Pharmacokinetic Comparison of Ezetimibe/Rosuvastatin/Telmisartan Fixed-Dose Combination versus Coadministration of Separate Treatments

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BACKGROUND

- Ezetimibe, rosuvastatin, and telmisartan are frequently co-administered in the management of dyslipidemia, leveraging their complementary mechanisms of action.
- Fixed-dose combination (FDC) therapy offers a promising strategy to enhance patient adherence by simplifying the regimen, compared to the administration of separate tablets.

OBJECTIVE

- This study aimed to evaluate the pharmacokinetics (PKs) for FDC of ezetimibe 10 mg/rosuvastatin 20 mg/telmisartan 80 mg (test) compared to separate tablets of ezetimibe 10 mg/rosuvastatin 20 mg FDC and telmisartan 80 mg (reference).

METHODS

Study Design

- A phase 1, randomized, open-label, 4-period, 2-sequence replicated crossover study was conducted in healthy participants and registered in Clinical Research information Service in Korea (KCT0009387).
- Each treatment group received a single oral dose of reference or test drug in each period.

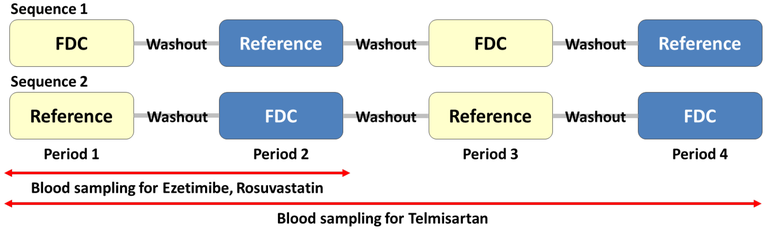

Figure 1. Study design.

Outcome Assessments

- PK samples were collected up to 72 hours, and PK samples at the 3rd and 4th period were only collected for telmisartan to evaluate intrasubject variability.
  - Blood sampling for free and total ezetimibe PK analysis was conducted at 0 h (pre-dose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, 72 h post-dose.
  - For rosuvastatin, samples were taken at 0 h (pre-dose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48 h post-dose.
  - Blood samples were collected at 0 h (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72 h (post-dose) for the PK analysis of telmisartan.
- Geometric mean ratios (GMRs) of PK parameters and their 90% confidence intervals (CIs) were calculated with linear mixed effect model between each treatment group.
- Also, intrasubject variability of log-transformed maximum plasma concentration (C_{max}) in each reference treatment was calculated for the assessment of intrasubject variability of telmisartan.
- Safety evaluations including physical examination, clinical laboratory test, electrocardiogram, vital sign, and adverse event (AE) monitoring were performed.

RESULTS

Disposition of Subjects

- A total of 58 participants were randomized and 49 participants completed the study and included in analysis.
- PK profiles were comparable between treatments.

Pharmacokinetic Results

- The GMR and 90% CIs (test-to-reference) of area under the concentration-time curve (AUC_t) and maximum plasma concentration (C_{max}) were 0.9835 (0.9260–1.0446) and 0.9873 (0.8830–1.1039) for free ezetimibe, and 0.9937 (0.9459–1.0440) and 1.0617 (0.9844–1.1415) for total ezetimibe. For rosuvastatin, corresponding values were 0.9465 (0.8883–1.0086) and 0.9062 (0.8135–1.0096); for telmisartan, 0.9728 (0.9315–1.0159) and 0.9724 (0.8846–1.0690), respectively.
- Intrasubject coefficient of variation of C_{max} of telmisartan was 41.7%.

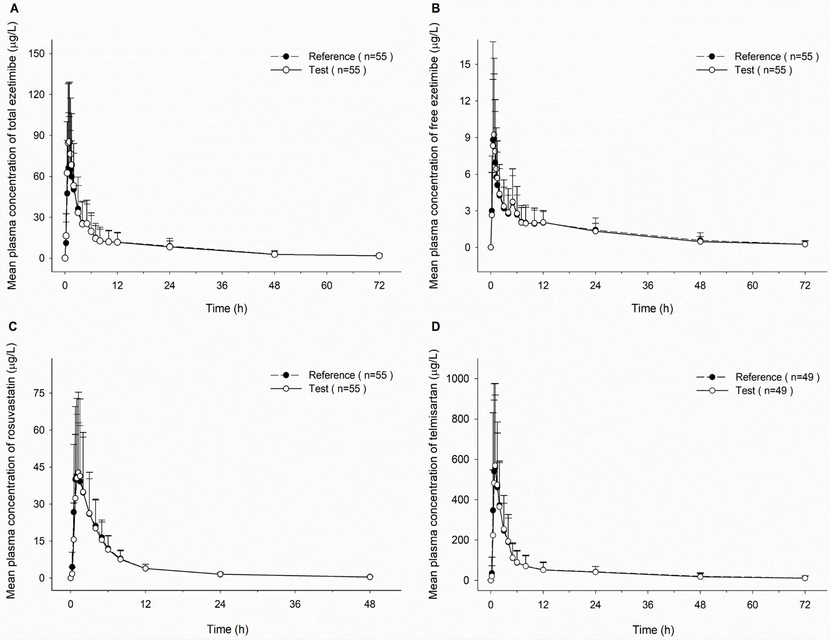

Figure 2. Mean plasma concentration-time profile of (A) total ezetimibe, (B) free ezetimibe, (C) rosuvastatin and (D) telmisartan after single oral administration of AD-201 (ezetimibe/rosuvastatin/telmisartan 10 mg/20 mg/80 mg FDC) as a FDC treatment or AD-2011 (ezetimibe/rosuvastatin 10 mg/20 mg FDC) and AD-2012 (telmisartan 80 mg) combination therapy as a reference treatment.
***Error bars denote standard deviation.**
***FDC; Fixed dose combination**

Table 1. GMRs (test-to-reference) and 90% CIs of total ezetimibe, free ezetimibe, rosuvastatin and telmisartan and intrasubject variability of telmisartan

Drug	Variables (unit)	Geometric Mean Ratio (90% Confidence Interval)	Intrasubject variability (%)
Free ezetimibe	AUC_t (hr·μg/L)	0.9835 (0.9260–1.0446)	
	C_{max} (μg/L)	0.9873 (0.8830–1.1039)	
Total ezetimibe	AUC_t (hr·μg/L)	0.9937 (0.9459–1.0440)	
	C_{max} (μg/L)	1.0617 (0.9844–1.1451)	
Rosuvastatin	AUC_t (hr·μg/L)	0.9465 (0.8883–1.0086)	
	C_{max} (μg/L)	0.9062 (0.8135–1.0096)	
Telmisartan	AUC_t (hr·μg/L)	0.9728 (0.9315–1.0159)	18.5
	C_{max} (μg/L)	0.9724 (0.8846–1.0690)	41.7

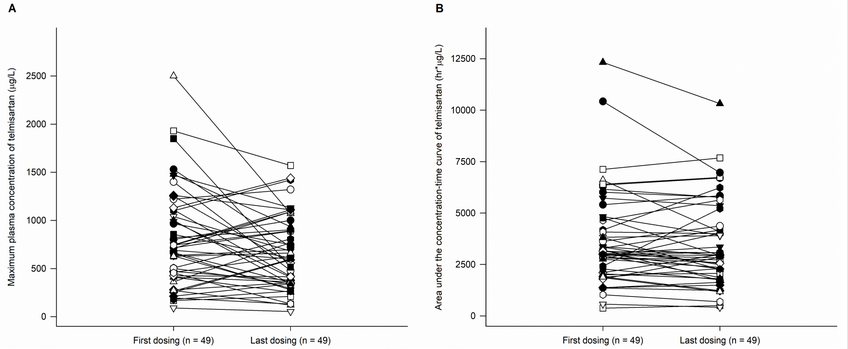

Figure 3. Telmisartan (A) C_{max} and (B) AUC_t of reference* treatment
AUC_t, area under the concentration-time curve; C_{max}, maximum plasma concentration; FDC, fixed dose combination;
*** AD-2012 (Telmisartan 80 mg) as a reference treatment.**

Safety Results

- Among the 14 participants, a total of 21 AEs occurred, of which 13 were considered adverse drug reactions (ADRs).
- All ADRs were mild in severity and recovered without sequelae.

CONCLUSIONS

- A fixed-dose combination of ezetimibe 10 mg/rosuvastatin 20 mg/telmisartan 80 mg demonstrated comparable pharmacokinetic and safety profiles to corresponding separate tablets.

CONFLICTS OF INTEREST

- This study was sponsored by Yuhan & Addpharma Pharmaceutical Corp., Korea.
- The authors do not have any conflicts of interest in this study.