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Long-term safety and efficacy of TAK-085 in Japanese subjects with hypertriglyceridemia undergoing lifestyle modification: The omega-3 fatty acids randomized long-term (ORL) study

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TAK-085

BACKGROUND: TAK-085 is an omega-3 preparation that contains eicosapentaenoic acid ethyl-ester (EPA-E) and docosahexaenoic acid-ethyl ester used in the management of hypertriglyceridemia.

OBJECTIVE: The aim of the study was to evaluate the long-term safety (adverse events [AEs], laboratory parameters, vital signs, weight, and electrocardiograms) and effects on lipid profiles, especially triglyceride levels, of TAK-085 in Japanese patients with hypertriglyceridemia (triglyceride levels ≥150 mg/dL and <750 mg/dL).

METHODS: In this multicenter, open-label, randomized study, adults with hypertriglyceridemia undergoing lifestyle modification received TAK-085 2 g (2 g once daily; n = 165) or 4 g (2 g twice daily; n = 171), or EPA-E 1.8 g (0.6 g three times daily; n = 167) for 52 weeks. Patients were stratified for co-administration of a statin.

RESULTS: TAK-085 was well tolerated throughout the 52-week study. Overall, no substantial differences were found in the tolerability of TAK-085 2 g, TAK-085 4 g, and EPA-E 1.8 g with incidence rates for AEs of 83.6%, 86.0%, and 89.2%, respectively. Most AEs were mild or moderate in severity. Triglyceride levels decreased from baseline in all groups by week 4, and the decreases were maintained throughout the study. At week 52 the reduction in triglycerides with TAK-085 2 g (–13.9%) was similar to that with EPA-E 1.8 g (–12.1%), whereas the reduction seen with TAK-085 4 g (–25.5%) was greater than that with EPA-E 1.8 g, as assessed by point estimates and 95% confidence intervals.

CONCLUSIONS: TAK-085 was safe and well tolerated for up to 52 weeks of treatment in Japanese patients with hypertriglyceridemia undergoing lifestyle modification. Reductions in triglyceride levels achieved after 4 weeks were maintained at 52 weeks.
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An elevated triglyceride level is recognized as an independent risk factor for cardiovascular events.[1–4] A number of pharmacotherapeutic options for reducing triglycerides are available; 3-hydroxy 3-methylglutaryl coenzyme A reductase inhibitors (statins) and ezetimibe can

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lower levels modestly, but agents such as niacin, fibrates, and omega-3 fatty acids target triglycerides more specifically.[5]

As well as lowering triglyceride levels,[6] omega-3 fatty acids have been shown to be associated with a reduced incidence of cardiovascular events.[7–11] In addition to dietary sources of omega-3 fatty acids, such as fatty fish, prescription formulations are available. One such preparation, an oral capsule that contains concentrated omega-3 fatty acid ethyl esters, primarily eicosapentaenoic acid ethyl-ester (EPA-E) and docosahexaenoic acid-ethyl ester (DHA-E), is available in a number of countries for the treatment of hypertriglyceridemia, under the trade name Omacor/Lovaza. This formulation is currently being evaluated in Japan as TAK-085 and has recently been compared in a head-to-head study with an EPA-E preparation that is already approved in Japan for the treatment of hypertriglyceridemia.[11,12] The study showed that, in Japanese patients with hypertriglyceridemia undergoing lifestyle modification, 12 weeks of treatment with TAK-085 2 g/day was as effective at lowering triglyceride levels as EPA-E 1.8 g/day and that TAK-085 4 g/day was associated with a significantly greater reduction in triglycerides than EPA-E 1.8 g/day.[12]

The aim of the present study was to evaluate the safety and efficacy of TAK-085 over a longer, 52-week, period of treatment.

Methods

Study design

This was a phase 3, multicenter, open-label, randomized, study to evaluate the safety and efficacy of TAK-085 administered orally at a dose of 2 g/day (2 g once daily) or 4 g/day (2 g twice daily) for 52 weeks to patients with hypertriglyceridemia undergoing lifestyle modification. Specific lifestyle guidance that was based on the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases was given at all visits by the attending physician.[13]

Each 1 g of fatty acid in TAK-085 capsules contains approximately 465 mg of EPA-E plus 375 mg of DHA-E. EPA-E 1.8 g/day (0.6 g three times daily, orally) was included as a reference for the safety evaluation of TAK-085, and all medications were taken immediately after a meal.

Patients participated in a 4-week screening period during which time demographic and baseline characteristics were recorded, and the patients then entered a 52-week study. The principle assessments included physical examinations, vital signs, weight, clinical laboratory tests (including serum lipid profiles), and treatment compliance which were monitored every 4 weeks. Waist circumference and 12-lead electrocardiograms (ECGs) were recorded at baseline and on weeks 12, 24, 36, and 52, or on early termination. In addition, a full medical history, including concurrent medical conditions and medication use, was obtained at screening.

Randomization, which was stratified according to statin use, was performed by an independent registration center. The study was performed at 50 centers in Japan between November 2009 and July 2011 in accordance with the ethical principles set out in the Declaration of Helsinki and the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice and was approved by the institutional review board at each study site in line with local regulations. All patients provided written informed consent.

Patients: inclusion/exclusion criteria

Eligible male and female subjects were outpatients aged 20 to 74 years undergoing lifestyle modification for hypertriglyceridemia and who had a fasting triglyceride level $\geq$150 mg/dL and $<$750 mg/dL at weeks –4 and –2 during the screening period and a variation in fasting low-density lipoprotein cholesterol (LDL-C) level between weeks –4 and –2 of $<$25% from the highest value. The hypertriglyceridemia criteria were based on the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases.[13] All subjects were advised about lifestyle modifications (dietary or exercise or both) at all visits during the study.

The main exclusion criteria were coronary artery disease, an aortic aneurysm, or significant hemorrhagic disease within 6 months before the study; pancreatitis; lipoprotein lipase deficiency, apolipoprotein C-II deficiency, and type III familial hyperlipidemia; Cushing syndrome, uremia, systemic lupus erythematosus, or serum dysproteinemia; type 1 or uncontrolled type 2 diabetes mellitus (hemoglobin A1c $\geq$8%); stage III hypertension; and hepatic impairment.

Use of concomitant medications that might affect the evaluation of efficacy was not permitted, such as fish oil supplements (including any other products, medications, or investigational drugs that contained EPA-E or DHA), insulin, androgens, estrogens, progesterones, and systemic steroids. Antihyperlipidemic drugs (with the exception of EPA-E) and antidiabetic drugs (except insulin) were allowed, provided they had been initiated at least 4 weeks before the study and the dose was not changed during the screening or treatment periods.

Outcome measures

The primary objective of the study was to evaluate the safety of TAK-085. Safety variables included adverse events (AEs), vital signs, weight, 12-lead ECG findings, and clinical laboratory tests.

Efficacy variables were secondary end points in this study. The main efficacy variables were triglycerides, LDL-C, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and non-HDL-C levels. Other efficacy

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