometric mean ratio; $t_{1/2,ss}$, half-life at steady state; $T_{max,ss}$, time to reach maximum plasma concentration at steady state; $V_{d,ss}/F$, apparent volume of distribution at steady state.

Regulatory guidelines suggest using the highest dose and strengths of investigational drugs when evaluating drug–drug interactions. However, in this study, the dose of amlodipine was reduced from 10 mg to 5 mg to avoid potential adverse drug reactions when the two FDCs were combined. A previous study evaluated the pharmacokinetic interactions between FDC tablets of telmisartan/amlodipine 80/10 mg and rosuvastatin 20 mg and reported a 2.83-fold increase in the $C_{max,ss}$ of rosuvastatin.[18] Considering a previous report that telmisartan increases the $C_{max,ss}$ of rosuvastatin by 2.01-fold, amlodipine is considered to increase the $C_{max,ss}$ by 82%.[18–20] This result was considered a potential risk factor that could affect safety and tolerability when coadministering the maximal tolerable dose of the three components. Therefore, the study doses were selected as ezetimibe/rosuvastatin 10/20 mg and telmisartan/amlodipine 80/5 mg.

In previous studies, bioequivalence has been established for ER FDC and the combination of ezetimibe and rosuvastatin, as well as for the TA FDC and the combination of telmisartan and amlodipine. Given the common clinical use and practical considerations for administration and research, this study aimed to evaluate drug–drug interactions by concurrently administering two FDCs containing four individual components. Instead of administering individual components for DDI assessment, a pragmatic approach involves coadministration of the two FDCs.

The washout period during the study schedule was set at 7 days after the last administration of the ER FDC, taking into account the reported elimination half-life of the medications in the literature.[16] However, between periods 2 and 3, we aimed to maximize subject safety and research efficiency by opting for continuous combined administration rather than introducing another washout phase. The selection of sampling points relied on the reported T_{max} and $T_{1/2}$ of each component, as indicated in the respected labels. Given that the primary objective of this study was to assess drug interactions under steady-state

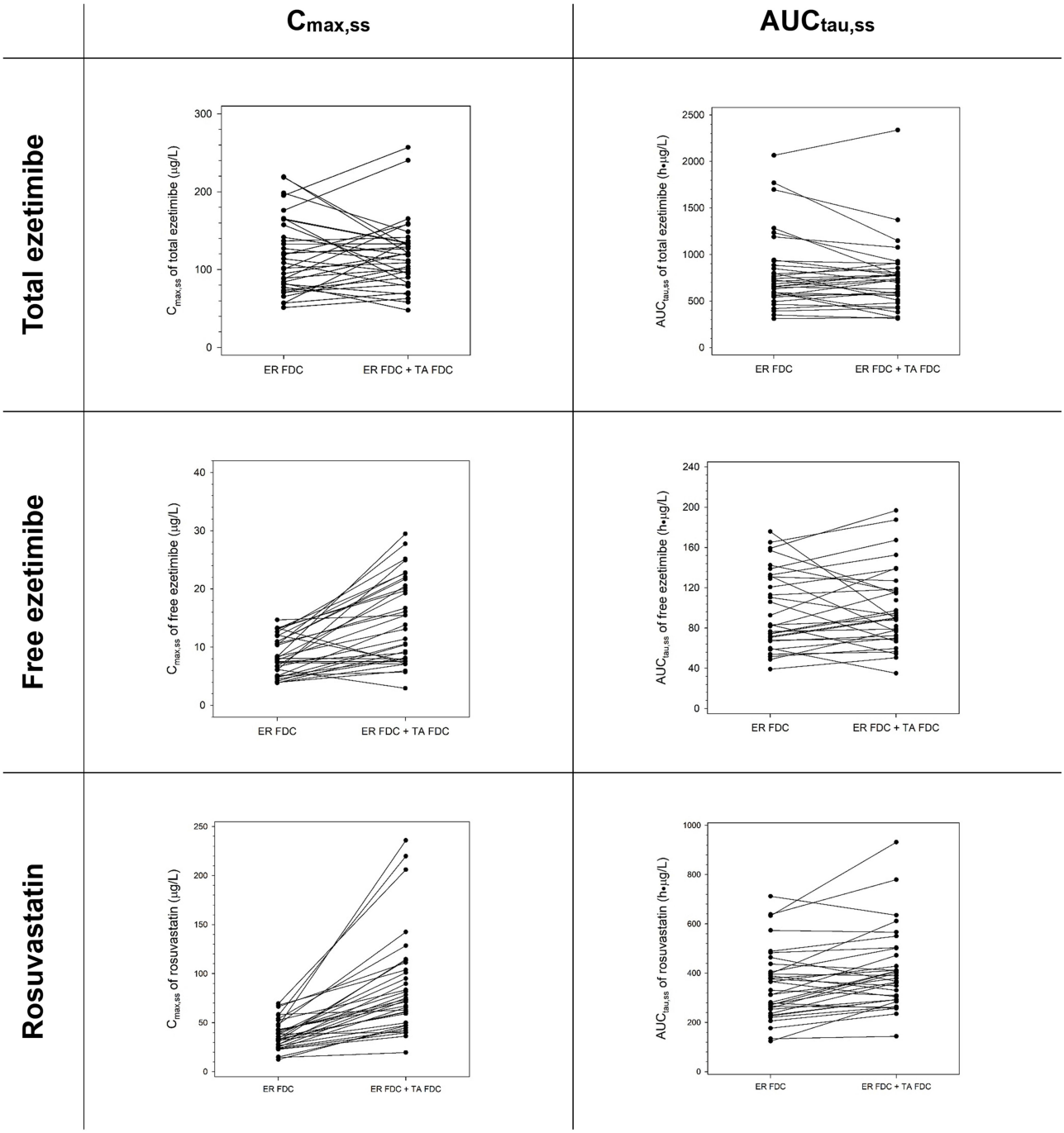

Figure 3 Comparison of $C_{max,ss}$ and $AUC_{tau,ss}$ for lipid-lowering agents, total ezetimibe, free ezetimibe, and rosuvastatin after multiple administrations of ER FDC alone and with TA FDC.

Abbreviations: $AUC_{tau,ss}$, area under the plasma concentration-time curve during the dosing interval at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; ER FDC, fixed-dose combination of ezetimibe 20 mg and rosuvastatin 10 mg; TA FDC, fixed-dose combination of telmisartan 80 mg and amlodipine 5 mg.

conditions, blood sampling was conducted only up to the time corresponding to the 24-hour dosing interval, with the main evaluative parameter being the AUC_{tau}.

A previous study revealed that the coadministration of ezetimibe and rosuvastatin did not significantly alter the $C_{max,ss}$ of free ezetimibe, suggesting that these two drugs have no significant pharmacokinetic interaction.[12,13] However, when telmisartan was added to the combination of ezetimibe and rosuvastatin, there was a notable increase in the $C_{max,ss}$ of free ezetimibe by 1.85-fold, accompanied by a smaller T_{max}.[15,21] An increase in the $C_{max,ss}$ of free

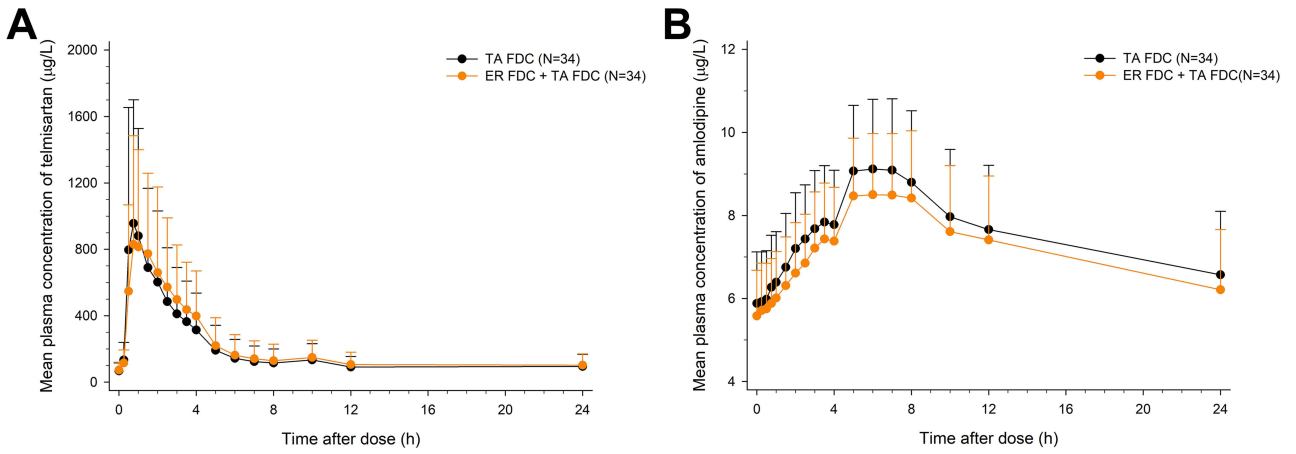

Figure 4 Mean plasma concentration–time profiles of antihypertensive agents, (**A**) telmisartan, and (**B**) amlodipine at steady state after multiple administrations of TA FDC alone and with ER FDC.

Note: Error bars represent the standard deviation.

Abbreviations: ER FDC, fixed-dose combination of 10 mg of ezetimibe and 20 mg of rosuvastatin; TA FDC, fixed-dose combination of 80 mg of telmisartan and 5 mg of amlodipine.

ezetimibe was also observed in this study after coadministration of two FDCs. Most ezetimibe undergoes metabolic conversion to form ezetimibe glucuronide in the liver and intestine via UDP glycosyltransferase (UGT) enzymes, especially 1A1, 1A3 and 2B15.[22] For telmisartan, the major elimination pathway involves glucuronidation, and it was shown that the pathway involves UGT 1A3.[23] These findings suggest that telmisartan may influence the glucuronidation of free ezetimibe. However, given that free ezetimibe constitutes only approximately 10–20% of the total ezetimibe concentration and that an increase in free ezetimibe concentration has been proven to have no correlation

Table 2 Pharmacokinetic Parameters of Telmisartan and Amlodipine After Multiple Administrations of the Fixed-Dose Combination (FDC) of Telmisartan 80 Mg and Amlodipine 5 Mg FDC, Both Alone and in Combination with Ezetimibe 20 Mg and Rosuvastatin 10 Mg

Pharmacokinetic Parameters	Monotherapy (N=34)	Combination Therapy (N=34)	GMR* (90% CIs)
Telmisartan			
$C_{max,ss}$ (μg/L)	1165.48 ± 821.91	1147.21 ± 620.47	1.0745 (0.8139–1.4186)
$AUC_{tau,ss}$ (h·μg/L)	4379.39 ± 2808.84	4794.81 ± 2903.07	1.1057 (0.8379–1.4591)
$T_{max,ss}$ (h)	0.75 [0.50–3.05]	0.77 [0.50–4.00]	
$t_{1/2,ss}$ (h)	13.16 ± 7.90	15.06 ± 8.93	
CL_{ss}/F (L/h)	28.76 ± 23.73	25.85 ± 20.18	
$V_{d,ss}/F$ (L)	469.07 ± 376.33	500.50 ± 369.63	
Amlodipine			
$C_{max,ss}$ (μg/L)	9.42 ± 1.76	8.83 ± 1.45	0.9421 (0.8764–1.0126)
$AUC_{tau,ss}$ (h·μg/L)	179.38 ± 34.75	172.20 ± 33.38	0.9603 (0.8862–1.0405)
$T_{max,ss}$ (h)	6.00 [3.00–8.00]	6.00 [3.50–10.00]	
$t_{1/2,ss}$ (h)	53.43 ± 24.49	55.08 ± 47.08	
CL_{ss}/F (L/h)	28.72 ± 6.07	30.15 ± 6.12	
$V_{d,ss}/F$ (L)	2125.74 ± 847.45	2273.08 ± 1460.18	

Notes: Values are presented as the mean ± standard deviation, except for $T_{max,ss}$, which is presented as the median [minimum–maximum]; *Geometric mean ratio of combination therapy to monotherapy.

Abbreviations: $AUC_{tau,ss}$, area under the plasma concentration-time curve during the dosing interval at steady state; CIs, confidence intervals; CL_{ss}/F, apparent clearance at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; GMR, geometric mean ratio; $t_{1/2,ss}$, half-life at steady state; $T_{max,ss}$, time to reach maximum plasma concentration at steady state; $V_{d,ss}/F$, apparent volume of distribution at steady state.

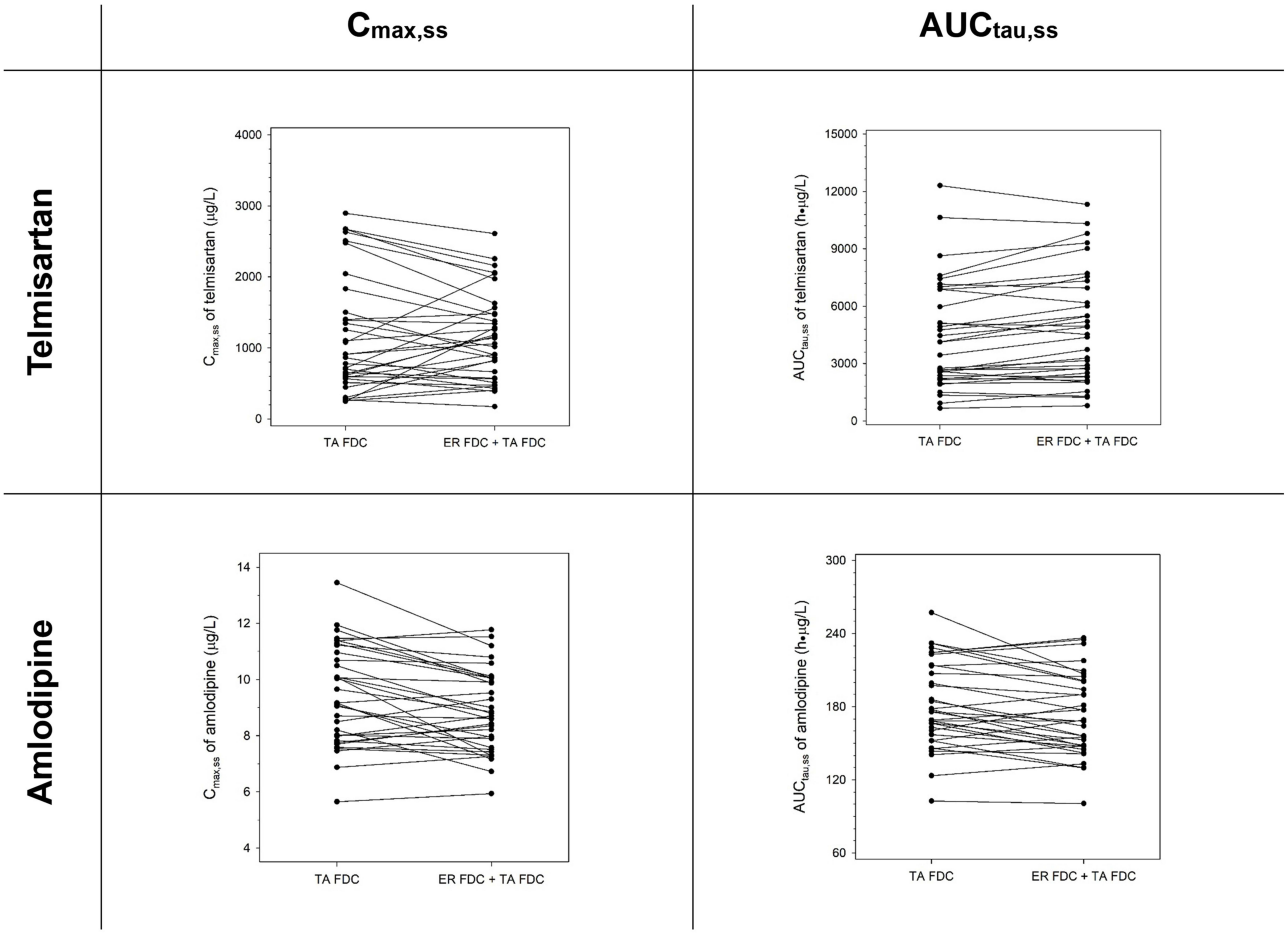

Figure 5 Comparison of $C_{max,ss}$ and $AUC_{tau,ss}$ for antihypertensive agents, telmisartan, and amlodipine after multiple administrations of TA FDC alone and with ER FDC.
Abbreviations: $AUC_{tau,ss}$, area under the plasma concentration-time curve during the dosing interval at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; ER FDC, fixed-dose combination of ezetimibe 20 mg and rosuvastatin 10 mg; TA FDC, fixed-dose combination of telmisartan 80 mg and amlodipine 5 mg.

with adverse events, a 1.57-fold increase in the free ezetimibe concentration may not have a clinically significant impact on ezetimibe therapy.[13,24,25]

The pharmacokinetic interactions among ezetimibe, rosuvastatin, telmisartan, and amlodipine were investigated in three separate studies, and the results indicated consistent findings.[13,15,19] In the study examining ezetimibe alone with rosuvastatin, no significant changes were observed in the C_{max} of rosuvastatin.[13] However, when telmisartan was combined with rosuvastatin, a notable 2.01-fold increase in the C_{max} of rosuvastatin was observed.[19] Similarly, when ezetimibe and telmisartan were added to rosuvastatin, a similar 2.13-fold increase in the C_{max} of rosuvastatin was noted.[15] In this trial investigating the combination of ezetimibe, rosuvastatin, telmisartan and amlodipine, a 2.17-fold increase in the C_{max} of rosuvastatin was detected. These consistent findings across the three studies suggest that amlodipine or ezetimibe alone does not significantly impact the PKs of rosuvastatin. Rather, the results indicated that telmisartan plays a role in elevating the exposure to rosuvastatin. The increase in rosuvastatin exposure is presumed to be due to competition between rosuvastatin and telmisartan for transporters (OATP1B3, BCRP, MDR1), which reduce rosuvastatin influx to the liver.[26,27]

In a previous modeling approach on the pharmacodynamics of rosuvastatin, a dose–response curve was observed to be flat beyond 10 mg, indicating that an increase in the dosage does not significantly influence the frequency of adverse events.[28] Given these findings, the incremental exposure identified in our study is expected to have minimal impact on the pharmacodynamics and safety of the treatment. For telmisartan and amlodipine, the coadministration of two FDCs had a negligible effect on the pharmacokinetic parameters, indicating that there were no significant interactions between the two FDCs.

Table 3 Summary of Adverse Drug Reactions

System Organ Class Preferred Terms	ER FDC (N=35)	TA FDC (N=35)	ER FDC + TA FDC (N=34)
Total	**3 (8.57) [6]**	**4 (11.43) [4]**	**7 (20.59) [9]**
Cardiac disorders	–	–	1 (2.94) [1]
Palpitations	–	–	1 (2.94) [1]
Eye disorders	–	–	1 (2.94) [1]
Photopsia	–	–	1 (2.94) [1]
Gastrointestinal System disorders	1 (2.86) [1]	–	–
Nausea	1 (2.86) [1]	–	–
General disorders and administration site conditions	–	–	1 (2.94) [1]
Noncardiac chest pain	–	–	1 (2.94) [1]
Investigations	–	–	1 (2.94) [1]
Electrocardiogram QT prolonged	–	–	1 (2.94) [1]
Musculoskeletal and connective tissue disorders	–	–	2 (5.88) [2]
Musculoskeletal pain	–	–	1 (2.94) [1]
Myalgia	–	–	1 (2.94) [1]
Nervous System disorders	3 (8.57) [5]	2 (5.71) [2]	2 (5.88) [3]
Dizziness	1 (2.86) [1]	1 (2.86) [1]	2 (5.88) [2]
Headache	3 (8.57) [4]	1 (2.86) [1]	1 (2.94) [1]
Skin and subcutaneous tissue disorders	–	2 (5.71) [2]	–
Rash	–	1 (2.86) [1]	–
Skin mass	–	1 (2.86) [1]	–

Note: The number of subjects (percentage of the subjects) (number of events) is presented.
Abbreviations: ER FDC, fixed-dose combination of ezetimibe 20 mg and rosuvastatin 10 mg; TA FDC, fixed-dose combination of telmisartan 80 mg and amlodipine 5 mg.

Conclusion

In conclusion, the coadministration of the FDC of ezetimibe (20 mg) and rosuvastatin (10 mg), along with the FDC of telmisartan (80 mg) and amlodipine (5 mg), did not result in clinically significant pharmacokinetic interactions and was well tolerated when administered together. Combining telmisartan, known for its superior tolerability among ARBs,[29] with rosuvastatin, which demonstrates a more potent lipid-lowering effect compared to other statins,[30] is anticipated to enhance the treatment of complex cardiovascular diseases. Therefore, the combination of these two FDCs may be considered a viable therapeutic option for treating complex cardiovascular diseases.

Data Sharing Statement

The data supporting the published results of this study will be shared upon a reasonable request made to the corresponding author or sponsor.

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Disclosure

Kyung Tae Kim is a full-time employee of Addpharma. The other authors report no conflicts of interest associated with this work.

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