

Pharmacokinetic Comparison Between a Fixed-Dose Combination of Atorvastatin/Omega-3-Acid Ethyl Esters and the Corresponding Loose Combination in Healthy Korean Male Subjects

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Purpose: Statins are widely used in combination with omega-3 fatty acids for the treatment of patients with dyslipidemia. The aim of this study was to compare the pharmacokinetic (PK) profiles of atorvastatin and omega-3-acid ethyl esters between fixed-dose combination (FDC) and loose combination in healthy subjects.

Methods: A randomized, open-label, single-dose, 2-sequence, 2-treatment, 4-period replicated crossover study was performed. Subjects were randomly assigned to one of the 2 sequences and alternately received four FDC soft capsules of atorvastatin/omega-3-acid ethyl esters (10/1000 mg) or a loose combination of atorvastatin tablets (10 mg × 4) and omega-3-acid ethyl ester soft capsules (1000 mg × 4) for four periods, each period accompanied by a high-fat meal. Serial blood samples were collected for PK analysis of atorvastatin, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). PK parameters were calculated by a non-compartmental analysis. The geometric mean ratio (GMR) and its 90% confidence interval (CI) of the FDC to the loose combination were calculated to compare PK parameters.

Results: A total of 43 subjects completed the study as planned. The GMR (90% CI) of FDC to loose combination for maximum concentration (C_{max}) and area under the time-concentration curve from zero to the last measurable point (AUC_{last}) were 1.0931 (1.0054–1.1883) and 0.9885 (0.9588–1.0192) for atorvastatin, 0.9607 (0.9068–1.0178) and 0.9770 (0.9239–1.0331) for EPA, and 0.9961 (0.9127–1.0871) and 0.9634 (0.8830–1.0512) for DHA, respectively. The intra-subject variability for C_{max} and AUC_{last} of DHA was 30.8% and 37.5%, respectively, showing high variability. Both the FDC and the loose combination were safe and well tolerated.

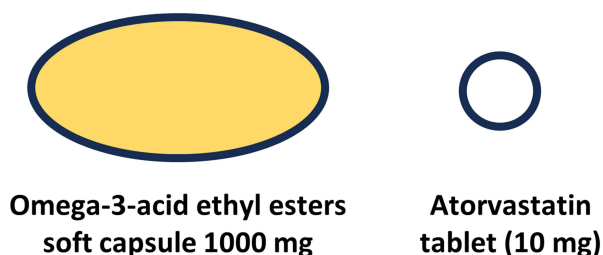
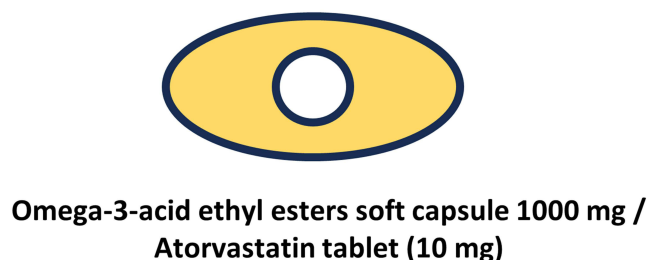
Conclusion: The FDC of atorvastatin and omega-3-acid ethyl esters showed comparable PK characteristics to the corresponding loose combination, offering a convenient therapeutic option for the treatment of dyslipidemia.

Keywords: pharmacokinetics, cardiovascular disease

Introduction

Dyslipidemia is defined as an imbalance in the lipid profile, including total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C), and is a clinically significant risk factor for atherosclerotic cardiovascular diseases (ASCVDs).^{1,2} The management of dyslipidemia and prevention of ASCVDs primarily focuses on maintaining LDL-C under certain levels through lifestyle modifications and lipid-lowering

Graphical Abstract

Loose combination**Fixed-dose combination**

therapies.³⁻⁷ According to current guidelines, patients with a very high risk of ASCVDs are recommended to achieve LDL-C levels of less than 55 mg/dL^{6,7} or achieve 50% or greater reduction from baseline.⁵

Statins are currently used as first-line therapies for dyslipidemia and the prevention of ASCVDs.^{5,7} By inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), statins lower LDL-C levels by inhibiting the cholesterol synthesis pathway. Although the management of dyslipidemia primarily focuses on lowering LDL-C levels, lipid profiles of TG, very-low-density lipoprotein (VLDL), and HDL-C may not improve sufficiently in patients treated with statin monotherapy.

In case of combined hyperlipidemia, combination therapy with statins and omega-3 fatty acids may lower TGs in greater amounts and reduce the risk of ASCVDs.⁸ The mechanism by which omega-3 fatty acid administration lowers TGs is not fully understood, but it has been suggested that omega-3 fatty acid administration contributes to hepatic lipogenesis suppression by increasing fatty acid oxidation.^{9,10} In a large-scale clinical study, combination therapy with omega-3 fatty acids and simvastatin significantly improved the non-HDL-C profile compared to simvastatin alone in hypertriglyceridemic patients.¹¹ Another large-scale clinical trial in Japan demonstrated a significant reduction in major coronary events following combination therapy with statins and omega-3 fatty acids in patients with hypercholesterolemia.¹²

For patients taking both atorvastatin and omega-3-acid ethyl esters, a fixed-dose combination (FDC) of atorvastatin and omega-3-acid ethyl esters (ATMEG CombiGel Softcap, Korea United Pharm. Inc., Korea) was developed to improve compliance and convenience. While the possibility of drug interactions between atorvastatin and omega-3-acid ethyl esters has been reported,¹³ the efficacy and safety of ATMEG CombiGel have been confirmed through a Phase 3 study.¹⁴ The FDC formulation of atorvastatin and omega-3-acid ethyl esters contains atorvastatin tablet inside the omega-3-acid ethyl esters

capsule. By applying the multilayer barrier coating technology developed by Korean United Pharm. Inc. (Seoul, Korea), the combination of different (solution and tablet) formulations was possible. With this approach, the pill size was maintained as a single omega-3-acid ethyl esters capsule, offering an advantage to patients who have difficulty swallowing larger pills.

The aim of this study was to compare the pharmacokinetic (PK) and safety profile of atorvastatin and omega-3-acid ethyl esters between the FDC and the corresponding loose combination in healthy Korean subjects.

Materials and Methods

This study (NCT05085184) was approved by the institutional review board (IRB) of Seoul National University Hospital (IRB number: H-2107-247-1241) and the Korea Ministry of Food and Drug Safety (MFDS). This study was conducted from 6 September to 10 December 2021. All study procedures were conducted in accordance with the principles of the Korean Good Clinical Practices and the ethical principles of the Declaration of Helsinki. Participants fully understood the objectives, expected results, and possible risks of this study and signed informed consent forms before enrollment.

Study Population

Healthy Korean adults aged between 19 and 45 years with a body mass index (BMI) of 18.0 to 27.0 kg/m² were eligible to participate in this study. The enrolled subjects had no clinically significant abnormalities considering medical history, vital signs, clinical laboratory tests, 12-lead electrocardiogram, and physical examinations. Subjects were excluded if they had any clinically significant hypersensitivity to atorvastatin, other HMG-CoA reductase inhibitors, omega-3 fatty acids or fish; history or family history of myopathy or hereditary muscular disorders; or current or history of obstructive bile disorders.

Study Design

A randomized, open-label, single-dose, 2-sequence, 2-treatment, 4-period replicated crossover study was performed. A replicated crossover design was applied owing to the highly variable characteristics of atorvastatin and omega-3 fatty acids.^{15,16} Subjects were randomly assigned to one of the 2 sequences (Figure 1) and received FDC soft capsules of atorvastatin/omega-3-acid ethyl esters (10/1000 mg × 4) or a loose combination of atorvastatin tablets (Lipitor, Pfizer Ltd., 10 mg × 4) and omega-3-acid ethyl ester soft capsules (Omacor, Kuhnlel Pharmaceutical, Co. Ltd., 1000 mg × 4) with a high-fat meal (≥900 kcal and ≥35% lipid content) in each period. The study dose was selected to evaluate the pharmacokinetics of atorvastatin and omega-3 fatty acids at the highest approved dosage. Wash-out between periods was 7 days, which was longer than 5 times the previously reported half-lives of atorvastatin and omega-3 fatty acids.^{16,17} PK blood samples for atorvastatin were collected at 0 (predose) and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, and 48 h postdose in each period. To adjust the baseline for the endogenous compounds of EPA and DHA, serial predose blood samples were also collected. PK blood samples for EPA were collected at -15, -14, -13, -12, -11, 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, 72, and 96 h postdose in each period. PK blood samples for DHA were collected at -15, -14, -13, -12, -11, 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12

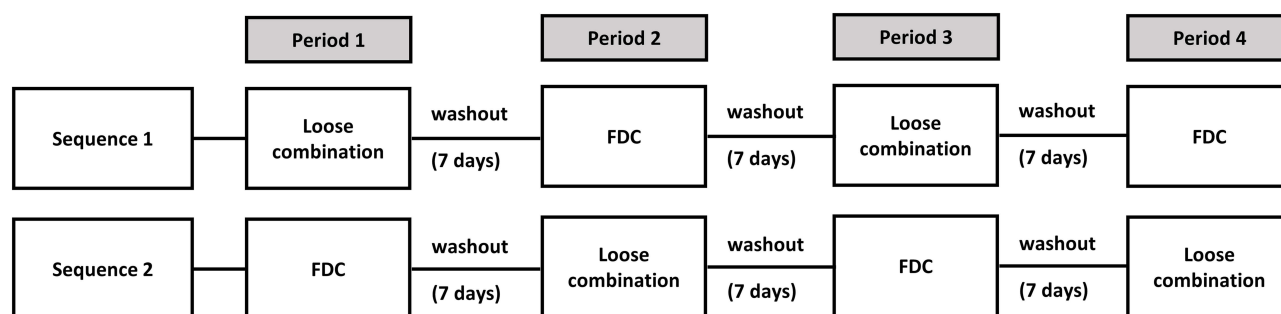


Figure 1 Summary of the study design.

Notes: Loose combination: atorvastatin tablet (10 mg × 4) and omega-3-acid ethyl esters soft capsule (1000 mg × 4). FDC: atorvastatin/omega-3-acid ethyl esters soft capsule (10/1000 mg × 4).

Abbreviation: FDC, fixed-dose combination.

h postdose in each period. The blood samples were centrifuged at 1912 g for 10 minutes and stored at -70°C until bioanalysis. To minimize the confounding effect of omega-3 fatty acids from food intake, study participants were hospitalized during the entire study period, and meals provided during the study were prepared without fish and consisted of a standard diet with restricted EPA and DHA content.

Determination of Plasma Concentration

The plasma concentration of atorvastatin was measured by ultra-performance liquid chromatography (ACQUITY UPLC I-CLASS System; Waters, Milford, MA, USA) coupled with tandem mass spectrometry (Xevo TQ-XS triple quadrupole MS/MS system; Waters, Milford, MA, USA). The samples were separated under an ACQUITY UPLC BEH C18, 1.7 μm column (2.1 mm \times 50 mm) (Waters, Milford, MA, USA). Atorvastatin-d5 was used as an internal standard (IS). The mobile phase was 10 mM ammonium formate (0.1% formic acid): acetonitrile 45:55 (v/v), with a flow rate of 0.35 mL/min. For the quality control samples, the accuracy was 98.7–100.3%, and the precision was $\leq 2.7\%$.

Plasma concentrations of EPA and DHA were measured by ultra-performance liquid chromatography (ACQUITY UPLC I-CLASS System; Waters, Milford, MA, USA) coupled with tandem mass spectrometry (Xevo TQ-XS triple quadrupole MS/MS system; Waters, Milford, MA, USA). The samples were separated under a Kinetex C18 100A 1.7 μm column (2.1 mm \times 50 mm) (Phenomenex, Torrance, CA, USA). The mobile phase was 5 mM ammonium formate (0.2% formic acid): acetonitrile 30:70 (v/v) and had a flow rate of 0.4 mL/min. For the quality control samples of EPA and DHA, the accuracy was 100.1–104.0% and 100.2–102.1%, respectively, and the precision was $\leq 4.1\%$ and $\leq 4.5\%$, respectively.

PK Assessment

The PKs were evaluated on subjects who had completed all the study procedures with no major protocol deviation. PK parameters were calculated by a non-compartmental analysis using Phoenix WinNonlin software (Version 8.2 Certara, NJ, USA). As EPA and DHA are endogenous compounds, baseline-adjusted plasma concentration was used for the calculation of the pharmacokinetic parameters of EPA and DHA. The average blood concentrations at -15 , -14 , -13 , -12 , -11 , and 0 h for each period were used to adjust the baseline EPA and DHA levels. If the baseline adjusted concentration value was negative, the value was replaced with 0 when calculating the PK parameters of EPA and DHA. For concentrations of atorvastatin, concentrations below the quantification limit were considered as 0, while concentrations after T_{max} were regarded as missing data. The area under the time-concentration curve (AUC) from zero to the last measurable point (AUC_{last}) was calculated using the linear-up/log-down trapezoidal method. The AUC from 0 to infinity (AUC_{inf}) was calculated as $\text{AUC}_{\text{last}} + C_{\text{last}}/\lambda_z$, where C_{last} is the last measurable concentration and λ_z is the terminal elimination rate constant estimated from linear regression of the terminal phase of the log-linear plot of the plasma concentration-time curve. The maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were obtained from the observed concentration data. Apparent clearance (CL/F) was calculated as $\text{dose}/\text{AUC}_{\text{inf}}$, and apparent volume of distribution (V_z/F) was calculated as $\text{CL}/F/\lambda_z$. The terminal elimination half-life ($t_{1/2}$) was calculated as $\ln(2)/\lambda_z$. The intra-subject coefficient of variation (CV, %) was calculated as $100 \times \sqrt{(e^{\text{SWR}^2} - 1)}$, where SWR is the within-subject standard deviation of the log transformed parameters.

Safety and Tolerability Assessment

Safety and tolerability were assessed in subjects who had taken the study drug at least once. All adverse events (AEs) that occurred during this study were recorded, and the severity and relationship of the AEs with the study drug were evaluated. Monitoring of vital signs, physical examination, 12-lead ECG, and clinical laboratory tests were also performed.

Statistical Analysis

SAS software (Version 9.3, SAS Institute Inc., Cary, NC, USA) was used for the statistical analysis. The geometric mean ratio (GMR) and its 90% confidence interval (CI) of the FDC to the loose combination were calculated to compare the PK parameters C_{max} and AUC_{last} . The sum of C_{max} and AUC_{last} after the first and second administration of the FDC and the loose combination were used for the calculation of the GMR and its 90% CI. Analysis of variance (ANOVA) was conducted using a linear mixed model with log transformed AUC_{last} and C_{max} as dependent variables, sequence, period,

and treatment as fixed effects and subjects nested within a sequence as a random effect. The GMRs and their 90% CIs were compared with the conventional bioequivalence range (0.8–1.25). The reported maximum intra-subject CVs (%) of AUC_{last} and C_{max} of omega-3-acid ethyl esters were 43.1%.¹⁶ When assuming there would be no pharmacokinetic difference between the FDC and the loose combination, the minimum number of subjects required to demonstrate the bioequivalence between the FDC and the loose combination with 80% statistical power at a 5% significance level was 30 subjects. Considering a dropout rate of 30%, a total sample size of 44 subjects was determined.

Results

Demographics

A total of 44 subjects were randomized, and 43 subjects completed the study as planned. One subject withdrew consent before the first study drug administration. All subjects were males, and the mean \pm SD values for age, height, body weight, and body mass index (BMI) were 30.53 ± 6.42 years, 172.12 ± 5.65 cm, 67.90 ± 7.75 kg and 22.92 ± 2.32 kg/m², respectively. There were no statistically significant differences in age, height, body weight, BMI, alcohol consumption or smoking status between the sequences.

Pharmacokinetics

The plasma concentration-time profile and PK parameters of atorvastatin, EPA and DHA were comparable between the FDC and loose combination (Figures 2–4, Tables 1–3). The 90% CIs of the GMRs of the FDC to the loose combination for C_{max} and AUC_{last} of atorvastatin, EPA, and DHA were all within the accepted bioequivalence range of 0.8–1.25 (Table 3). The baseline EPA and DHA levels were stable. The intra-subject CVs (%) for C_{max} and AUC_{last} of DHA were 30.8% and 37.5%, respectively, showing high variability. The corresponding values for EPA were 24.0% and 25.6%, respectively, and 27.5% and 10.4% for atorvastatin, respectively.

Safety and Tolerability

A total of 19 treatment emergent adverse events (TEAEs) occurred in 10 (23.3%) subjects (Table 4). Thirteen TEAEs occurred in 6 subjects (14%) after administration of the FDC, and 6 TEAEs occurred in 5 subjects (11.6%) after administration of the loose combination. Among the 19 TEAEs, 15 TEAEs in 8 (18.6%) subjects were considered to be related to the study drug and classified as ADRs. Chapped lips, oral macule, limb mass, and neck pain were TEAEs considered unrelated to the study drug. All TEAEs were resolved without sequelae and were mild in severity, except for 1 moderate migraine. The frequency of TEAEs for both the FDC and the corresponding loose combination was also comparable. No serious adverse events were reported during the study. No clinically significant abnormalities or changes from baseline were observed in the vital signs, physical examination, 12-lead ECG, or clinical laboratory tests. Both the FDC and the loose combination were safe and well tolerated.

Discussion

This study aimed to compare the pharmacokinetic characteristics and safety of atorvastatin and omega-3-acid ethyl esters (EPA and DHA) between the FDC formulation (atorvastatin/omega-3-acid ethyl esters 10/1000 mg \times 4) and the corresponding loose combination (atorvastatin tablet 10 mg \times 4 and omega-3-acid ethyl esters soft capsule 1000 mg \times 4) in healthy subjects. The GMR and its 90% CI of the FDC to loose combination for C_{max} and AUC_{last} of atorvastatin, EPA, and DHA were all within the bioequivalence range of 0.8–1.25, demonstrating comparable PK profiles between the FDC and loose combination. Both the FDC and the loose combination were safe and well tolerated. The multilayer barrier coating technology developed by Korean United Pharm. Inc. was applied and enabled both the omega-3 and atorvastatin substances to remain intact within the FDC. Therefore, the clinical impact of the formulation on the PK and safety profiles of the FDC would likely be minimal. This multilayer barrier coating technology could be further applied to the development of FDCs of other drug substances.

Generally, a 3-period partial replicated crossover design (RRT – RTR – TRR) or a 4-period replicated crossover design (RTRT – TRTR) is recommended in bioequivalence studies of highly variable drugs.¹⁸ The replicated crossover

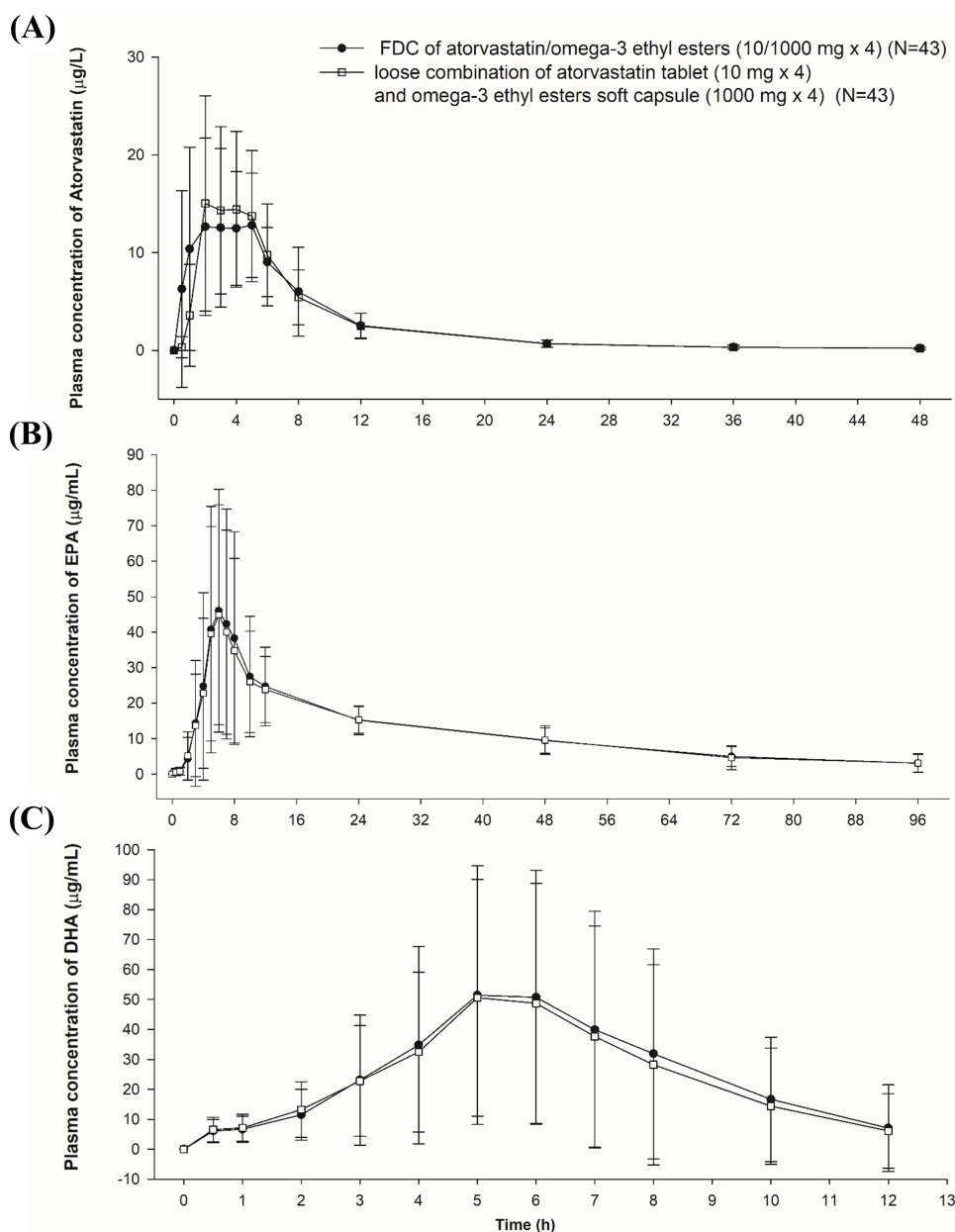


Figure 2 Mean plasma concentration-time profiles of (A) atorvastatin, baseline adjusted (B) EPA, and (C) DHA in linear scale following administration of FDC of atorvastatin/omega-3-acid ethyl esters (10/1000 mg × 4) or loose combination of atorvastatin tablet (10 mg × 4) and omega-3-acid ethyl esters soft capsule (1000 mg × 4). **Abbreviations:** DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FDC, fixed-dose combination.

study design has the advantage of reducing the sample size compared to the conventional crossover design. For instance, 62 subjects were needed to obtain a similar power for the conventional 2×2 crossover study design with the intra-subject CV (%) of the C_{max} for omega-3-acid ethyl esters (43.1%).¹⁶ Considering these highly variable characteristics of the active compounds, a 2×2×4 replicate crossover design was applied to evaluate the bioequivalence between the FDC formulation of atorvastatin and omega-3-acid ethyl esters and the corresponding loose combination. The 4-way replicated crossover design was successfully applied in this study with a relatively small sample size compared to the sample size required for the 2-way crossover design (44 vs 62 subjects, respectively). The reduction in sample size contributed to the efficient recruitment of participants. As the overall study time of replicated crossover design is longer than the conventional 2-way crossover design, it may lead to a higher dropout rate of subjects. Those designs' pros and cons must be thoroughly considered before the initiation of comparative pharmacokinetic studies.

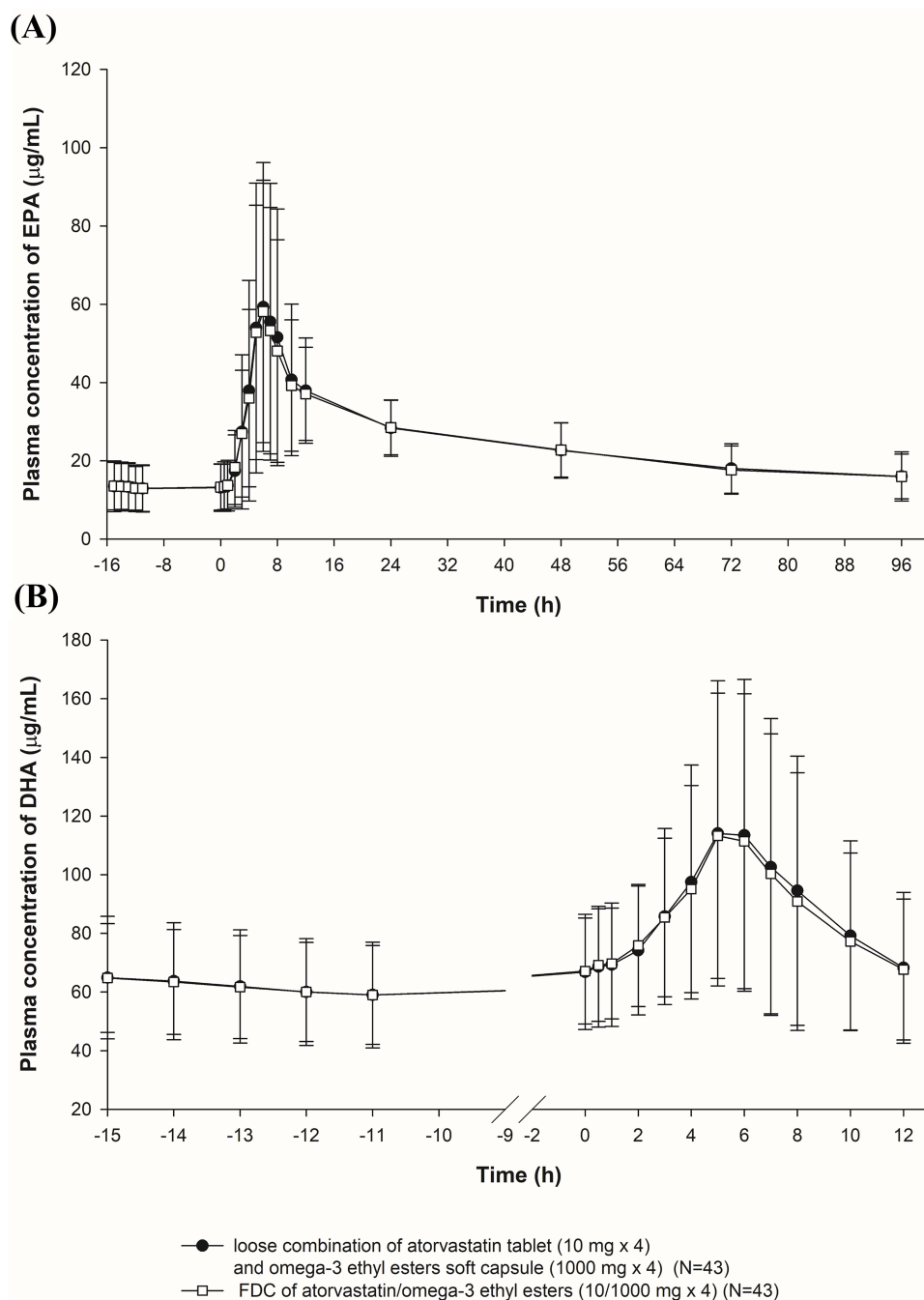


Figure 3 Mean plasma concentration-time profiles of **(A)** EPA and **(B)** DHA on a linear scale following administration of FDCs of atorvastatin/omega-3-acid ethyl esters (10/1000 mg \times 4) or a loose combination of atorvastatin tablet (10 mg \times 4) and omega-3-acid ethyl ester soft capsule (1000 mg \times 4).

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FDC, fixed-dose combination.

In this clinical study, the intra-subject CVs (%) for C_{\max} and AUC_{last} of DHA were 30.8% and 37.5%, respectively, showing high variability. The intra-subject CVs (%) for the C_{\max} of atorvastatin and the C_{\max} and AUC_{last} of EPA were approximately 25%, showing a variability close to 30%. According to the MFDS and European Medicines Association, the reference scaled bioequivalence approach can be used in the bioequivalence assessment of highly variable drugs. If the observed reference within-subject standard deviation of the C_{\max} of DHA were applied, the bioequivalence acceptance range of the C_{\max} of DHA could have been scaled to 0.7956–1.2570. However, as the GMRs and 90% CIs

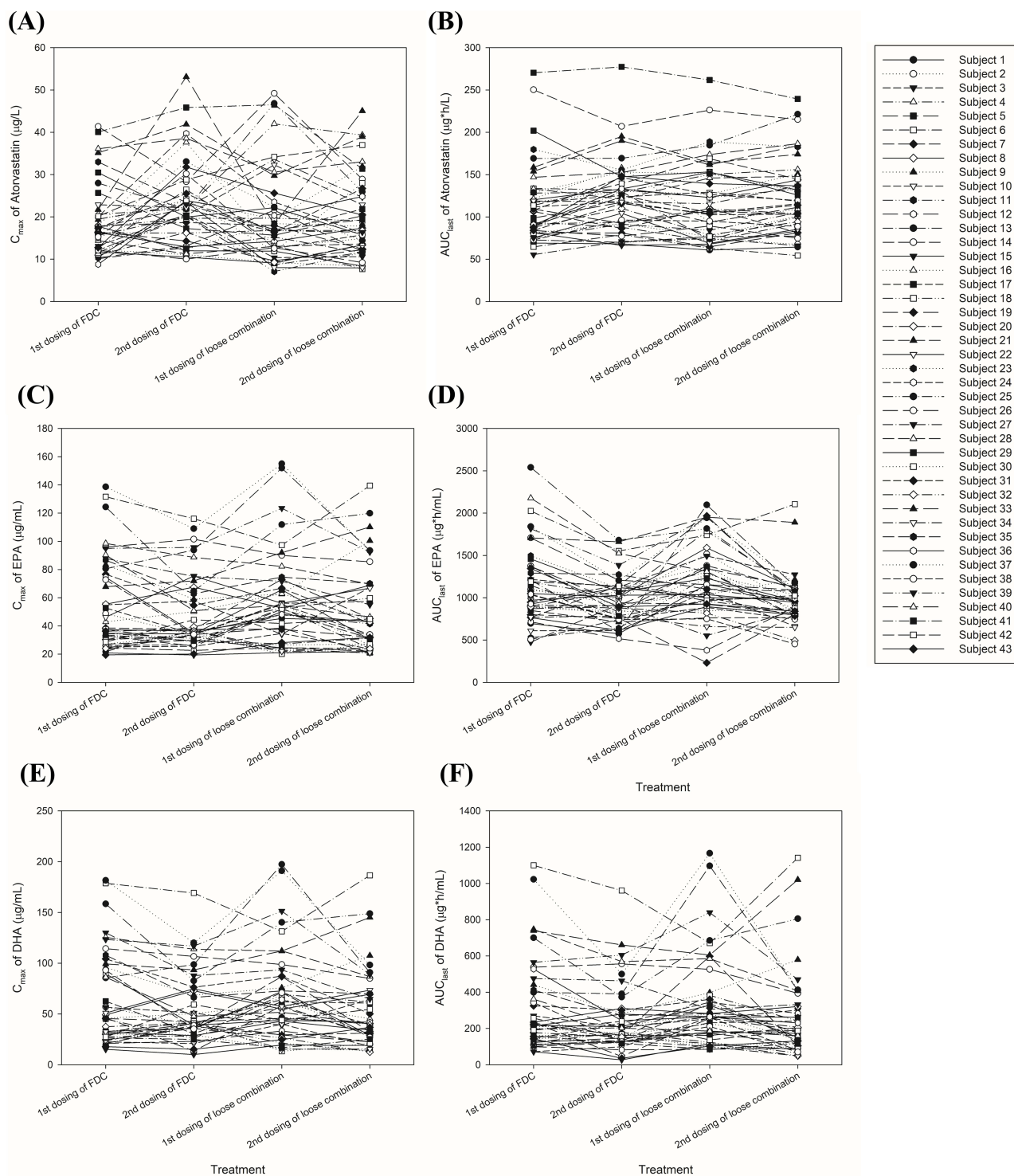


Figure 4 Individual (A) C_{max} and (B) AUC_{last} of atorvastatin, baseline adjusted (C) C_{max} and (D) AUC_{last} of EPA, baseline adjusted (E) C_{max} and (F) AUC_{last} of DHA following administration of FDC of atorvastatin/omega-3-acid ethyl esters (10/1000 mg \times 4) or loose combination of atorvastatin tablet (10 mg \times 4) and omega-3-acid ethyl esters soft capsule (1000 mg \times 4).

Note: Symbols represent each subject.

Abbreviations: AUC_{last} , area under the plasma concentration-time curve from time zero to the last observed time point; C_{max} , maximum plasma concentration; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FDC, fixed-dose combination.

Table 1 Summary of Pharmacokinetic Parameters of Atorvastatin Following Administration of FDC of Atorvastatin/Omega-3-Acid Ethyl Esters (10/1000 mg × 4) or Loose Combination of Atorvastatin Tablet (10 mg × 4) and Omega-3-Acid Ethyl Esters Soft Capsule (1000 mg × 4)

Parameter	FDC (N=43)		Loose Combination (N=43)	
	1st Dosing	2nd Dosing	1st Dosing	2nd Dosing
T_{max} (h)	3.00 [1.00–6.00]	3.00 [1.00–8.00]	2.00 [0.50–5.02]	3.00 [0.50–8.00]
C_{max} (µg/L)	18.85 ± 8.24	23.25 ± 10.07	20.04 ± 11.00	19.72 ± 9.54
AUC_{last} (µg h/L)	113.86 ± 46.21	123.32 ± 42.95	118.89 ± 46.12	122.25 ± 43.94
AUC_{inf} (µg h/L)	116.62 ± 47.32	126.72 ± 43.76	121.6 ± 46.88	125.12 ± 45.08
t_{1/2} (h)	9.26 ± 2.88	10.64 ± 3.40	8.85 ± 2.80	9.56 ± 2.97
CL/F (L/h)	387.62 ± 124.34	351.40 ± 115.40	375.63 ± 133.43	360.36 ± 125.65
V_Z/F (L)	5023.1 ± 1773.04	5269.35 ± 2073.25	4686.46 ± 1980.27	4880.78 ± 2349.28

Notes: Data are presented as the arithmetic mean ± standard deviation except for T_{max}, for which the median [minimum - maximum] is presented.

Abbreviations: AUC_{last}, area under the plasma concentration-time curve (AUC) from time zero to the last observed time point; AUC_{inf}, AUC from time zero to infinity; C_{max}, maximum plasma concentration; CI, confidence interval; CL/F, apparent clearance; FDC, fixed-dose combination; t_{1/2}, terminal elimination half-life; T_{max}, time to reach maximum plasma concentration; V_Z/F, apparent volume of distribution.

Table 2 Summary of Pharmacokinetic Parameters of Baseline Adjusted EPA and DHA Following Administration of FDC of Atorvastatin/Omega-3-Acid Ethyl Esters (10/1000 mg × 4) or Loose Combination of Atorvastatin Tablet (10 mg × 4) and Omega-3-Acid Ethyl Esters Soft Capsule (1000 mg × 4)

Parameter	FDC (N=43)		Loose Combination (N=43)	
	1st Dosing	2nd Dosing	1st Dosing	2nd Dosing
EPA				
T_{max} (h)	6.00 [4.07–23.98]	6.00 [4.00–12.00]	6.02 [4.00–12.05]	7.00 [4.00–12.05]
C_{max} (µg/L)	54.74 ± 32.50	49.32 ± 25.87	57.82 ± 32.73	51.31 ± 30.40
AUC_{last} (µg h/L)	1141.77 ± 458.99	979.88 ± 287.31	1198.05 ± 442.61	974.11 ± 291.35
AUC_{inf} (µg h/L)	1399.77 ± 743.54	1078.2 ± 321.53	1446.24 ± 640.13	1117.20 ± 517.46
t_{1/2} (h)	31.79 ± 14.95	24.43 ± 8.42	31.63 ± 18.83	28.03 ± 22.87
CL/F (L/h)	1602.09 ± 673.21	1857.98 ± 558.14	1626.77 ± 1111.44	1823.34 ± 504.41
V_Z/F (L)	63,122.62 ± 17,515.87	63,215.07 ± 23,547.44	59,134.7 ± 24,159.46	66,156.51 ± 21,699.08
DHA				
T_{max} (h)	6.00 [2.00–10.10]	5.00 [3.00–10.00]	5.02 [4.00–12.00]	6.00 [3.00–12.05]
C_{max} (µg/L)	63.65 ± 45.67	54.74 ± 34.37	66.04 ± 44.45	53.92 ± 39.10
AUC_{last} (µg h/L)	311.67 ± 245.97	253.90 ± 190.21	331.56 ± 255.50	263.98 ± 238.18
AUC_{inf} (µg h/L)	413.38 ± 469.35	320.26 ± 257.06	399.5 ± 269.55	313.16 ± 270.96
t_{1/2} (h)	2.06 ± 2.68	2.12 ± 1.68	1.92 ± 1.21	1.99 ± 1.61
CL/F (L/h)	6437.29 ± 4185.55	7171.00 ± 5329.73	5422.46 ± 3297.18	7850.59 ± 5299.01
V_Z/F (L)	14,999.4 ± 11,257.07	18,993.63 ± 13,933.13	15,191.96 ± 14,225.62	22,115.06 ± 24,385.73

Notes: Data are presented as the arithmetic mean ± standard deviation except for T_{max}, for which the median [minimum - maximum] is presented.

Abbreviations: AUC_{last}, area under the plasma concentration-time curve (AUC) from time zero to the last observed time point; AUC_{inf}, AUC from time zero to infinity; C_{max}, maximum plasma concentration; CI, confidence interval; CL/F, apparent clearance; DHA, docosahexaenoic acid; t_{1/2}, terminal elimination half-life; EPA, eicosapentaenoic acid; FDC, fixed-dose combination; T_{max}, time to reach maximum plasma concentration; V_Z/F, apparent volume of distribution.

of the C_{max} of DHA were within the conventional bioequivalence acceptance range (0.8–1.25), the scaled bioequivalence approach was not used.

Absorption of omega-3-acid ethyl esters requires stimulation of pancreatic lipase by a high-fat meal.¹⁹ In a randomized, open-label study to compare the pharmacokinetics of two different omega-3 fatty acid formulations, the bioavailability of both formulations (omega-3 carboxylic acids and ethyl esters) dramatically increased when they were consumed with a high-fat meal.¹¹ To fully compare the pharmacokinetic characteristics of the FDC and

Table 3 Geometric Mean Ratio (90% CI) of FDC to Loose Combination for Atorvastatin, EPA, and DHA

Parameter	FDC [†] (N=43)	Loose Combination [†] (N=43)	Geometric Mean Ratio* (90% CI)	Intra-Subject CV [‡] (%)
Atorvastatin				
C _{max} (µg/L)	19.23	17.60	1.0931 (1.0054–1.1883)	27.5
AUC _{last} (µg h/L)	111.45	112.74	0.9885 (0.9588–1.0192)	10.4
EPA				
C _{max} (µg/L)	45.04	46.88	0.9607 (0.9068–1.0178)	24.0
AUC _{last} (µg h/L)	996.23	1019.72	0.9770 (0.9239–1.0331)	25.6
DHA				
C _{max} (µg/L)	47.60	47.79	0.9961 (0.9127–1.0871)	30.8
AUC _{last} (µg h/L)	218.33	226.62	0.9634 (0.8830–1.0512)	37.5

Notes: Data are presented as the geometric mean. [†]The pharmacokinetic parameters are the sum of PK data collected after the first and second administration of FDC or loose combination. *Geometric mean ratio of FDC to loose combination was calculated from the sum of parameters after the 1st and 2nd administrations of the FDC or the loose combination. [‡]Intra-subject CV of the loose combination.

Abbreviations: AUC_{last}, area under the plasma concentration-time curve from time zero to the last observed time point; C_{max}, maximum plasma concentration; CI, confidence interval; CV, coefficient of variation; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FDC, fixed-dose combination.

Table 4 Summary of the Treatment-Emergent Adverse Events (TEAEs) Following Administration of FDC of Atorvastatin/Omega-3-Acid Ethyl Esters (10/1000 mg × 4) or Loose Combination of Atorvastatin Tablet (10 mg × 4) and Omega-3-Acid Ethyl Esters Soft Capsule (1000 mg × 4)

System Organ Class (SOC) / Preferred Term (PT)	FDC [†] (N=43)	Loose Combination [†] (N=43)	All Subjects (N=43)
Treatment-emergent adverse events	6 (14.0) [13]	5 (11.6) [6]	10 (23.3) [19]
Eye disorders		1 (2.3) [1]	1 (2.3) [1]
Ocular hyperemia		1 (2.3) [1]	1 (2.3) [1]
Gastrointestinal disorders	3 (7.0) [6]	4 (9.3) [4]	7 (16.3) [10]
Abdominal pain	1 (2.3) [1]		1 (2.3) [1]
Chapped lips		1 (2.3) [1]	1 (2.3) [1]
Diarrhea	2 (4.7) [3]	2 (4.7) [2]	4 (9.3) [5]
Faeces discoloured	1 (2.3) [1]		1 (2.3) [1]
Oral macule		1 (2.3) [1]	1 (2.3) [1]
Stomatitis	1 (2.3) [1]		1 (2.3) [1]
Musculoskeletal and connective tissue disorders	1 (2.3) [1]	1 (2.3) [1]	2 (4.7) [2]
Limb mass	1 (2.3) [1]		1 (2.3) [1]
Neck pain		1 (2.3) [1]	1 (2.3) [1]
Nervous system disorders	2 (4.7) [3]		2 (4.7) [3]
Dizziness	1 (2.3) [1]		1 (2.3) [1]
Headache	1 (2.3) [1]		1 (2.3) [1]
Migraine	1 (2.3) [1]		1 (2.3) [1]
Respiratory, thoracic and mediastinal disorders	2 (4.7) [2]		2 (4.7) [2]
Oropharyngeal pain	1 (2.3) [1]		1 (2.3) [1]
Rhinorrhoea	1 (2.3) [1]		1 (2.3) [1]
Skin and subcutaneous tissue disorders	1 (2.3) [1]		1 (2.3) [1]
Rash	1 (2.3) [1]		1 (2.3) [1]

Notes: Data are displayed as the number of subjects (percentage of subjects) [number of events]. [†]The sum of TEAEs that occurred after the first and second administration of the FDC or loose combination.

Abbreviation: FDC, fixed-dose combination.

loose combination, a high-fat meal (≥ 900 kcal and $\geq 35\%$ lipid content) was given before administration of the study drug. In addition, omega-3 fatty acid consumption from food was controlled by excluding fish-containing meals during the study period.

According to FDA draft guidance on omega-3-acid ethyl esters, baseline measurement should be calculated from an average of three or more samples collected between 24 and 0 hours (inclusive) prior to dosing.²⁰ In this study, six PK blood samples for baseline adjustment were collected at -15, -14, -13, -12, -11, and 0 h predose. Although it was reported that there is a circadian variation in lipid metabolism due to high tissue uptake of fatty acids during sleep,²¹ the extent of oscillation was not substantial. Additionally, compared to previous PK studies of omega-3 fatty acids,^{16,22,23} we intensively assessed baseline PK samples, and the baseline fluctuation observed from this study was marginal.

Given that this study was conducted among healthy Korean male participants, potential variations in the PK of endogenous DHA and EPA based on gender, ethnicity, and renal or hepatic impairment remain plausible. However, we suggest that these differences are minimized due to the implementation of the extensive baseline adjustments. Furthermore, considering the study's findings demonstrating comparable PK and safety between the FDC and the loose combination, these outcomes are anticipated to remain consistent across diverse patient populations.

DHA is an endogenous compound. In the administration of omega-3 fatty acids, findings from a prior clinical trial and published data showed a reduction in plasma DHA concentration for 12 hours after peak levels, followed by a subsequent increase.^{24,25} An isotope analysis study after EPA supplementation in humans demonstrated a substantial conversion of EPA to DHA, without retroconversion of DHA to EPA.²⁶ In addition, an animal study to investigate the plasma and brain synthesis pathways of DHA also proposed that free plasma EPA entering the liver is desaturated to DHA and secreted into the plasma.²⁷ The plasma DHA level observed after 12 hours is likely to be the concentration of DHA synthesized from EPA rather than the concentration administered as a study drug. Therefore, we planned to collect blood samples for DHA until 12 hours postdose to observe the exact elimination phase.

Conclusion

The FDC of atorvastatin and omega-3-acid ethyl esters showed comparable PK characteristics to the corresponding loose combination, offering a convenient therapeutic option for the treatment of combined hyperlipidemia.

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

Won-Ho Kang, Youn Woong Choi, Dae Chul Ha, RaeHoon Jung, Min-Gu Han, Won Tae Jung, Kyu-Yeol Nam, and YeSeul Kim are employees of Korea United Pharm. Inc. Hye Jung Lee, Kyu Yeon Kim, Ki-Sun Jeong, and Chongho Won are employees of Caleb Multilab, Inc. The other authors do not have any conflicts of interest for this study.

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