ORIGINAL RESEARCH ARTICLE

Cardiovascular Therapeutics

Effect of TAK-085 on Low-density Lipoprotein Particle Size in Patients with Hypertriglyceridemia: A Double-blind Randomized Clinical Study

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SUMMARY

Background: Low-density lipoproteins (LDLs) comprise a heterogeneous group of particles with various size and density. A shift to larger LDL particle size is mainly the result of a decrease in small dense LDL (sd-LDL) levels and an increase in large buoyant LDL (lb-LDL) levels. **Methods:** In a randomized, double-blind study of TAK-085 (containing docosahexaenoic and eicosapentaenoic acid-ethyl esters [EPA-E]) and an EPA-E product in Japanese patients with hypertriglyceridemia, exploratory evaluations of the effects of the LDL particle size were performed on the basis of LDL-cholesterol/apolipoprotein B ratios and LDL subfractions, which were analyzed with a polyacrylamide gel electrophoresis system. **Results:** Patients were randomized to 12-week treatment with TAK-085 4 g/day (N = 210), TAK-085 2 g/day (N = 205), or EPA-E 1.8 g/day (N = 195). Treatment with TAK-085 4 g/day, TAK-085 2 g/day, and EPA-E 1.8 g/day caused an increase in the LDL cholesterol/apolipoprotein B ratios (3.99%, 3.35%, and 0.66%, respectively), the mean diameter of LDL particles (1.12%, 0.84%, and 0.67%, respectively), and the level of lb-LDL at the end of the study (16.37%, 9.51%, and 7.31%, respectively). The increases in the LDL cholesterol/apolipoprotein B ratios and the mean diameter of LDL particles from baseline to the end of the study were greater with TAK-085 4 g/day than EPA-E 1.8 g/day. TAK-085 4 g/day and TAK-085 2 g/day caused a decrease in the sd-LDL levels (−16.21% and −6.96%, respectively). **Conclusion:** TAK-085 produced a favorable shift in the LDL particle size in Japanese patients with hypertriglyceridemia. JAPIC Clinical Trials Information: Japic CTI-090937.

Introduction

Hypertriglyceridemia is an independent risk factor for cardiovascular diseases, and a number of large cohort studies/meta-analyses have confirmed that fasting triglyceride (TG) levels are associated with increased rates of coronary heart diseases [1–3]. Increased levels of TG are often associated with, and may contribute to, the presence of highly atherogenic small dense low-density lipoprotein (sd-LDL) particles that are associated with an increased risk of cardiovascular diseases [4]. The US National Cholesterol Education Program Adult Treatment Panel III recognizes that sd-LDL is a risk factor contributing to atherogenic development [5]. Therefore, reducing the sd-LDL levels with a shift toward large buoyant LDL (lb-LDL) is often described as a less atherogenic state and might balance the increased risk due to a rise in total LDL cholesterol (LDL-C).

Omega-3 polyunsaturated fatty acids (n-3 PUFAs), which have been shown to reduce TG concentrations, are widely utilized for the treatment of hypertriglyceridemia [6,7]. TAK-085 is an oral capsule containing highly concentrated n-3 PUFAs, mainly eicosapentaenoic acid-ethyl ester (EPA-E) and docosahexaenoic acid-ethyl ester (DHA-E). We investigated the TG-lowering effects of TAK-085 in comparison with an EPA-E product in Japanese patients with hypertriglyceridemia and reported that TAK-085 4 g/day caused greater reductions in the levels of TG than EPA-E 1.8 g/day, and TAK-085 2 g/day had similar effects on TG as EPA-E 1.8 g/day [8]. In addition to evaluating TG as the primary endpoint, we measured the various lipid parameters, apolipoproteins, such as apolipoprotein (Apo) B and LDL subfractions with a quantitative linear polyacrylamide gel electrophoresis system in this study. Each LDL particle has one Apo B molecule, which is recognized by the LDL receptors that remove LDL from the plasma. The Apo B concentration indicates the number of LDL particles in the plasma [9]. Thus, the LDL-C/Apo B ratios reflect the LDL particle size [10]. A quantitative linear polyacrylamide gel electrophoresis system is used to measure LDL subfractions and

the diameter of LDL particles directly; however, these methods are difficult to apply in clinical settings due to their high cost and complex procedures.

Understanding the effect of TAK-085 on the LDL particle size in patients with hypertriglyceridemia may help to determine the optimal treatment in Japanese patients with hypertriglyceridemia.Therefore, we evaluated the effects of treatment with TAK-085 and an EPA-E product on LDL particle size using LDL-C/Apo B ratios and LDL subfractions in Japanese patients with hypertriglyceridemia.

Materials and Method

Study Population

The full details of the study design, patients, primary endpoints, and statistical analyses have been described previously [8]. All patients provided written informed consent before entry into the study. Japanese men and women, who were outpatients, aged ≥20 to <75 years and had hypertriglyceridemia defined as a fasting TG of ≥150 mg/dL according to the current Japan Atherosclerosis Society guideline [11], and were undergoing lifestyle modification, were enrolled. Patients with unstable TG during the screening period were excluded from the study. Patients were allowed to continue receiving statin treatment, but changes in dosage were not permitted except for the management of adverse events. All other lipid-lowering drugs were prohibited in this study.

Study Design

The study was performed in accordance with the ethical principles set out in the Declaration of Helsinki and the ICH Harmonised Tripartite Guideline for Good Clinical Practice and was approved by the appropriate Institutional Review Boards on the basis of local regulations.

The design of this study was a multicenter, randomized, clinical study comprising an 8-week screening period followed by a 12-week double-blind parallel group comparison of n-3 PUFAs 2 g once (TAK-085 2 g/day) or twice daily (TAK-085 4 g/day), and EPA-E 0.6 g three times daily (EPA-E 1.8 g/day). Each 1-g capsule of TAK-085 (Pronova BioPharma/BASF, Oslo, Norway, and Takeda, Osaka, Japan) contained approximately 465 mg EPA-E and 375 mg DHA-E. TAK-085 is now available as a prescription medicine in Japan for the treatment of hyperlipidemia.

Patients fulfilling the entry criteria were randomly assigned to treatment with TAK-085 4 g/day, TAK-085 2 g/day, or EPA-E 1.8 g/day at Week 0. Randomization was stratified according to the use of statins. Clinic visits were scheduled at weeks −8, −4, −2, 0, 4, 8, 10, and 12. TG, total cholesterol (TC), LDL-C, and high-density lipoprotein cholesterol were measured at all visits. Very LDL cholesterol (VLDL-C), Apo A1, B, and C-III, lipoprotein (a), remnant-like particles cholesterol, fatty acids arachidonic acid, DHA, and EPA were measured at baseline (Week 0) and at all treatment visits. Lipoprotein subfraction measurements including lb-LDL, sd-LDL, and the mean diameter of the LDL particles were performed at baseline and at the end of the study using the commercially available Quantimetrix Lipoprint® system (Quantimetrix Corporation, Redondo Beach, CA, USA) LDL subfractions kit, which uses a linear polyacrylamide gel electrophoresis method that has previously been described [12]. LDL subfractions 1 and 2 represent lb-LDL, while subfractions 3–7 represent sd-LDL. Areas under the curve for each fraction were measured, and the fractions of lb-LDL and sd-LDL were calculated. All clinical laboratory tests were performed at a central independent laboratory (Mitsubishi Chemical Medience Corporation, Tokyo, Japan).

Statistical Analysis

Data analysis was performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA). For LDL subfraction analyses, descriptive statistics and two-sided 95% confidence intervals (CIs) of means for observed values, and corresponding absolute changes from baseline, were calculated by treatment group. SDs and 95% CIs of the differences between the TAK-085 4 g/day and 2 g/day groups and the EPA-E 1.8 g/day group were calculated.

Results

Demographic and Baseline Characteristics

Details of the three randomly assigned treatment groups have previously been described [8]. There were no clinically relevant differences in demographic or baseline characteristics such as age, gender, body mass index, concurrent diseases (e.g., diabetes mellitus or hypertension), concomitant treatment with 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, or baseline TG levels between the three groups (Table 1).

Changes in Plasma Fatty Acids

Changes from baseline in plasma fatty acids are documented in Table S1. Plasma EPA levels increased in all three treatment groups. The increases in the TAK-085 4 g/day and EPA-E 1.8 g/day groups were similar, but the increase in the TAK-085 2 g/day group was much smaller. Plasma DHA levels markedly increased in the TAK-085 groups, but decreased in the EPA-E 1.8 g/day group after 12-week treatment. These results confirmed both EPA and DHA were absorbed following the administration of the three products.

Changes in Low-Density Lipoprotein Particle Size

The summary statistics, the percent changes from baseline, and the point estimates of differences between the TAK-085 groups and the EPA-E 1.8 g/day group concerning the LDL-C/Apo B ratios and the mean diameter of LDL particles at the end of the study are shown in Table 2. Treatment with TAK-085 4 g/day, TAK-085 2 g/day, and EPA-E 1.8 g/day increased the mean LDL-C/Apo B ratios (Figure 1A) and the diameter of LDL particles (Figure 1B). The point estimates of the differences in the mean percent changes of the LDL-C/Apo B ratios at the end of the study between the TAK-085 groups and the EPA-E 1.8 g group were 3.33% [0.66, 5.99] in the TAK-085 4 g group and 2.69% [0.64, 4.74] in the TAK-085 2 g group. The upper limit of the 2-sided 95% CI was above 0, and the increases in the LDL-C/Apo B ratios

Table 1 Demographic and baseline characteristics in the TAK-085 4 g/day, TAK-085 2 g/day, and eicosapentaenoic acid-ethyl ester (EPA-E) 1.8 g/day groups

	TAK-085 4 g/day	TAK-085 2 g/day	EPA-E 1.8 g/day	Total
N	210	206	195	611
Age (years [Mean ± SD])	55.0 ± 10.5	53.9 ± 10.8	55.6 ± 10.5	54.8 ± 10.6
Gender, men	157 (74.8)	160 (77.7)	157 (80.5)	474 (77.6)
Body mass index (kg/m^2 [Mean ± SD]) at Week 0	26.3 ± 3.8	26.6 ± 3.7*	26.3 ± 3.6	26.4 ± 3.7
Hypertension, yes	127 (60.5)	123 (59.7)	131 (67.2)	381 (62.4)
Diabetes mellitus, yes	70 (33.3)	62 (30.1)	67 (34.4)	199 (32.6)
Administration of HMG-CoA reductase inhibitor, yes	89 (42.4)	89 (43.2)	83 (42.6)	261 (42.7)
TG levels at baseline (mg/dL [Mean ± SD])	277.5 ± 97.29	269.0 ± 77.52*	271.8 ± 91.53	272.8 ± 89.12

Values represent n (%), unless otherwise stated. HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; TG, triglyceride. *N = 205.

Table 2 Mean (95% confidence interval [CI]) percent changes in the low-density lipoprotein cholesterol (LDL-C)/apolipoprotein (Apo) B ratios and the mean diameter of LDL particles endpoints (end of the study vs. baseline) in patients with hypertriglyceridemia treated with TAK-085 4 g/day, TAK-085 2 g/day, or eicosapentaenoic acid-ethyl ester (EPA-E) 1.8 g/day for 12 weeks

	Variable	TAK-085 4 g/day	TAK-085 2 g/day	EPA-E 1.8 g/day
LDL-C/Apo B ratio	Baseline (Mean ± SD)	1.14 ± 0.17	1.14 ± 0.13	1.14 ± 0.17
	End of the study (Mean ± SD)	1.17 ± 0.15	1.17 ± 0.14	1.18 ± 0.17
	% change (Mean ± SD)	3.99 ± 16.53	3.35 ± 11.22	0.66 ± 9.46
	Point estimate vs. EPA-E 1.8 g [95% CI]	3.33 [0.66, 5.99]	2.69 [0.64, 4.74]	–
LDL-C (mg/dL)	Baseline (Mean ± SD)	125.7 ± 28.5	127.4 ± 29.1	130.1 ± 30.5
	End of the study (Mean ± SD)	123.6 ± 29.0	124.0 ± 31.8	123.3 ± 28.3
	% change (Mean ± SD)	−1.08 ± 16.67	−2.10 ± 14.45	−4.25 ± 13.29
	Point estimate vs. EPA-E 1.8 g [95% CI]	3.17 [0.20, 6.14]	2.14 [−0.60, 4.89]	–
Apo B (mg/dL)	Baseline (Mean ± SD)	108.5 ± 18.9	110.4 ± 18.7	110.2 ± 20.2
	End of the study (Mean ± SD)	105.2 ± 18.6	105.6 ± 20.6	104.7 ± 19.8
	% change (Mean ± SD)	−2.73 ± 12.82	−3.87 ± 11.91	−4.31 ± 13.24
	Point estimate vs. EPA-E 1.8 g [95% CI]	1.58 [−0.97, 4.14]	0.44 [−2.04, 2.92]	–
Diameter of LDL particles (angstrom)	Baseline (Mean ± SD)	260.6 ± 5.9	260.7 ± 5.2	260.8 ± 5.4
	End of the study (Mean ± SD)	263.5 ± 5.3	262.7 ± 5.5	262.5 ± 5.7
	% change (Mean ± SD)	1.12 ± 1.87	0.84 ± 1.81	0.67 ± 1.69
	Point estimate vs. EPA-E 1.8 g [95% CI]	0.45 [0.09, 0.80]	0.16 [−0.18, 0.51]	–

from baseline to the end of the study were greater in both TAK-085 groups than the EPA-E 1.8 g/day group. The point estimate of the differences in the percent changes of the mean diameters of LDL particles at the end of the study between TAK-085 4 g/day and EPA-E 1.8 g/day was 0.45% [0.09, 0.80]. The increase in the level of the mean diameters of LDL particles from baseline to the end of the study was greater in the TAK-085 4 g/day group than the EPA-E 1.8 g/day group.

Changes in Small Dense Low-Density Lipoprotein and Large Buoyant Low-Density Lipoprotein

The summary statistics, the percent changes from baseline, and the point estimates of differences between the TAK-085 groups and the EPA-E 1.8 g/day group concerning sd-LDL and lb-LDL at the end of the study are shown in Table 3. Both TAK-085 4 g/day and TAK-085 2 g/day decreased the level of sd-LDL (−16.21% and −6.96%, respectively). There was a marked increase in the level of lb-LDL with TAK-085 4 g/day, TAK-085 2 g/day, and EPA-E 1.8 g/day at the end of the study (16.37%, 9.51%, and 7.31%, respectively). The point estimate of the differences in the percent changes of lb-LDL at the end of the study between TAK-085 4 g/day and EPA-E 1.8 g/day was 9.07% [2.93, 15.20]. The increase in the level of lb-LDL from baseline to the end of the study was greater with TAK-085 4 g/day than EPA-E 1.8 g/day (Figure 2A). Concerning individual LDL subfractions, all sd-LDL subfractions from LDL-3 to LDL-6 decreased, while the lb-LDL subfractions of LDL-1 and LDL-2 both increased, in all treatment groups (Figure 2B).

Discussion

The exploratory evaluation of the effects on LDL particle size in this randomized clinical study in Japanese patients with hypertriglyceridemia demonstrated that treatment with TAK-085 and EPA-E products is associated with an increase in the LDL particle size and a less atherogenic LDL profile, which can be explained by a shift from sd-LDL to lb-LDL particles. This observation is

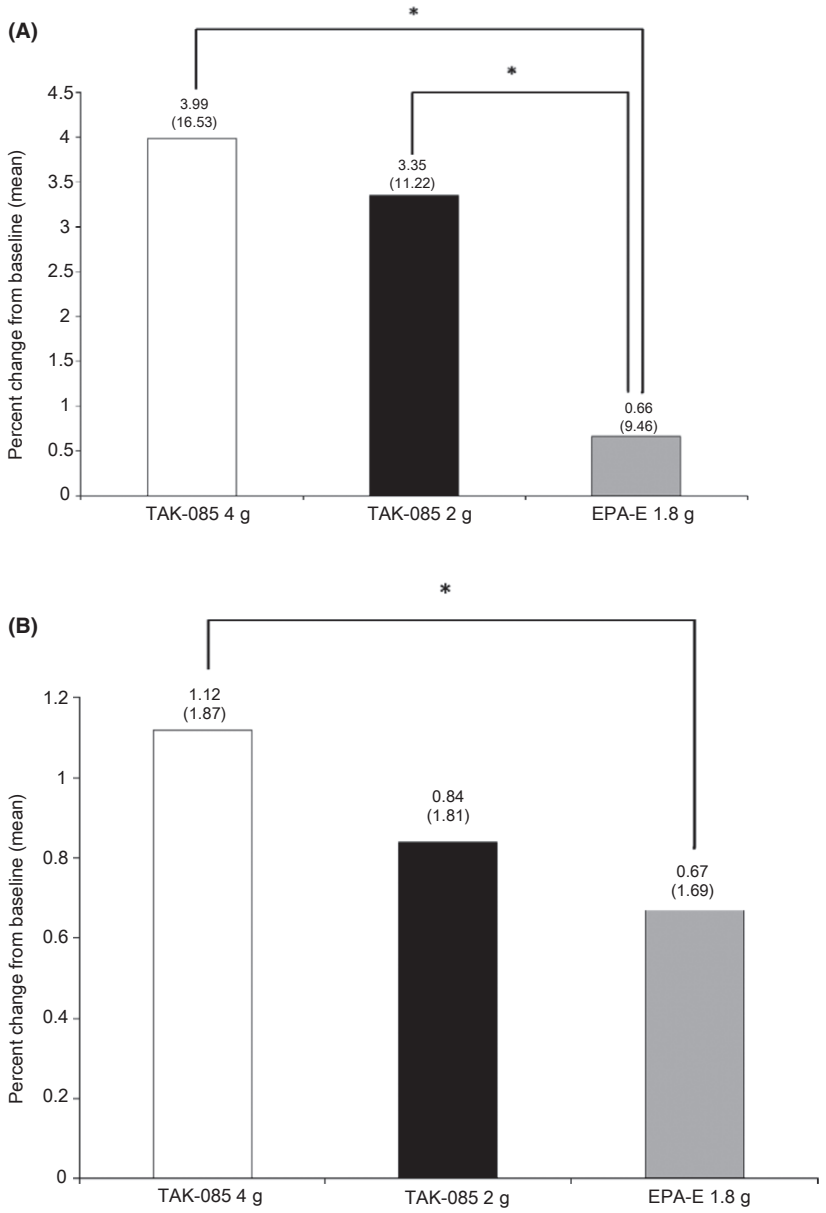

Figure 1 Mean changes in the low-density lipoprotein (LDL) particle size (end of the study vs. baseline) in patients with hypertriglyceridemia treated with TAK-085 4 g/day, TAK-085 2 g/day, or eicosapentaenoic acid-ethyl ester (EPA-E) 1.8 g/day for 12 weeks. (**A**) Percent changes in LDL-cholesterol/apolipoprotein B. (**B**) Percent changes in the mean diameter of LDL particles. Numerical values represent mean (SD). The asterisk indicates that the lower limit of the 95% confidence interval of the point estimate difference between TAK-085 vs. EPA-E was above 0.

consistent with the results of double-blind, randomized studies in patients with mixed dyslipidemia who received omega-3 fatty acids and atorvastatin [13] or simvastatin [14].

Under hypertriglyceridemic, for example, VLDL-rich conditions, sd-LDL is likely to be formed. The mechanism leading to the formation of sd-LDL under hypertriglyceridemic conditions is now well established. Two enzymes are involved in this process. Firstly, cholesteryl ester transfer protein facilitates the transfer of TGs from VLDL to LDL (and that of cholesteryl esters from LDL to VLDL) [15]. As a result of this first process, the LDL particles did not form cholesterol-rich LDL, but TG-rich LDL. Secondly, hepatic lipase increases lipolysis of TG-rich LDL resulting in the formation of sd-LDL [15]. We previously reported the results with TG as the primary endpoint in a study [8]. In all treatment groups, the TG levels were reduced at the end of the study from baseline (TAK-085 4 g/day, −22.87%; TAK-085 2 g/day, −10.78%; and EPA-E 1.8 g/day, −11.23% [Table S2]). TAK-085 4 g/day caused a markedly greater reduction in the TG levels than TAK-085 2 g/day and EPA-E 1.8 g/day. The increases in the LDL-C/Apo B ratios and the mean diameter of the LDL particles were also the largest with TAK-085 4 g/day in this exploratory evaluation. As the plasma TG levels play a central role in regulating LDL particle size,

Table 3 Mean (95% confidence interval [CI]) percent changes in the small dense low-density lipoprotein (sd-LDL) and the large buoyant LDL (lb-LDL) endpoints (end of the study vs. baseline) in patients with hypertriglyceridemia treated with TAK-085 4 g/day, TAK-085 2 g/day, or eicosapentaenoic acid-ethyl ester (EPA-E) 1.8 g/day for 12 weeks

	Variable	TAK-085 4 g/day	TAK-085 2 g/day	EPA-E 1.8 g/day
sd-LDL (mg/dL)	Baseline (Mean ± SD)	22.2 ± 14.4	23.2 ± 13.6	23.9 ± 14.7
	End of the study (Mean ± SD)	16.5 ± 12.6	18.5 ± 14.3	18.8 ± 14.1
	% change (Mean ± SD)	−16.21 ± 74.81	−6.96 ± 101.69	1.07 ± 137.49
	Point estimate vs. EPA-E 1.8 g [95% CI]	−17.28 [−39.01, 4.44]	−8.03 [−32.09, 16.04]	–
lb-LDL (mg/dL)	Baseline (Mean ± SD)	56.4 ± 19.0	58.4 ± 18.4	58.5 ± 19.0
	End of the study (Mean ± SD)	63.4 ± 20.1	61.7 ± 18.8	60.7 ± 19.2
	% change (Mean ± SD)	16.37 ± 34.13	9.51 ± 29.80	7.31 ± 27.35
	Point estimate vs. EPA-E 1.8 g [95% CI]	9.07 [2.93, 15.20]	2.21 [−3.48, 7.89]	–

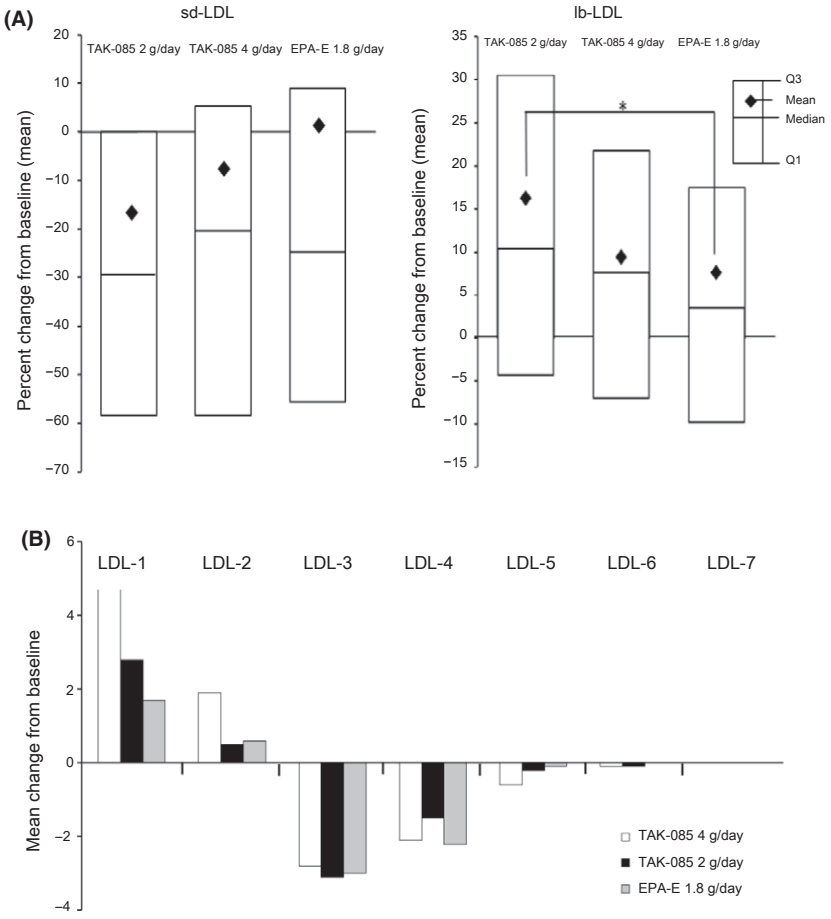

Figure 2 Mean changes in the small dense low-density lipoprotein (sd-LDL) and large buoyant LDL (lb-LDL) (end of the study vs. baseline) in patients with hypertriglyceridemia treated with TAK-085 4 g/day, TAK-085 2 g/day, or eicosapentaenoic acid-ethyl ester (EPA-E) 1.8 g/day for 12 weeks. (**A**) Percent changes in sd-LDL and lb-LDL. (**B**) Percent changes in individual LDL subfractions based on a representative electrophoresis chart. The asterisk indicates that the lower limit of the 95% confidence interval of the point estimate difference between TAK-085 vs. EPA-E was above 0.

omega-3 fatty acids such as TAK-085 and an EPA-E product are assumed to modulate the LDL particle size by lowering the plasma TG levels [16].

Omega-3 fatty acids are considered to indirectly cause an increase in the LDL particle size through their TG level-lowering effects. The reductions in the TG levels were similar in the TAK-085 2 g/day and the EPA-E 1.8 g/day group in a recent study [8]. However, we found differences in the effects of TAK-085 2 g/day and EPA-E 1.8 g/day on LDL particle size in this exploratory evaluation. The difference was found in the LDL-C/

Apo B ratio which increased more with TAK-085 2 g/day than with EPA-E 1.8 g/day. A greater effect on mean diameter of LDL particles was also observed with TAK-085 2 g/day, followed by EPA-E 1.8 g/day. Therefore, the differences in the effects on LDL particle size cannot be fully explained by a reduction in the TG levels alone.

The greater increases in the LDL-C/Apo B ratios and the mean diameter of LDL particles with TAK-085 2 g/day than EPA-E 1.8 g/day is possibly explained by the premise that TAK-085, which contains DHA-E and EPA-E, caused more cholesterol-rich LDL particles. Although LDL-C decreased in all treatment groups, the decrease was smaller in the TAK-085 groups than the EPA-E 1.8 g/day group as shown in Table 2. As it has been reported that the numbers of LDL particles are not changed by DHA-E treatment [17], it means that TAK-085 must have caused each LDL particle to become more cholesterol-rich, reflecting the increase in the LDL particle size. The difference in the effects of DHA-E and EPA-E on Apo C-III may also possibly explain our current results. Apo C-III knockout animals show more rapid conversion of VLDL to LDL particles in the circulation [18]. The increase in the LDL particle size was significantly inversely correlated with the degree of Apo C-III lowering in patients with hypertriglyceridemia due to treatment with EPA-E and DHA-E [13,19]. In the current study, we confirmed that there was a markedly greater decrease in the level of Apo C-III at the end of the study in the TAK-085 4 g/day and TAK-085 2 g/day groups than in the EPA-E 1.8 g/day group (−9.23%, −4.54%, and −2.23%, respectively [Table S2]). It is possible that TAK-085, which contains DHA-E and EPA-E, regulates different hepatic transcription factors more than an EPA-E product, which results in enhanced conversion of VLDL to LDL and the formation of lb-LDL. These findings are consistent with an earlier report that EPA and DHA have different effects on serum lipids, lipoproteins, and LDL particle size [20].

The current evaluations have some limitations. Firstly, the study was conducted in a highly selective group of Japanese patients with hypertriglyceridemia who were undergoing lifestyle modification. The findings, therefore, may not be generalizable to other ethnic groups. Secondly, the lipoprotein profile analyses that were performed were not predefined as the primary study endpoints. We also did not compare pure EPA-E and DHA-E, and thus, to clarify the differential effects of EPA-E and DHA-E on LDL subfractions, additional studies have to be conducted in the future.

Conclusion

The exploratory evaluation of effects on LDL particle size in our randomized clinical study demonstrated that TAK-085 produced a favorable shift in LDL particle size in Japanese patients with hypertriglyceridemia.

Author Contribution

All authors designed the study and contributed to the data interpretation. IT and TK drafted the manuscript, and all authors revised it critically. KK performed the statistical analysis. KK and TK conducted the data collection. All authors read and approved the final manuscript.

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This clinical study was funded by Takeda Pharmaceutical Co., Ltd. The funder was involved in study design, data collection, data analysis, manuscript preparation, and publication decisions.

Conflict of Interest

KK and TK are employees of Takeda Pharmaceutical Co., Ltd. IT has acted as a consultant to Takeda Pharmaceutical Co., Ltd.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Mean changes in plasma fatty acids in patients with hypertriglyceridemia treated with TAK-085 4 g/day, TAK-085 2 g/day, or eicosapentaenoic acid-ethyl ester (EPA-E) 1.8 g/day for 12 weeks.

Table S2. Mean percent changes in the triglyceride (TG), total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), very low density lipoprotein-cholesterol (VLDL-C), apolipoprotein (Apo) A1, Apo C-III, lipoprotein (a), and remnant-like particle-cholesterol (RLP-C) endpoints (end of the study vs. baseline) in patients with hypertriglyceridemia treated with TAK-085 4 g/day, TAK-085 2 g/day, or eicosapentaenoic acid-ethyl ester (EPA-E) 1.8 g/day for 12 weeks.