Exhibit V

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Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

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ABSTRACT

BACKGROUND

Patients with elevated triglyceride levels are at increased risk for ischemic events. Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowers triglyceride levels, but data are needed to determine its effects on ischemic events.

METHODS

We performed a multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg per deciliter (1.52 to 5.63 mmol per liter) and a low-density lipoprotein cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter). The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS

A total of 8179 patients were enrolled (70.7% for secondary prevention of cardiovascular events) and were followed for a median of 4.9 years. A primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.68 to 0.83; P<0.001); the corresponding rates of the key secondary end point were 11.2% and 14.8% (hazard ratio, 0.74; 95% CI, 0.65 to 0.83; P<0.001). The rates of additional ischemic end points, as assessed according to a prespecified hierarchical schema, were significantly lower in the icosapent ethyl group than in the placebo group, including the rate of cardiovascular death (4.3% vs. 5.2%; hazard ratio, 0.80; 95% CI, 0.66 to 0.98; P=0.03). A larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%, P=0.004). Serious bleeding events occurred in 2.7% of the patients in the icosapent ethyl group and in 2.1% in the placebo group (P=0.06).

CONCLUSIONS

Among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo. (Funded by Amarin Pharma; REDUCE-IT ClinicalTrials.gov number, NCT01492361.)

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*A complete list of the REDUCE-IT trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Among patients with cardiovascular risk factors who are receiving treatment for secondary or primary prevention, the rates of cardiovascular events remain high.[1-3] Even in patients receiving appropriate treatment with statins, a substantial residual cardiovascular risk remains.[4] In such patients, an elevated triglyceride level serves as an independent marker for an increased risk of ischemic events, as shown in epidemiologic and mendelian randomization studies.[5-9] In randomized trials, medications that reduce triglyceride levels, such as extended-release niacin and fibrates, have not reduced the rates of cardiovascular events when administered in addition to appropriate medical therapy, including statins.[10] Contemporary trials and recent meta-analyses of n–3 fatty acid products have not shown a benefit in patients receiving statin therapy.[11-13]

In the Japan EPA Lipid Intervention Study (JELIS), 18,645 Japanese patients with hypercholesterolemia were randomly assigned to receive either low-intensity statin therapy plus 1.8 g of eicosapentaenoic acid (EPA) daily or statin therapy alone (there was no placebo group). The risk of major coronary events was significantly lower, by 19%, in the group that received EPA plus statin therapy than in the group that received statin therapy alone.[14]

These considerations led to the design of the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT).[15] Icosapent ethyl is a highly purified and stable EPA ethyl ester that has been shown to lower triglyceride levels and is used as an adjunct to diet in adult patients who have triglyceride levels of at least 500 mg per deciliter (5.64 mmol per liter).[16,17] In addition, icosapent ethyl may have antiinflammatory, antioxidative, plaque-stabilizing, and membrane-stabilizing properties.[18-21] We hypothesized that the risk of cardiovascular events would be lower with icosapent ethyl therapy than with placebo among patients in whom elevated triglyceride levels served as a marker of residual risk despite statin therapy.

Methods

Trial Design

The design of REDUCE-IT has been published previously.[15] In brief, REDUCE-IT was a phase 3b randomized, double-blind, placebo-controlled trial comparing icosapent ethyl (2 g twice daily with food [total daily dose, 4 g]) with a placebo that contains mineral oil to mimic the color and consistency of icosapent ethyl. Randomization was stratified according to cardiovascular risk stratum (secondary-prevention cohort or primary-prevention cohort, with primary prevention capped at 30% of enrolled patients), use or no use of ezetimibe, and geographic region. Further details of the study design are provided in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. Patients were enrolled and followed at 473 participating sites in 11 countries. The first patient underwent randomization on November 28, 2011, and the last on August 4, 2016.

The trial was sponsored by Amarin Pharma. The steering committee, which consisted of academic physicians (see the Supplementary Appendix), and representatives of the sponsor developed the protocol, available at NEJM.org, and were responsible for the conduct and oversight of the study, as well as the interpretation of the data. The sponsor was responsible for the collection and management of the data. The protocol was approved by the relevant health authorities, institutional review boards, and ethics committees. All the data analyses were performed by the sponsor, and the primary, secondary, and tertiary adjudicated end-point analyses were validated by an independent statistician from the data and safety monitoring committee. The first author vouches for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol.

Eligibility

Patients could be enrolled if they were 45 years of age or older and had established cardiovascular disease or were 50 years of age or older and had diabetes mellitus and at least one additional risk factor. Eligible patients had a fasting triglyceride level of 150 to 499 mg per deciliter (1.69 to 5.63 mmol per liter) and a low-density lipoprotein (LDL) cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter) and had been receiving a stable dose of a statin for at least 4 weeks; because of the intraindividual variability of triglyceride levels, the initial protocol allowed for a 10% lower triglyceride level from the target lower limit, which permitted patients to be enrolled if they had a triglyceride level of at least 135 mg per deciliter (1.52 mmol per liter). The first protocol amendment in May 2013 changed the lower limit of the acceptable triglyceride level

from 150 mg per deciliter to 200 mg per deciliter (2.26 mmol per liter), with no allowance for variability. Patients were excluded if they had severe heart failure, active severe liver disease, a glycated hemoglobin level greater than 10.0%, a planned coronary intervention or surgery, a history of acute or chronic pancreatitis, or known hypersensitivity to fish, shellfish, or ingredients of icosapent ethyl or placebo. Further details regarding inclusion and exclusion criteria are provided in Tables S1 and S2 in the Supplementary Appendix. Written informed consent was obtained from all patients.

END POINTS

The primary efficacy end point was a composite of cardiovascular death, nonfatal myocardial infarction (including silent myocardial infarction), nonfatal stroke, coronary revascularization, or unstable angina in a time-to-event analysis. While the steering committee and the sponsor remained unaware of the trial-group assignments, a second protocol amendment in July 2016 designated the key secondary end point as a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis. After the primary efficacy end-point analysis was performed, the prespecified secondary efficacy end points were examined in a hierarchical fashion in the following order: the key secondary efficacy end point; a composite of cardiovascular death or nonfatal myocardial infarction; fatal or nonfatal myocardial infarction; emergency or urgent revascularization; cardiovascular death; hospitalization for unstable angina; fatal or nonfatal stroke; a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke; and death from any cause. Prespecified tertiary end points are listed in the Supplementary Appendix. Adjudication of all the above events was performed by an independent clinical end-point committee whose members were unaware of the trial-group assignments and lipid levels.

STATISTICAL ANALYSIS

In this event-driven trial, it was estimated that approximately 1612 adjudicated primary end-point events would be necessary to provide the trial with 90% power to detect a 15% lower risk of the primary composite end point in the icosapent ethyl group than in the placebo group. We estimated that a sample size of approximately 7990 patients would be required to reach that number of primary end-point events. The primary efficacy analysis was based on the time from randomization to the first occurrence of any component of the primary composite end point. If the risk of the primary composite end point was significantly lower with icosapent ethyl than with placebo at a final two-sided alpha level of 0.0437 (as determined with the use of O'Brien–Fleming boundaries generated with the Lan–DeMets alpha-spending function approach after accounting for two prespecified interim efficacy analyses), the key secondary end point and other prespecified secondary end points were to be tested in a hierarchical fashion at the same final alpha level of 0.0437. All analyses were performed according to the intention-to-treat principle. Hazard ratios and 95% confidence intervals were generated with the use of a Cox proportional-hazards model that included trial-group assignment as a covariate, stratified according to cardiovascular risk category, geographic region, and use of ezetimibe. Log-rank P values from a Kaplan–Meier analysis that was stratified according to the three randomization factors are reported to evaluate the timing of events in the two trial groups. With respect to the tertiary and subgroup efficacy analyses, 95% confidence intervals (which were not adjusted for multiple comparisons) are reported. An independent data and safety monitoring committee oversaw the study and performed two prespecified interim efficacy reviews.

RESULTS

PATIENTS

A total of 19,212 patients were screened, of whom 8179 (43%) underwent randomization. At the time of database lock, vital status was available for 99.8% of the patients; 152 patients (1.9%) did not complete the final study visits, and 578 patients (7.1%) withdrew consent. Details regarding the disposition of the patients are provided in Figure S2 in the Supplementary Appendix.

The baseline characteristics of the patients are shown in Table 1. Among the patients who underwent randomization, 70.7% were enrolled on the basis of secondary prevention (i.e., patients had established cardiovascular disease) and 29.3% on the basis of primary prevention (i.e., patients had diabetes mellitus and at least one additional risk factor). The median age of the patients was 64 years; 28.8% were female, and 38.5% were from the United States. At baseline, the median

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age		
Median (IQR) — yr	64.0 (57.0–69.0)	64.0 (57.0–69.0)
≥65 yr — no. (%)	1857 (45.4)	1906 (46.6)
Male sex — no. (%)	2927 (71.6)	2895 (70.8)
White race — no. (%)†	3691 (90.3)	3688 (90.2)
Body-mass index‡		
Median (IQR)	30.8 (27.8–34.5)	30.8 (27.9–34.7)
≥30 — no. (%)	2331 (57.0)	2362 (57.8)
Geographic region — no. (%)§		
United States, Canada, the Netherlands, Australia, New Zealand, and South Africa	2906 (71.1)	2905 (71.0)
Eastern European	1053 (25.8)	1053 (25.7)
Asia–Pacific	130 (3.2)	132 (3.2)
Cardiovascular risk stratum — no. (%)		
Secondary-prevention cohort	2892 (70.7)	2893 (70.7)
Primary-prevention cohort	1197 (29.3)	1197 (29.3)
Ezetimibe use — no. (%)	262 (6.4)	262 (6.4)
Statin intensity — no. (%)		
Low	254 (6.2)	267 (6.5)
Moderate	2533 (61.9)	2575 (63.0)
High	1290 (31.5)	1226 (30.0)
Data missing	12 (0.3)	22 (0.5)
Diabetes — no. (%)		
Type 1	27 (0.7)	30 (0.7)
Type 2	2367 (57.9)	2363 (57.8)
No diabetes at baseline	1695 (41.5)	1694 (41.4)
Data missing	0	3 (0.1)
Median high-sensitivity CRP level (IQR) — mg/liter	2.2 (1.1–4.5)	2.1 (1.1–4.5)
Median triglyceride level (IQR) — mg/dl	216.5 (176.5–272.0)	216.0 (175.5–274.0)
Median HDL cholesterol level (IQR) — mg/dl	40.0 (34.5–46.0)	40.0 (35.0–46.0)
Median LDL cholesterol level (IQR) — mg/dl	74.0 (61.5–88.0)	76.0 (63.0–89.0)
Distribution of triglyceride levels — no./total no. (%)		
<150 mg/dl	412/4086 (10.1)	429/4089 (10.5)
≥150 to <200 mg/dl	1193/4086 (29.2)	1191/4089 (29.1)
≥200 mg/dl	2481/4086 (60.7)	2469/4089 (60.4)
Triglyceride level ≥200 mg/dl and HDL cholesterol level ≤35 mg/dl — no. (%)	823 (20.1)	794 (19.4)
Median eicosapentaenoic acid level (IQR) — μg/ml	26.1 (17.1–40.1)	26.1 (17.1–39.9)

* Median low-density lipoprotein (LDL) cholesterol level at baseline differed significantly between the trial groups (P=0.03); there were no other significant between-group differences in baseline characteristics. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. In general, the baseline value was defined as the last nonmissing measurement obtained before randomization. The baseline LDL cholesterol value as measured by means of preparative ultracentrifugation was used in our analyses; however, if the preparative ultracentrifugation value was missing, the LDL cholesterol value measured by another method was used in the following order of priority: the value obtained by means of direct measurement of LDL cholesterol, the value derived with the use of the Friedewald equation (only for patients with a triglyceride level <400 mg per deciliter), and the value derived with the use of the calculation published by Johns Hopkins University investigators.[22] At the first and second screening visits, the LDL cholesterol value obtained by direct measurement was used if at the same visit the triglyceride level was higher than 400 mg per deciliter. At all remaining visits, the LDL cholesterol value was obtained by means of direct measurement or preparative ultracentrifugation if at the same visit the triglyceride level was higher than 400 mg per deciliter. For all other measures of lipid and lipoprotein markers, whenever possible, the baseline value was derived as the arithmetic mean of the value obtained at visit 2 (day 0) and the value obtained at the preceding screening visit. If only one of these values was available, that single value was used as the baseline value. CRP denotes C-reactive protein, HDL high-density lipoprotein, and IQR interquartile range. Percentages may not total 100 because of rounding.

† Race was reported by the investigators.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Eastern European region includes Poland, Romania, Russia, and Ukraine, and Asia–Pacific region includes India.

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