Pharmacokinetic comparison between fixed-dose combination of rosuvastatin/ezetimibe 2.5/10 mg and the coadministration of individual formulations in healthy subjects

Dowon Lee[1], Sejung Hwang, Pharm.D., PhD[1], Kyung-Sang Yu MD, PhD[1], SeungHwan Lee MD, PhD[1]

[1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea

BACKGROUND

- Dyslipidemia is a common chronic disease and a major risk factor for atherosclerotic cardiovascular disease (ASCVD), and the statins are the first-line for dyslipidemia.
- However, it has been reported that Asian tend to experience higher statin exposure, which raises safety concern.
- Previous studies have shown that the combination of rosuvastatin (a type of statin, 5-40 mg) and ezetimibe demonstrates superior efficacy compared to statin monotherapy.
- A combination therapy with a lower dose of statin (e.g., rosuvastatin 2.5 mg) and ezetimibe may enhance safety while maintaining efficacy compared to conventional combination therapy.
- As a result, such a fixed-dose combination (FDC) has been developed.

OBJECTIVE

- This study aimed to compare the pharmacokinetics (PKs) between the FDC of rosuvastatin/ezetimibe 2.5/10 mg and the coadministration of individual formulations.

METHODS

<Study design>

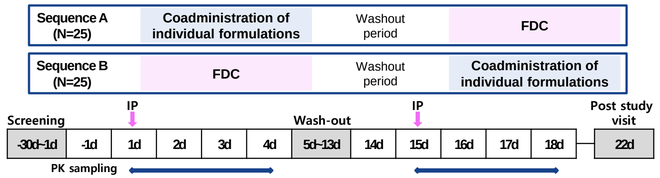

Figure 1. Study design.

- A randomized, open-label, single-dose, 2-sequence, 2-period, crossover study was conducted in healthy volunteers.
- Subjects were randomized in one of the two sequence and received a single dose of FDC of rosuvastatin/ezetimibe 2.5/10 mg or the coadministration of individual formulations in each period with a 14-day washout.

<Pharmacokinetic Assessment>

- Serial blood samples for PK assessment were collected up to 48 hours post-dose for rosuvastatin and 72 hours post-dose for ezetimibe.
  - At 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.25, 2, 3, 4, 5, 6, 8, 12, 24, 48 h post-dose for rosuvastatin
  - At 0 (pre-dose), 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72 h post-dose for total and free ezetimibe
- Plasma concentrations of rosuvastatin, total and free ezetimibe were determined by liquid chromatography with tandem mass spectrometry.
- PK parameters were estimated using noncompartmental analysis using Phoenix WinNonlin® 8.0.
- The geometric least squares mean ratios (GMRs) and 90% confidence intervals (CIs) for C_{max} and AUC_{last} of FDC to coadministration of individual formulations were calculated and evaluated if these values were within the conventional bioequivalence criteria of 0.8 to 1.25.

<Safety and Tolerability Assessment>

- Physical examinations, concomitant medications, clinical laboratory tests (hematology, blood chemistry, urinalysis), vital signs, 12-lead ECGs, and adverse events (AEs) monitoring were performed throughout the study.

RESULTS

- Forty-seven healthy subjects randomized, and 41 subjects completed the study and included in PK analyses.
- The GMRs (90% CIs) of C_{max} and AUC_{last} for rosuvastatin were 0.9789 (0.9020–1.0622) and 0.9741 (0.9105–1.0422).
- The corresponding values were 1.0419 (0.9219–1.1776) and 0.9983 (0.9522–1.0465) for total ezetimibe, and 1.0396 (0.9087–1.1893) and 0.9743 (0.8997–1.0550) for free ezetimibe, respectively.
- All the values were within the conventional bioequivalence criteria of 0.8 to 1.25.
- There were no significant differences in the safety between the FDC and the coadministration of individual formulations.

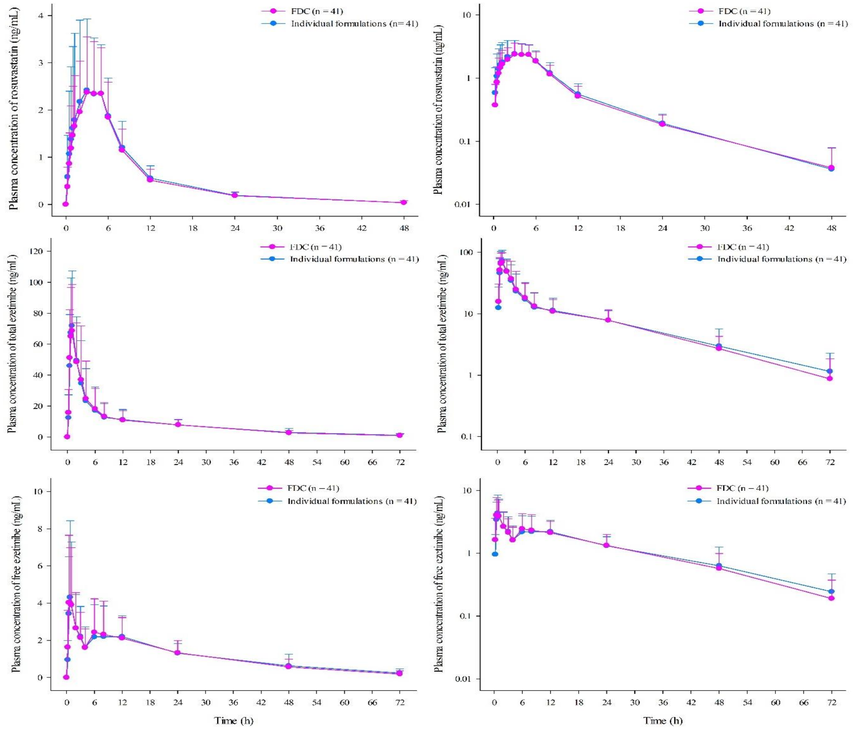

Figure 2. Mean plasma concentration-time profiles of rosuvastatin, total and free ezetimibe after a single oral administration of FDC of rosuvastatin/ezetimibe 2.5/10 mg or the coadministration of individual formulations.

Table 1. Summary of pharmacokinetic parameters of rosuvastatin after a single oral administration of FDC of rosuvastatin/ezetimibe 2.5 mg/10 mg or coadministration of individual formulations.

Parameter	FDC (n = 41)	Individual formulations (n = 41)	Geometric mean ratio (90% CIs)
C_{max} (μg/L)	2.60 ± 1.19	2.74 ± 1.83	0.9789 (0.9020 – 1.0622)
AUC_{last} (hr·μg/L)	23.72 ± 9.97	24.77 ± 12.33	0.9741 (0.9105 – 1.0422)
AUC_{inf} (hr·μg/L)	25.01 ± 10.05	26.14 ± 12.36	
T_{max} (hr)	4.00 (1.25 – 6.00)	5.00 (0.75 – 6.00)	
$t_{1/2}$ (hr)	8.92 ± 4.66	8.52 ± 3.31	
CL/F (L/h)	117.00 ± 47.29	114.96 ± 48.96	
V_d/F (L)	1463.77 ± 933.34	1341.82 ± 644.83	

Table 2. Summary of pharmacokinetic parameters of total ezetimibe and free ezetimibe after a single oral administration of FDC of rosuvastatin/ezetimibe 2.5 mg/10 mg or coadministration of individual formulations.

Parameter	FDC (n = 41)	Individual formulations (n = 41)	Geometric mean ratio (90% CIs)
Total ezetimibe			
C_{max} (μg/L)	86.09 ± 31.90	85.52 ± 36.94	1.0419 (0.9219 – 1.1776)
AUC_{last} (hr·μg/L)	571.97 ± 256.26	578.18 ± 267.69	0.9983 (0.9522 – 1.0465)
AUC_{inf} (hr·μg/L)	611.07 ± 263.32	640.66 ± 293.78	
T_{max} (hr)	1.00 (0.50 – 4.00)	1.00 (0.50 – 3.00)	
$t_{1/2}$ (hr)	17.04 ± 6.81	20.27 ± 14.20	
CL/F (L/h)	18.56 ± 6.00	18.25 ± 7.03	
V_d/F (L)	450.02 ± 232.99	494.56 ± 272.67	
Free ezetimibe			
C_{max} (μg/L)	5.59 ± 3.50	5.52 ± 3.98	1.0396 (0.9087 – 1.1893)
AUC_{last} (hr·μg/L)	80.41 ± 38.66	82.29 ± 39.61	0.9743 (0.8997 – 1.0550)
AUC_{inf} (hr·μg/L)	87.29 ± 42.23	94.33 ± 48.36	
T_{max} (hr)	1.00 (0.25 – 8.00)	1.00 (0.50 – 24.00)	
$t_{1/2}$ (hr)	17.89 ± 7.64	21.53 ± 15.36	

CONCLUSION

- The FDC of rosuvastatin/ezetimibe 2.5/10 mg showed comparable PK with the coadministration of individual formulations.

CONFLICTS OF INTEREST

- This study was sponsored by Addpharma Co., Ltd., and Yuhan Corporation, Republic of Korea.
- Authors do not have any conflicts of interest for this study.