No. 24-889

In the Supreme Court of the United States

HIKMA PHARMACEUTICALS USA INC. AND
HIKMA PHARMACEUTICALS PLC, PETITIONERS

v.

AMARIN PHARMA, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

JOINT APPENDIX

VOLUME 2 of 2

PAGES 66–207

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(12) **United States Patent**
Yokoyama et al.

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(45) **Date of Patent: *Jul. 11, 2017**

(54) **COMPOSITION FOR PREVENTING THE OCCURRENCE OF CARDIOVASCULAR EVENT IN MULTIPLE RISK PATIENT**

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A61K 31/351	(2006.01)

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CPC ***A61K 31/22*** (2013.01); ***A61K 31/202*** (2013.01); ***A61K 31/225*** (2013.01); ***A61K 31/232*** (2013.01); ***A61K 31/351*** (2013.01); ***A61K 31/366*** (2013.01); ***A61K 31/40*** (2013.01); *A61K 2300/00* (2013.01)

(58) **Field of Classification Search**

USPC 514/560

See application file for complete search history.

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(57) **ABSTRACT**

Disclosed is a composition which is useful for preventing the occurrence of a cardiovascular event, particularly a composition which is expected to show a prophylactic effect on a cardiovascular event occurring in a hypercholesterolemia patient despite providing the patient with a treatment with HMG-CoA RI or a cardiovascular event occurring in a multiple risk patient.

16 Claims, 1 Drawing Sheet

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FIG. 1

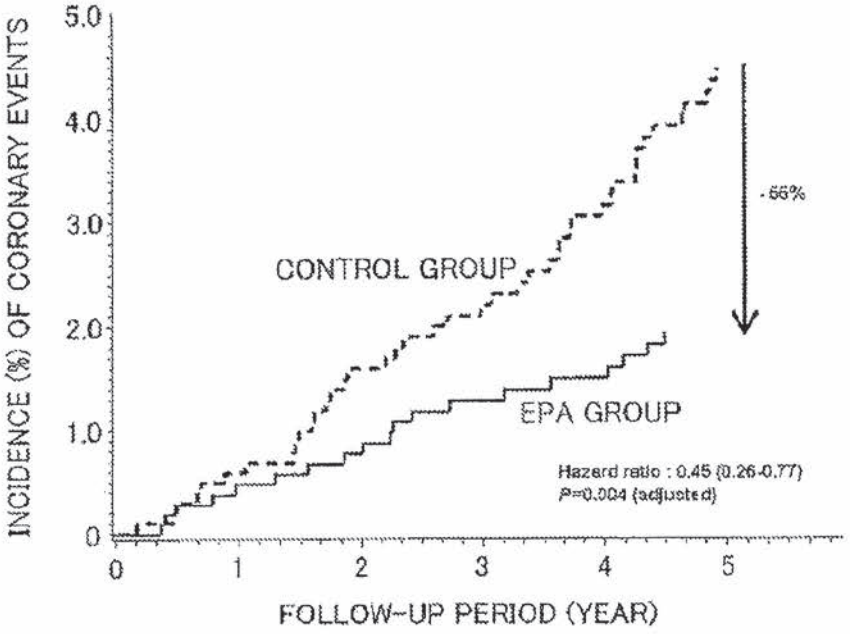
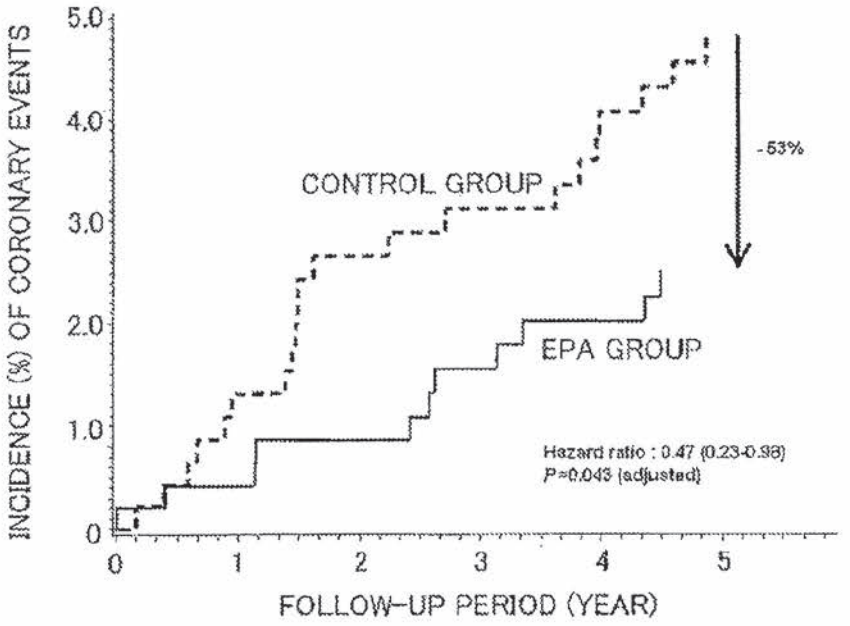

INCIDENCE (%) OF CORONARY EVENTS
5.0
4.0
3.0
2.0
1.0
0
0
1
2
3
4
5
FOLLOW-UP PERIOD (YEAR)
CONTROL GROUP
EPA GROUP
-55%
Hazard ratio : 0.45 (0.26-0.77)
P=0.004 (adjusted)

FIG. 2


INCIDENCE (%) OF CORONARY EVENTS
5.0
4.0
3.0
2.0
1.0
0
0
1
2
3
4
5
FOLLOW-UP PERIOD (YEAR)
CONTROL GROUP
EPA GROUP
-53%
Hazard ratio : 0.47 (0.23-0.98)
P=0.043 (adjusted)

COMPOSITION FOR PREVENTING THE OCCURRENCE OF CARDIOVASCULAR EVENT IN MULTIPLE RISK PATIENT

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a 37 C.F.R. §1.53(b) divisional of U.S. application Ser. No. 14/963,291 filed Dec. 9, 2015, which is a 37 C.F.R. §1.53(b) divisional of U.S. application Ser. No. 14/474,955 filed Sep. 2, 2014 (abandoned), which is a 37 C.F.R. §1.53(b) divisional of U.S. application Ser. No. 12/302,790 filed Nov. 26, 2008 (now U.S. Pat. No. 8,853,256 B2 issued Oct. 7, 2014), which is the National Phase of PCT International Application No. PCT/JP2007/061099 filed May 31, 2007, which in turn claims priority on Japanese Patent Application No. 2006-152740 filed May 31, 2006. The entire contents of each application is hereby incorporated by reference.

TECHNICAL FIELD

This invention relates to a composition for preventing occurrence of cardiovascular events (primary prevention) in multiple risk patients, the composition containing at least ethyl icosapentate (hereinafter abbreviated as EPA-E).

BACKGROUND ART

Westernization of diet has resulted in the increase of patients suffering from lifestyle-related diseases such as diabetes, hyperlipidemia, and hypertension. Some of these diseases finally lead to arteriosclerotic diseases such as myocardial infarction, angina pectoris, and cerebral infarction. Treatment of the lifestyle-related diseases is based on the improvement of lifestyle, and more specifically, on the alimentary therapy and kinesitherapy. However, such improvement of the dietary life or the lack of exercise is often difficult in the patients suffering from the "lifestyle-related diseases," and they usually transfer to pharmacotherapy in order to prevent poor prognosis, for example, onset of myocardial infarction or cerebral infarction.

An exemplary compound having the action of improving such lifestyle-related diseases is polyunsaturated fatty acid. The polyunsaturated fatty acid is defined as a fatty acid including two or more carbon-carbon double bonds in one molecule, and the polyunsaturated fatty acids are categorized by the position of the double bond into ω3 fatty acid, ω6 fatty acid, and the like. The ω3 polyunsaturated fatty acids include α-linolenic acid, icosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), and the ω6 polyunsaturated fatty acids include linoleic acid, γ-linolenic acid, and arachidonic acid. Polyunsaturated fatty acids are derived from natural products, and exhibit various actions including antiarteriosclerotic action, platelet aggregation inhibitory action, hypolipidemic action, antiinflammatory action, antitumor action, and central action, and due to the high safety, polyunsaturated fatty acids are incorporated in various kinds of food, or sold as a health food or drug.

Decrease in the death rate in the patients who have history of suffering from myocardial infarction has been reported for the administration of a mixture of ethyl ester of an ω-3 polyunsaturated fatty acid EPA (EPA-E) and ethyl ester of an ω-3 polyunsaturated fatty acid DHA (DHA-E) for 3.5 years (see Patent Document. 1). However, the results disclosed in Patent Document 1 relates to the secondary prevention, that is, prevention of recurrence, and the drug which is effective in the secondary prevention is not always effective in the primary prevention.

Based on the results of animal experiments and small scale clinical observations, many large scale clinical trials have been recently planned and conducted for the purpose of confirming whether various drugs which are effective in improving the lifestyle-related diseases can also prevent arteriosclerotic diseases in human. The results, however, have not necessarily been as intended, and the situation is still severe for the prevention of the occurrence of cardiovascular events in the case of patients suffering from a plurality of risk factors.

High purity EPA-E is commercially available in the trade names of Epadel™ and Epadel S™ (manufactured by Mochida Pharmaceutical Co., Ltd.) as therapeutic drugs for hyperlipidemia. There has been reported that when such high purity EPA-E is orally administered at 600 mg per administration and 3 times a day immediately after meal (when TG is abnormal, the dose is increased to the level of 900 mg per administration and 3 times a day), serum T-Cho concentration can be reduced by 3 to 6%, and serum TG can be reduced by 14 to 20% (see Non-Patent Document 1). There has also been reported in The Heart Failure Society of America 2005 Annual Meeting that, based on such action, such high purity EPA-E was expected to have the effects of improving cardiovascular events in hyperlipidemia patients, and combined use with HMG-CoA RI was effective in inhibiting cardiac events in a large scale clinical trial. In this large scale clinical trial (DELIS, Japan EPA Lipid Intervention Study), statistically significant suppression of the cardiac events by the EPA-E was confirmed for the total of the primary prevention patients and secondary prevention patients, and for the secondary prevention patients. On the other hand, in the analysis limited to the primary prevention patients, the incidence of the events was lower in the EPA-E group (the group administered with EPA-E in combination with HMG-CoA RI) compared to the control group (the group administered with solely with HMG-CoA RI), while this difference was not statistically significant. This trial also revealed that after 5 years from the start of the trial, the LDL-cholesterol value reduced by 26% in both of the EPA-E group and control group, that no significant difference was found between these groups, and that change of the HDL-cholesterol value was slight in both groups (see Non-Patent Document 2). This trial also revealed that the total cholesterol and the LDL-cholesterol decreased by 19% and 25%, respectively, in both the EPA-E group and the control group, and that triglyceride decreased by 9% (significant) and 4% in the EPA-E group and the control group, respectively, while little change in HDL-C was noted in both the EPA-E group and the control group (see Non-Patent Document 3). There is so far no report that has analyzed prevention of the occurrence of the cardiovascular events in the case of patients having two or more risk factors.

Patent Document 1: WO 00/48592 (JP 2002-537252 A)

Non-Patent Document 1: Drug Interview Form "EPA preparation, Epadel capsule 300", revised in July, 2002, and February, 2004, version 21 issued in December, 2004; pp. 21-22.

Non-Patent Document 2: Medical Tribune, issue of Nov. 17, 2005, Feature article 3, pp. 75-76.

Non-Patent Document 3: Lancet, vol. 369, pages 1090 to 1098 (2007).

DISCLOSURE OF THE INVENTION

Problems to be Solved by the Invention

In view of the situation that there is a serious problem that death from the cardiovascular disease is still a major cause of the death, and many cases of cardiovascular events are still impossible to prevent by the HMG-CoA RI therapy, an object of the present invention is to provide a composition for preventing onset of the cardiovascular events.

Means to Solve the Problems

In order to solve the problems as described above, the inventors of the present invention made an extensive study on a therapy of hypercholesterolemia patients and found that EPA-E has the effect of preventing occurrence of the cardiovascular events in patients suffering from multiple risk factors, and in particular, the effect of preventing occurrence of the cardiovascular events in male patients suffering from multiple risk factors. The present invention has been completed on the bases of such finding. Accordingly, the present invention is directed to the following:

(1) A composition for preventing occurrence of a cardiovascular event (primary prevention) in a hypercholesterolemia patient, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,

(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDL cholesterolemia.

(2) A composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E as its effective component, wherein the hypercholesterolemia patient is a patient also suffering from two or more of the risk factors.

(3) A composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from at least one of risk factors as defined by a body mass index (BMI) of at least 25 for the obesity; by a systolic blood pressure (SBP) of at least 140 mmHg or a diastolic blood pressure (DBP) of at least 90 mmHg for the hypertension or the prehypertension; by a fasting blood glucose (FBS) of at least 126 mg/dL or a hemoglobin Alc (HbAlc) of at least 6.5% for the diabetes, the prediabetes, or the abnormal glucose tolerance; and by triglyceride (TG) of at least 150 mg/dL and/or a HDL-C of less than 40 mg/dL for the hypertriglyceridemia and/or the low HDL cholesterolemia.

(4) The composition according to any one of (1) to (3) above, wherein the content of the EPA-E is at least 96.5% by weight in relation to the total content of fatty acid and derivatives thereof.

(5) The composition according to any one of (1) to (4) above, wherein the EPA-E is orally administered at a dose of 1.8 g/day to 2.7. g/day.

(6) The composition according to any one of (1) to (5) above, wherein the composition is used in combination with HMG-CoA RI.

(7) The composition according to any one of (1) to (6) above, wherein the hypercholesterolemia patient is a male patient.

(8) The composition according to any one of (1) to (7) above, wherein the hypercholesterolemia patient is a patient also suffering from hypertriglyceridemia and low HDL cholesterolemia.

(9) A method for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient by administering the patient with the composition according to any one of (1) to (8) above.

(10) Use of the composition according to any one of (1) to (8) above for the manufacture of an agent for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient.

Merits of the Invention

The above-mentioned composition of the present invention containing at least EPA-E as its effective component is effective in preventing occurrence of cardiovascular events in hypercholesterolemia patients, and in particular, in preventing occurrence of cardiovascular events in hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the risk of the cardiovascular events, or more particularly, in preventing occurrence of cardiovascular events in hypercholesterolemia patients also suffering from at least one risk factor selected from the group consisting of

(1) obesity,

(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDI, cholesterolemia.

The effect of the composition of the present Invention will be synergistically improved by combined use with the HMG-CoA RI, and such use of the composition of the present invention with the HMG-CoA RI has clinical utility since the effect of preventing the cardiovascular event occurrence is expected to be improved.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a graph prepared by plotting the incidence of the cardiovascular events in Y-axis and the time after the start of the trial in X-axis for male patients having at least 2 risk factors.

FIG. **2** is a graph prepared by plotting the incidence of the cardiovascular event in Y-axis and the time after the start of the trial in X-axis for patients having the risk factors of a triglyceride (TG) of at least 150 mg/dL and a HDL-C of less than 40 mg/dL.

BEST MODE FOR CARRYING OUT THE INVENTION

Next, the present invention is described in detail.

A first aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event (primary prevention) in a hypercholesterolemia patient, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,

(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDL cholesterolemia.

Alternatively, the first aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event (primary prevention) in a hypercholesterolemia patient, the composition containing at least EPA-E and/or DHA-E as its effective component, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,
(2) hypertension or prehypertension,
(3) diabetes, prediabetes, or abnormal glucose tolerance, and
(4) hypertriglyceridemia and/or low HDL cholesterolemia.

The prevention of the occurrence of the cardiovascular events include all cases of primary prevention, and exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest angina and exercise-induced angina, and destabilization of the angina. The composition of the present invention may be administered to any person who needs prevention of the occurrence of the cardiovascular events, and typical such patients are hypercholesterolemia patients.

A second aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient undergoing a HMG-CoA RI therapy, the composition containing at least EPA-E, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,
(2) hypertension or prehypertension,
(3) diabetes, prediabetes, or abnormal glucose tolerance, and
(4) hypertriglyceridemia and/or low HDL cholesterolemia.

Alternatively, the second aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient undergoing a HMG-CoA RI therapy, the composition containing at least EPA-E and/or DHA-E, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,
(2) hypertension or prehypertension,
(3) diabetes, prediabetes, or abnormal glucose tolerance, and
(4) hypertriglyceridemia and/or low HDL cholesterolemia.

While HMG-CoA RI includes all those having inhibitory action for 3-hydroxy-3-methylglutaryl coenzyme A reductase, the one used in the present invention is preferably a pharmaceutically administrable inhibitor which is preferably at least one member selected from the group consisting of pravastatin, simvastatin, lovastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin, rosuvastatin, and salts and derivatives thereof, and more preferably, pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin, or rosuvastatin, and most preferably, pravastatin or simvastatin. All salts are included as long as they are pharmaceutically administrable, and preferred are sodium and calcium salts such as pravastatin sodium, fluvastatin sodium, cerivastatin sodium, atorvastatin calcium, pitavastatin calcium, and rosuvastatin calcium. In the present invention, "pravastatin," for example, also includes the pravastatin in the form of a salt unless otherwise noted.

A third aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from at least two risk factors selected from the group consisting of

(1) obesity,
(2) hypertension or prehypertension,
(3) diabetes, prediabetes, or abnormal glucose tolerance, and
(4) hypertriglyceridemia and/or low HDL cholesterolemia; namely; obesity, and hypertension or prehypertension; obesity, and diabetes, prediabetes, or abnormal glucose tolerance; obesity, and hypertriglyceridemia and/or low HDL cholesterolemia; hypertension or prehypertension, and diabetes, prediabetes or abnormal glucose tolerance; hypertension or prehypertension, and hypertriglyceridemia and/or low HDL cholesterolemia; diabetes, prediabetes, or abnormal glucose tolerance, and hypertriglyceridemia and/or low HDL cholesterolemia; obesity, and hypertension or prehypertension, and diabetes, prediabetes, or abnormal glucose tolerance; obesity, and hypertension or prehypertension, and hypertriglyceridemia and/or low HDL cholesterolemia; obesity, and diabetes, prediabetes, or abnormal glucose tolerance, and hypertriglyceridemia and/or low HDL cholesterolemia; hypertension or prehypertension, and diabetes, prediabetes, or abnormal glucose tolerance, and hypertriglyceridemia and/or low HDL cholesterolemia; obesity, and hypertension or prehypertension, and diabetes, prediabetes, or abnormal glucose tolerance, and hypertriglyceridemia and/or low HDL cholesterolemia.

Alternatively, the third aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E and/or DHA-E as its effective component, wherein the patient also suffers from at least two risk factors selected from the group consisting of

(1) obesity,
(2) hypertension or prehypertension,
(3) diabetes, prediabetes, or abnormal glucose tolerance, and
(4) hypertriglyceridemia and/or low HDL cholesterolemia.

A fourth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from at least one, and more preferably, at least two risk factors selected from the group consisting of

(1) obesity,
(2) hypertension or prehypertension,
(3) diabetes, prediabetes, or abnormal glucose tolerance, and
(4) hypertriglyceridemia and/or low HDL cholesterolemia. In this case, the hypercholesterolemia patient is preferably a male patient.

Alternatively, the fourth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E and/or DHA-E as its effective component, wherein the patient also suffers from at least one, and more preferably, at least two risk factors selected from the group consisting of

(1) obesity,
(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDL cholesterolemia. In this case, the hypercholesterolemia patient is preferably a male patient.

A fifth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from risk factors of hypertriglyceridemia and low HDL cholesterolemia, and more specifically, hypertriglyceridemia and low HDL cholesterolemia with a serum triglyceride (TG) concentration of at least 150 mg/dl and a serum HDL-C concentration of less than 40 mg/dl, or serum TG/HDL-C ratio of at least 3.75. In this case, the hypercholesterolemia patient is preferably a male patient. Alternatively, the fifth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E and/or DHA-E as its effective component, wherein the patient also suffers from risk factors of hypertriglyceridemia and low HDL cholesterolemia, and more specifically, hypertriglyceridemia and low HDL cholesterolemia with a serum triglyceride (TG) concentration of at least 150 mg/dl and a serum HDL-C concentration of less than 40 mg/dl, or a serum TG/HDL-C ratio of at least 3.75. In this case, the hypercholesterolemia patient is preferably a male patient.

A sixth aspect of the present invention provides a composition containing at least EPA-E as its effective component, the composition exhibiting an excellent effect of preventing occurrence of a cardiovascular event in a patient suffering from multiple risk factors who has been administered with this composition for at least 2 years since the start of the administration. Alternatively, the sixth aspect of the present invention provides a composition containing at least EPA-E and/or DHA-E as its effective component, the composition exhibiting an excellent effect of preventing recurrence of a cardiovascular event in a patient suffering from multiple risk factors who has been administered with this composition for at least 2 years since the start of the administration. The hypercholesterolemia patient is preferably a male patient.

A seventh aspect of the present invention provides a method for preventing occurrence of a cardiovascular event in a patient suffering from multiple risk factors by continuously administering the patient with a composition containing at least EPA-E as its effective component for at least 2 years. Alternatively, the seventh aspect of the present invention provides a method for preventing occurrence of a cardiovascular event in a patient suffering from multiple risk factors by continuously administering the patient with a composition containing at least EPA-E and/or DHA-E as its effective component for at least 2 years. The hypercholesterolemia patient is preferably a male patient.

An eighth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event (primary prevention) in a dyslipidemia patient, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,

(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDL cholesterolemia.

Alternatively, the eighth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event (primary prevention) in a dyslipidemia patient, the composition containing at least EPA-E and/or DHA-E as its effective component, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,

(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDL cholesterolemia.

A ninth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event (primary prevention) in a hypercholesterolemia patient to be able to administered with HMG-CoA RI, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,

(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDL cholesterolemia.

Alternatively, the ninth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event (primary prevention) in a hypercholesterolemia patient to be able to administered with HMG-CoA RI, the composition containing at least EPA-E and/or DHA-E as its effective component, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,

(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDL cholesterolemia.

While the EPA-E content in the total fatty acid and dosage are not particularly limited as long as intended effects of the present invention are attained, the EPA-E used is preferably the one having a high purity, for example, the one having the proportion of the EPA-E in the total fatty acid and derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or higher, and still more preferably 96.5% by weight or higher. The daily dose in terms of EPA-E is typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8 g/day. Another preferable fatty acid included is DHA-E. While the compositional ratio of EPA-E/DHA-E, content of EPA-E and DHA-E (hereinafter referred to as (EPA-E+DHA-E)) in the total fatty acid, and dosage of (EPA-E+DHA-E) are not particularly limited as long as intended effects of the present invention are attained, the composition is preferably the one having a high purity of EPA-E and DHA-E, for example, the one having a proportion of the (EPA-E+DHA-E) in the total fatty acid and derivatives thereof of preferably 40% by weight or higher, more preferably 80% by weight or higher, and still more preferably 90% by weight or higher. The daily dose in terms of EPA-E+DHA-E is typically 0.3 to 10 g/day, preferably 0.5 to 6 g/day, and still more preferably 1 to 4 g/day. Another preferable daily dose is 0.3 to 6 g/day, 0.3 to 4 g/day, and 0.3 to 1 g/day. The content of other long chain saturated fatty acids is preferably low, and among the long

chain unsaturated fatty acids, the content of ω6 fatty acids, and in particular, the content of arachidonic acid is preferably as low as less than 2% by weight, and more preferably less than 1% by weight.

The composition of the present invention contains EPA-E and/or DHA-E, and has the effect of preventing occurrence of cardiovascular events in healthy people or those suffering from the risk factors of hyperlipidemia, diabetes, and hypertension when the composition is orally administered, and in particular, of preventing occurrence of cardiovascular events in hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffering from the risk of the cardiovascular events. The composition of the present invention may also be used in combination with the HMG-CoA RI, and such combination may further prevent the occurrence of the cardiovascular events.

The composition of the present invention may be used with other drugs, for example, antiplatelet drugs such as aspirin, ticlopidine, clopidogrel, prasugrel, and cilostazol; anticoagulants such as warfarin, heparin, and ximelagatran; antihypertensive drugs such as angiotensin II receptor antagonists (candesartan, losartan, valsartan, etc.), angiotensin converting enzyme inhibitors, calcium channel antagonists (amlodipine, cilnidipine, etc.), and al blockers; diabetes drugs or abnormal glucose tolerance stimulants such as α-glucosidase inhibitors (voglibose, acarbose, etc.), biguanide drugs, thiazolidinedione drugs (pioglitazone, rosiglitazone, rivoglitazone, etc.), and prompt insulin release promoters (mitiglinide, nateglinide, etc.); antilipotropic drugs and antiarteriosclerotic drugs such as HMG-CoA RI as described above, fibrate drugs, squalene synthetase inhibitors (TAK-475, etc.), and cholesterol absorption inhibitors (ezetimibe, etc.), probucol, anion exchange resin, nicotinic acid drugs, phytostero, elastase, dextran sulfate sodium sulfur, pantothenic acid, and polyenephosphatidylcholine.

The composition of the present invention contains smaller amounts of impurities such as saturated fatty acids and arachidonic acid which are unfavorable for cardiovascular events compared to fish oil or fish oil concentrate, and accordingly, the intended effects can be attained without causing problems like overnutrition or excessive intake of vitamin A. In addition, since the effective component of the present composition is in the form of an ester, the effective component is more stable to oxidation compared to the case of fish oil in which the effective component is in the form of a triglyceride, and a sufficiently stable composition can be produced by adding a conventional antioxidant. In other words, it is the use of the EPA-E that has for the first time enabled production of a composition for preventing onset of cardiovascular events which can be used in clinical practice.

In the present invention, the term "icosapentaenoic acid" designates all-cis-5,8,11,14,17-icosapentaenoic acid.

In the present invention, the term "hypercholesterolemia patient" means the patient with increased serum T-Cho concentration or serum LDL-Cho concentration. In a narrower sense, this term means the patient suffering from hypercholesterolemia (serum T-Cho concentration of at least about 220 mg/dl, and in more strict sense, at least 250 mg/dl) or high LDL cholesterolemia (serum LDL-Cho concentration of at least 140 mg/dL).

In the present invention, the term "dyslipidemia" is the condition which satisfies at least one of high LDL cholesterolemia (i.e. fasting serum LDL cholesterol value of at least 140 mg/dL), low HDL cholesterolemia (i.e. fasting serum HDL cholesterol value of less than 40 mg/dL), and hypertriglyceridemia (i.e. fasting serum triglyceride value of at least 150 mg/dL) according to the diagnostic criteria described in "Guideline for Preventing Arteriosclerotic diseases, 2007" (edited and published by Japan Atherosclerosis Society).

Of the risk factors treated in the present invention, "obesity" is the state with excessive accumulation of fats in the body. For example, non-limiting examples of the obesity include a body mass index (BMI) of at least 25, a waist measurement of at least 85 cm in male and at least 90 cm in female. "Hypertension" is the state with an abnormal increase in resting arterial blood pressure of the greater circulatory system. For example, in the criteria proposed by Japanese Society of Hypertension at the time of the filing of this application, hypertension is defined as a systolic blood pressure (SBP) of at least 140 mmHg or a diastolic blood pressure (DBP) of at least 90 mmHg. "Prehypertension" is the condition with the blood pressure between the normal blood pressure (or optimal blood pressure) and the blood pressure in the hypertension, and this condition is also referred to as "mild elevated blood pressure" or "borderline hypertension." Non-limiting exemplary criteria for such condition include a systolic blood pressure (SEP) of 120 to 139 mmHg or a diastolic blood pressure (DBP) of 80 to 89 mmHg. In the present invention, "hypertension or prehypertension" means a condition with a systolic blood pressure (SBP) of at least 120 mmHg or a diastolic blood pressure (DBP) of at least 80 mmHg, more strictly, a systolic blood pressure (SHP) of at least 135 mmHg or a diastolic blood pressure (DBP) of at least 85 mmHg, even more strictly a systolic blood pressure (SBP) of at least 140 mmHg or a diastolic blood pressure (DBP) of at least 90 mmHg. "Diabetes" is the glucose metabolism disorder caused by hyposecretion of insulin from the insulin-producing cell (β cell) in the pancreas or insufficient action of the insulin in the target cell. Exemplary non-limiting criteria proposed by Japan Diabetes Society at the time of the filing of this application is one of 1) fasting blood glucose of at least 126 mg/dL, 2) 75 g glucose tolerance test at 2 hours of at least 200 mg/dL, and 3) casual blood glucose level of at least 200 mg/dL; or a hemoglobin Alc (HbAlc) of at least 6.5%. The criteria, however, are not limited to these. "Prediabetes" is the condition in which the blood glucose level is between the normal value and the value in the diabetes. "Abnormal glucose tolerance" is the condition in which the blood glucose level in the glucose tolerance test is between the normal value and the value in the diabetes. These conditions are also referred to as the borderline diabetes, prediabetic state, and the diabetic high-risk group. For these conditions, exemplary non-limiting criteria include a fasting blood glucose of 110 to 125 mg/dL, a 75 g glucose tolerance test at 2 hours of 140 to 199 mg/dL, and a hemoglobin Alc (HbAlc) of 5.6 to 6.4%. In the present invention, "diabetes, prediabetes, or abnormal glucose tolerance" means a condition with a fasting blood glucose (FBS) of at least 110 mg/dL or a hemoglobin Alc (HbAlc) of at least 5.6%, more strictly, a fasting blood glucose (FBS) of at least 110 mg/dL or a hemoglobin Alc (HbAlc) of at least 5.9%, and even more strictly with a fasting blood glucose (FBS) of at least 126 mg/dL or a hemoglobin Alc (HbAlc) of at least 6.5%. "Hypertriglyceridemia" is the condition with an increased serum triglyceride (TG) concentration, and strictly, with the serum TG concentration of at least 150 mg/dL. "Low HDL cholesterolemia" is the condition with a reduced serum HDL-C concentration, and strictly, with the serum HDL-C concentration of less than 40 mg/dL. In the present invention, "hypertriglyceridemia and/or low HDL cholesterolemia" means the state with a serum TG concentration of at least 150 mg/dL and/or a serum HDL-C concentration of

less than 40 mg/dL. The hypertriglyceridemia and the low HDL cholesterolemia are both diseases included in the category of dyslipidemia, and they are mutually independent risk factors. Combination of these risk factors, however, is known to result in an increased risk of the occurrence of an arteriosclerotic disease. In the present invention, "the hypertriglyceridemia and/or the low HDL cholesterolemia" is treated as a single risk factor.

In the present invention, the term "combined use of EPA-E with HMG-CoA RI" include both the embodiment in which the EPA-E and the HMG-CoA RI are simultaneously administered and the embodiment in which both agents are separately administered. When these agents are simultaneously administered, they may be formulated either as a single combined drug or separate drugs. When these agents are separately administered, EPA-E may be administered either before or after the HMG-CoA RI. The doses and ratio of the EPA-E and the HMG-CoA RI may be adequately selected.

In the present invention, the term "combined use of EPA-E and/or DHA-E with HMG-CoA RI" include both the embodiment in which the EPA-E and/or DHA-E and the HMG-CoA RI are simultaneously administered and the embodiment in which these agents are separately administered. When these agents are simultaneously administered, they may be formulated either as a single combined drug or separate drugs. When these agents are separately administered, EPA-E and/or DHA-E may be administered either before or after the HMG-CoA RI. The doses and ratio of the EPA-E and/or DHA-E and the HMG-CoA RI may be adequately selected.

The composition of the present invention has the action of preventing onset of the cardiovascular events by the sole administration of the composition, and in particular, the present composition is expected to have the effect of preventing onset of the cardiovascular events which could not be prevented by the sole administration of the HMG-CoA RI. In addition, EPA-E has not only the action of reducing the serum T-Cho concentration and the serum TG, but also the action of suppressing platelet aggregation based on inhibition of arachidonic acid cascade, which is a pharmacological action different from the HMG-CoA RI. Therefore, the action as described above can also be exerted by combined administration with the HMG-CoA RI.

Since EPA-E and DHA-E are highly unsaturated, inclusion of an effective amount of an antioxidant such as butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, gallic acid, and pharmaceutically acceptable quinone, or α-tocopherol is preferable.

The preparation may be orally administered to the patient in the dosage form of tablet, capsule, microcapsule, granules, fine granules, powder, oral liquid preparation, syrup, or jelly. Preferably, the preparation is orally administered by filling in a capsule such as soft capsule or microcapsule.

The soft capsules containing high purity EPA-E (Epadel™ and Epadel S™) are commercially available in Japan as safe therapeutic agents for arteriosclerosis obliterans and hyperlipidemia with reduced side effects, and in such products, proportion of EPA-E in total fatty acid is at least 96.5% by weight. The soft capsule (Omacor™, Ross products, Reliant, and Pronova) containing about 46% by weight of EPA-E and about 38% by weight of DHA-E is commercially available in the U.S., Europe, and other countries as a drug applied for hypertriglyceridemia. These drugs may be purchased for use in the present invention.

The dose and administration period of the composition of the present invention for preventing the onset of the cardiovascular events is the dose and period sufficient for the expression of the intended action, and the dose and administration period may be adequately adjusted depending on the dosage form, administration route, daily frequency, severity of the symptoms, body weight, age, and the like. When orally administered, the composition may be administered at a dose in terms of EPA-E of 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and more preferably 1.8 to 2.7 g/day, and while such dose is typically administered in 3 divided doses, if desired, such dose may be administered in a single dose or in several divided doses. The composition is preferably administered during or after the meal, and more preferably, immediately (within 30 minutes) after the meal. When such dose is orally administered, the administration period is typically at least 1 year, preferably at least 2 years, more preferably at least 3 years and still more preferably at least 5 years. The administration, however, is preferably continued as long as there is a considerable risk of onset of the cardiovascular events. If necessary, drug holidays of about 1 day to 3 months, and preferably about 1 week to 1 month may be given.

The HMG-CoA RI is preferably used according to the dosage regimen recommended for the particular drug used, and the dose may be adequately adjusted depending on the type, dosage form, administration route, daily frequency, severity of the symptoms, body weight, gender, age, and the like. When orally administered, the HMG-CoA RI is typically administered at a dose of 0.05 to 200 mg/day, and preferably 0.1 to 100 mg/day in a single dose or in two divided doses. If necessary, the total dose may be administered in several divided doses. The dose of the HMG-CoA RI may be reduced depending on the dose of the EPA-E.

It is to be noted that pravastatin sodium (Mevalotin™ tablets and fine granules, Daiichi Sankyo Co., Ltd.), simvastatin (Lipovas™ tablets, Banyu Pharmaceutical Co., Ltd.), fluvastatin sodium (Lochol™ Tablets, Novartis Pharma K.K. and Tanabe Seiyaku Co., Ltd.), atorvastatin calcium hydrate (Lipitor™ tablets, Astellas Pharma Inc. and Pfizer Inc.), pitavastatin calcium (Livalo™, Kowa Company, Ltd. and Daiichi Sankyo Co., Ltd.), and rosuvastatin calcium (Crestor™ tablets, AstraZeneca and Shionogi & Co., Ltd.) are commercially available in Japan as drugs for treating hyperlipidemia, and lovastatin (Mevacor™ tablets, Merck) is commercially available in the U.S. as a drug for treating hyperlipidemia. These drugs may be purchased and used according to the prescribed dosing schedules.

In the case of pravastatin sodium, the preferable daily dose is 5 to 60 mg, and more preferably 10 to 20 mg, and in the case of simvastatin, the preferable daily dose is 2.5 to 60 mg, and more preferably 5 to 20 mg. In the case of fluvastatin sodium, the preferable daily dose is 10 to 180 mg, and more preferably 20 to 60 mg, and in the case of atorvastatin calcium hydrate, the preferable daily dose is 5 to 120 mg, and more preferably 10 to 40 mg. In the case of pitavastatin calcium, the preferable daily dose is 0.5 to 12 mg, and more preferably 1 to 4 mg, and in the case of rosuvastatin calcium, the preferable daily dose is 1.25 to 60 mg, and more preferably 2.5 to 20 mg. in the case of lovastatin, the preferable daily dose is 5 to 160 mg, and more preferably 10 to 80 mg, and in the case of cerivastatin sodium, the preferable daily dose is 0.075 to 0.9 mg, and more preferably 0.15 to 0.3 mg. The dose, however, is not limited to those as described above.

EXAMPLES

Next, the effects of the composition of the present invention are demonstrated by referring to Examples, which by no means limit the scope of the present invention.

Example 1: Effect of the EPA-E in Preventing Occurrence of Cardiovascular Events in Patients Having Multiple Risk Factors

Trial Procedure

This trial corresponds to a partial analysis of the results obtained in JELIS (Japan EPA Lipid Intervention Study) which is a large scale clinical trial of high purity EPA preparation which was presented in The Heart Failure Society of America 2005 Annual Meeting (for general information on JELIS, see Medical Tribune, issue of Nov. 17, 2005, Feature article 3, pp. 75-76).

More specifically, for the EPA-E group (7503 cases) and the control group (7478 cases) evaluated for the primary prevention effect in the 18,645 subject patients of the DELIS trial (EPA-E group (9,326 cases) and control group (9,319 cases)), occurrence of the cardiovascular events was observed and analysed for 5 years from the start of the administration in relation to the number of risk factors at the registration as defined by the following (1) to (4):

(1) obesity: body mass index (BMI) of at least 25;

(2) hypertension or prehypertension: systolic blood pressure (SBP) of at least 140 mmHg or diastolic blood pressure (DBP) of at least 90 mmHg;

(3) diabetes, prediabetes, or abnormal glucose tolerance: fasting blood glucose (FBS) of at least 126 mg/dL or hemoglobin Alc (HbAlc) of at least 6.5%;

(4) hypertriglyceridemia or low HDL cholesterolemia: a triglyceride (TG) of at least 150 mg/dL or a HDL-C of less than 40 mg/dL.

The EPA-E group was orally administered with Epadel (Mochida Pharmaceutical Co., Ltd.) typically at an adult dose of 600 mg per administration and 3 times a day after the meal. However, in the case of abnormal serum TG, the dose could be increased to 900 mg per administration and 3 times a day. In both groups, pravastatin sodium (Mevalotin™ tablets and fine granules, Daiichi Sankyo Co., Ltd.), simvastatin (Lipovas™ tablets, Banyu Pharmaceutical Co., Ltd.), or atorvastatin calcium hydrate (Lipitor™ tablets, Astellas Pharma Inc. and Pfizer Inc.) was used for the base drug, and these drugs were orally administered according to the prescribed dosage regimen. More specifically, pravastatin sodium was orally administered at a daily dose of 10 to 20 mg in a single dose or two divided doses; simvastatin was orally administered at a daily dose of 5 to 20 mg in a single dose; atorvastatin calcium hydrate was orally administered at a daily dose of 10 to 40 mg in a single dose.

Results

The number of occurrence of cardiovascular events in the observation period of 5 years, incidence (%), and rate of suppression of the incidence of the cardiovascular events in the EPA-E group with respect to the control group are shown in Table 1 for each number of risk factors. The rate of suppression of the incidence of the cardiovascular events was calculated by the formula: [{(incidence in the control group)−(incidence in the EPA-E group)}/incidence in the control group]×100.

TABLE 1

Number of risk factors	Incidence in the control group (cases of occurrence/ all cases, %)	Incidence in the EPA-E group (cases of occurrence/ all cases, %)	Rate of Suppression (%)
0	14/1309 (1.1)	11/1326 (0.8)	22
1	29/2424 (1.2)	25/2468 (1.0)	15
2	46/2324 (2.0)	34/2238 (1.5)	23
3	29/1205 (2.4)	28/1229 (2.3)	5
4	9/216 (4.2)	6/242 (2.5)	40
1-2	75/4748 (1.6)	59/4706 (1.3)	21
1-3	104/5953 (1.7)	87/5935 (1.5)	18
1-4	113/6169 (1.8)	93/6177 (1.5)	18
2-3	75/3529 (2.1)	62/3467 (1.8)	16
2-4	84/3745 (2.2)	68/3709 (1.8)	18
3-4	38/1421 (2.7)	34/1471 (2.3)	14

The incidence (%) of cardiovascular events was found to increase with the increase in the number of risk factors. While the incidence was 1.1% for the risk factor number of 0 and 4.2% for the risk factor number 4 in the control group, the incidence was 0.8% in the risk factor number 0 and 2.5% for the case of risk factor number 4 in the group administered with the EPA-E. As evident from Table 1, for all cases of both groups with 1 to 4 risk factors, the cardiovascular event incidence was lower in the group administered with the EPA-E compared to the control group, and the cardiovascular events were suppressed by 5 to 40%. The effect of preventing occurrence of the cardiovascular events by the administration of the EPA-E was thereby confirmed for the hypercholesterolemia patients having the risk factors.

From the results of the trial as described above, the number of occurrence of cardiovascular events in the observation period of 5 years, incidence (%), and rate of suppression of the incidence of the cardiovascular events in the EPA-E group with respect to the control group were calculated for the male patients having at least two risk factors. The results are shown in Table 2. (The calculation was conducted by the same procedure as described above.)

TABLE 2

Number of risk factors	Incidence in the control group (cases of occurrence/ all cases, %)	Incidence in the EPA-E group (cases of occurrence/ all cases, %)	Rate of Suppression (%)
2-4	43/1053 (4.1)	19/1065 (1.8)	56

FIG. 1 is a graph prepared by plotting the incidence of the cardiovascular events in Y-axis and time after the start of the trial in X-axis.

As evident from Table 2 and FIG. 1, in the case of male patients having two or more risk factors, EPA-E significantly suppressed the occurrence of cardiovascular events. It was also confirmed that decrease in the incidence of the cardiovascular events was significant after 2 years or more from

the start of the administration. At the end of the trial, the rate of suppression of the cardiovascular event occurrence was 56% compared to the control group (the value after correcting the dispersion between groups was 55%; see FIG. **1**).

From the results of the trial as described above, the number of occurrence of cardiovascular events in the observation period of 5 years, incidence (%), and rate of suppression of the incidence of the cardiovascular events in the EPA-E group with respect to the control group were calculated for the patients exhibiting a triglyceride (TG) of at least 150 mg/dL and a HDL-C of less than 40 mg/dL as the risk factors. The results are shown in Table 3. (The calculation was conducted by the same procedure as described above.)

TABLE 3

Risk factor	Incidence in the control group (cases of occurrence/ all cases, %)	Incidence in the EPA-E group (cases of occurrence/ all cases, %)	Rate of Suppression (%)
TG of at least 150 mg/dL and HDL-C of less than 40 mg/dL	21/475 (4.4)	11/482 (2.3)	48

FIG. **2** is a graph prepared by plotting the incidence of the cardiovascular events in Y-axis and time after the start of the trial in X-axis.

As evident from Table 3 and FIG. **2**, EPA-E significantly suppressed occurrence of cardiovascular events in the patients having the risk factors of the triglyceride (TG) of at least 150 mg/dL and the HDL-C of less than 40 mg/dL. It was also confirmed that decrease in the incidence of the cardiovascular events was significant after 2 years or more from the start of the administration. At the end of the trial, the rate of suppression of the cardiovascular event occurrence was 48% compared to the control group (the value after correcting the dispersion between groups was 53%; see FIG. **2**). This suggests that the composition containing EPA-E as its effective component effectively prevents the occurrence of the cardiovascular event in the patient having the serum TG/HDL-C ratio of at least 3.75. It is also to be noted that, while the events that occurred in the control group were fatal myocardial infarction, nonfatal myocardial infarction, new occurrence of angina and cardiovascular angioplasty, the events that occurred in the EPA-E group were either nonfatal myocardial infarction or new occurrence of angina, and occurrence of fatal events was not found in the EPA-E group.

In addition, in the group of patients having the risk factor of the triglyceride of at least 150 mg/dL, the occurrence of the cardiovascular events was suppressed by 15% in the EPA-E group compared to the control group; and in the group of patients having the risk factor of HDL-C of less than 40 mg/dL, the occurrence of the cardiovascular events was suppressed by 35% compared to the control group (both values are uncorrected values).

As described above, a significant effect of the EPA-E administration was confirmed for the prevention of the occurrence of the cardiovascular events in the hypercholesterolemia patients having the risk factors.

What is claimed:

1. A method of reducing occurrence of a cardiovascular event in a hypercholesterolemia patient consisting of:

identifying a patient having triglycerides (TG) of at least 150 mg/DL and HDL-C of less than 40 mg/dL in a blood sample taken from the patient as a risk factor of a cardiovascular event, wherein the patient has not previously had a cardiovascular event, and administering ethyl icosapentate in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor,

wherein said 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitor is administered to the patient at least one of before, during and after administering the ethyl icosapentate; and

wherein the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor is selected from the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin, rosuvastatin, and salts thereof, and

wherein daily dose of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor are 5 to 60 mg for pravastatin, 2.5 to 60 mg for simvastatin, 10 to 180 mg for fluvastatin sodium, 5 to 120 mg for atorvastatin calcium hydrate, 0.5 to 12 mg for pitavastatin calcium, 1.25 to 60 mg for rosuvastatin calcium, 5 to 160 mg for lovastatin, and 0.075 to 0.9 mg for cerivastatin sodium.

2. The method according to claim **1**, wherein the ethyl icosapentate is orally administered at a dose of 1.8 g/day to 2.7 g/day.

3. The method according to claim **1**, wherein the hypercholesterolemia patient is a male patient.

4. The method according to claim **1**, wherein the ethyl icosapentate is administered daily for two years or more.

5. The method according to claim **1**, wherein the cardiovascular event is a fatal cardiovascular event.

6. The method according to claim **1**, wherein the hypercholesterolemia patient has a serum [triglyceride (TG)/ HDL-C] ratio of at least 3.75.

7. The method according to claim **1**, wherein the ethyl icosapentate is orally administered at a dose of 0.3 g/day to 6 g/day.

8. The method according to claim **1**, wherein the content of the ethyl icosapentate is at least 96.5% by weight in relation to the total content of fatty acid that is simultaneously administered with the ethyl icosapentate.

9. A method of reducing occurrence of a cardiovascular event in a hypercholesterolemia patient consisting of:

identifying a patient having (i) total cholesterol (TC) of at least 220 mg/dL or LDL-cholesterol (LDL-C) of at least 140 mg/dL, and (ii) triglycerides (TG) of at least 150 mg/dL and HDL-C of less than 40 mg/dL in a blood sample taken from the patient as a risk factors of a cardiovascular event, wherein the patient has not previously had a cardiovascular event, and

administering ethyl icosapentate in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor,

wherein said 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitor is administered to the patient at least one of before, during and after administering the ethyl icosapentate; and

wherein the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor is selected from the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin, rosuvastatin, and salts thereof, and

wherein daily dose of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor are 5 to 60 mg for pravastatin, 2.5 to 60 mg for simvastatin, 10 to 180 mg for fluvastatin sodium, 5 to 120 mg for atorvastatin calcium hydrate, 0.5 to 12 mg for pitavastatin calcium,

1.25 to 60 mg for rosuvastatin calcium, 5 to 160 mg for lovastatin, and 0.075 to 0.9 mg for cerivastatin sodium.

10. The method according to claim **9**, wherein the ethyl icosapentate is orally administered at a dose of 1.8 g/day to 2.7 g/day.

11. The method according to claim **9**, wherein the hypercholesterolemia patient is a male patient.

12. The method according to claim **9**, wherein the ethyl icosapentate is administered daily for two years or more.

13. The method according to claim **9**, wherein the cardiovascular event is a fatal cardiovascular event.

14. The method according to claim **9**, wherein the hypercholesterolemia patient has a serum [triglyceride (TG)/HDL-C] ratio of at least 3.75.

15. The method according to claim **9**, wherein the ethyl icosapentate is orally administered at a dose of 0.3 g/day to 6 g/day.

16. The method according to claim **9**, wherein the content of the ethyl icosapentate is at least 96.5% by weight in relation to the total content of fatty acid that is simultaneously administered with the ethyl icosapentate.

* * * * *

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VASCEPA® safely and effectively. See full prescribing information for VASCEPA.

VASCEPA® (icosapent ethyl) capsules, for oral use
Initial U.S. Approval: 2012

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	12/2019
Warnings and Precautions, Atrial Fibrillation/Flutter (5.1)	12/2019
Warnings and Precautions, Bleeding (5.3)	12/2019

----------INDICATIONS AND USAGE----------

VASCEPA is an ethyl ester of eicosapentaenoic acid (EPA) indicated:

- as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dL) and
  - established cardiovascular disease or
  - diabetes mellitus and 2 or more additional risk factors for cardiovascular disease. (1)
- as an adjunct to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. (1)

Limitations of Use:

- The effect of VASCEPA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined. (1)

----------DOSAGE AND ADMINISTRATION----------

- Assess lipid levels before initiating therapy. Identify other causes of high triglyceride levels and manage as appropriate. (2.1)
- Patients should engage in appropriate nutritional intake and physical activity before receiving VASCEPA, which should continue during treatment. (2.1)
- The daily dose of VASCEPA is 4 grams per day taken as either
  - four 0.5 gram capsules twice daily with food or
  - two 1 gram capsules twice daily with food. (2.2)
- Advise patients to swallow capsules whole. Do not break open, crush, dissolve, or chew VASCEPA. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 0.5 gram and 1 gram (3)

----------CONTRAINDICATIONS----------

VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components. (4)

----------WARNINGS and PRECAUTIONS----------

Atrial Fibrillation/Flutter: VASCEPA was associated with an increased risk of atrial fibrillation or atrial flutter requiring hospitalization in a double-blind, placebo-controlled trial. The incidence of atrial fibrillation was greater in patients with a previous history of atrial fibrillation or atrial flutter. (5.1)
Potential for Allergic Reactions in Patients with Fish Allergy: VASCEPA contains ethyl esters of the omega-3 fatty acid, eicosapentaenoic acid (EPA), obtained from the oil of fish. It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to VASCEPA. Inform patients with known hypersensitivity to fish and/or shellfish about the potential for allergic reactions and advise them to discontinue VASCEPA and seek medical attention if any reactions occur. (5.2)
Bleeding: VASCEPA was associated with an increased risk of bleeding in a double-blind, placebo-controlled trial. The incidence of bleeding was greater in patients receiving concomitant antithrombotic medications, such as aspirin, clopidogrel, or warfarin. (5.3)

----------ADVERSE REACTIONS----------

Common adverse reactions in the cardiovascular outcomes trial (incidence ≥3% and ≥1% more frequent than placebo): musculoskeletal pain, peripheral edema, constipation, gout, and atrial fibrillation (6.1)
Common adverse reactions in the hypertriglyceridemia trials (incidence ≥1% more frequent than placebo): arthralgia and oropharyngeal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amarin Pharma, Inc. at 1-855-VASCEPA (1-855-827-2372) or contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Increased Bleeding Risk with Anticoagulants and Antiplatelet Agents: Some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. Monitor patients receiving VASCEPA and concomitant anticoagulants and/or antiplatelet agents for bleeding. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VASCEPA® (icosapent ethyl) is indicated:

- as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dL) and
  - established cardiovascular disease or
  - diabetes mellitus and 2 or more additional risk factors for cardiovascular disease.
- as an adjunct to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.

Limitations of Use:

The effect of VASCEPA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of VASCEPA

- Assess lipid levels before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate.
- Patients should engage in appropriate nutritional intake and physical activity before receiving VASCEPA, which should continue during treatment with VASCEPA.

2.2 Dosage and Administration

- The daily dose of VASCEPA is 4 grams per day taken as either:
  - four 0.5 gram capsules twice daily with food; or as
  - two 1 gram capsules twice daily with food.
- Advise patients to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA.

3 DOSAGE FORMS AND STRENGTHS

VASCEPA capsules are supplied as:

- 0.5 gram amber-colored, oval, soft-gelatin capsules imprinted with V500
- 1 gram amber-colored, oblong, soft-gelatin capsules imprinted with VASCEPA

4 CONTRAINDICATIONS

VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components.

5 WARNINGS AND PRECAUTIONS

5.1 Atrial Fibrillation/Flutter

VASCEPA is associated with an increased risk of atrial fibrillation or atrial flutter requiring hospitalization. In a double-blind, placebo-controlled trial of 8,179 statin-treated subjects with established cardiovascular disease (CVD) or diabetes plus an additional risk factor

for CVD, adjudicated atrial fibrillation or atrial flutter requiring hospitalization for 24 or more hours occurred in 127 (3%) patients treated with VASCEPA compared to 84 (2%) patients receiving placebo [HR= 1.5 (95% CI 1.14, 1.98)]. The incidence of atrial fibrillation was greater in patients with a previous history of atrial fibrillation or atrial flutter.

5.2 Potential for Allergic Reactions in Patients with Fish Allergy

VASCEPA contains ethyl esters of the omega-3 fatty acid, eicosapentaenoic acid (EPA), obtained from the oil of fish. It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to VASCEPA. Inform patients with known hypersensitivity to fish and/or shellfish about the potential for allergic reactions to VASCEPA and advise them to discontinue VASCEPA and seek medical attention if any reactions occur.

5.3 Bleeding

VASCEPA is associated with an increased risk of bleeding. In a double-blind, placebo-controlled cardiovascular outcomes trial of 8,179 patients, 482 (12%) patients receiving VASCEPA experienced a bleeding event compared to 404 (10%) patients receiving placebo. Serious bleeding events occurred in 111 (3%) of patients on VASCEPA vs. 85 (2%) of patients receiving placebo. The incidence of bleeding was greater in patients receiving concomitant antithrombotic medications, such as aspirin, clopidogrel, or warfarin.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Atrial Fibrillation or Atrial Flutter *[see Warnings and Precautions (5.1)]*
- Potential for Allergic Reactions in Patients with Fish Allergy *[see Warnings and Precautions (5.2)]*
- Bleeding *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Cardiovascular Outcomes Trial

In a double-blind, randomized, placebo-controlled cardiovascular outcomes trial, 8,179 statin-stabilized patients were randomized to receive VASCEPA or placebo and followed for a median of 4.9 years *[see Clinical Studies (14.1)]*. The median age at baseline was 64 years, 29% were women, 90% White, 5% Asian, 2% were Black, and 4% identified as Hispanic ethnicity.

Common adverse reactions (incidence ≥3% on VASCEPA and ≥1% more frequent than placebo) included musculoskeletal pain, peripheral edema, constipation, gout, and atrial fibrillation.

Hypertriglyceridemia Trials

In two randomized, double-blind, placebo-controlled trials in patients with triglyceride levels between 200 and 2000 mg/dL treated for 12 weeks, adverse reactions reported with

VASCEPA at an incidence ≥1% more frequent than placebo based on pooled data included arthralgia and oropharyngeal pain.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during post-approval use of VASCEPA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Diarrhea
- Blood triglycerides increased
- Abdominal discomfort
- Pain in the extremities

7 DRUG INTERACTIONS

7.1 Increased Bleeding Risk with Anticoagulants and Antiplatelet Agents

Some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in those studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Monitor patients receiving VASCEPA and concomitant anticoagulants and/or antiplatelet agents for bleeding.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The available data from published case reports and the pharmacovigilance database on the use of VASCEPA in pregnant women are insufficient to identify a drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies in pregnant rats, non-dose-related imbalances for some minor developmental findings were observed with oral administration of icosapent ethyl during organogenesis at exposures that were equivalent to the clinical exposure at the human dose of 4 g/day, based on body surface area comparisons. In a study in pregnant rabbits orally administered icosapent ethyl during organogenesis, there were no clinically relevant adverse developmental effects at exposures that were 5 times the clinical exposure, based on body surface area comparisons *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In pregnant rats given oral gavage doses of 0.3, 1 and 2 g/kg/day icosapent ethyl from gestation through organogenesis all drug treated groups had non-dose-related imbalances in visceral and skeletal findings, including 13th reduced ribs, additional liver lobes, testes medially

displaced and/or not descended, at human systemic exposures following a maximum oral dose of 4 g/day based on body surface comparisons.

In a multigenerational developmental study in pregnant rats given doses of 0.3, 1, 3 g/kg/day icosapent ethyl by oral gavage from gestation day 7-17, icosapent ethyl did not affect viability in fetuses (F_1 or F_2). Non-dose-related imbalances in findings of absent optic nerves and unilateral testes atrophy at human exposures based on the maximum dose of 4 g/day and on body surface area comparisons. Additional variations consisting of early incisor eruption and increased percent cervical ribs were observed at the same exposures. Pups from high dose treated dams exhibited decreased copulation rates, delayed estrus, decreased implantations and decreased surviving fetuses (F2) suggesting potential multigenerational effects of icosapent ethyl at 7 times human systemic exposure following 4 g/day dose based on body surface area comparisons across species.

In pregnant rabbits given oral gavage doses of 0.1, 0.3, and 1 g/kg/day icosapent ethyl from gestation through organogenesis, a decrease in body weight and food consumption was observed at the high dose of 1 g/kg/day (5 times the human exposure at the maximum dose of 4 g/day, based on body surface area comparisons). Slight increases in resorbed and dead fetuses were noted in the 1 g/kg/day group, but these were not significantly different from the control group. There were no differences between the icosapent ethyl groups and control group as to the number of *corpora lutea*, number of implantations, number of surviving fetuses, sex ratio, body weight of female fetuses or placental weight. There were no treatment-related malformations or skeletal anomalies.

In pregnant rats given icosapent ethyl from gestation day 17 through lactation day 20 at 0.3, 1, 3 g/kg/day no adverse maternal or developmental effects were observed. However, complete litter loss (not dose-related) was noted in 2/23 litters at the low dose and 1/23 mid-dose dams by post-natal day 4 at human exposures at a maximum dose of 4 g/day, based on body surface area comparisons.

8.2 Lactation

Risk Summary

Published studies have detected omega-3 fatty acids, including EPA, in human milk. Lactating women receiving oral omega-3 fatty acids for supplementation have resulted in higher levels of omega-3 fatty acids in human milk. There are no data on the effects of omega-3 fatty acid ethyl esters on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VASCEPA and any potential adverse effects on the breastfed child from VASCEPA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in well-controlled clinical studies of VASCEPA, 45% were 65 years of age and over. No overall differences in safety or effectiveness were observed

between these patients and younger groups. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

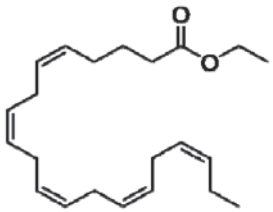
8.7 Hepatic Impairment

In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored periodically during therapy with VASCEPA.

11 DESCRIPTION

VASCEPA, a lipid-regulating agent, is supplied as either a 0.5 gram or a 1 gram amber-colored, liquid-filled soft gelatin capsule for oral use.

Each VASCEPA capsule contains either 0.5 grams of icosapent ethyl (in a 0.5 gram capsule) or 1 gram of icosapent ethyl (in a 1 gram capsule). Icosapent ethyl is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA). The empirical formula of icosapent ethyl is $C_{22}H_{34}O_2$ and the molecular weight is 330.51. The chemical name for icosapent ethyl is ethyl all-cis-5,8,11,14,17-icosapentaenoate with the following chemical structure:



VASCEPA capsules also contain the following inactive ingredients: tocopherol, gelatin, glycerin, maltitol, sorbitol, and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Studies suggest that EPA reduces hepatic very low-density lipoprotein triglycerides (VLDL-TG) synthesis and/or secretion and enhances TG clearance from circulating VLDL particles. Potential mechanisms of action include increased β-oxidation; inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase (DGAT); decreased lipogenesis in the liver; and increased plasma lipoprotein lipase activity.

The mechanisms of action contributing to reduction of cardiovascular events with VASCEPA (icosapent ethyl) are not completely understood but are likely multi-factorial. Increased EPA lipid composition from carotid plaque specimens and increased circulating EPA/arachidonic acid ratio have been observed following EPA treatment. EPA inhibits platelet aggregation under some ex vivo conditions. However, the direct clinical meaning of individual findings is not clear.

12.2 Pharmacodynamics

In a 12-week, dose-ranging study in patients with severe hypertriglyceridemia and in the event-driven REDUCE-IT® trial, VASCEPA 4 grams per day reduced median TG from baseline relative to placebo [see Clinical Studies (14)].

12.3 Pharmacokinetics

Absorption

After oral administration, VASCEPA is de-esterified during the absorption process and the active metabolite EPA is absorbed in the small intestine and enters the systemic circulation mainly via the thoracic duct lymphatic system. Peak plasma concentrations of EPA were reached approximately 5 hours following oral doses of VASCEPA.

VASCEPA was administered with or following a meal in all clinical studies; no food effect studies were performed. Take VASCEPA with or following a meal.

Distribution

The mean volume of distribution at steady state of EPA is approximately 88 liters. The majority of EPA circulating in plasma is incorporated in phospholipids, triglycerides and cholesteryl esters, and <1% is present as the unesterified fatty acid. Greater than 99% of unesterified EPA is bound to plasma proteins.

Elimination

Metabolism

EPA is mainly metabolized by the liver via beta-oxidation similar to dietary fatty acids. Beta oxidation splits the long carbon chain of EPA into acetyl Coenzyme A, which is converted into energy via the Krebs cycle. Cytochrome P450-mediated metabolism is a minor pathway of elimination of EPA.

Excretion

The total plasma clearance of EPA at steady state is 684 mL/hr. The plasma elimination half-life ($t_{1/2}$) of EPA is approximately 89 hours. VASCEPA does not undergo renal excretion.

Specific Populations

Gender

When administered VASCEPA in clinical trials, plasma total EPA concentrations did not differ significantly between men and women.

Pediatric

The pharmacokinetics of VASCEPA have not been studied in pediatric patients.

Hepatic or Renal Impairment

VASCEPA has not been studied in patients with renal or hepatic impairment.

Drug Interaction Studies

Omeprazole

In a drug-drug interaction study with 28 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the steady-state AUC_{τ} or C_{max} of omeprazole when co-administered at 40 mg/day to steady-state.

Rosiglitazone

In a drug-drug interaction study with 28 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the single dose AUC or C_{max} of rosiglitazone at 8 mg.

Warfarin

In a drug-drug interaction study with 25 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the single dose AUC or C_{max} of *R*- and *S*-warfarin or the anti-coagulation pharmacodynamics of warfarin when co-administered as racemic warfarin at 25 mg.

Atorvastatin

In a drug-drug interaction study of 26 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the steady-state AUC_{τ} or C_{max} of atorvastatin, 2-hydroxyatorvastatin, or 4-hydroxyatorvastatin when co-administered with atorvastatin 80 mg/day at steady-state.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year rat carcinogenicity study with oral gavage doses of 0.09, 0.27, and 0.91 g/kg/day icosapent ethyl, respectively, males did not exhibit drug-related neoplasms. Hemangiomas and hemangiosarcomas of the mesenteric lymph node, the site of drug absorption, were observed in females at clinically relevant exposures based on body surface area comparisons across species relative to the maximum clinical dose of 4 g/day. Overall incidence of hemangiomas and hemangiosarcomas in all vascular tissues did not increase with treatment.

In a 6-month carcinogenicity study in Tg.rasH2 transgenic mice with oral gavage doses of 0.5, 1, 2, and 4.6 g/kg/day icosapent ethyl, drug-related incidences of benign squamous cell papilloma in the skin and subcutis of the tail was observed in high dose male mice. The papillomas were considered to develop secondary to chronic irritation of the proximal tail associated with fecal excretion of oil and therefore not clinically relevant. Drug-related neoplasms were not observed in female mice.

Icosapent ethyl was not mutagenic with or without metabolic activation in the bacterial mutagenesis (Ames) assay or in the *in vivo* mouse micronucleus assay. A chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells was positive for clastogenicity with and without metabolic activation.

In an oral gavage rat fertility study, ethyl-EPA, administered at doses of 0.3, 1, and 3 g/kg/day to male rats for 9 weeks before mating and to female rats for 14 days before mating through day 7 of gestation, increased anogenital distance in female pups and increased cervical ribs were observed at 3 g/kg/day (7 times human systemic exposure with 4 g/day clinical dose based on a body surface area comparison).

14 CLINICAL STUDIES

14.1 Prevention of Cardiovascular Events

REDUCE-IT (NCT01492361) was a multinational, double-blind, randomized, placebo-controlled, event-driven trial in 8,179 (4,089 VASCEPA, 4,090 placebo) statin-treated adult patients enrolled with LDL-C >40 mg/dL and ≤100 mg/dL and elevated TG levels (90% of enrolled patients had TG ≥ 150 mg/dL and <500 mg/dL) and either established cardiovascular disease (71%) or diabetes and other risk factors for cardiovascular disease (29%). Patients with established cardiovascular disease were defined as being at least 45 years of age and having a documented history of coronary artery disease, cerebrovascular or carotid disease, or peripheral artery disease. Patients with other risk factors for cardiovascular disease were defined as being at least 50 years of age with diabetes and at least one additional risk factor. Patients were randomly assigned 1:1 to receive either VASCEPA (4 grams daily) or placebo. The median follow-up duration was 4.9 years. Overall, 99.8% of patients were followed for vital status until the end of the trial or death.

The median age at baseline was 64 years and 29% were women. The trial population was 90% White, 5% Asian, 2% Black; 4% identified as Hispanic ethnicity. Selected additional baseline risk factors included hypertension (87%), type 2 diabetes mellitus (58%), eGFR < 60 mL/min per 1.73 m^2 (22%), congestive heart failure (18%), and current daily cigarette smoking (15%).

Most patients were taking moderate-intensity (63%) or high-intensity (31%) statin therapy at baseline. Most patients at baseline were taking at least one other cardiovascular medication, including anti-platelet agents (79%) or anti-hypertensives (95%), including beta blockers (71%), angiotensin converting enzyme (ACE) inhibitors (52%), or angiotensin receptor blockers (ARB; 27%).

On stable background lipid-lowering therapy, the median [Q1, Q3] LDL-C at baseline was 75.0 [62.0, 89.0] mg/dL; the mean (SD) was 76.2 (20.3) mg/dL. The median [Q1, Q3] fasting TG was 216.0 [176.0, 272.5] mg/dL; the mean (SD) was 233.2 (80.1) mg/dL.

VASCEPA significantly reduced the risk for the primary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina; p<0.0001) and the key secondary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, or stroke; p<0.0001). The results of the primary, key secondary, and other secondary efficacy endpoints in the prespecified testing hierarchy to control for type 1 error are shown in Table 2. The Kaplan-Meier estimates of the cumulative incidence of the primary composite endpoints over time are shown in Figure 1.

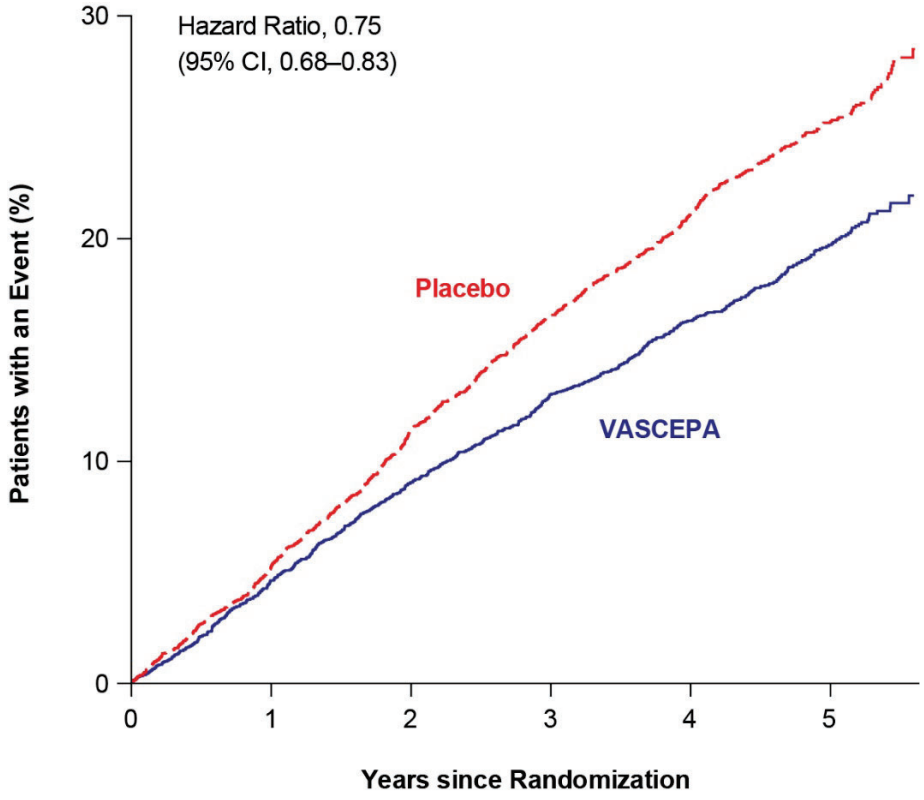
Table 1. Effect of VASCEPA on Time to First Occurrence of Cardiovascular Events in Patients with Elevated Triglyceride Levels and Other Risk Factors for Cardiovascular Disease in REDUCE-IT

	VASCEPA		Placebo		VASCEPA vs Placebo
	N = 4089 n (%)	Incidence Rate (per 100 patient years)	N = 4090 n (%)	Incidence Rate (per 100 patient years)	Hazard Ratio (95% CI)
Primary composite endpoint					
Cardiovascular death, myocardial infarction, stroke, coronary revascularization, hospitalization for unstable angina (5-point MACE)	705 (17.2)	4.3	901 (22.0)	5.7	0.75 (0.68, 0.83)
Key secondary composite endpoint					
Cardiovascular death, myocardial infarction, stroke (3-point MACE)	459 (11.2)	2.7	606 (14.8)	3.7	0.74 (0.65, 0.83)
Other secondary endpoints					
Fatal or non-fatal myocardial infarction	250 (6.1)	1.5	355 (8.7)	2.1	0.69 (0.58, 0.81)
Emergent or urgent coronary revascularization	216 (5.3)	1.3	321 (7.8)	1.9	0.65 (0.55, 0.78)
Cardiovascular death [1]	174 (4.3)	1.0	213 (5.2)	1.2	0.80 (0.66, 0.98)
Hospitalization for unstable angina [2]	108 (2.6)	0.6	157 (3.8)	0.9	0.68 (0.53, 0.87)

	VASCEPA		Placebo		VASCEPA vs Placebo
	N = 4089 n (%)	Incidence Rate (per 100 patient years)	N = 4090 n (%)	Incidence Rate (per 100 patient years)	Hazard Ratio (95% CI)
Fatal or non-fatal stroke	98 (2.4)	0.6	134 (3.3)	0.8	0.72 (0.55, 0.93)

[1] Includes adjudicated cardiovascular deaths and deaths of undetermined causality.
[2] Determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

Figure 1. Kaplan-Meier Estimated Cumulative Incidence of Primary Composite Endpoint in REDUCE-IT



No. at Risk						
Placebo	4090	3743	3327	2807	2347	1358
VASCEPA	4089	3787	3431	2951	2503	1430

CI=confidence interval

The median TG and LDL-C baseline values were similar between the VASCEPA group and placebo group. The median change in TG from baseline to Year 1 was -39 mg/dL (-18%) in the VASCEPA group and 5 mg/dL (2%) in the placebo group. The median change in LDL-C from baseline to Year 1 was 2 mg/dL (3%) in the VASCEPA group and 7 mg/dL (10%) in the placebo group.

14.2 Severe Hypertriglyceridemia

The effects of VASCEPA 4 grams per day were assessed in a randomized, placebo-controlled, double-blind, parallel-group study of adult patients (76 on VASCEPA, 75 on placebo) with severe hypertriglyceridemia. Patients whose baseline TG levels were between 500 and 2,000 mg/dL were enrolled in this study for 12 weeks. The median baseline TG and LDL-C levels in these patients were 684 mg/dL and 86 mg/dL, respectively. Median baseline HDL-C level was 27 mg/dL. The randomized population in this study was mostly Caucasian (88%) and male (76%). The mean age was 53 years and the mean body mass index was 31 kg/m^2. Twenty-five percent of patients were on concomitant statin therapy, 28% were diabetics, and 39% of the patients had TG levels >750 mg/dL.

The changes in the major lipoprotein lipid parameters for the groups receiving VASCEPA or placebo are shown in Table 2.

Table 2. Median Baseline and Percent Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia (≥500 mg/dL)

Parameter	VASCEPA 4 g/day N=76		Placebo N=75		Difference (95% Confidence Interval)
	Baseline	% Change	Baseline	% Change	
TG (mg/dL)	680	-27	703	+10	-33* (-47, -22)
LDL-C (mg/dL)	91	-5	86	-3	-2 (-13, +8)
Non-HDL-C (mg/dL)	225	-8	229	+8	-18 (-25, -11)
TC (mg/dL)	254	-7	256	+8	-16 (-22, -11)
HDL-C (mg/dL)	27	-4	27	0	-4 (-9, +2)
VLDL-C (mg/dL)	123	-20	124	+14	-29** (-43, -14)
Apo B (mg/dL)	121	-4	118	+4	-9**(-14, -3)

% Change= Median Percent Change from Baseline
Difference= Median of [VASCEPA % Change – Placebo % Change] (Hodges-Lehmann Estimate)
p-values from Wilcoxon rank-sum test

*p-value < 0.001 (primary efficacy endpoint)

**p-value < 0.05 (key secondary efficacy endpoints determined to be statistically significant according to the pre-specified multiple comparison procedure)

VASCEPA 4 grams per day reduced median TG, VLDL-C, and Apo B levels from baseline relative to placebo. The reduction in TG observed with VASCEPA was not associated with elevations in LDL-C levels relative to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

VASCEPA (icosapent ethyl) capsules are supplied as:

Strength	Quantity	Description	NDC
0.5 gram capsules	Bottles of 240	amber-colored soft-gelatin capsules imprinted with V500	52937-003-40
1 gram capsules	Bottles of 120	amber-colored soft-gelatin capsules imprinted with VASCEPA	52937-001-20

Store at 20° to 25° C (68° to 77°F); excursions permitted to 15° to 30° C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling before starting VASCEPA (Patient Information).

Inform patients that VASCEPA may increase their risk for atrial fibrillation or atrial flutter *[see Warnings and Precautions (5.1)]*.

Inform patients with known hypersensitivity to fish and/or shellfish about the potential for allergic reactions to VASCEPA and advise them to discontinue VASCEPA and seek medical attention if any reactions occur *[see Warnings and Precautions (5.2)]*.

Inform patients that VASCEPA may increase their risk for bleeding, especially if they are receiving other antithrombotic agents *[see Warnings and Precautions (5.3)]*.

Advise patients to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA *[see Dosage and Administration (2.2)]*.

Instruct patients to take VASCEPA as prescribed. If a dose is missed, patients should take it as soon as they remember. However, if they miss one day of VASCEPA, they should not double the dose when they take it.

For more information about VASCEPA, go to www.VASCEPA.com or call 1-855-VASCEPA (1-855-827-2372).

AMARIN®

VASCEPA® (icosapent ethyl)

Distributed by:
Amarin Pharma, Inc.
Bridgewater, NJ, USA

Manufactured for:
Amarin Pharmaceuticals Ireland Limited
Dublin, Ireland

VASCEPA is a registered trademark of the Amarin group of companies

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P00120L 12/2019

PATIENT INFORMATION
VASCEPA® (vas-EE-puh) (icosapent ethyl)
capsules

What is VASCEPA?
VASCEPA is a prescription medicine used:

- along with certain medicines (statins) to reduce the risk of heart attack, stroke, and certain types of heart issues requiring hospitalization in adults with heart (cardiovascular) disease, or diabetes and 2 or more additional risk factors for heart disease.
- along with a low-fat and low-cholesterol diet to lower high levels of triglycerides (fats) in adults.

It is not known if VASCEPA changes your risk of having inflammation of your pancreas (pancreatitis).
It is not known if VASCEPA is safe and effective in children.

Do not take VASCEPA if you are allergic to icosapent ethyl or any of the ingredients in VASCEPA.
See the end of this leaflet for a complete list of ingredients in VASCEPA.

Before taking VASCEPA, tell your doctor about all of your medical conditions, including if you:

- have diabetes.
- have a low thyroid problem (hypothyroidism).
- have a liver problem.
- have a pancreas problem.
- are allergic to fish or shellfish. It is not known if people who are allergic to fish or shellfish are also allergic to VASCEPA.
- are pregnant, or planning to become pregnant. It is not known if VASCEPA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. VASCEPA can pass into your breast milk, and may harm your baby. Talk to your doctor about the best way to feed your baby if you take VASCEPA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and dietary or herbal supplements.
VASCEPA can interact with certain other medicines that you are taking.
Especially tell your doctor if you take medicines that affect your blood clotting (anticoagulants or blood thinners).

How should I take VASCEPA?

- Take VASCEPA exactly as your doctor tells you to take it.
- Do not change your dose or stop taking VASCEPA without talking to your doctor.
- Do not take more capsules than what is prescribed by your doctor.
  - If you are prescribed the 0.5 gram capsules, you should not take more than 8 capsules each day with food.
  - If you are prescribed the 1 gram capsules, you should not take more than 4 capsules each day with food.
- Take VASCEPA capsules whole. Do not break, crush, dissolve, or chew VASCEPA capsules before swallowing.
- If you miss a dose of VASCEPA, take it as soon as you remember. However, if you miss one day of VASCEPA, do not double your dose when you take it.
- Your doctor may start you on a diet that is low in saturated fat, cholesterol, carbohydrates, and low in added sugars before giving you VASCEPA. Stay on this diet while taking VASCEPA.
- Your doctor may do blood tests to check your triglyceride and other lipid levels while you take VASCEPA.

What are the possible side effects of VASCEPA?
VASCEPA may cause serious side effects, including:

- **Heart rhythm problems (atrial fibrillation and atrial flutter).** Heart rhythm problems which can be serious and cause hospitalization have happened in people who take VASCEPA, especially in people who have heart (cardiovascular) disease or diabetes with a risk factor for heart (cardiovascular) disease, or who have had heart rhythm problems in the past. Tell your doctor if you get any symptoms of heart rhythm problems such as feeling as if your heart is beating fast and irregular, lightheadedness, dizziness, shortness of breath, chest discomfort, or you faint.
- **Possible allergic reactions if you are allergic to fish or shellfish.** Stop taking VASCEPA and tell your doctor right away or get emergency medical help if you have any signs or symptoms of an allergic reaction.

- **Bleeding.** Serious bleeding can happen in people who take VASCEPA. Your risk of bleeding may increase if you are also taking a blood thinner medicine.

If you have liver problems and are taking VASCEPA, your doctor should do blood tests during treatment.

The most common side effects of VASCEPA include:

- Muscle and joint pain.
- Swelling of the hands, legs, or feet.
- Constipation
- Gout
- Heart rhythm problems (atrial fibrillation).

These are not all the possible side effects of VASCEPA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VASCEPA?

- Store VASCEPA at room temperature between 68° to 77° F (20° to 25° C).
- Safely throw away medicine that is out of date or no longer needed.

Keep VASCEPA and all medicine out of the reach of children.

General information about the safe and effective use of VASCEPA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VASCEPA for a condition for which it was not prescribed. Do not give VASCEPA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about VASCEPA that is written for health professionals.

What are the ingredients in VASCEPA?

Active ingredient: icosapent ethyl

Inactive ingredients: tocopherol, gelatin, glycerin, maltitol, sorbitol, and purified water

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PP00120L
Distributed by: Amarin Pharma, Inc. Bridgewater, NJ, USA
Manufactured for: Amarin Pharmaceuticals Ireland Limited Dublin, Ireland +1-855-VASCEPA (+1-855-827-2372) www.vascepa.com
For more information, go to www.vascepa.com or call 1-855-VASCEPA (1-855-827-2372).
This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 12/2019

HIGHLIGHTS OF PRESCRIBING INFORMATION

VASCEPA™ (icosapent ethyl) Capsules, for oral use
Initial U.S. Approval: 2012

These highlights do not include all of the information needed to use VASCEPA™ safely and effectively. See full prescribing information for VASCEPA.

----------INDICATIONS AND USAGE----------

VASCEPA is an ethyl ester of eicosapentaenoic acid (EPA) indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. (1)

Limitations of Use:

•The effect of VASCEPA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined. (1)

•The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined. (1)

----------DOSAGE AND ADMINISTRATION----------

The daily dose of VASCEPA is 4 grams per day taken as 2 capsules twice daily with food. (2)

Patients should be advised to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 1 gram (3)

----------CONTRAINDICATIONS----------

VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components. (4)

----------WARNINGS and PRECAUTIONS----------

In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy. (5.1)

Use with caution in patients with known hypersensitivity to fish and/or shellfish. (5.2)

----------ADVERSE REACTIONS----------

The most common reported adverse reaction (incidence >2% and greater than placebo) was arthralgia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amarin Pharma Inc. at 1-855-VASCEPA (1-855-827-2372) or contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Omega-3 acids may prolong bleeding time. Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically. (7)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)

Pediatric Use: The safety and effectiveness in pediatric patients have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2012

FULL PRESCRIBING INFORMATION:

CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VASCEPA™ (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

Usage Considerations: Patients should be placed on an appropriate lipid-lowering diet and exercise regimen before receiving VASCEPA and should continue this diet and exercise regimen with VASCEPA.

Attempts should be made to control any medical problems such as diabetes mellitus, hypothyroidism, and alcohol intake that may contribute to lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed, if possible, prior to consideration of TG-lowering drug therapy.

Limitations of Use:

The effect of VASCEPA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

2 DOSAGE AND ADMINISTRATION

Assess lipid levels before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate. *[see Indications and Usage (1)]*.

Patients should engage in appropriate nutritional intake and physical activity before receiving VASCEPA, which should continue during treatment with VASCEPA.

The daily dose of VASCEPA is 4 grams per day taken as 2 capsules twice daily with food.

Patients should be advised to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA.

3 DOSAGE FORMS AND STRENGTHS

VASCEPA capsules are supplied as 1-gram amber-colored soft-gelatin capsules imprinted with VASCEPA.

4 CONTRAINDICATIONS

VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components.

5 WARNINGS AND PRECAUTIONS

5.1 Monitoring: Laboratory Tests

In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored periodically during therapy with VASCEPA.

5.2 Fish Allergy

VASCEPA contains ethyl esters of the omega-3 fatty acid, eicosapentaenoic acid (EPA), obtained from the oil of fish. It is not known whether patients with allergies to fish and/or

shellfish are at increased risk of an allergic reaction to VASCEPA. VASCEPA should be used with caution in patients with known hypersensitivity to fish and/or shellfish.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions reported in at least 2% and at a greater rate than placebo for patients treated with VASCEPA based on pooled data across two clinical studies are listed in Table 1.

Table 1. Adverse Reactions Occurring at Incidence >2% and Greater than Placebo in Double-Blind, Placebo-Controlled Trials*

	Placebo (N=309)		VASCEPA (N=622)	
Adverse Reaction	**n**	**%**	**n**	**%**
Arthralgia	3	1.0	14	2.3

*Studies included patients with triglycerides values of 200 to 2000 mg/dL.

An additional adverse reaction from clinical studies was oropharyngeal pain.

7 DRUG INTERACTIONS

7.1 Anticoagulants

Some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in those studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. It is unknown whether VASCEPA can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. VASCEPA should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

In pregnant rats given oral gavage doses of 0.3, 1 and 2 g/kg/day icosapent ethyl from gestation through organogenesis all drug treated groups had visceral or skeletal abnormalities including: 13th reduced ribs, additional liver lobes, testes medially displaced and/or not descended at human systemic exposures following a maximum oral dose of 4 g/day based on body surface comparisons. Variations including incomplete or abnormal ossification of various skeletal bones were observed in the 2 g/kg/day group at 5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison.

In a multigenerational developmental study in pregnant rats given oral gavage doses of 0.3, 1, 3 g/kg/day ethyl-EPA from gestation day 7-17, an increased incidence of absent optic nerves and unilateral testes atrophy were observed at ≥0.3 g/kg/day at human systemic exposure following an oral dose of 4 g/day based on body surface area comparisons across species.

Additional variations consisting of early incisor eruption and increased percent cervical ribs were observed at the same exposures. Pups from high dose treated dams exhibited decreased copulation rates, delayed estrus, decreased implantations and decreased surviving fetuses (F2) suggesting multigenerational effects of ethyl-EPA at 7 times human systemic exposure following 4 g/day dose based on body surface area comparisons across species.

In pregnant rabbits given oral gavage doses of 0.1, 0.3, and 1 g/kg/day from gestation through organogenesis there were increased dead fetuses at 1 g/kg/day secondary to maternal toxicity (significantly decreased food consumption and body weight loss).

In pregnant rats given ethyl-EPA from gestation day 17 through lactation day 20 at 0.3, 1, 3 g/kg/day complete litter loss was observed in 2/23 litters at the low dose and 1/23 mid-dose dams by post-natal day 4 at human exposures based on a maximum dose of 4 g/day comparing body surface areas across species.

8.3 Nursing Mothers

Studies with omega-3-acid ethyl esters have demonstrated excretion in human milk. The effect of this excretion is unknown; caution should be exercised when VASCEPA is administered to a nursing mother. In lactating rats, given oral gavage ^{14}C-ethyl EPA, drug levels were 6 to 14 times higher in milk than in plasma.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of VASCEPA, 33% were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

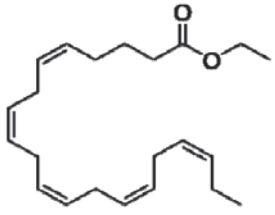
9 DRUG ABUSE AND DEPENDENCE

VASCEPA does not have any known drug abuse or withdrawal effects.

11 DESCRIPTION

VASCEPA, a lipid-regulating agent, is supplied as a 1-gram amber-colored, liquid-filled soft gelatin capsule for oral administration.

Each VASCEPA capsule contains 1 gram of icosapent ethyl. Icosapent ethyl is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA). The empirical formula of icosapent ethyl is $C_{22}H_{34}O_2$ and the molecular weight is 330.51. The chemical name for icosapent ethyl is ethyl all-cis-5,8,11,14,17-icosapentaenoate with the following chemical structure:



VASCEPA 1 gram capsules also contain the following inactive ingredients: tocopherol, gelatin, glycerin, maltitol, sorbitol, and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Studies suggest that EPA reduces hepatic very low-density lipoprotein triglycerides (VLDL-TG) synthesis and/or secretion and enhances TG clearance from circulating VLDL particles. Potential mechanisms of action include increased β-oxidation; inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase (DGAT); decreased lipogenesis in the liver; and increased plasma lipoprotein lipase activity.

12.3 Pharmacokinetics

Absorption: After oral administration, VASCEPA is de-esterified during the absorption process and the active metabolite EPA is absorbed in the small intestine and enters the systemic circulation mainly via the thoracic duct lymphatic system. Peak plasma concentrations of EPA were reached approximately 5 hours following oral doses of VASCEPA.

VASCEPA was administered with or following a meal in all clinical studies; no food effect studies were performed. Take VASCEPA with or following a meal.

Distribution: The mean volume of distribution at steady-state of EPA is approximately 88 liters. The majority of EPA circulating in plasma is incorporated in phospholipids, triglycerides and cholesteryl esters, and <1% is present as the unesterified fatty acid. Greater than 99% of unesterified EPA is bound to plasma proteins.

Metabolism and Excretion: EPA is mainly metabolized by the liver via beta-oxidation similar to dietary fatty acids. Beta oxidation splits the long carbon chain of EPA into acetyl Coenzyme A, which is converted into energy via the Krebs cycle. Cytochrome P450-mediated metabolism is a minor pathway of elimination of EPA. The total plasma clearance of EPA at steady state is 684 mL/hr. The plasma elimination half-life ($t_{1/2}$) of EPA is approximately 89 hours. VASCEPA does not undergo renal excretion.

Drug-Drug Interactions

VASCEPA was studied at the 4 g/day dose level with the following medications which are typical substrates of cytochrome P450 enzymes, and no drug-drug interactions were observed:

Omeprazole: In a drug-drug interaction study with 28 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the steady-state AUC_τ or C_{max} of omeprazole when co-administered at 40 mg/day to steady-state.

Rosiglitazone: In a drug-drug interaction study with 28 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the single dose AUC or C_{max} of rosiglitazone at 4 mg.

Warfarin: In a drug-drug interaction study with 25 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the single dose AUC or C_{max} of *R*- and *S*-warfarin or the anti-coagulation pharmacodynamics of warfarin when co-administered as racemic warfarin at 25 mg.

Atorvastatin: In a drug-drug interaction study of 26 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the steady-state AUC_τ or C_{max} of atorvastatin,

2-hydroxyatorvastatin, or 4-hydroxyatorvastatin when co-administered with atorvastatin 80 mg/day to steady-state.

Specific Populations

Gender: When administered VASCEPA in clinical trials, plasma total EPA concentrations did not differ significantly between men and women.

Pediatric: The pharmacokinetics of VASCEPA has not been studied in pediatric patients.

Hepatic or Renal Impairment: VASCEPA has not been studied in patients with renal or hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year rat carcinogenicity study with oral gavage doses of 0.09, 0.27, and 0.91 g/kg/day icosapent ethyl, respectively, males did not exhibit drug-related neoplasms. Hemangiomas and hemangiosarcomas of the mesenteric lymph node, the site of drug absorption, were observed in females at clinically relevant exposures based on body surface area comparisons across species relative to the maximum clinical dose of 4 g/day. Overall incidence of hemangiomas and hemangiosarcomas in all vascular tissues did not increase with treatment.

In a 6-month carcinogenicity study in Tg.rasH2 transgenic mice with oral gavage doses of 0.5, 1, 2, and 4.6 g/kg/day icosapent ethyl, drug-related incidences of benign squamous cell papilloma in the skin and subcutis of the tail was observed in high dose male mice. The papillomas were considered to develop secondary to chronic irritation of the proximal tail associated with fecal excretion of oil and therefore not clinically relevant. Drug-related neoplasms were not observed in female mice.

Icosapent ethyl was not mutagenic with or without metabolic activation in the bacterial mutagenesis (Ames) assay or in the *in vivo* mouse micronucleus assay. A chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells was positive for clastogenicity with and without metabolic activation.

In an oral gavage rat fertility study, ethyl-EPA, administered at doses of 0.3, 1, and 3 g/kg/day to male rats for 9 weeks before mating and to female rats for 14 days before mating through day 7 of gestation, increased anogenital distance in female pups and increased cervical ribs were observed at 3 g/kg/day (7 times human systemic exposure with 4 g/day clinical dose based on a body surface area comparison).

14 CLINICAL STUDIES

14.1 Severe Hypertriglyceridemia

The effects of VASCEPA 4 grams per day were assessed in a randomized, placebo-controlled, double-blind, parallel-group study of adult patients (76 on VASCEPA, 75 on placebo) with severe hypertriglyceridemia. Patients whose baseline TG levels were between 500 and 2,000 mg/dL were enrolled in this study for 12 weeks. The median baseline TG and LDL-C levels in these patients were 684 mg/dL and 86 mg/dL, respectively. Median baseline HDL-C level was 27 mg/dL. The randomized population in this study was mostly Caucasian (88%) and male (76%). The mean age was 53 years and the mean body mass index was 31 kg/m^2. Twenty-five percent of patients were on concomitant statin therapy, 28% were diabetics, and 39% of the patients had TG levels >750 mg/dL.

The changes in the major lipoprotein lipid parameters for the groups receiving VASCEPA or placebo are shown in Table 2.

Table 2. Median Baseline and Percent Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia (≥500 mg/dL)

Parameter	Vascepa 4 g/day N=76		Placebo N=75		Difference (95% Confidence Interval)
	Baseline	% Change	Baseline	% Change	
TG (mg/dL)	680	-27	703	+10	-33* (-47, -22)
LDL-C (mg/dL)	91	-5	86	-3	-2 (-13, +8)
Non-HDL-C (mg/dL)	225	-8	229	+8	-18 (-25, -11)
TC (mg/dL)	254	-7	256	+8	-16 (-22, -11)
HDL-C (mg/dL)	27	-4	27	0	-4 (-9, +2)
VLDL-C (mg/dL)	123	-20	124	+14	-29** (-43, -14)
Apo B (mg/dL)	121	-4	118	+4	-9**(-14, -3)

% Change= Median Percent Change from Baseline
Difference= Median of [VASCEPA % Change – Placebo % Change] (Hodges-Lehmann Estimate)
p-values from Wilcoxon rank-sum test

*p-value < 0.001 (primary efficacy endpoint)

**p-value < 0.05 (key secondary efficacy endpoints determined to be statistically significant according to the pre-specified multiple comparison procedure)

VASCEPA 4 grams per day reduced median TG, VLDL-C, and Apo B levels from baseline relative to placebo. The reduction in TG observed with VASCEPA was not associated with elevations in LDL-C levels relative to placebo.

The effect of VASCEPA on the risk of pancreatitis in patients with severe hypertriglyceridemia has not been determined.

The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia levels has not been determined.

16 HOW SUPPLIED/STORAGE AND HANDLING

VASCEPA (icosapent ethyl) capsules are supplied as 1-gram amber-colored soft-gelatin capsules imprinted with VASCEPA.

Bottles of 120: NDC 52937-001-20.

Store at 20° to 25° C (68° to 77°F); excursions permitted to 15° to 30° C (59° to 86°F) [see USP Controlled Room Temperature]. Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

VASCEPA should be used with caution in patients with known sensitivity or allergy to fish and/or shellfish *[see Warnings and Precautions (5.2)]*.

Patients should be advised that use of lipid-regulating agents does not reduce the importance of appropriate nutritional intake and physical activity *[see Dosage and Administration (2)]*.

Patients should be advised not to alter VASCEPA capsules in any way and to ingest intact capsules only *[see Dosage and Administration (2)]*.

Instruct patients to take VASCEPA as prescribed. If a dose is missed, patients should take it as soon as they remember. However if they miss one day of VASCEPA, they should not double the dose when they take it.

Distributed by:
Amarin Pharma Inc.
Bedminster, NJ, USA

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Manufactured for:
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www.VASCEPA.com

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P00120A 7/12

PATIENT INFORMATION
VASCEPA™ (pronounced vas-EE-puh)
(icosapent ethyl)
Capsules

Read this Patient Information before you start taking VASCEPA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is VASCEPA?

VASCEPA is a prescription medicine used along with a low-fat and low-cholesterol diet to lower high levels of triglycerides (fats) in adults.

It is not known if VASCEPA changes your risk of having inflammation of your pancreas (pancreatitis).

It is not known if VASCEPA prevents you from having a heart attack or stroke.

It is not known if VASCEPA is safe and effective in children.

Who should not take VASCEPA?

Do not take VASCEPA if you are allergic to icosapent ethyl or any of the ingredients in VASCEPA. See the end of this leaflet for a complete list of ingredients in VASCEPA.

What should I tell my doctor before taking VASCEPA?

Before you take VASCEPA, tell your doctor if you:

- have diabetes.
- have a low thyroid problem (hypothyroidism).
- have a liver problem.
- have a pancreas problem.
- are allergic to fish or shellfish. It is not known if people who are allergic to fish or shellfish are also allergic to VASCEPA.
- are pregnant, or planning to become pregnant. It is not known if VASCEPA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. VASCEPA can pass into your milk, and may harm your baby. Talk to your doctor about the best way to feed your baby if you take VASCEPA.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and dietary or herbal supplements.

VASCEPA can interact with certain other medicines that you are taking.

Especially tell your doctor if you take medicines that affect your blood clotting (anticoagulants or blood thinners).

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take VASCEPA?

- Take VASCEPA exactly as your doctor tells you to take it.
- Do not change your dose or stop taking VASCEPA without talking to your doctor.
- You should not take more than 4 capsules of VASCEPA each day. Do not take more capsules than what is prescribed by your doctor.
- Take VASCEPA capsules whole. Do not break, crush, dissolve, or chew VASCEPA capsules before swallowing.

- If you miss a dose of VASCEPA, take it as soon as you remember. However, if you miss one day of VASCEPA, do not double your dose when you take it.
- Your doctor may start you on a diet that is low in saturated fat, cholesterol, carbohydrates, and low in added sugars before giving you VASCEPA. Stay on this diet while taking VASCEPA.
- Your doctor may do blood tests to check your triglyceride and other lipid levels while you take VASCEPA.

What are the possible side effects of VASCEPA?

If you have liver problems and are taking VASCEPA, your doctor should do blood tests during treatment.

The most common side effect of VASCEPA is joint pain. **As with all drugs, you may experience a serious side effect when taking VASCEPA.** Talk to your doctor if you have a side effect that bothers you or does not go away.

This is not the only side effect of VASCEPA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VASCEPA?

- Store VASCEPA at room temperature between 68° to 77° F (20° to 25° C).
- Safely throw away medicine that is out of date or no longer needed.

Keep VASCEPA and all medicine out of the reach of children.

General information about the safe and effective use of VASCEPA.

Medicines are sometimes prescribed for purposes other than those listed in Patient Information Leaflets. Do not use VASCEPA for a condition for which it was not prescribed. Do not give VASCEPA to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information summarizes the most important information about VASCEPA. If you would like more information, talk with your doctor or pharmacist. You can ask your doctor or pharmacist for information about VASCEPA that is written for health professionals.

For more information, go to www.vascepa.com or call 1-855-VASCEPA (1-855-827-2372).

What are the ingredients in VASCEPA?

Active Ingredient: icosapent ethyl
Inactive Ingredients: tocopherol, gelatin, glycerin, maltitol, sorbitol, and purified water

This patient information has been approved by the U.S. Food and Drug Administration.

VASCEPA is a trademark of Amarin Pharmaceuticals Ireland Ltd.
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PP00120A 07/2012

AMARIN

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HIGHLIGHTS OF PRESCRIBING INFORMATION

VASCEPA® (icosapent ethyl) Capsules, for oral use
Initial U.S. Approval: 2012

These highlights do not include all the information needed to use VASCEPA® safely and effectively. See full prescribing information for VASCEPA.

----------INDICATIONS AND USAGE----------

VASCEPA is an ethyl ester of eicosapentaenoic acid (EPA) indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia. (1)

Limitations of Use:
•The effect of VASCEPA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined. (1)

•The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined. (1)

----------DOSAGE AND ADMINISTRATION----------

The daily dose of VASCEPA is 4 grams per day taken as four 0.5-gram capsules or two 1-gram capsules twice daily with food. (2)
Patients should be advised to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 0.5-gram and 1-gram (3)

----------CONTRAINDICATIONS----------

VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components. (4)

----------WARNINGS and PRECAUTIONS----------

In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy. (5.1)

Use with caution in patients with known hypersensitivity to fish and/or shellfish. (5.2)

----------ADVERSE REACTIONS----------

The most common reported adverse reaction (incidence >2% and greater than placebo) was arthralgia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amarin Pharma Inc. at 1-855-VASCEPA (1-855-827-2372) or contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Omega-3 acids may prolong bleeding time. Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically. (7)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2017

FULL PRESCRIBING INFORMATION:

CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VASCEPA® (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

Usage Considerations: Patients should be placed on an appropriate lipid-lowering diet and exercise regimen before receiving VASCEPA and should continue this diet and exercise regimen with VASCEPA.

Attempts should be made to control any medical problems such as diabetes mellitus, hypothyroidism, and alcohol intake that may contribute to lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed, if possible, prior to consideration of TG-lowering drug therapy.

Limitations of Use:

The effect of VASCEPA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

2 DOSAGE AND ADMINISTRATION

Assess lipid levels before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate. *[see Indications and Usage (1)]*.

Patients should engage in appropriate nutritional intake and physical activity before receiving VASCEPA, which should continue during treatment with VASCEPA.

The daily dose of VASCEPA is 4 grams per day taken as either:

- four 0.5-gram capsules twice daily with food; or as
- two 1-gram capsules twice daily with food

Patients should be advised to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA.

3 DOSAGE FORMS AND STRENGTHS

VASCEPA capsules are supplied in the following dosage form strengths:

- 0.5-gram amber-colored, oval, soft-gelatin capsules imprinted with V500.
- 1-gram amber-colored, oblong, soft-gelatin capsules imprinted with VASCEPA.

4 CONTRAINDICATIONS

VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components.

5 WARNINGS AND PRECAUTIONS

5.1 Monitoring: Laboratory Tests

In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored periodically during therapy with VASCEPA.

5.2 Fish Allergy

VASCEPA contains ethyl esters of the omega-3 fatty acid, eicosapentaenoic acid (EPA), obtained from the oil of fish. It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to VASCEPA. VASCEPA should be used with caution in patients with known hypersensitivity to fish and/or shellfish.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions reported in at least 2% and at a greater rate than placebo for patients treated with VASCEPA based on pooled data across two clinical studies are listed in Table 1.

Table 1. Adverse Reactions Occurring at Incidence >2% and Greater than Placebo in Double-Blind, Placebo-Controlled Trials*

	Placebo (N=309)		VASCEPA (N=622)	
Adverse Reaction	**n**	**%**	**n**	**%**
Arthralgia	3	1.0	14	2.3

*Studies included patients with triglycerides values of 200 to 2000 mg/dL.

An additional adverse reaction from clinical studies was oropharyngeal pain.

7 DRUG INTERACTIONS

7.1 Anticoagulants

Some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in those studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. It is unknown whether VASCEPA can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. VASCEPA should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

In pregnant rats given oral gavage doses of 0.3, 1 and 2 g/kg/day icosapent ethyl from gestation through organogenesis all drug treated groups had visceral or skeletal abnormalities including: 13th reduced ribs, additional liver lobes, testes medially displaced and/or not descended at human systemic exposures following a maximum oral dose of 4 g/day based on body surface comparisons. Variations including incomplete or abnormal ossification of various skeletal bones were observed in the 2 g/kg/day group at 5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison.

In a multigenerational developmental study in pregnant rats given oral gavage doses of 0.3, 1, 3 g/kg/day ethyl-EPA from gestation day 7-17, an increased incidence of absent optic

nerves and unilateral testes atrophy were observed at ≥0.3 g/kg/day at human systemic exposure following an oral dose of 4 g/day based on body surface area comparisons across species. Additional variations consisting of early incisor eruption and increased percent cervical ribs were observed at the same exposures. Pups from high dose treated dams exhibited decreased copulation rates, delayed estrus, decreased implantations and decreased surviving fetuses (F2) suggesting multigenerational effects of ethyl-EPA at 7 times human systemic exposure following 4 g/day dose based on body surface area comparisons across species.

In pregnant rabbits given oral gavage doses of 0.1, 0.3, and 1 g/kg/day from gestation through organogenesis there were increased dead fetuses at 1 g/kg/day secondary to maternal toxicity (significantly decreased food consumption and body weight loss).

In pregnant rats given ethyl-EPA from gestation day 17 through lactation day 20 at 0.3, 1, 3 g/kg/day complete litter loss was observed in 2/23 litters at the low dose and 1/23 mid-dose dams by post-natal day 4 at human exposures based on a maximum dose of 4 g/day comparing body surface areas across species.

8.3 Nursing Mothers

Studies with omega-3-acid ethyl esters have demonstrated excretion in human milk. The effect of this excretion on the infant of a nursing mother is unknown; caution should be exercised when VASCEPA is administered to a nursing mother. An animal study in lactating rats given oral gavage ^{14}C-ethyl EPA demonstrated that drug levels were 6 to 14 times higher in milk than in plasma.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of VASCEPA, 33% were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

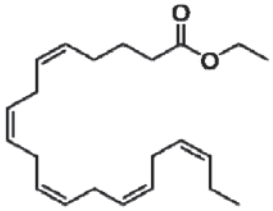
9 DRUG ABUSE AND DEPENDENCE

VASCEPA does not have any known drug abuse or withdrawal effects.

11 DESCRIPTION

VASCEPA, a lipid-regulating agent, is supplied as either a 0.5-gram or a 1-gram amber-colored, liquid-filled soft gelatin capsule for oral administration.

Each VASCEPA capsule contains either 0.5 grams of icosapent ethyl (in a 0.5 gram capsule) or 1 gram of icosapent ethyl (in a 1 gram capsule). Icosapent ethyl is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA). The empirical formula of icosapent ethyl is $C_{22}H_{34}O_2$ and the molecular weight is 330.51. The chemical name for icosapent ethyl is ethyl all-cis-5,8,11,14,17-icosapentaenoate with the following chemical structure:



VASCEPA capsules also contain the following inactive ingredients: tocopherol, gelatin, glycerin, maltitol, sorbitol, and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Studies suggest that EPA reduces hepatic very low-density lipoprotein triglycerides (VLDL-TG) synthesis and/or secretion and enhances TG clearance from circulating VLDL particles. Potential mechanisms of action include increased β-oxidation; inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase (DGAT); decreased lipogenesis in the liver; and increased plasma lipoprotein lipase activity.

12.3 Pharmacokinetics

Absorption: After oral administration, VASCEPA is de-esterified during the absorption process and the active metabolite EPA is absorbed in the small intestine and enters the systemic circulation mainly via the thoracic duct lymphatic system. Peak plasma concentrations of EPA were reached approximately 5 hours following oral doses of VASCEPA.

VASCEPA was administered with or following a meal in all clinical studies; no food effect studies were performed. Take VASCEPA with or following a meal.

Distribution: The mean volume of distribution at steady-state of EPA is approximately 88 liters. The majority of EPA circulating in plasma is incorporated in phospholipids, triglycerides and cholesteryl esters, and <1% is present as the unesterified fatty acid. Greater than 99% of unesterified EPA is bound to plasma proteins.

Metabolism and Excretion: EPA is mainly metabolized by the liver via beta-oxidation similar to dietary fatty acids. Beta oxidation splits the long carbon chain of EPA into acetyl Coenzyme A, which is converted into energy via the Krebs cycle. Cytochrome P450-mediated metabolism is a minor pathway of elimination of EPA. The total plasma clearance of EPA at steady state is 684 mL/hr. The plasma elimination half-life ($t_{1/2}$) of EPA is approximately 89 hours. VASCEPA does not undergo renal excretion.

Drug-Drug Interactions

VASCEPA was studied at the 4 g/day dose level with the following medications which are typical substrates of cytochrome P450 enzymes, and no drug-drug interactions were observed:

Omeprazole: In a drug-drug interaction study with 28 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the steady-state AUC_{τ} or C_{max} of omeprazole when co-administered at 40 mg/day to steady-state.

Rosiglitazone: In a drug-drug interaction study with 28 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the single dose AUC or C_{max} of rosiglitazone at 8 mg.

Warfarin: In a drug-drug interaction study with 25 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the single dose AUC or C_{max} of *R*- and *S*-warfarin or the anti-coagulation pharmacodynamics of warfarin when co-administered as racemic warfarin at 25 mg.

Atorvastatin: In a drug-drug interaction study of 26 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the steady-state AUC_{τ} or C_{max} of atorvastatin, 2-hydroxyatorvastatin, or 4-hydroxyatorvastatin when co-administered with atorvastatin 80 mg/day to steady-state.

Specific Populations

Gender: When administered VASCEPA in clinical trials, plasma total EPA concentrations did not differ significantly between men and women.

Pediatric: The pharmacokinetics of VASCEPA has not been studied in pediatric patients.

Hepatic or Renal Impairment: VASCEPA has not been studied in patients with renal or hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year rat carcinogenicity study with oral gavage doses of 0.09, 0.27, and 0.91 g/kg/day icosapent ethyl, respectively, males did not exhibit drug-related neoplasms. Hemangiomas and hemangiosarcomas of the mesenteric lymph node, the site of drug absorption, were observed in females at clinically relevant exposures based on body surface area comparisons across species relative to the maximum clinical dose of 4 g/day. Overall incidence of hemangiomas and hemangiosarcomas in all vascular tissues did not increase with treatment.

In a 6-month carcinogenicity study in Tg.rasH2 transgenic mice with oral gavage doses of 0.5, 1, 2, and 4.6 g/kg/day icosapent ethyl, drug-related incidences of benign squamous cell papilloma in the skin and subcutis of the tail was observed in high dose male mice. The papillomas were considered to develop secondary to chronic irritation of the proximal tail associated with fecal excretion of oil and therefore not clinically relevant. Drug-related neoplasms were not observed in female mice.

Icosapent ethyl was not mutagenic with or without metabolic activation in the bacterial mutagenesis (Ames) assay or in the *in vivo* mouse micronucleus assay. A chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells was positive for clastogenicity with and without metabolic activation.

In an oral gavage rat fertility study, ethyl-EPA, administered at doses of 0.3, 1, and 3 g/kg/day to male rats for 9 weeks before mating and to female rats for 14 days before mating through day 7 of gestation, increased anogenital distance in female pups and increased cervical ribs were observed at 3 g/kg/day (7 times human systemic exposure with 4 g/day clinical dose based on a body surface area comparison).

14 CLINICAL STUDIES

14.1 Severe Hypertriglyceridemia

The effects of VASCEPA 4 grams per day were assessed in a randomized, placebo-controlled, double-blind, parallel-group study of adult patients (76 on VASCEPA, 75 on placebo) with severe hypertriglyceridemia. Patients whose baseline TG levels were between 500

and 2,000 mg/dL were enrolled in this study for 12 weeks. The median baseline TG and LDL-C levels in these patients were 684 mg/dL and 86 mg/dL, respectively. Median baseline HDL-C level was 27 mg/dL. The randomized population in this study was mostly Caucasian (88%) and male (76%). The mean age was 53 years and the mean body mass index was 31 kg/m^2. Twenty-five percent of patients were on concomitant statin therapy, 28% were diabetics, and 39% of the patients had TG levels >750 mg/dL.

The changes in the major lipoprotein lipid parameters for the groups receiving VASCEPA or placebo are shown in Table 2.

Table 2. Median Baseline and Percent Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia (≥500 mg/dL)

	VASCEPA 4 g/day N=76		Placebo N=75		Difference (95% Confidence
Parameter	Baseline	% Change	Baseline	% Change	Interval)
TG (mg/dL)	680	-27	703	+10	-33* (-47, -22)
LDL-C (mg/dL)	91	-5	86	-3	-2 (-13, +8)
Non-HDL-C (mg/dL)	225	-8	229	+8	-18 (-25, -11)
TC (mg/dL)	254	-7	256	+8	-16 (-22, -11)
HDL-C (mg/dL)	27	-4	27	0	-4 (-9, +2)
VLDL-C (mg/dL)	123	-20	124	+14	-29** (-43, -14)
Apo B (mg/dL)	121	-4	118	+4	-9**(-14, -3)

% Change= Median Percent Change from Baseline
Difference= Median of [VASCEPA % Change – Placebo % Change] (Hodges-Lehmann Estimate)
p-values from Wilcoxon rank-sum test

*p-value < 0.001 (primary efficacy endpoint)

**p-value < 0.05 (key secondary efficacy endpoints determined to be statistically significant according to the pre-specified multiple comparison procedure)

VASCEPA 4 grams per day reduced median TG, VLDL-C, and Apo B levels from baseline relative to placebo. The reduction in TG observed with VASCEPA was not associated with elevations in LDL-C levels relative to placebo.

The effect of VASCEPA on the risk of pancreatitis in patients with severe hypertriglyceridemia has not been determined.

The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

16 HOW SUPPLIED/STORAGE AND HANDLING

VASCEPA (icosapent ethyl) capsules are supplied as 0.5-gram amber-colored soft-gelatin capsules imprinted with V500 or as 1-gram amber-colored soft-gelatin capsules imprinted with VASCEPA.

Bottles of 240 (0.5-gram): NDC 52937-001-40.

Bottles of 120 (1-gram): NDC 52937-001-20.

Store at 20° to 25° C (68° to 77°F); excursions permitted to 15° to 30° C (59° to 86°F) [see USP Controlled Room Temperature]. Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

VASCEPA should be used with caution in patients with known sensitivity or allergy to fish and/or shellfish *[see Warnings and Precautions (5.2)]*.

Patients should be advised that use of lipid-regulating agents does not reduce the importance of appropriate nutritional intake and physical activity *[see Dosage and Administration (2)]*.

Patients should be advised not to alter VASCEPA capsules in any way and to ingest intact capsules only *[see Dosage and Administration (2)]*.

Instruct patients to take VASCEPA as prescribed. If a dose is missed, patients should take it as soon as they remember. However if they miss one day of VASCEPA, they should not double the dose when they take it.

Distributed by:
Amarin Pharma Inc.
Bedminster, NJ, USA

Manufactured for:
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www.VASCEPA.com

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P00120H 8/2016

PATIENT INFORMATION
VASCEPA (vas-EE-puh) (icosapent ethyl)
capsules

What is VASCEPA?
VASCEPA is a prescription medicine used along with a low-fat and low-cholesterol diet to lower high levels of triglycerides (fats) in adults.
It is not known if VASCEPA changes your risk of having inflammation of your pancreas (pancreatitis).
It is not known if VASCEPA prevents you from having a heart attack or stroke.
It is not known if VASCEPA is safe and effective in children.

Do not take VASCEPA if you are allergic to icosapent ethyl or any of the ingredients in VASCEPA. See the end of this leaflet for a complete list of ingredients in VASCEPA.

Before taking VASCEPA, tell your doctor about all of your medical conditions, including if you:
- have diabetes.
- have a low thyroid problem (hypothyroidism).
- have a liver problem.
- have a pancreas problem.
- are allergic to fish or shellfish. It is not known if people who are allergic to fish or shellfish are also allergic to VASCEPA.
- are pregnant, or planning to become pregnant. It is not known if VASCEPA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. VASCEPA can pass into your milk, and may harm your baby. Talk to your doctor about the best way to feed your baby if you take VASCEPA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and dietary or herbal supplements. VASCEPA can interact with certain other medicines that you are taking.
Especially tell your doctor if you take medicines that affect your blood clotting (anticoagulants or blood thinners).

How should I take VASCEPA?
- Take VASCEPA exactly as your doctor tells you to take it.
- Do not change your dose or stop taking VASCEPA without talking to your doctor.
- Do not take more capsules than what is prescribed by your doctor.
  - If you are prescribed the 0.5 gram capsules, you should not take more than 8 capsules each day.
  - If you are prescribed the 1 gram capsules, you should not take more than 4 capsules per day.
- Take VASCEPA capsules whole. Do not break, crush, dissolve, or chew VASCEPA capsules before swallowing.
- If you miss a dose of VASCEPA, take it as soon as you remember. However, if you miss one day of VASCEPA, do not double your dose when you take it.
- Your doctor may start you on a diet that is low in saturated fat, cholesterol, carbohydrates, and low in added sugars before giving you VASCEPA. Stay on this diet while taking VASCEPA.
- Your doctor may do blood tests to check your triglyceride and other lipid levels while you take VASCEPA.

What are the possible side effects of VASCEPA?
If you have liver problems and are taking VASCEPA, your doctor should do blood tests during treatment.
The most common side effect of VASCEPA is joint pain. As with all drugs, you may experience a serious side effect when taking VASCEPA. Talk to your doctor if you have a side effect that bothers you or does not go away.
These are not all the possible side effects of VASCEPA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VASCEPA?
- Store VASCEPA at room temperature between 68° to 77° F (20° to 25° C).
- Safely throw away medicine that is out of date or no longer needed.

Keep VASCEPA and all medicine out of the reach of children.

General information about the safe and effective use of VASCEPA.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VASCEPA for a condition for which it was not prescribed. Do not give VASCEPA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about VASCEPA that is written for health professionals.

What are the ingredients in VASCEPA?

Active ingredient: icosapent ethyl

Inactive ingredients: tocopherol, gelatin, glycerin, maltitol, sorbitol, and purified water

Distributed by: Amarin Pharma Inc. Bedminster, NJ, USA

Manufactured for: Amarin Pharmaceuticals Ireland Limited Dublin, Ireland +1-855-VASCEPA (+1-855-827-2372) www.vascepa.com

For more information, go to www.vascepa.com or call 1-855-VASCEPA (1-855-827-2372).

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 2/2017

ICOSAPENT ETHYL- icosapent ethyl capsule
Hikma Pharmaceuticals USA Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ICOSAPENT ETHYL CAPSULES safely and effectively. See full prescribing information for ICOSAPENT ETHYL CAPSULES.

ICOSAPENT ETHYL capsules, for oral use
Initial U.S. Approval: 2012

RECENT MAJOR CHANGES

Warnings and Precautions, Atrial Fibrillation/Flutter (5.1)	12/2019
Warnings and Precautions, Bleeding (5.3)	12/2019

INDICATIONS AND USAGE

Icosapent ethyl capsules are an ethyl ester of eicosapentaenoic acid (EPA) indicated:

- as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. (1)

Limitations of Use:

- The effect of icosapent ethyl on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined. (1)

DOSAGE AND ADMINISTRATION

- Assess lipid levels before initiating therapy. Identify other causes of high triglyceride levels and manage as appropriate. (2.1)
- Patients should engage in appropriate nutritional intake and physical activity before receiving icosapent ethyl capsules, which should continue during treatment. (2.1)
- The daily dose of icosapent ethyl is 4 grams per day taken as
    - two 1-gram capsules twice daily with food. (2.2)
- Advise patients to swallow capsules whole. Do not break open, crush, dissolve, or chew icosapent ethyl capsules. (2.2)

DOSAGE FORMS AND STRENGTHS

Capsules: 1 gram (3)

CONTRAINDICATIONS

Icosapent ethyl is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to icosapent ethyl or any of its components. (4)

WARNINGS AND PRECAUTIONS

Atrial Fibrillation/Flutter: Icosapent ethyl was associated with an increased risk of atrial fibrillation or atrial flutter requiring hospitalization in a double-blind, placebo-controlled trial. The incidence of atrial fibrillation was greater in patients with a previous history of atrial fibrillation or atrial flutter. (5.1)
Potential for Allergic Reactions in Patients with Fish Allergy: Icosapent ethylcontains ethyl esters of the omega-3 fatty acid, eicosapentaenoic acid (EPA), obtained from the oil of fish. It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to icosapent ethyl. Inform patients with known hypersensitivity to fish and/or shellfish about the potential for allergic reactions and advise them to discontinue icosapent ethyl and seek medical attention if any reactions occur. (5.2)
Bleeding: Icosapent ethylwas associated with an increased risk of bleeding in a double-blind, placebo-controlled trial. The incidence of bleeding was greater in patients receiving concomitant antithrombotic medications, such as aspirin, clopidogrel, or warfarin. (5.3)

ADVERSE REACTIONS

Common adverse reactions (incidence ≥3% and ≥1% more frequent than placebo): musculoskeletal pain, peripheral edema, constipation, gout, and atrial fibrillation (6.1)
Common adverse reactions in the hypertriglyceridemia trials (incidence ≥1% more frequent than placebo): arthralgia and

oropharyngeal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-800-962-8364 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Increased Bleeding Risk with Anticoagulants and Antiplatelet Agents: Some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. Monitor patients receiving icosapent ethyl capsules and concomitant anticoagulants and/or antiplatelet agents for bleeding. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Icosapent ethyl is indicated:

- as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

Limitations of Use

The effect of icosapent ethyl on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of Icosapent Ethyl

- Assess lipid levels before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate.
- Patients should engage in appropriate nutritional intake and physical activity before receiving icosapent ethyl, which should continue during treatment with icosapent ethyl.

2.2 Dosage and Administration

- The daily dose of icosapent ethyl is 4 grams per day taken as:
  - two 1 gram capsules twice daily with food.
- Advise patients to swallow icosapent ethyl capsules whole. Do not break open, crush, dissolve, or chew icosapent ethyl capsules.

3 DOSAGE FORMS AND STRENGTHS

Icosapent Ethyl Capsules are supplied as a 1 gram, clear, oblong capsule with product identification “54 648” on one side.

4 CONTRAINDICATIONS

Icosapent ethyl is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to icosapent ethyl or any of its components.

5 WARNINGS AND PRECAUTIONS

5.1 Atrial Fibrillation/Flutter

Icosapent ethyl is associated with an increased risk of atrial fibrillation or atrial flutter requiring hospitalization. In a double-blind, placebo-controlled trial of 8,179 subjects, adjudicated atrial fibrillation or atrial flutter requiring hospitalization for 24 or more hours occurred in 127 (3%) patients treated with icosapent ethyl compared to 84 (2%) patients receiving placebo [HR= 1.5 (95% CI 1.14, 1.98)]. The incidence of atrial fibrillation was greater in patients with a previous history of atrial fibrillation or atrial flutter.

5.2 Potential for Allergic Reactions in Patients with Fish Allergy

Icosapent ethyl contains ethyl esters of the omega-3 fatty acid, eicosapentaenoic acid (EPA), obtained

from the oil of fish. It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to icosapent ethyl. Inform patients with known hypersensitivity to fish and/or shellfish about the potential for allergic reactions to icosapent ethyl and advise them to discontinue icosapent ethyl and seek medical attention if any reactions occur.

5.3 Bleeding

Icosapent ethyl is associated with an increased risk of bleeding. In a double-blind, placebo-controlled trial of 8,179 patients, 482 (12%) patients receiving icosapent ethyl experienced a bleeding event compared to 404 (10%) patients receiving placebo. Serious bleeding events occurred in 111 (3%) of patients on icosapent ethyl vs. 85 (2%) of patients receiving placebo. The incidence of bleeding was greater in patients receiving concomitant antithrombotic medications, such as aspirin, clopidogrel, or warfarin.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Atrial Fibrillation or Atrial Flutter *[see Warnings and Precautions (5.1)]*
- Potential for Allergic Reactions in Patients with Fish Allergy *[see Warnings and Precautions (5.2)]*
- Bleeding *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Common adverse reactions (incidence ≥3% on icosapent ethyl and ≥1% more frequent than placebo) included musculoskeletal pain, peripheral edema, constipation, gout, and atrial fibrillation.

Hypertriglyceridemia Trials

In two randomized, double-blind, placebo-controlled trials in patients with triglyceride levels between 200 and 2000 mg/dL treated for 12 weeks, adverse reactions reported with icosapent ethyl at an incidence ≥1% more frequent than placebo based on pooled data included arthralgia and oropharyngeal pain.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during post-approval use of icosapent ethyl. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Diarrhea
- Blood triglycerides increased
- Abdominal discomfort
- Pain in the extremities

7 DRUG INTERACTIONS

7.1 Increased Bleeding Risk with Anticoagulants and Antiplatelet Agents

Some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in those studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Monitor patients receiving icosapent ethyl and

concomitant anticoagulants and/or antiplatelet agents for bleeding.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The available data from published case reports and the pharmacovigilance database on the use of icosapent ethyl in pregnant women are insufficient to identify a drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies in pregnant rats, non-dose-related imbalances for some minor developmental findings were observed with oral administration of icosapent ethyl during organogenesis at exposures that were equivalent to the clinical exposure at the human dose of 4 g/day, based on body surface area comparisons. In a study in pregnant rabbits orally administered icosapent ethyl during organogenesis, there were no clinically relevant adverse developmental effects at exposures that were 5 times the clinical exposure, based on body surface area comparisons *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In pregnant rats given oral gavage doses of 0.3, 1 and 2 g/kg/day icosapent ethyl from gestation through organogenesis all drug treated groups had non-dose-related imbalances in visceral and skeletal findings, including 13th reduced ribs, additional liver lobes, testes medially displaced and/or not descended, at human systemic exposures following a maximum oral dose of 4 g/day based on body surface comparisons.

In a multigenerational developmental study in pregnant rats given doses of 0.3, 1, 3 g/kg/day icosapent ethyl by oral gavage from gestation day 7-17, icosapent ethyl did not affect viability in fetuses (F1 or F2). Non-dose-related imbalances in findings of absent optic nerves and unilateral testes atrophy at human exposures based on the maximum dose of 4 g/day and on body surface area comparisons. Additional variations consisting of early incisor eruption and increased percent cervical ribs were observed at the same exposures. Pups from high dose treated dams exhibited decreased copulation rates, delayed estrus, decreased implantations and decreased surviving fetuses (F2) suggesting potential multigenerational effects of icosapent ethyl at 7 times human systemic exposure following 4 g/day dose based on body surface area comparisons across species.

In pregnant rabbits given oral gavage doses of 0.1, 0.3, and 1 g/kg/day icosapent ethyl from gestation through organogenesis, a decrease in body weight and food consumption was observed at the high dose of 1 g/kg/day (5 times the human exposure at the maximum dose of 4 g/day, based on body surface area comparisons). Slight increases in resorbed and dead fetuses were noted in the 1 g/kg/day group, but these were not significantly different from the control group. There were no differences between the icosapent ethyl groups and control group as to the number of corpora lutea, number of implantations, number of surviving fetuses, sex ratio, body weight of female fetuses or placental weight. There were no treatment-related malformations or skeletal anomalies.

In pregnant rats given icosapent ethyl from gestation day 17 through lactation day 20 at 0.3, 1, 3 g/kg/day no adverse maternal or developmental effects were observed. However, complete litter loss (not dose-related) was noted in 2/23 litters at the low dose and 1/23 mid-dose dams by post-natal day 4 at human exposures at a maximum dose of 4 g/day, based on body surface area comparisons.

8.2 Lactation

Risk Summary

Published studies have detected omega-3 fatty acids, including EPA, in human milk. Lactating women receiving oral omega-3 fatty acids for supplementation have resulted in higher levels of omega-3 fatty acids in human milk. There are no data on the effects of omega-3 fatty acid ethyl esters on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for icosapent ethyl and any potential adverse effects on the breastfed child from icosapent ethyl or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in well-controlled clinical studies of icosapent ethyl, 45% were 65 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger groups. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

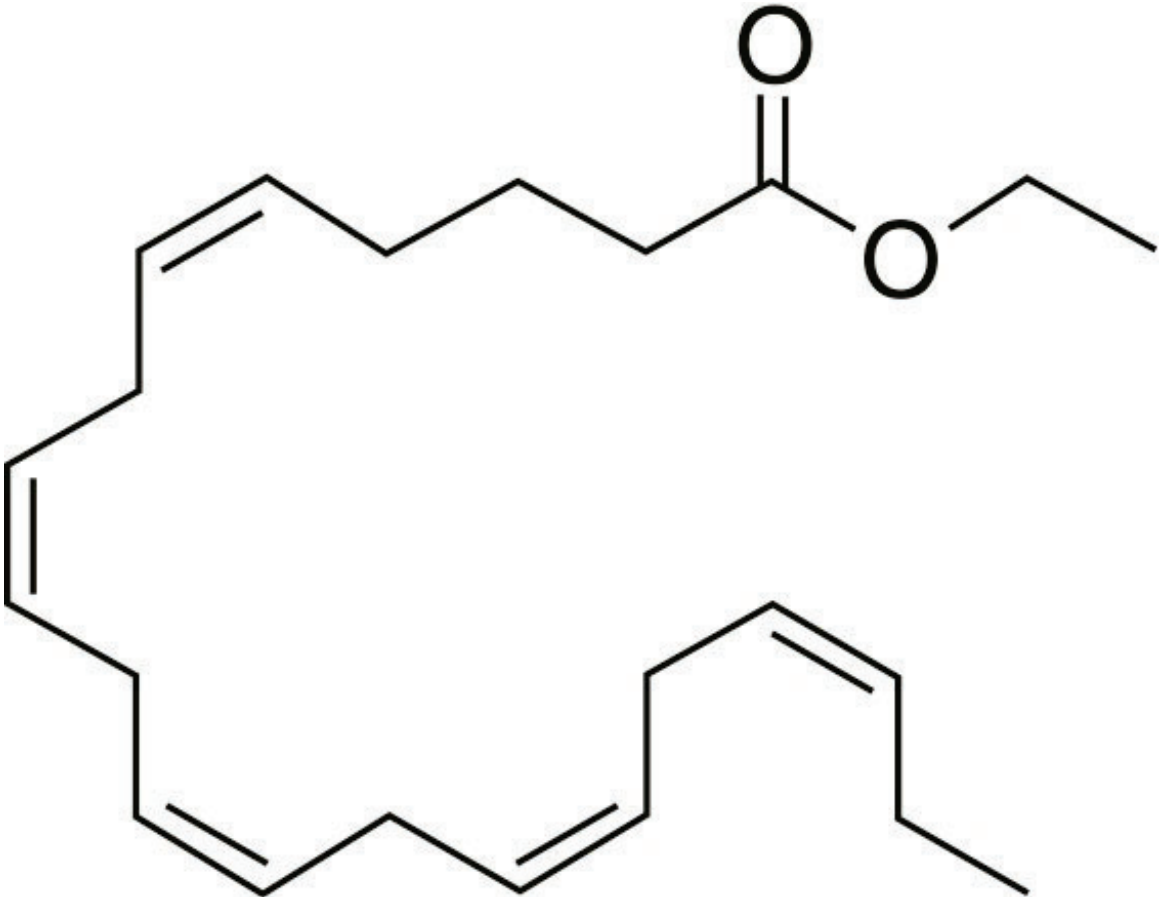
8.7 Hepatic Impairment

In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored periodically during therapy with icosapent ethyl.

11 DESCRIPTION

Icosapent ethyl, a lipid-regulating agent, is supplied as a 1 gram, liquid-filled soft gelatin capsule for oral administration.

Icosapent ethyl is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA). The empirical formula of icosapent ethyl is $C_{22}H_{34}O_2$ and the molecular weight is 330.51. The chemical name for icosapent ethyl is ethyl all-cis-5,8,11,14,17-icosapentaenoate with the following chemical structure:



Each capsule contains the following inactive ingredients: gelatin, glycerin, purified water, sorbitol, sorbitan and tocopherol. The monogramming ink ingredients contain: ammonium hydroxide, iron oxide black, isopropyl alcohol, macrogol, polyvinyl acetate phthalate, propylene glycol, purified water and SDA alcohol (ethanol and ethyl acetate).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Studies suggest that EPA reduces hepatic very low-density lipoprotein triglycerides (VLDL-TG) synthesis and/or secretion and enhances TG clearance from circulating VLDL particles. Potential mechanisms of action include increased β-oxidation; inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase (DGAT); decreased lipogenesis in the liver; and increased plasma lipoprotein lipase activity.

12.2 Pharmacodynamics

In a 12-week, dose-ranging study in patients with severe hypertriglyceridemia, icosapent ethyl 4 grams per day reduced median TG from baseline relative to placebo *[see Clinical Studies (14)]*.

12.3 Pharmacokinetics

Absorption

After oral administration, icosapent ethyl is de-esterified during the absorption process and the active metabolite EPA is absorbed in the small intestine and enters the systemic circulation mainly via the thoracic duct lymphatic system. Peak plasma concentrations of EPA were reached approximately 5 hours following oral doses of icosapent ethyl.

Icosapent ethyl was administered with or following a meal in all clinical studies; no food effect studies

were performed. Take icosapent ethyl with or following a meal.

Distribution

The mean volume of distribution at steady state of EPA is approximately 88 liters. The majority of EPA circulating in plasma is incorporated in phospholipids, triglycerides and cholesteryl esters, and <1% is present as the unesterified fatty acid. Greater than 99% of unesterified EPA is bound to plasma proteins.

Elimination

Metabolism

EPA is mainly metabolized by the liver via beta-oxidation similar to dietary fatty acids. Beta oxidation splits the long carbon chain of EPA into acetyl Coenzyme A, which is converted into energy via the Krebs cycle. Cytochrome P450-mediated metabolism is a minor pathway of elimination of EPA.

Excretion

The total plasma clearance of EPA at steady state is 684 mL/hr. The plasma elimination half-life ($t_{1/2}$) of EPA is approximately 89 hours. Icosapent ethyl does not undergo renal excretion.

Specific Populations

Gender

When administered icosapent ethyl in clinical trials, plasma total EPA concentrations did not differ significantly between men and women.

Pediatric

The pharmacokinetics of icosapent ethyl has not been studied in pediatric patients.

Hepatic or Renal Impairment

Icosapent ethyl has not been studied in patients with renal or hepatic impairment.

Drug Interaction Studies

Omeprazole: In a drug-drug interaction study with 28 healthy adult subjects, icosapent ethyl 4 g/day at steady-state did not significantly change the steady-state AUC_{τ} or C_{max} of omeprazole when co-administered at 40 mg/day to steady-state.

Rosiglitazone: In a drug-drug interaction study with 28 healthy adult subjects, icosapent ethyl 4 g/day at steady-state did not significantly change the single dose AUC or C_{max} of rosiglitazone at 8 mg.

Warfarin: In a drug-drug interaction study with 25 healthy adult subjects, icosapent ethyl 4 g/day at steady-state did not significantly change the single dose AUC or C_{max} of *R*- and *S*-warfarin or the anti-coagulation pharmacodynamics of warfarin when co-administered as racemic warfarin at 25 mg.

Atorvastatin: In a drug-drug interaction study of 26 healthy adult subjects, icosapent ethyl 4 g/day at steady-state did not significantly change the steady-state AUC_{τ} or C_{max} of atorvastatin, 2-hydroxyatorvastatin, or 4-hydroxyatorvastatin when co-administered with atorvastatin 80 mg/day at steady-state.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year rat carcinogenicity study with oral gavage doses of 0.09, 0.27, and 0.91 g/kg/day icosapent ethyl, respectively, males did not exhibit drug-related neoplasms. Hemangiomas and hemangiosarcomas of the mesenteric lymph node, the site of drug absorption, were observed in females at clinically relevant exposures based on body surface area comparisons across species relative to the maximum clinical dose of 4 g/day. Overall incidence of hemangiomas and hemangiosarcomas in all vascular tissues did not increase with treatment.

In a 6-month carcinogenicity study in Tg.rasH2 transgenic mice with oral gavage doses of 0.5, 1, 2, and 4.6 g/kg/day icosapent ethyl, drug-related incidences of benign squamous cell papilloma in the skin and subcutis of the tail was observed in high dose male mice. The papillomas were considered to develop secondary to chronic irritation of the proximal tail associated with fecal excretion of oil and therefore not clinically relevant. Drug-related neoplasms were not observed in female mice.

Icosapent ethyl was not mutagenic with or without metabolic activation in the bacterial mutagenesis (Ames) assay or in the *in vivo* mouse micronucleus assay. A chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells was positive for clastogenicity with and without metabolic activation.

In an oral gavage rat fertility study, ethyl-EPA, administered at doses of 0.3, 1, and 3 g/kg/day to male rats for 9 weeks before mating and to female rats for 14 days before mating through day 7 of gestation, increased anogenital distance in female pups and increased cervical ribs were observed at 3 g/kg/day (7 times human systemic exposure with 4 g/day clinical dose based on a body surface area comparison).

14 CLINICAL STUDIES

14.2 Severe Hypertriglyceridemia

The effects of icosapent ethyl 4 grams per day were assessed in a randomized, placebo-controlled, double-blind, parallel-group study of adult patients (76 on icosapent ethyl, 75 on placebo) with severe hypertriglyceridemia. Patients whose baseline TG levels were between 500 and 2,000 mg/dL were enrolled in this study for 12 weeks. The median baseline TG and LDL-C levels in these patients were 684 mg/dL and 86 mg/dL, respectively. Median baseline HDL-C level was 27 mg/dL. The randomized population in this study was mostly Caucasian (88%) and male (76%). The mean age was 53 years and the mean body mass index was 31 kg/m^2. Twenty-five percent of patients were on concomitant statin therapy, 28% were diabetics, and 39% of the patients had TG levels >750 mg/dL.

The changes in the major lipoprotein lipid parameters for the groups receiving icosapent ethyl or placebo are shown in Table 2.

Table2. Median Baseline and Percent Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia (≥500 mg/dL)

	Icosapent Ethyl 4 g/day N=76		Placebo N=75		Difference (95% Confidence Interval)
Parameter	**Baseline**	**% Change**	**Baseline**	**% Change**	
TG (mg/dL)	680	-27	703	+10	-33[1], -47, -22)
LDL-C (mg/dL)	91	-5	86	-3	-2 (-13, +8)
Non-HDL-C (mg/dL)	225	-8	229	+8	-18 (-25, -11)
TC (mg/dL)	254	-7	256	+8	-16 (-22, -11)
HDL-C (mg/dL)	27	-4	27	0	-4 (-9, +2)
VLDL-C (mg/dL)	123	-20	124	+14	-29[2] (-43, -14)
Apo B (mg/dL)	121	-4	118	+4	-9[2] (-14, -3)

% Change = Median Percent Change from Baseline
Difference = Median of [Icosapent ethyl % Change – Placebo % change] (Hodges-Lehmann Estimate)
p-values from Wilcoxon rank-sum test

Icosapent ethyl 4 grams per day reduced median TG, VLDL-C, and Apo B levels from baseline relative to placebo. The reduction in TG observed with icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

Icosapent Ethyl Capsules

1 gram capsules are supplied as a clear, oblong capsule filled with colorless to pale yellow oily liquid and printed with "54 648" in black ink on one side.

NDC 0054-0508-23: Bottle of 120 Capsules

Store at 20° to 25° C (68° to 77°F). [See USP Controlled Room Temperature.] Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling before starting icosapent ethyl (Patient Information).

Inform patients that icosapent ethyl may increase their risk for atrial fibrillation or atrial flutter *[see Warnings and Precautions (5.1)]*.

Inform patients with known hypersensitivity to fish and/or shellfish about the potential for allergic reactions to icosapent ethyl and advise them to discontinue icosapent ethyl and seek medical attention if any reactions occur *[see Warnings and Precautions (5.2)]*.

Inform patients that icosapent ethyl may increase their risk for bleeding, especially if they are receiving other antithrombotic agents *[see Warnings and Precautions (5.3)]*.

Advise patients to swallow icosapent ethyl capsules whole. Do not break open, crush, dissolve, or chew icosapent ethyl *[see Dosage and Administration (2.2)]*.

Instruct patients to take icosapent ethyl as prescribed. If a dose is missed, patients should take it as soon as they remember. However, if they miss one day of icosapent ethyl, they should not double the dose when they take it.

For more information about icosapent ethyl, please call Hikma Pharmaceuticals USA Inc. at 1-800-962-8364.

Mfg. by:

Catalent Pharma Solutions, LLC.

St. Petersburg, Florida 33716

Distr. by: **Hikma**

Pharmaceuticals USA Inc.

Eatontown, NJ 07724

C50000421/01

Revised January 2020

PATIENT INFORMATION

Icosapent Ethyl
Capsules
(eye koe' sa pent eth' il)
Rx Only

What is icosapent ethyl?
Icosapent ethyl is a prescription medicine used:

- along with a low-fat and low-cholesterol diet to lower high levels of triglycerides (fats) in

adults.

It is not known if icosapent ethyl changes your risk of having inflammation of your pancreas (pancreatitis).
It is not known if icosapent ethyl is safe and effective in children.

Do not take icosapent ethyl capsules if you are allergic to icosapent ethyl or any of the ingredients in icosapent ethyl capsules. See the end of this leaflet for a complete list of ingredients in icosapent ethyl capsules.

Before taking icosapent ethyl, tell your doctor about all of your medical conditions, including if you:

- have diabetes.
- have a low thyroid problem (hypothyroidism).
- have a liver problem.
- have a pancreas problem.
- are allergic to fish or shellfish. It is not known if people who are allergic to fish or shellfish are also allergic to icosapent ethyl.
- are pregnant, or planning to become pregnant. It is not known if icosapent ethyl will harm your unborn baby.
- are breastfeeding or plan to breastfeed. Icosapent ethyl can pass into your breast milk, and may harm your baby. Talk to your doctor about the best way to feed your baby if you take icosapent ethyl.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and dietary or herbal supplements.
Icosapent ethyl can interact with certain other medicines that you are taking.
Especially tell your doctor if you take medicines that affect your blood clotting (anticoagulants or blood thinners).

How should I take icosapent ethyl?

- Take icosapent ethyl exactly as your doctor tells you to take it.
- Do not change your dose or stop taking icosapent ethyl without talking to your doctor.
- Do not take more capsules than what is prescribed by your doctor.
    - If you are prescribed the 1 gram capsules, you should not take more than 4 capsules each day with food.
- Take icosapent ethyl capsules whole. Do not break, crush, dissolve, or chew icosapent ethyl capsules before swallowing.
- If you miss a dose of icosapent ethyl, take it as soon as you remember. However, if you miss one day of icosapent ethyl, do not double your dose when you take it.
- Your doctor may start you on a diet that is low in saturated fat, cholesterol, carbohydrates, and low in added sugars before giving you icosapent ethyl. Stay on this diet while taking icosapent ethyl.
- Your doctor may do blood tests to check your triglyceride and other lipid levels while you take icosapent ethyl.

What are the possible side effects of icosapent ethyl?
Icosapent ethyl may cause serious side effects, including:

- **Heart rhythm problems (atrial fibrillation and atrial flutter).** Heart rhythm problems which can

be serious and cause hospitalization have happened in people who take icosapent ethyl, especially in people who have heart (cardiovascular) disease or diabetes with a risk factor for heart (cardiovascular) disease, or who have had heart rhythm problems in the past. Tell your doctor if you get any symptoms of heart rhythm problems such as feeling as if your heart is beating fast and irregular, lightheadedness, dizziness, shortness of breath, chest discomfort, or you faint.

- **Possible allergic reactions if you are allergic to fish or shellfish.** Stop taking icosapent ethyl and tell your doctor right away or get emergency medical help if you have any signs or symptoms of an allergic reaction.
- **Bleeding**. Serious bleeding can happen in people who take icosapent ethyl. Your risk of bleeding may increase if you are also taking a blood thinner medicine.

If you have liver problems and are taking icosapent ethyl, your doctor should do blood tests during treatment.
The most common side effects of icosapent ethyl include:

- Muscle and joint pain.
- Swelling of the hands, legs, or feet.
- Constipation
- Gout
- Heart rhythm problems (atrial fibrillation).

These are not all the possible side effects of icosapent ethyl. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Icosapent Ethyl Capsules?

- Store icosapent ethyl at room temperature between 68° to 77° F (20° to 25° C).
- Safely throw away medicine that is out of date or no longer needed.

Keep icosapent ethyl and all medicine out of the reach of children.

General information about the safe and effective use of icosapent ethyl.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use icosapent ethyl for a condition for which it was not prescribed. Do not give icosapent ethyl to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about icosapent ethyl that is written for health professionals.

What are the ingredients in Icosapent Ethyl Capsules?
Active ingredient: icosapent ethyl
Inactive ingredients: gelatin, glycerin, purified water, sorbitol, sorbitan and tocopherol. The monogramming ink ingredients contain: ammonium hydroxide, iron oxide black, isopropyl alcohol, macrogol, polyvinyl acetate phthalate, propylene glycol, purified water and SDA alcohol (ethanol and ethyl acetate).

This Patient Information has been approved by the U.S. Food and Drug Administration.

Mfg. by:

Catalent Pharma Solutions, LLC.

St. Petersburg, Florida 33716

Distr. by: **Hikma**

Pharmaceuticals USA Inc.

Eatontown, NJ 07724

C50000421/01

Revised January 2020

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

Icosapent Ethyl Capsules, 1 gram
NDC 0054-0508-23: Bottle of 120 Capsules

Rx Only

ICOSAPENT ETHYL
icosapent ethyl capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0054-0508
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ICOSAPENT ETHYL (UNII: 6GC8A4PAYH) (ICOSAPENT - UNII:AAN7QOV9EA)	ICOSAPENT ETHYL	1 g

Inactive Ingredients

Ingredient Name	Strength
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
GLYCERIN (UNII: PDC6A3C0OX)	
SORBITOL (UNII: 506T60A25R)	
.ALPHA.-TOCOPHEROL (UNII: H4N855PNZ1)	2 mg
AMMONIA (UNII: 5138Q19F1X)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POLYVINYL ACETATE PHTHALATE (UNII: 58QVG85GW3)	
ALCOHOL (UNII: 3K9958V90M)	
ETHYL ACETATE (UNII: 76845O8NMZ)	
SORBITAN (UNII: 6O92ICV9RU)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	

Product Characteristics

Color	YELLOW	**Score**	no score
Shape	CAPSULE	**Size**	25mm
Flavor		**Imprint Code**	54;648
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0054-0508-23	120 in 1 BOTTLE; Type 0: Not a Combination Product	11/04/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA209457	11/04/2020	

Labeler - Hikma Pharmaceuticals USA Inc. (080189610)

Establishment

Name	Address	ID/FEI	Business Operations
West-Ward Columbus Inc.		058839929	MANUFACTURE(0054-0508)

Revised: 11/2020 Hikma Pharmaceuticals USA Inc.

US010568861B1

(12) **United States Patent**
Soni

(10) **Patent No.: US 10,568,861 B1**
(45) **Date of Patent: *Feb. 25, 2020**

(54) **METHODS OF REDUCING THE RISK OF A CARDIOVASCULAR EVENT IN A SUBJECT AT RISK FOR CARDIOVASCULAR DISEASE**

(71) Applicant: **Amarin Pharmaceuticals Ireland Limited**, Dublin (IE)

(72) Inventor: **Paresh Soni**, Mystic, CT (US)

(73) Assignee: **Amarin Pharmaceuticals Ireland Limited** (IE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **16/599,374**

(22) Filed: **Oct. 11, 2019**

Related U.S. Application Data

(60) Division of application No. 16/502,621, filed on Jul. 3, 2019, which is a continuation of application No. 16/287,157, filed on Feb. 27, 2019, now Pat. No. 10,383,840, which is a continuation of application No. 16/005,852, filed on Jun. 12, 2018, now Pat. No. 10,278,935, which is a continuation of application No. 15/886,422, filed on Feb. 1, 2018, now Pat. No. 10,016,386, which is a continuation of application No. 15/607,084, filed on May 26, 2017, now Pat. No. 9,918,955, which is a continuation of application No. 15/427,238, filed on Feb. 8, 2017, now Pat. No. 9,693,986, which is a continuation of application No. 15/333,991, filed on Oct. 25, 2016, now Pat. No. 9,610,272, which is a continuation of application No. 14/411,815, filed as application No. PCT/US2013/048559 on Jun. 28, 2013, now Pat. No. 9,603,826.

(60) Provisional application No. 61/666,447, filed on Jun. 29, 2012.

(51) **Int. Cl.**

A61K 31/232	(2006.01)
A61K 31/397	(2006.01)
A61K 45/06	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/232*** (2013.01); ***A61K 31/397*** (2013.01); ***A61K 45/06*** (2013.01); *A61K 2300/00* (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/232; A61K 31/397; A61K 45/06; A61K 2300/00
USPC 548/400
See application file for complete search history.

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(Continued)

Primary Examiner — Kristin A Vajda

(74) *Attorney, Agent, or Firm* — Perkins Coie LLP

(57) **ABSTRACT**

In various embodiments, the present invention provides methods of reducing the risk of a cardiovascular event in a subject on statin therapy and, in particular, a method of reducing the risk of a cardiovascular event in a subject on statin therapy having a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, and administering to the subject a pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester or a derivative thereof.

7 Claims, No Drawings

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METHODS OF REDUCING THE RISK OF A CARDIOVASCULAR EVENT IN A SUBJECT AT RISK FOR CARDIOVASCULAR DISEASE

PRIORITY CLAIM

This application is a divisional of U.S. patent application Ser. No. 16/502,621 filed Jul. 3, 2019, which is a continuation of U.S. patent application Ser. No. 16/287,157 filed Feb. 27, 2019 (now U.S. Pat. No. 10,383,840), which is a continuation of U.S. patent application Ser. No. 16/005,852 filed Jun. 12, 2018 (now U.S. Pat. No. 10,278,935), which is a continuation of U.S. patent application Ser. No. 15/886,422 filed Feb. 1, 2018 (now U.S. Pat. No. 10,016,386), which is a continuation application of U.S. patent application Ser. No. 15/607,084 filed May 26, 2017 (now U.S. Pat. No. 9,918,955), which is a continuation of U.S. patent application Ser. No. 15/427,238 filed Feb. 8, 2017 (now U.S. Pat. No. 9,693,986), which is a continuation application of U.S. patent application Ser. No. 15,333,991 filed Oct. 25, 2016 (now U.S. Pat. No. 9,610,272), which is a continuation of U.S. patent application Ser. No. 14/411,815, filed Dec. 29, 2014 (now U.S. Pat. No. 9,603,826), which is a 371 national stage application of PCT/US2013/048559 filed Jun. 28, 2013, and which claims priority to U.S. provisional patent application Ser. No. 61/666,447, filed Jun. 29, 2012, the entire contents of which are incorporated herein by reference.

BACKGROUND

Cardiovascular disease is one of the leading causes of death in the United States and most European countries. It is estimated that over 70 million people in the United States alone suffer from a cardiovascular disease or disorder including but not limited to high blood pressure, coronary heart disease, dyslipidemia, congestive heart failure and stroke.

Lovaza®, a lipid regulating agent, is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with very high triglyceride levels. Unfortunately, Lovaza® can significantly increase LDL-C and/or non-HDL-C levels in some patients. A need exists for improved treatments for cardiovascular diseases and disorders.

SUMMARY

In various embodiments, the present invention provides methods of reducing the risk of a cardiovascular event in a subject on statin therapy. In one embodiment, the method comprises administering to the subject a pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester or a derivative thereof. In another embodiment, the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL. In another embodiment, the composition contains not more than 10%, by weight, docosahexaenoic acid or derivative thereof, substantially no docosahexaenoic acid or derivative thereof, or no docosahexaenoic acid or derivative thereof. In another embodiment, eicosapentaenoic acid ethyl ester comprises at least 96%, by weight, of all fatty acids present in the composition; the composition contains not more than 4%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; and/or the composition contains about 0.1% to about 0.6% of at least one fatty acid other than eicosapentaenoic acid ethyl ester and docosahexaenoic acid.

In another embodiment, the invention provides a method of treating hypertriglyceridemia comprising administering a composition as described herein to a subject in need thereof one to about four times per day.

These and other embodiments of the present invention will be disclosed in further detail herein below.

DETAILED DESCRIPTION

While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention, and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any manner. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

The use of numerical values in the various quantitative values specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about." Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values recited as well as any ranges that can be formed by such values. Also disclosed herein are any and all ratios (and ranges of any such ratios) that can be formed by dividing a disclosed numeric value into any other disclosed numeric value. Accordingly, the skilled person will appreciate that many such ratios, ranges, and ranges of ratios can be unambiguously derived from the numerical values presented herein and in all instances such ratios, ranges, and ranges of ratios represent various embodiments of the present invention.

Compositions

In one embodiment, a composition of the invention is administered to a subject in an amount sufficient to provide a daily dose of eicosapentaenoic acid of about 1 mg to about 10,000 mg, 25 about 5000 mg, about 50 to about 3000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about

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In one embodiment, a composition for use in methods of the invention comprises eicosapentaenoic acid, or a pharmaceutically acceptable ester, derivative, conjugate or salt thereof, or mixtures of any of the foregoing, collectively referred to herein as "EPA." The term "pharmaceutically acceptable" in the present context means that the substance in question does not produce unacceptable toxicity to the subject or interaction with other components of the composition.

In another embodiment, the EPA comprises an eicosapentaenoic acid ester. In another embodiment, the EPA comprises a C_1-C_5 alkyl ester of eicosapentaenoic acid. In another embodiment, the EPA comprises eicosapentaenoic acid ethyl ester, eicosapentaenoic acid methyl ester, eicosapentaenoic acid propyl ester, or eicosapentaenoic acid butyl ester.

In another embodiment, the EPA is in the form of ethyl-EPA, lithium EPA, mono-, di- or triglyceride EPA or any other ester or salt of EPA, or the free acid form of EPA. The EPA may also be in the form of a 2-substituted derivative or other derivative which slows down its rate of oxidation but does not otherwise change its biological action to any substantial degree.

In another embodiment, EPA is present in a composition useful in accordance with methods of the invention in an amount of about 50 mg to about 5000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225

mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg, about 2500 mg, about 2525 mg, about 2550 mg, about 2575 mg, about 2600 mg, about 2625 mg, about 2650 mg, about 2675 mg, about 2700 mg, about 2725 mg, about 2750 mg, about 2775 mg, about 2800 mg, about 2825 mg, about 2850 mg, about 2875 mg, about 2900 mg, about 2925 mg, about 2950 mg, about 2975 mg, about 3000 mg, about 3025 mg, about 3050 mg, about 3075 mg, about 3100 mg, about 3125 mg, about 3150 mg, about 3175 mg, about 3200 mg, about 3225 mg, about 3250 mg, about 3275 mg, about 3300 mg, about 3325 mg, about 3350 mg, about 3375 mg, about 3400 mg, about 3425 mg, about 3450 mg, about 3475 mg, about 3500 mg, about 3525 mg, about 3550 mg, about 3575 mg, about 3600 mg, about 3625 mg, about 3650 mg, about 3675 mg, about 3700 mg, about 3725 mg, about 3750 mg, about 3775 mg, about 3800 mg, about 3825 mg, about 3850 mg, about 3875 mg, about 3900 mg, about 3925 mg, about 3950 mg, about 3975 mg, about 4000 mg, about 4025 mg, about 4050 mg, about 4075 mg, about 4100 mg, about 4125 mg, about 4150 mg, about 4175 mg, about 4200 mg, about 4225 mg, about 4250 mg, about 4275 mg, about 4300 mg, about 4325 mg, about 4350 mg, about 4375 mg, about 4400 mg, about 4425 mg, about 4450 mg, about 4475 mg, about 4500 mg, about 4525 mg, about 4550 mg, about 4575 mg, about 4600 mg, about 4625 mg, about 4650 mg, about 4675 mg, about 4700 mg, about 4725 mg, about 4750 mg, about 4775 mg, about 4800 mg, about 4825 mg, about 4850 mg, about 4875 mg, about 4900 mg, about 4925 mg, about 4950 mg, about 4975 mg, or about 5000 mg.

In another embodiment, a composition useful in accordance with the invention contains not more than about 10%, not more than about 9%, not more than about 8%, not more than about 7%, not more than about 6%, not more than about 5%, not more than about 4%, not more than about 3%, not more than about 2%, not more than about 1%, or not more than about 0.5%, by weight, docosahexaenoic acid (DHA), if any. In another embodiment, a composition of the invention contains substantially no docosahexaenoic acid. In still another embodiment, a composition useful in the present invention contains no docosahexaenoic acid and/or derivative thereof.

In another embodiment, EPA comprises at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, by weight, of all fatty acids present in a composition that is useful in methods of the present invention.

In some embodiments, the composition comprises at least 96% by weight of eicosapentaenoic acid ethyl ester and less than about 2% by weight of a preservative. In some embodiments, the preservative is a tocopherol such as all-racemic α-tocopherol.

In another embodiment, a composition useful in accordance with methods of the invention contains less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5% or less than 0.25%, by weight of the total composition or by weight of the total fatty acid content, of any fatty acid other than EPA. Illustrative examples of a "fatty acid other than EPA" include linolenic acid (LA), arachidonic acid (AA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), stearadonic acid (STA), eicosatrienoic acid (ETA) and/or docosapentaenoic acid (DPA). In another embodiment, a composition useful in accordance with methods of the invention contains about 0.1% to about 4%, about 0.5% to about 3%, or about 1% to about 2%, by weight, of total fatty acids other than EPA and/or DHA.

In another embodiment, a composition useful in accordance with the invention has one or more of the following features: (a) eicosapentaenoic acid ethyl ester represents at least about 96%, at least about 97%, or at least about 98%, by weight, of all fatty acids present in the composition; (b) the composition contains not more than about 4%, not more than about 3%, or not more than about 2%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; (c) the composition contains not more than about 0.6%, not more than about 0.5%, or not more than about 0.4% of any individual fatty acid other than eicosapentaenoic acid ethyl ester; (d) the composition has a refractive index (20° C.) of about 1 to about 2, about 1.2 to about 1.8 or about 1.4 to about 1.5; (e) the composition has a specific gravity (20° C.) of about 0.8 to about 1.0, about 0.85 to about 0.95 or about 0.9 to about 0.92; (e) the composition contains not more than about 20 ppm, not more than about 15 ppm or not more than about 10 ppm heavy metals, (f) the composition contains not more than about 5 ppm, not more than about 4 ppm, not more than about 3 ppm, or not more than about 2 ppm arsenic, and/or (g) the composition has a peroxide value of not more than about 5 meq/kg, not more than about 4 meq/kg, not more than about 3 meq/kg, or not more than about 2 meq/kg.

In another embodiment, compositions useful in accordance with methods of the invention are orally deliverable. The terms "orally deliverable" or "oral administration" herein include any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration. In one embodiment, the composition is present in a capsule, for example a soft gelatin capsule.

A composition for use in accordance with the invention can be formulated as one or more dosage units. The terms "dose unit" and "dosage unit" herein refer to a portion of a pharmaceutical composition that contains an amount of a therapeutic agent suitable for a single administration to provide a therapeutic effect. Such dosage units may be administered one to a plurality (i.e. 1 to about 10, 1 to 8, 1 to 6, 1 to 4 or 1 to 2) of times per day, or as many times as needed to elicit a therapeutic response.

In one embodiment, compositions of the invention, upon storage in a closed container maintained at room temperature, refrigerated (e.g. about 5 to about 5-10° C.) temperature, or frozen for a period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, exhibit at least about 90%, at least about 95%, at least about 97.5%, or at least about 99% of the active ingredient(s) originally present therein.

Therapeutic Methods

In one embodiment, the invention provides a method for treatment and/or prevention of cardiovascular-related disease and disorders. The term "cardiovascular-related disease and disorders" herein refers to any disease or disorder of the heart or blood vessels (i.e. arteries and veins) or any symptom thereof. Non-limiting examples of cardiovascular-related disease and disorders include hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, coronary heart disease, vascular disease, stroke, atherosclerosis, arrhythmia, hypertension, myocardial infarction, and other cardiovascular events.

The term "treatment" in relation a given disease or disorder, includes, but is not limited to, inhibiting the disease

or disorder, for example, arresting the development of the disease or disorder; relieving the disease or disorder, for example, causing regression of the disease or disorder; or relieving a condition caused by or resulting from the disease or disorder, for example, relieving, preventing or treating symptoms of the disease or disorder. The term "prevention" in relation to a given disease or disorder means: preventing the onset of disease development if none had occurred, preventing the disease or disorder from occurring in a subject that may be predisposed to the disorder or disease but has not yet been diagnosed as having the disorder or disease, and/or preventing further disease/disorder development if already present.

In various embodiments, the present invention provides methods of reducing a risk of a cardiovascular event in a subject on statin therapy. In some embodiments, the method comprises (a) identifying a subject on statin therapy and having a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, wherein said subject has established cardiovascular disease or has a high risk of developing cardiovascular disease; and (b) administering to the subject a pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester per day, wherein the composition contains substantially no docosahexaenoic acid.

In some embodiments, the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, for example 135 mg/dL to 500 mg/dL, 150 mg/dL to 500 mg/dL, or 200 mg/dL to <500 mg/dL. In some embodiments, the subject or subject group has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, of about 135 mg/dL, about 140 mg/dL, about 145 mg/dL, about 150 mg/dL, about 155 mg/dL, about 160 mg/dL, about 165 mg/dL, about 170 mg/dL, about 175 mg/dL, about 180 mg/dL, about 185 mg/dL, about 190 mg/dL, about 195 mg/dL, about 200 mg/dL, about 205 mg/dL, about 210 mg/dL, about 215 mg/dL, about 220 mg/dL, about 225 mg/dL, about 230 mg/dL, about 235 mg/dL, about 240 mg/dL, about 245 mg/dL, about 250 mg/dL, about 255 mg/dL, about 260 mg/dL, about 265 mg/dL, about 270 mg/dL, about 275 mg/dL, about 280 mg/dL, about 285 mg/dL, about 290 mg/dL, about 295 mg/dL, about 300 mg/dL, about 305 mg/dL, about 310 mg/dL, about 315 mg/dL, about 320 mg/dL, about 325 mg/dL, about 330 mg/dL, about 335 mg/dL, about 340 mg/dL, about 345 mg/dL, about 350 mg/dL, about 355 mg/dL, about 360 mg/dL, about 365 mg/dL, about 370 mg/dL, about 375 mg/dL, about 380 mg/dL, about 385 mg/dL, about 390 mg/dL, about 395 mg/dL, about 400 mg/dL, about 405 mg/dL, about 410 mg/dL, about 415 mg/dL, about 420 mg/dL, about 425 mg/dL, about 430 mg/dL, about 435 mg/dL, about 440 mg/dL, about 445 mg/dL, about 450 mg/dL, about 455 mg/dL, about 460 mg/dL, about 465 mg/dL, about 470 mg/dL, about 475 mg/dL, about 480 mg/dL, about 485 mg/dL, about 490 mg/dL, about 495 mg/dL, or about 500 mg/dL.

In some embodiments, the subject or subject group is also on stable therapy with a statin (with or without ezetimibe). In some embodiments, the subject or subject group also has established cardiovascular disease, or is at high risk for establishing cardiovascular disease. In some embodiments, the subject's statin therapy includes administration of one or more statins. For example and without limitation, the subject's statin therapy may include one or more of: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. In some embodiments, the subject is additionally administered one or more of: amlodipine, ezetimibe, niacin, and sitagliptin. In some embodiments, the subject's statin therapy includes administration of a statin and ezetimibe. In some embodiments, the subject's statin therapy includes administration of a statin without ezetimibe.

In some embodiments, the subject's statin therapy does not include administration of 200 mg or more per day of niacin and/or fibrates. In some embodiments, the subject is not on concomitant omega-3 fatty acid therapy (e.g., is not being administered or co-administered a prescription and/or over-the-counter composition comprising an omega-3 fatty acid active agent). In some embodiments, the subject is not administered or does not ingest a dietary supplement comprising an omega-3 fatty acid.

In some embodiments, the subject has established cardiovascular disease ("CV disease" or "CVD"). The status of a subject as having CV disease can be determined by any suitable method known to those skilled in the art. In some embodiments, a subject is identified as having established CV disease by the presence of any one of: documented coronary artery disease, documented cerebrovascular disease, documented carotid disease, documented peripheral arterial disease, or combinations thereof. In some embodiments, a subject is identified as having CV disease if the subject is at least 45 years old and: (a) has one or more stenosis of greater than 50% in two major epicardial coronary arteries; (b) has had a documented prior MI; (c) has been hospitalized for high-risk NSTE ACS with objective evidence of ischemia (e.g., ST-segment deviation and/or biomarker positivity); (d) has a documented prior ischemic stroke; (e) has symptomatic artery disease with at least 50% carotid arterial stenosis; (0 has asymptomatic carotid artery disease with at least 70% carotid arterial stenosis per angiography or duplex ultrasound; (g) has an ankle-brachial index ("ABI") of less than 0.9 with symptoms of intermittent claudication; and/or (h) has a history of aorto-iliac or peripheral arterial intervention (catheter-based or surgical).

In some embodiments, the subject or subject group being treated in accordance with methods of the invention has a high risk for developing CV disease. For example and without limitation, a subject or subject group has a high risk for developing CV disease if the subject or subject in a subject group is age 50 or older, has diabetes mellitus (Type 1 or Type 2), and at least one of: (a) is a male age 55 or older or a female age 65 or older; (b) is a cigarette smoker or was a cigarette smoker who stopped less than 3 months prior; (c) has hypertension (e.g., a blood pressure of 140 mmHg systolic or higher, or greater than 90 mmHg diastolic); (d) has an HDL-C level of ≤40 mg/dL for men or ≤50 mg/dL for women; (e) has an hs-CRP level of >3.0 mg/L; (0 has renal dysfunction (e.g., a creatinine clearance ("CrCL") of greater than 30 mL/min and less than 60 mL/min); (g) has retinopathy (e.g., defined as any of: non-proliferative retinopathy, preproliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease, or history of photocoagulation); (h) has microalbuminuria (e.g., a positive micral or other strip test, an albumin/creatinine ratio of ≥2.5 mg/mmol, or an albumin excretion rate on timed collection of ≥20 mg/min all on at least two successive occasions); (i) has macroalbuminuria (e.g., albumix or other dip stick evidence of gross proteinuria, an albumin/creatinine ratio of ≥25 mg/mmol, or an albumin excretion rate on timed collection of ≥200 mg/min all on at least two successive occasions); and/or (j) has an ankle-brachial index of <0.9 without symptoms of intermittent claudication.

In some embodiments, the subject's baseline lipid profile is measured or determined prior to administering the pharmaceutical composition to the subject. Lipid profile characteristics can be determined by any suitable method known to those skilled in the art including, for example, by testing a fasting or non-fasting blood sample obtained from the subject using standard blood lipid profile assays. In some embodiments, the subject has one or more of: a baseline non-HDL-C value of about 200 mg/dL to about 300 mg/dL; a baseline total cholesterol value of about 250 mg/dL to about 300 mg/dL; a baseline VLDL-C value of about 140 mg/dL to about 200 mg/dL; a baseline HDL-C value of about 10 to about 30 mg/dL; and/or a baseline LDL-C value of about 40 to about 100 mg/dL.

In some embodiments, the cardiovascular event for which risk is reduced is one or more of: cardiovascular death; nonfatal myocardial infarction; nonfatal stroke; coronary revascularization; unstable angina (e.g., unstable angina determined to be caused by myocardial ischemia by, for example, invasive or non-invasive testing, and requiring hospitalization); cardiac arrest; peripheral cardiovascular disease requiring intervention, angioplasty, bypass surgery or aneurysm repair; death; and onset of new congestive heart failure.

In some embodiments, the subject is administered about 1 g to about 4 g of the pharmaceutical composition per day for about 4 months, about 1 year, about 2 years, about 3 years, about 4 years, about 5 years, or more than about 5 years. Thereafter, in some embodiments the subject exhibits one or more of

(a) reduced triglyceride levels compared to baseline;

(b) reduced Apo B levels compared to baseline;

(c) increased HDL-C levels compared to baseline;

(d) no increase in LDL-C levels compared to baseline;

(e) a reduction in LDL-C levels compared to baseline;

(f) a reduction in non-HDL-C levels compared to baseline;

(g) a reduction in VLDL levels compared to baseline;

(h) a reduction in total cholesterol levels compared to baseline;

(i) a reduction in high sensitivity C-reactive protein (hs-CRP) levels compared to baseline; and/or

(j) a reduction in high sensitivity troponin (hsTnT) levels compared to baseline.

In some embodiments, the subject exhibits one or more of: (a) a reduction in triglyceride level of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 55% as compared to baseline;

(b) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in non-HDL-C levels or a reduction in non-HDL-C levels of at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% as compared to baseline;

(c) an increase in HDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% as compared to baseline; and/or

(d) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in LDL-C levels or a reduction in LDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 55% as compared to baseline.

In one embodiment, the subject or subject group being treated has a baseline EPA blood level on a (mol %) basis of less than 2.6, less than 2.5, less than 2.4, less than 2.3, less than 2.2, less than 2.1, less than 2, less than 1.9, less than 1.8, less than 1.7, less than 1.6, less than 1.5, less than 1.4, less than 1.3, less than 1.2, less than 1.1 or less than 1.

In another embodiment, the subject or subject group being treated has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, of about 135 mg/dL to about In some embodiments, the subject or subject group being treated in accordance with methods of the invention is on stable therapy with a statin (with or without ezetimibe). As used herein, the phrase "on stable therapy with a statin" means that the subject or subject group has been on the same daily dose of the same statin for at least 28 days and, if applicable, the same daily dose of ezetimibe for at least 28 days. In some embodiments, the subject or subject group on stable statin therapy has an LDL-C level of about 40 mg/dL to about 100 mg/dL.

In some embodiments, safety laboratory tests of subject blood samples include one or more of: hematology with complete blood count ("CBC"), including RBC, hemoglobin (Hgb), hematocrit (Hct), white cell blood count (WBC), white cell differential, and platelet count; and biochemistry panel including total protein, albumin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), total bilirubin, glucose, calcium, electrolytes, (sodium, potassium, chloride), blood urea nitrogen (BUN), serum creatinine, uric acid, creatine kinase, and HbA_{1c}.

In some embodiments, a fasting lipid panel associated with a subject includes TG, TC, LDL-C, HDL-C, non-HDL-C, and VLDL-C. In some embodiments, LDL-C is calculated using the Friedewald equation, or is measured by preparative ultracentrifugation (Beta Quant) if the subject's triglyceride level is greater than 400 mg/dL. In some embodiments, LDL-C is measured by ultracentrifugation (Beta Quant) at randomization and again after about one year after randomization.

In some embodiments, a biomarker assay associated with blood obtained from a subject includes hs-CRP, Apo B and hsTnT.

In some embodiments, a medical history associated with a subject includes family history, details regarding all illnesses and allergies including, for example, date(s) of onset, current status of condition(s), and smoking and alcohol use.

In some embodiments, demographic information associated with a subject includes day, month and year of birth, race, and gender.

In some embodiments, vital signs associated with a subject include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (e.g., oral body temperature).

In some embodiments, a physical examination of a subject includes assessments of the subject's general appearance, skin, head, neck, heart, lung, abdomen, extremities, and neuromusculature.

In some embodiments, the subject's height and weight are measured. In some embodiments, the subject's weight is recorded with the subject wearing indoor clothing, with shoes removed, and with the subject's bladder empty.

In some embodiments, a waist measurement associated with the subject is measured. In some embodiments, the

waist measurement is determined with a tape measure at the top of the subject's hip bone.

In some embodiments, an electrocardiogram associated with the subject is obtained. In some embodiments, an ECG is obtained every year during the treatment/follow-up portion of the study. In some embodiments, the ECG is a 12-lead ECG. In some embodiments, the ECG is analyzed for detection of silent MI.

In some embodiments, subjects randomly assigned to the treatment group receive 4 g per day of a composition comprising at least 96% by weight of eicosapentaenoic acid ethyl ester. In some embodiments, the composition is encapsulated in a gelatin capsule. In some embodiments, subjects in this treatment group continue to take 4 g per day of the composition for about 1 year, about 2 years, about 3 years, about 4 years, about 4.75 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, about 10 years, or more than about 10 years. In some embodiments, a median treatment duration is planned to be about 4 years.

In some embodiments, the present invention provides a method of reducing a risk of cardiovascular events in a subject. In some embodiments, the method comprises administering to the subject a composition comprising at least 96% by weight of eicosapentaenoic acid ethyl ester. In some embodiments, the subject is administered about 1 g to about 4 g of the composition per day.

In some embodiments, the reduced risk of CV events is indicated or determined by comparing an amount of time (e.g., an average amount of time) associated with a subject or subject group from first dosing to a first CV event selected from the group consisting of: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization (e.g., emergent hospitalization) for unstable angina determined to be caused by myocardial ischemia (e.g., by invasive or non-invasive testing), to an amount of time (e.g., an average amount of time) associated with a placebo or untreated subject or group of subjects from first dosing with a placebo to a first CV event selected from the group consisting of: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization (e.g., emergent hospitalization) for unstable angina determined to be caused by myocardial ischemia (e.g., by invasive or non-invasive testing), wherein said placebo does not include eicosapentaenoic acid ethyl ester. In some embodiments, the amount of time associated with the subject or group of subjects are compared to the amount of time associated with the placebo or untreated subject or group of subjects are compared using a log-rank test. In some embodiments, the log-rank test includes one or more stratification factors such as CV Risk Category, use of ezetimibe, and/or geographical region.

In some embodiments, the present invention provides a method of reducing risk of CV death in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the subject a composition as disclosed herein.

In another embodiment, the present invention provides a method of reducing risk of recurrent nonfatal myocardial infarction (including silent MI) in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the patient one or more compositions as disclosed herein.

In some embodiments, the present invention provides a method of reducing risk of nonfatal stroke in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the subject a composition as disclosed herein.

In some embodiments, the present invention provides a method of reducing risk of coronary revascularization in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the subject a composition as disclosed herein.

In some embodiments, the present invention provides a method of reducing risk of developing unstable angina caused by myocardial ischemia in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the subject a composition as disclosed herein.

In another embodiment, any of the methods disclosed herein are used in treatment or prevention of a subject or subjects that consume a traditional Western diet. In one embodiment, the methods of the invention include a step of identifying a subject as a Western diet consumer or prudent diet consumer and then treating the subject if the subject is deemed a Western diet consumer. The term "Western diet" herein refers generally to a typical diet consisting of, by percentage of total calories, about 45% to about 50% carbohydrate, about 35% to about 40% fat, and about 10% to about 15% protein. A Western diet may alternately or additionally be characterized by relatively high intakes of red and processed meats, sweets, refined grains, and desserts, for example more than 50%, more than 60% or more or 70% of total calories come from these sources.

In another embodiment, a composition as described herein is administered to a subject once or twice per day. In another embodiment, 1, 2, 3 or 4 capsules, each containing about 1 g of a composition as described herein, are administered to a subject daily. In another embodiment, 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the morning, for example between about 5 am and about 11 am, and 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the evening, for example between about 5 pm and about 11 pm.

In some embodiments, the risk of a cardiovascular event in a subject is reduced compared to a control population. In some embodiments, a plurality of control subjects to a control population, wherein each control subject is on stable statin therapy, has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, and has established cardiovascular disease or a high risk of developing cardiovascular disease, and wherein the control subjects are not administered the pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester per day.

In some embodiments, a first time interval beginning at (a) an initial administration of a composition as disclosed herein to the subject to (b) a first cardiovascular event of the subject is greater than or substantially greater than a first control time interval beginning at (a') initial administration of a placebo to the control subjects to (b') a first cardiovascular event in the control subjects. In some embodiments, the first cardiovascular event of the subject is a major cardiovascular event selected from the group consisting of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina caused by myocardial ischemia. In some embodiments, the first cardiovascular event of the control subjects is a major cardiovascular event selected from the group consisting of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina caused by myocardial ischemia. In some embodiments, the first cardiovascular event of the subject and the first cardio-

vascular event of the control subjects is any of: death (from any cause), nonfatal myocardial infarction, or nonfatal stroke. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death from a cardiovascular cause, nonfatal myocardial infarction, coronary revascularization, unstable angina, peripheral cardiovascular disease, or cardiac arrhythmia requiring hospitalization. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death from a cardiovascular cause, nonfatal myocardial infarction, and coronary revascularization, unstable angina. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death from a cardiovascular cause and nonfatal myocardial infarction. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is death (from any cause). In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: fatal myocardial infarction and nonfatal myocardial infarction (optionally including silent MI). In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is coronary revascularization. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is hospitalization (e.g. emergent hospitalization) for unstable angina (optionally unstable angina caused by myocardial ischemia). In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any one of: fatal stroke or nonfatal stroke. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any one of: new coronary heart failure, new coronary heart failure leading to hospitalization, transient ischemic attack, amputation for coronary vascular disease, and carotid revascularization. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any one of: elective coronary revascularization and emergent coronary revascularization. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is an onset of diabetes. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is cardiac arrhythmia requiring hospitalization. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is cardiac arrest.

In some embodiments, a second time interval beginning at (a) an initial administration of the pharmaceutical composition to the subject to (c) a second cardiovascular event of the subject is greater than or substantially greater than a second control time interval beginning at (a') initial administration of a placebo to the control subjects to (c') a second cardiovascular event in the control subjects. In some embodiments, the second cardiovascular event of the subject and the second cardiovascular event of the control subjects is a major cardiovascular event selected from the group consisting of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina caused by myocardial ischemia.

In some embodiments, the subject has diabetes mellitus and the control subjects each have diabetes mellitus. In some embodiments, the subject has metabolic syndrome and the control subjects each have metabolic syndrome.

In some embodiments, the subject exhibits one or more of (a) reduced triglyceride levels compared to the control population; (b) reduced Apo B levels compared to the control population; (c) increased HDL-C levels compared to the control population; (d) no increase in LDL-C levels compared to the control population; (e) a reduction in LDL-C levels compared to the control population; (f) a reduction in non-HDL-C levels compared to the control population; (g) a reduction in VLDL levels compared to the control population; (h) a reduction in total cholesterol levels compared to the control population; (i) a reduction in high sensitivity C-reactive protein (hs-CRP) levels compared to the control population; and/or (j) a reduction in high sensitivity troponin (hsTnT) levels compared to the control population.

In some embodiments, the subject's weight after administration of the composition is less than a baseline weight determined before administration of the composition. In some embodiments, the subject's waist circumference after administration of the composition is less than a baseline waist circumference determined before administration of the composition.

In methods of the present invention in which a time interval is determined or assessed, the time interval may be for example an average, a median, or a mean time interval. For example, in embodiments wherein a first control time interval is associated with a plurality of control subjects, the first control time interval is an average, a median, or a mean of a plurality of first control time intervals associated with each control subject. Similarly, in embodiments wherein a second control time interval is associated with a plurality of control subjects, the second control time interval is an average, a median, or a mean of a plurality of second control time intervals associated with each control subject.

In some embodiments, the reduced risk of cardiovascular events is expressed as a difference in incident rates between a study group and a control population. In some embodiments, the subjects in the study group experience a first major cardiovascular event after an initial administration of a composition as disclosed herein at a first incidence rate which is less than a second incidence rate, wherein the second incidence rate is associated with the rate of cardiovascular events in the subjects in the control population. In some embodiments, the first major cardiovascular event is any one of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina (optionally determined to be caused by myocardial ischemia). In some embodiments, the first and second incidence rates are determined for a time period beginning on the date of the initial administration and ending about 4 months, about 1 year, about 2 years, about 3 years, about 4 years, or about 5 years after the date of initial administration.

In another embodiment, the invention provides use of any composition described herein for treating hypertriglyceridemia in a subject in need thereof, comprising: providing a subject having a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL and administering to the subject a pharmaceutical composition as described herein. In one embodiment, the composition comprises about 1 g to about 4 g of eicosapentaenoic acid ethyl ester, wherein the composition contains substantially no docosahexaenoic acid.

EXAMPLES

A phase 3, multi-center, placebo-controlled randomized, double-blind, 12-week study with an open-label extension is

performed to evaluate the efficacy and safety of AMR101 in patients with fasting triglyceride levels≥150 mg/dL and <500 mg/dL. The primary objective is, in patients at LDL-C goal while on statin therapy, with established cardiovascular disease (CVD) or at high risk for CVD, and hypertriglyceridemia (fasting triglycerides, TG, ≥200 mg/dL and <500 mg/dL, determine the efficacy of AMR101 4 g daily, compared to placebo, in preventing the occurrence of a first major cardiovascular event of the composite endpoint that includes:

- cardiovascular ("CV") death;
- nonfatal myocardial infarction ("MI");
- nonfatal stroke;
- coronary revascularization; and
- unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emertgent hospitalization.

The secondary objectives of this study are the following:

To evaluate the effect of therapy on the composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or peripheral CV disease requiring intervention, angioplasty, bypass surgery, and aneurysm repair;

To evaluate the effect of therapy on combinations of each of the clinical events listed in secondary objective #1, supra, in addition to cardiac arrhythmia requiring hospitalization, cardiac arrest, peripheral CV disease requiring intervention, angioplasty, bypass surgery, aneurysm repair, and total mortality;

To evaluate the effect of therapy on the occurrence of a second, third, fourth and fifth major cardiovascular event (e.g., occurrence of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization after a first occurrence of any of same);

To evaluate the effect of therapy on the first occurrence of a major cardiovascular event in subgroups of patients including (a) those with diabetes mellitus, and (b) those with metabolic syndrome (e.g., as defined by the NCEP ATP III or future criteria as may evolve therefrom);

To evaluate the effect of therapy on new congestive heart failure ("CHF"), on new CHF as a primary cause of hospitalization, on transient ischemic attack, on amputation for CV disease, and on carotid revascularization;

To evaluate the effect of therapy on occurrence of elective coronary revascularization and emergent coronary revascularization;

To evaluate the effects of therapy on lipids, lipoproteins and inflammatory markers including triglycerides, total cholesterol, low-density lipoprotein cholesterol ("LDL-C"), high-density lipoprotein cholesterol ("HDL-C"), non-HDL-C, very low-density lipoprotein cholesterol ("VLDL-C"), apoliporpotein B ("apo B"), high-sensitivity C-reactive protein ("hs-CRP"), and high-sensitivity troponin ("hsTnT") as follows:

Evaluation of the effect of therapy on each marker;

Evaluation of the effect of the baseline value of each marker on therapy effects; and

Evaluation of the effect of therapy for preventing clinical events as defined above among all patients in the study and in sub-groups such as patients with diabetes mellitus and patients with substantial on-treatment changes of any of the markers;

To evaluate the effect of therapy on new onset diabetes; and

To explore the effect of therapy on weight and waist circumference.

Study Population

The population for this study is men and women≥45 years of age with established CVD, or men and women≥50 years of age with diabetes in combination with one additional risk factor for CVD. In addition, all patients will have atherogenic dyslipidemia defined as on treatment for hypercholesterolemia (but at treatment goal for LDL-C, by treatment with a statin) and hypertriglyceridemia. More details are listed in the inclusion criteria.

The patients will need to provide consent to participate in the study and be willing and able to comply with the protocol and the study procedures.

Study Periods

This study consists of the following study periods:

Screening Period: During the screening period, patients will be evaluated for inclusion/exclusion criteria.

At the first visit to the Research Unit (Visit 1), study procedures will be performed for evaluation of patient's eligibility in the study. At this screening visit, patients will sign an informed consent form before any study procedure is performed; the informed consent form will cover the treatment/follow-up period. Based on the evaluation from Visit 1, the following situations may occur:

Patients who are eligible for participation based on the study procedures on Visit 1 will return to the Research Unit for Visit 2 (randomization visit) to start the treatment/follow-up period. This case includes, for example, patients at Visit lwho are on a stable dose of a statin, are planning to stay on the same statin and the same dose of the statin, and who not need to wash out any non-statin lipid-altering medications.

Patients who are not eligible for participation based on the study procedures on Visit 1 and are unlikely to become eligible in the next 28 days (for example: unlikely to stabilize statin dose, unable to wash out non-statin lipid-altering medications, etc.): these patients will be screen failed after Visit 1.

Patients not eligible for participation in the study based on the study procedures on Visit 1 may possibly become eligible in the next 28 days: these patients may return at the discretion of the investigator for a second optional screening visit (Visit 1.1) at which time the procedures needed for re-evaluation of the previously failed inclusion/exclusion criteria will be repeated. This case includes, for example, patients who are started on a statin at Visit 1, whose statin dose is changed at Visit 1, and/or needed to wash out non-statin lipid-altering medications. The following applies for these patients:

Patients with a change in the statin or statin dose on Visit 1 will need to be on a stable statin dose for at least 28 days before the lipid qualifying measurements at Visit 1.1. Other concomitant medications (antidiabetic therapy, for example) can be optimized or stabilized during this period.

Patients starting a washout at Visit 1 will have a washout period of at least 28 days (only 7 days for bile acid sequestrants) before the lipid qualifying measurements at Visit 1.1.

Patients at Visit 1 who are on a stable dose of a statin, are planning to stay on the same statin at the same dose, and who do not need any medication washout, but were asked to return for Visit 1.1 to repeat one or more of the other study procedures not related to concomitant medications

Patients who become eligible for participation based on the additional study procedures at Visit 1.1 will return to the Research Unit for Visit 2 (randomization visit) to start the treatment/follow-up period.

At the end of the screening period, patients will need to meet all inclusion/exclusion criteria before they can be randomized. Patients who are not eligible for participation after the screening period (based on study procedures at Visit 1 and/or Visit 1.1) may return at a later date for rescreening. These patients will need to re-start with all procedures starting with Visit 1. This includes patients who need more time to stabilize one or more conditions or therapies (for example: statin, antidiabetic, antihypertensive, thyroid hormone, HIV-protease inhibitor therapy).

Treatment/Follow-Up Period: Within 42 days after the first screening visit (Visit 1) or within 60 days after the first screening visit (Visit 1) for those patients that have a second screening visit (Visit 1.1), eligible patients will enter the treatment/follow-up period. During this period, the patients will receive study drug during the planned visits at the Research Site and take the study drug while away from the Research Site.

During the visits, study procedures will be performed for evaluation of efficacy and safety. A detailed schedule of procedures is provided in Table 1.

Study Duration

The estimated study duration includes a planned 18-month enrollment period followed by a follow-up period of approximately 3.5 years in expected duration (approximately 5 years in total). Patients will be randomized at different times during the enrollment period but will all end the study at the same date (study end date). It is planned that all randomized patients will receive study medication and be followed-up until the study end date. This is an event-driven trial and patients will continue in the trial if the trial runs longer than expected, or will terminate earlier if the trial runs shorter than expected.

The total duration of the trial is based on a median 4-year follow-up period across patients. The first patient randomized would be followed for 4.75 years (the longest individual follow-up duration), and the last patient randomized would be followed for 3.25 year (the shortest individual follow-up duration).

Study Groups

At Visit 2 (Day 0), eligible study patients will be randomly assigned to the following treatment groups:

Group 1: AMR101 4 g daily (four 1000 mg capsules daily)

Group 2: placebo (four capsules daily)

The four AMR101 or placebo capsules daily will be taken as two capsules in the morning and two capsules in the evening (twice-per-day dosing regimen).

Number of Patients

This is an event-driven trial: It is expected that a minimum of 1612 primary efficacy endpoint events will be required during the study. A total of approximately 7990 patients will be entered into the study to either receive AMR101 or placebo (approximately 3995 patients per treatment group) in order to observe an estimated 1612 events that make up the primary composite endpoint for efficacy.

Number of Study Sites

Participants will be enrolled at multiple Research Sites in multiple countries.

Randomization

On Day 0, eligible patients will be randomized to one of 2 study groups using a computer-generated randomization schema. Randomized treatment assignment to either AMR101 or placebo in a 1:1 ratio will be provided using the internet (IWR).

Blinding

This is a double-blind study. Patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors supporting the study will be unaware of the randomization code (i.e., they will not know which study participants are receiving the experimental drug and which are receiving the placebo drug). The study medication AMR101 and placebo capsules will be similar in size and appearance to maintain blinding.

During the double-blind treatment/follow-up period, everyone (patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors managing/supporting the study), with the exception of the laboratory personnel performing the analysis, will be blinded to individual results of the efficacy laboratory measurements (including lipid values). Individual results from the lipid profile may be unblinded in the event of an emergency for a patient.

Stratification

Participants will be assigned to treatment groups stratified by CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries). There are two CV risk categories:

CV Risk Category 1: patients with established CVD defined in the inclusion criteria. Patients with diabetes and established CVD are included in this category.

CV Risk Category 2: patients with diabetes and at least one additional risk factor for CVD, but no established CVD.

Stratification will be recorded in the IWR at the time of enrollment. Approximately 70% of randomized patients will be in the CV Risk Category 1 and approximately 30% of randomized patients will be in the CV Risk Category 2. Enrollment with patients of a CV risk category will be stopped when the planned number of patients in that risk category is reached.

Study Population

Inclusion Criteria

Patients meeting the following criteria will be eligible to participate in the study:

Fasting TG levels of ≥200 mg/dL (2.26 mmol/L) and <500 mg/dL (5.64 mmol/L).

LDL-C>40 mg/dL (1.04 mmol/L) and ≤100 mg/dL (2.60 mmol/L) and on stable therapy with a statin (with or without ezetimibe) for at least 4 weeks prior to the LDL-C/TG baseline qualifying measurements for randomization

Stable therapy is defined as the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C) and, if applicable, the same daily dose of ezetimibe for at least 28 days before the lipid qualification measurements (TG and LDL-C). Patients who have their statin therapy or use of ezetimibe initiated at Visit 1, or have their statin, statin dose and/or ezetimibe dose changed at Visit 1, will need to go through a stabilization period of at least 28 days since initiation/change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).

Statins may be administered with or without ezetimibe.

If patients qualify at the first qualification visit (Visit 1) for TG and LDL-C, and meet all other inclusion/exclusion criteria, they may be randomized at Visit 2. If patients don't qualify at the first qualifying visit (Visit 1), a second

re-qualifying visit (Visit 1.1) is allowed. For some patients, because they need to stabilize medications and/or need to washout medications, the second re-qualifying visit (Visit 1.1) will be needed after the stabilization/washout period.

Either having established CVD (in CV Risk Category 1) or at high risk for CVD (in CV Risk Category 2). The CV risk categories are defined as follows:

CV Risk Category 1: defined as men and women≥45 years of age with one or more of the following:

Documented coronary artery disease (CAD; one or more of the following primary criteria must be satisfied):

Documented multivessel CAD (>50% stenosis in at least two major epicardial coronary arteries—with or without antecedent revascularization)

Documented prior MI

Hospitalization for high-risk NSTE-ACS (with objective evidence of ischemia: ST-segment deviation or biomarker positivity)

Documented cerebrovascular or carotid disease (one of the following primary criteria must be satisfied):

Documented prior ischemic stroke

Symptomatic carotid artery disease with ≥50% carotid arterial stenosis

Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound

History of carotid revascularization (catheter-based or surgical)

Documented peripheral arterial disease (PAD; one or more of the following primary criteria must be satisfied):

ABI<0.9 with symptoms of intermittent claudication

History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical)

OR

CV Risk Category 2: defined as patients with:

Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication AND

Men and women≥50 years of age AND

One of the following at Visit 1 (additional risk factor for CVD):

Men≥55 years of age or women≥65 years of age;

Cigarette smoker or stopped smoking within 3 months before Visit 1;

Hypertension (blood pressure≥140 mmHg systolic OR≥90 mmHg diastolic) or on antihypertensive medication;

HDL-C≤40 mg/dL for men or ≤50 mg/dL for women;

Hs-CRP>3.00 mg/L (0.3 mg/dL);

Renal dysfunction: CrCL>30 and <60 mL/min (>0.50 and <1.00 mL/sec);

Retinopathy, defined as any of the following: non-proliferative retinopathy, preproliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease or a history of photocoagulation;

Micro- or macroalbuminuria. Microalbuminuria is defined as either a positive micral or other strip test (may be obtained from medical records), an albumin creatinine ratio≥2.5 mg/mmol or an albumin excretion rate on timed collection≥20 mg/min all on at least two successive occasions; macroalbuminuria, defined as albustix or other dipstick evidence of gross proteinuria, an albumin:creatinine ratio≥25 mg/mmol or an albumin excretion rate on timed collection≥200 mg/min all on at least two successive occasions;

ABI<0.9 without symptoms of intermittent claudication (patients with ABI<0.9 with symptoms of intermittent claudication are counted under CV Risk Category 1).

Patients with diabetes with CVD as defined above are eligible based on the CVD requirements and will be counted under CV Risk Category 1. Only patients with diabetes and no documented CVD as defined above need at least one additional risk factor as listed, and will be counted under CV Risk Category 2.

Women may be enrolled if all 3 of the following criteria are met:

They are not pregnant;

They are not breastfeeding;

They do not plan on becoming pregnant during the study.

Women of child-bearing potential must have a negative urine pregnancy test before randomization.

Women are not considered to be of childbearing potential if they meet one of the following criteria as documented by the investigator:

They have had a hysterectomy, tubal ligation or bilateral oophorectomy prior to signing the informed consent form;

They are post-menopausal, defined as ≥1 year since their last menstrual period or have a follicle-stimulating hormone (FSH) level in a menopausal range.

Women of childbearing potential must agree to use an acceptable method of avoiding pregnancy from screening to the end of the study, unless their sexual partner(s) is/are surgically sterile or the woman is abstinent.

Understanding of the study procedures, willing to adhere to the study schedules, and agreement to participate in the study by giving informed consent prior to screening.

Agree to follow a physician recommended diet and to maintain it through the duration of the study.

Exclusion Criteria

Patients are excluded from participation in the study if any of the following criteria apply:

Severe (class IV) heart failure.

Any life-threatening disease expected to result in death within the next 2 years (other than CVD).

Active severe liver disease (evaluated at Visit 1): cirrhosis, active hepatitis, ALT or AST>3×ULN, or biliary obstruction with hyperbilirubinemia (total bilirubin>2× ULN).

Hemoglobin A1c>10.0% (or 86 mmol/mol IFCC units) at screening (Visit 1). If patients fail this criterion (HbA1c>10.0% or 86 mmol/mol IFCC units) at Visit 1, they may have their antidiabetic therapy optimized and be retested at Visit 1.1.

Poorly controlled hypertension: blood pressure≥200 systolic mmHg OR≥100 mmHg diastolic (despite antihypertensive therapy).

Planned coronary intervention (such as stent placement or heart bypass) or any non-cardiac major surgical procedure. Patients can be (re)evaluated for participation in the trial (starting with Visit 1.1) after their recovery from the intervention/surgery.

Known familial lipoprotein lipase deficiency (Fredrickson Type I), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type III)].

Participation in another clinical trial involving an investigational agent within 90 days prior to screening (Visit 1). Patients cannot participate in any other investigational medication or medical device trial while participating in this study (participation in a registry or observational study without an additional therapeutic intervention is allowed).

Intolerance or hypersensitivity to statin therapy.

Known hypersensitivity to any ingredients of the study product or placebo; known hypersensitivity to fish and or shellfish.

History of acute or chronic pancreatitis.

Malabsorption syndrome and/or chronic diarrhea (Note: patients who have undergone gastric/intestinal bypass sur-

gery are considered to have malabsorption, hence are excluded; patients who have undergone gastric banding are allowed to enter the trial).

Non-study drug related, non-statin, lipid-altering medications, supplements or foods:

Patients are excluded if they used niacin>200 mg/day or fibrates during the screening period (after Visit 1) and/or plan to use during the study; patients who are taking niacin>200 mg/day or fibrates during the last 28 days before Visit 1 need to go through washout of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (Visit 1.1);

Patients are excluded if they take any omega-3 fatty acid medications (prescription medicines containing EPA and/or DHA) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking omega-3 fatty acid medications during the last 28 days before Visit 1 (except patients in The Netherlands), need to go through a washout period of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (at Visit 1.1);

For patients in The Netherlands only: patients being treated with omega-3 fatty acid medications containing EPA and/or DHA are excluded; no washout is allowed.

Patients are excluded if they use dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking >300 mg/day omega-3 fatty acids (combined amount of EPA and DHA) within 28 days before Visit 1 (except patients in The Netherlands), need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);

For patients in The Netherlands only: patients being treated with dietary supplements containing omega-3 fatty acids of >300 mg/day EPA and/or DHA are excluded; no washout is allowed.

Patients are excluded if they use bile acid sequestrants during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking bile acid sequestrants within 7 days before Visit 1, need to go through a washout period of at least 7 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);

Other medications (not indicated for lipid alteration):

Treatment with tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are allowed), HIV-protease inhibitors that have not been stable for ≥28 days prior to the qualifying lipid measurements (TG and LDL-C) during screening. To be eligible for participation in the study, patients who are not taking a stable dose of these medications within 28 days before Visit 1, need to go through a stabilization period of at least 28 days since their last dose change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).

Patients are excluded if they use cyclophosphamide or systemic retinoids during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking these medications within 28 days before Visit 1, need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).

Known to have AIDS (patients who are HIV positive without AIDS are allowed).

Requirement for peritoneal dialysis or hemodialysis for renal insufficiency or if creatinine clearance (CrCL)<30 mL/min (0.50 mL/sec).

Unexplained creatine kinase concentration>5×ULN or creatine kinase elevation due to known muscle disease (e.g., polymyositis, mitochondrial dysfunction) at Visit 1.

Any condition or therapy which, in the opinion of the investigator, might pose a risk to the patient or make participation in the study not in the patient's best interest.

Drug or alcohol abuse within the past 6 months, and unable/unwilling to abstain from drug abuse and excessive alcohol consumption during the study or drinking 5 units or more for men or 4 units or more for women in any one hour (episodic excessive drinking or binge drinking). Excessive alcohol consumption is on average>2 units of alcohol per day. A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.

Mental/psychological impairment or any other reason to expect patient difficulty in complying with the requirements of the study or understanding the goal and potential risks of participating in the study (evaluated at Visit 1).

Study Procedures

Assessment Schedule

Screening Period

Screening Visit (Visit 1)

Patients will come to the Research Site for Visit 1. They will be instructed to fast for at least 10 hours before their visit.

If patients qualify for randomization based on the procedures at Visit 1, they need to be randomized within 60 days after Visit 1. The following procedures will be performed at the screening visit:

Obtain signed informed consent

Assign the patient a patient number

Obtain medical, surgical and family history

Record demographics

Obtain height, weight, and body mass index

Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

Obtain a 12-lead electrocardiogram

Evaluate inclusion/exclusion criteria

This includes procedures and (fasting) blood samples (for example, hs-CRP, calculated creatinine clearance) as needed to determine the CV risk category (see inclusion criteria)

Obtain fasting blood samples for chemistry and hematology testing

Obtain a fasting blood sample for the lipid profile (TG, TC, HDL-C, LDL-C, non-HDL-C, VLDL-C)

Perform a urine pregnancy test on women of childbearing potential

Record concomitant medication(s)

Instruct patient to fast for at least 10 hours prior to the next visit

Screening Visit (Visit 1.1)

Some patients will skip Visit 1.1: Patients who qualify for study participation after Visit 1 because they meet all inclusion criterion and none of the exclusion criteria, may return to the Research Site for Visit 2 to be randomized and to start the treatment/follow-up period of the study. For these patients, Visit 2 will occur soon after Visit 1.

Patients, who do not qualify at Visit 1, may return to the Research Site for a second qualifying visit (Visit 1.1) at the discretion of the investigator. At Visit 1.1, procedures that caused failure of eligibility at Visit 1 will be repeated. Patients will be eligible for randomization after Visit 1.1 if they meet all inclusion criteria and if they no longer fail the exclusion criteria. If patients are evaluated at Visit 1.1 and qualify for randomization based on the repeated procedures at Visit 1.1, they need to be randomized within 60 days after Visit 1.

For some patients, Visit 1.1 will be mandatory at least 28 days after Visit 1 in order to check eligibility. These are patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications (see inclusion/exclusion criteria for details). Any of these changes at Visit 1 may affect the qualifying lipid levels and therefore, patients will need to have Visit 1.1 to determine whether they qualify based on lipid level requirements (TG and LDL-C) determined at Visit 1. Other procedures that caused failure of eligibility at Visit 1 will also be repeated at Visit 1.1.

The following procedures will be performed at the screening visit:

Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

Evaluate inclusion/exclusion criteria; only those evaluations will be repeated that deemed the patient not eligible on Visit 1.

Obtain fasting blood samples for chemistry and hematology testing. Only those samples will be obtained that deemed the patient not eligible on Visit 1.

Obtain a fasting blood sample for the lipid profile (TG, TC, HDL-C, LDL-C, non-HDL-C, VLDL-C) if the patient was deemed not eligible on Visit 1. This includes patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications (see inclusion/exclusion criteria for details). These patients will have a fasting blood sample collected at Visit 1.1 for the qualifying lipid values (TG and LDL-C), and the TG and LDL-C inclusion criteria will be evaluated.

Record concomitant medication(s)

Treatment/Follow-Up Period

Every attempt should be made to complete the follow-up visits during the defined window periods.

Randomization visit (Visit 2; Day 0)

Qualified patients will return to the Research Site for Visit 2.

The following procedures will be performed at Visit 2:

Perform physical examination

Obtain weight

Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

Measure waist circumference (one of the factors to diagnose metabolic syndrome)

Obtain a 12-lead electrocardiogram

Evaluate inclusion/exclusion criteria

Obtain fasting blood samples for:

Chemistry and hematology testing

Lipid profile (baseline)

Biomarker assays (baseline)

Genetic testing (optional blood sample)

Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)

Perform a urine pregnancy test on women of childbearing potential (must be negative for randomization)

Dispense study drug and record randomization number

Instruct patient on how to take study drug

Administer study drug—Note: Study drug should be taken orally with food following the collection of all fasting blood samples

Assess for and record adverse events

Record concomitant medication(s)

Instruct patient:

To bring all study supplies with them to the next visit

Not to take study drug on the morning of their next visit

To fast for ≥10 hours prior to the next visit

Visit 3 (Day 120; ~4 Months)

Patients will return to the Research Site for Visit 3 on Day 120±10 days.

The following procedures will be performed:

Perform physical examination

Obtain weight

Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

Obtain fasting blood samples for:

Chemistry and hematology testing

Lipid profile

Review study drug compliance by unused capsule count; discuss with and counsel patients about compliance if needed

Administer study drug—Note: Study drug should be taken orally with food following the collection of all fasting blood samples

Assess and record efficacy events

Assess for and record adverse events

Record concomitant medication(s)

Instruct patient:

To bring all study supplies with them to the next visit

Not to take study drug on the morning of their next visit

To fast for ≥10 hours prior to the next visit

Visits 4, 5, 6 and 7

At Visit 4: Day 360±10; Visit 5: Day 720±10; Visit 6: Day 1080±10; and Visit 7: Day 1440±10, the following procedures will be performed:

Perform physical examination

Obtain weight

Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

Measure waist circumference (collected at Visit 5 only)

Obtain a 12-lead electrocardiogram

Obtain fasting blood samples for:

Chemistry and hematology testing

Lipid profile

Biomarker assays (collected at Visit 5 only)

Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)

Review study drug compliance by unused capsule count; discuss with and counsel patients about compliance if needed

Administer study drug—Note: Study drug should be taken orally with food following the collection of all fasting blood samples

Assess and record efficacy events

Assess for and record adverse events

Record concomitant medication(s)

Instruct patient:

To bring all study supplies with them to the next visit

Not to take study drug on the morning of their next visit

To fast for ≥10 hours prior to the next visit

Additional Visits

The end date of the study is expected for Day 1800 but the actual end date will be dependent on the determination of the study end date by the DMC. The study end date is determined to be when approximately 1612 primary efficacy events have occurred. If the actual study end date is later than the expected end date, additional visits will be planned between Visit 7 and the Last Visit with a maximum of 360±10 days between visits. If the actual study end date is sooner than the expected end date, fewer visits will occur, and the last visit (See Section 6.1.2.5) will occur sooner.

On additional visits the same procedures will be performed as listed in Section 6.1.2.3. Irrespective of the number of additional visits, after the DMC has established the end of the study date, there will be a last visit with procedures as listed in Section 6.1.2.5.

Last Visit—End of Study

All patients will complete the study at the same time (within a 30-day window after the study end date), irrespective of the date that they were randomized. The end date of the study is planned for Day 1800 but the actual end date will be dependent on the determination of the study end date when approximately 1612 primary efficacy events have occurred (event-driven trial). For each patient, the last visit may occur within 30 day after the actual study end date. However, for the efficacy endpoints based on CV events, only events occurring up to and including the scheduled actual study end date will be included in the efficacy analyses.

A final follow-up visit is required for all patients. In the rare cases that a final follow-up visit cannot occur within the 30-day timeframe following the study end date, any attempt to contact the patient must be recorded on a special contact form, until/unless appropriate information is obtained.

At the Last Visit, the following procedures will be performed:

Perform physical examination

Obtain weight

Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

Measure waist circumference

Obtain a 12-lead electrocardiogram

Obtain fasting blood samples for:

Chemistry and hematology testing

Lipid profile

Biomarker assays

Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)

Determine study drug compliance by unused capsule count

Assess and record efficacy events

Assess for and record adverse events

Record concomitant medication(s)

Telephone Follow-up Contact

Site personnel will contact each patient by telephone on the following study days:

Day 60±3 days

Day 180±5 days

Day 270±5 days

Day 450±5 days

Day 540±5 days

Day 630±5 days

Day 810±5 days

Day 900±5 days

Day 990±5 days

Day 1170±5 days

Day 1260±5 days

Day 1350±5 days

Day 1530±5 days

Day 1620±5 days

Day 1710±5 days

If the treatment/follow-up period of the study is extended beyond the expected end date (Day 1800), additional follow-up phone calls will be made every 3 months in-between additional visits±5 days. If the treatment/follow period of the study is shorter than the expected end date, less follow-up phone calls will be needed.

Every attempt will be made to talk to each patient within this time frame.

The following information will be collected from the patient:

Possible efficacy endpoints related to CV events. Patients will be asked to return to the Research Site to assess for any endpoints or events identified.

Adverse events

Concomitant medications

Current address and contact information (update if changed or will be changing)

Patients will be reminded about the following items:

To take the study medication according to the dosing schedule assigned, with food

When to return to the Research Center for the next visit

To bring the unused study medication to the next visit

To not take study drug on the morning of their next visit

To fast for at least 10 hours prior to the next visit

Laboratory Procedures

Clinical Laboratory Procedures

All clinical laboratory determinations for screening and safety will be performed by a certified clinical laboratory under the supervision of the Sponsor or its designee.

Whenever possible and appropriate, samples for the clinical laboratory procedures will be collected after fasting for at least 10 hours. For the purposes of this study, fasting is defined as nothing by mouth except water (and any essential medications).

The investigator must review and sign all laboratory test reports. At screening, patients who have laboratory values that are outside the exclusionary limits specified in the exclusion criteria may not be enrolled in the study (patients can be considered for the study if values are classified as not clinically significant by the investigator). After randomization, the investigator will be notified if laboratory values are outside of their normal range. In this case, the investigator will be required to conduct clinically appropriate follow-up procedures.

Safety Laboratory Tests

The safety laboratory tests include:

Hematology with complete blood count (CBC), including RBC, hemoglobin (Hgb), hematocrit (Hct), white cell blood count (WBC), white cell differential, and platelet count

Biochemistry panel including total protein, albumin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), total bilirubin, glucose, calcium, electrolytes (sodium, potassium, chloride), blood urea nitrogen (BUN), serum creatinine, uric acid, creatine kinase, and HbA1c.

Fasting Lipid Profile

The fasting lipid panel includes: TG, TC, LDL-C, HDL-C, non-HDL-C, and VLDL-C.

At all visits, LDL-C will be calculated using the Friedewald equation. At Visit 1 and Visit 1.1 Direct LDL-C will be used if at the same visit TG>400 mg/dL (4.52 mmol/L). These LDL-C values will be used for the evaluation of the LDL-C inclusion criterion (LDL-C qualifying measure-

ments for randomization) and for the assessment of changes in the statin therapy when LDL-C is not at goal. At all remaining visits (except Visit 2 and Visit 4) LDL-C will be measured by Direct LDL Cholesterol or by Preparative Ultracentrifugation if at the same visit TG>400 mg/dL (4.52 mmol/L). In addition, irrespective of the TG levels, at Visit 2 (0 Months of Follow-up, baseline) and at Visit 4 (12 Months of Follow-up), LDL-C will be measured by Preparative Ultracentrifugation. These Preparative Ultracentrifugation LDL-C measurements will be used in the statistical analysis including the calculation of the percent change from baseline (1 year versus baseline).

Genetic Testing

A fasting blood sample will be stored for future genetic testing at the discretion of the sponsor. The specifics of this test will be determined at a later date. This sample is optional as local regulations may prohibit genetic samples to be collected or shipped outside the country, or patients may not consent.

Research on genetic testing will look for links between genes and certain diseases, including their treatment(s) such as medicines and medical care. The blood samples will be collected in the study center with the regular protocol-required labs. Each patient tube with sample for genetic testing will be labeled with patient number only. The site will maintain a Subject Code Identification List for cross-reference. The patient number does not contain any identifiable information (i.e. Patient initials, date of birth, etc). Un-analyzed samples will be stored frozen by the sponsor for a period of up to 2 years following the end of the study, at which time they will be destroyed. If samples are tested, results will not be reported to the patient, parents, relatives, or attending physician and will not be recorded in the patient's medical records. There will be no follow-up contact with the sites or patients regarding this sample. The subject can withdraw their consent for genetic testing at any time up to analysis, even after the sample has been obtained. The subject can notify the site in writing that they withdraw their consent for the genetic testing portion of the study, and it will be documented by the site in the subject chart, as well as captured in the CRF. The lab will be notified to pull the sample and destroy it.

Biomarkers Assays

The biomarker assays include: hs-CRP, Apo B and hsTnT.

Additional laboratory tests

Additional laboratory tests include:

A urine pregnancy test will be administered to women of childbearing potential at certain visits as listed in schedule of procedures (Table 1). The urine pregnancy tests will be performed at the Research Site utilizing marketed test kits, or at a certified clinical laboratory.

A fasting blood sample (12 mL) for archiving. This sample will be collected only at sites in countries where allowed by local regulations and at sites for which approved by the IRB or IEC. The plasma from the archiving sample will be stored frozen in 2 separate equal aliquots, and will be used at the Sponsor's discretion to perform repeat analyses described in the protocol or to perform other tests related to cardiovascular health.

Blinding of Laboratory Results

All efficacy laboratory results during the double-blind period of the trial will be blinded (values not provided) to patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors managing and/or supporting the study, with the exception of the laboratory personnel conducting the assays. To ensure patient safety, hsTnT values will be reported to the site.

Flagging of Critical Lab Values

Critical lab values are values that may warrant medical intervention to avoid possible harm to a patient. Critical lab values will be defined in the Laboratory Manual for the study, and the Research Site will be notified of the occurrence of a critical lab value (critical high or critical low) by a special annotation (flag) in the laboratory reports provided to the Research Sites. Although laboratory values that are part of the efficacy endpoints during the double-blind period of the study will not be provided to the Research Site (see Section 6.3.1.6), the sites will be notified when the TG value of a patient sample is >1000 mg/dL (11.29 mmol/L) (critical high TG value) or if the LDL-C values of a patient sample is >130 mg/dL (3.37 mmol/L) (critical high LDL-C value). These critical high values will need to be confirmed by a repeat measurement (new fasting blood sample) within 7 days. TG value of >2000 mg/dL (22.58 mmol/L) will also be flagged, so that appropriate medical action can be taken by the investigator as soon as possible.

If TG values are confirmed critically high, patients may be discontinued from study drug with the option to remain on study. The investigator should use the best clinical judgment for each patient which could include the use of approved TG-lowering medications after patients have been discontinued from study drug.

If LDL-C values are confirmed critically high, the investigator may need to take appropriate medical action which could include: reinforce/intensify therapeutic lifestyle changes (including diet and physical activity), increase the dose of the present statin therapy, add ezetimibe, or prescribe a more potent statin to lower LDL-C. The investigator should use the best clinical judgment for each patient.

Medical Procedures

Medical, Surgical and Family History

Medical history, including family history and details regarding all illnesses and allergies, date(s) of onset, status of current condition, and smoking and alcohol use will be collected on all patients.

Demographics

Demographic information including day, month, and year of birth, race, and gender will be collected for all patients.

Vital Signs

Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Blood pressure will be measured using a standardized process:

Patient should sit for ≥5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level.

Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery.

Blood pressure should be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device. A blood pressure reading should be repeated 1 to 2 minutes later, and the second reading should also be recorded to the nearest 2 mmHg mark.

Physical Examination

A physical examination must include source documentation of general appearance, skin, and specific head and neck, heart, lung, abdomen, extremities, and neuromuscular assessments.

Height, Weight and Body Mass Index

Height and weight will be measured. Measurement of weight should be performed with the patient dressed in indoor clothing, with shoes removed, and bladder empty.

Waist Circumference

Waist circumference will be measured with a tape measure, as follows: Start at the top of the hip bone then bring the tape measure all the way around—level with the navel. Make sure the tape measure is snug, but without compressing the skin, and that it is parallel with the floor.

Patients should not hold their breath while measuring waist circumference.

Electrocardiogram (ECG)

ECGs (standard 12-lead) will be obtained annually. Site personnel should make every attempt to perform a patient's ECG using the same equipment at each visit. ECGs will be reviewed by the site for the detection of silent MI. Silent MIs will be sent for event adjudication.

Treatment and Restrictions

Treatment

Treatment Regimen, Dosage, and Duration

Eligible study patients will be randomly assigned on Day 0 to one of the 2 treatment groups. Patients in each group will receive either 4 g/day AMR101 or placebo for up to 4.75 years (4 years planned median treatment duration) according to Table 2.

The daily dose of study drug is 4 capsules per day taken as two capsules take on two occasions per day (2 capsules given twice daily).

TABLE 2

Dosing Schedule during the Treatment Period

Treatment Group	Daily Dose	Number of Capsules per Day
1	4 g	4 capsules of 1000 mg AMR101
2	Placebo	4 capsules of matching placebo

Patients will be instructed to take study drug with food (i.e., with or at the end of their morning and evening meals). On days that patients are scheduled for study visits, the daily dose of study drug will be administered by site personnel with food provided by the site following collection of all fasting blood samples. For the purposes of this study, fasting is defined as nothing by mouth except water (and any essential medications) for at least 10 hours.

Treatment Assignment

Identification Number

A unique patient identification number (patient number) will be established for each patient at each site. The patient number will be used to identify the patient throughout the study and will be entered on all documentation. If a patient is not eligible to receive treatment, or if a patient discontinues from the study, the patient number cannot be reassigned to another patient. The patient number will be used to assign patients to one of the 2 treatment groups according to the randomization schedule.

Drug Randomization

Only qualified patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized and will receive study medication starting at Visit 2 (Day 0). Eligible patients will be randomly assigned to one of the 2 treatment groups. Randomization will be stratified by CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries) (See Section 3.10). Approximately 70% of randomized patients will be in the CV Risk Category 1, including patients with established CVD, and approximately 30% of randomized patients will be in the CV Risk Category 2, including patients with diabetes and at least one additional risk factor but no established CVD. Enrollment with patients of a CV risk category will be stopped when the planned number of patients in that risk category is reached.

Emergency Unblinding

In an emergency, when knowledge of the patient's treatment assignment is essential for the clinical management or welfare of the patient, the investigator may request the patient's treatment assignment for unblinding. Prior to unblinding the patient's individual treatment assignment, the investigator should assess the relationship of an adverse event to the administration of the study drug (Yes or No). If the blind is broken for any reason, the investigator must record the date and reason for breaking the blind on the appropriate Case Report Form (CRF) and source documents.

Compliance Control

It is recommended that, unless clear contraindications arise, patients be strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any interruptions of therapy should, if possible, be brief (e.g., <4 weeks) and only for clinically indicated reasons, such as adverse events. Discontinuations will be discouraged as much as possible. Any discontinuations should be based on compelling clinical reasons.

For every patient, an assessment of compliance to the study drug treatment regimen must be obtained at each scheduled visit. Study medication will be dispensed in amounts exceeding the amount required for the study. Patients will be instructed to return all unused study medication at the next visit. Compliance to the study drug regimen will be evaluated at each visit by counting unused capsules. Discrepancies will be evaluated and discussed with each patient to assess compliance. If compliance is unsatisfactory, the patient will be counseled about the importance of compliance to the dosing regimen. At the end of the study, the final study medication compliance will be determined by unused capsule count.

Study Restrictions

Concomitant Medications During Treatment/Follow-Up Period

Any medications administered during the study period must be documented on the Concomitant Medication CRF. Patients must not have taken any investigational agent within 90 days prior to screening. Patients cannot participate in any other investigational medication trial while participating in this study.

The following non-study drug related, non-statin, lipid-altering medications and supplements, and foods are prohibited during the study (from Visit 1 until after the Last Visit-End of Study), except for compelling medical reasons in ODIS patients:

niacin>200 mg/day;

fibrates;

prescription omega-3 fatty acid medications;

dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils);

bile acid sequestrants;

cyclophosphamide;

systemic retinoids

If any of these products would be used during the treatment/follow-up period of the study, it should be for compelling medical reasons in ODIS patients, and it should be documented in the Concomitant Medication CRF. If the

ODIS patient agrees to restart study medication, the use of excluded medication must be discontinued.

Foods enriched with omega-3 fatty acids are strongly discouraged after Visit 1 for the duration of the study (does not apply to The Netherlands or Canada only. Therefore, all centers in The Netherlands and Canada must ignore this request).

The following products are allowed: statins, ezetimibe, and herbal products & dietary supplements not containing omega-3 fatty acids.

Statins:

The same statin at the same dose should be continued until the end of the study, unless deemed medically necessary to change because of an adverse event or lack of efficacy (LOE). It is preferred that if LOE is the determining factor that ezetimibe be added to the present dose.

Switching between a brand name statin and the generic version of the same statin is allowed at any time during the study.

Statins may be administered with or without ezetimibe.

Based on the FDA recommendation, simvastatin 80 mg be used only in patients who have been taking this dose for 12 months or more and have not experienced any muscle toxicity. (See reference: FDA Drug Safety Communication: Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury. (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204882.htm)

Changing of the type of statin or the statin dose during the treatment/follow-up period of the study should only be done for compelling medical reasons and must be documented in the CRF.

LDL-C Rescue:

If the level of LDL-C exceeds 130 mg/dL (3.37 mmol/L) during the study (initial measurement and confirmed by a second determination at least 1 week later), the investigator may either increase the dose of the present statin therapy or may add ezetimibe to lower LDL-C. The investigator should use the best clinical judgment for each patient.

No data are available with regard to potential interactions between ethyl-EPA and oral contraceptives. There are no reports suggesting that omega-3 fatty acids, including ethyl-EPA, would decrease the efficacy of oral contraceptives.

Patient Restrictions

Beginning at the screening visit, all patients should be instructed to refrain from excessive alcohol consumption, to follow a physician recommended diet and to maintain it through the duration of the study. Excessive alcohol consumption is on average 2 units of alcohol per day or drinking 5 units or more for men or 4 units or more for women in any one hour (episodic excessive drinking or binge drinking). A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.

Investigational Product

Clinical Trial Material

The following will be supplied by the Sponsor:

AMR101 1000 mg capsules

Placebo capsules

The Sponsor will supply sufficient quantities of AMR101 1000 mg capsules and placebo capsules to allow for completion of the study. The lot numbers of the drugs supplied will be recorded in the final study report.

Records will be maintained indicating the receipt and dispensation of all drug supplies. At the conclusion of the study, any unused study drug will be destroyed.

Pharmaceutical Formulations

AMR101 1000 mg and placebo capsules (paraffin) are provided in liquid-filled, oblong, gelatin capsules. Each capsule is filled with a clear liquid (colorless to pale yellow in color). The capsules are approximately 25.5 mm in length with a diameter of approximately 9.5 mm.

Labeling and Packaging

Study medication will be packaged in high-density polyethylene bottles. Labeling and packaging will be performed according to GMP guidelines and all applicable country-specific requirements. The bottles will be numbered for each patient based on the randomization schedule. The patient randomization number assigned by IWR or a designee of the Sponsor for the study (if no IWR system is used), will correspond to the number on the bottles. The bottle number for each patient will be recorded in the Electronic Data Capture (EDC) system for the study.

Dispensing Procedures and Storage Conditions

Dispensing Procedures

At Visit 2 (Day 0), patients will be assigned study drug according to their treatment group determined by the randomization schedule. Once assigned to a treatment group, patients will receive study drug supplies. At each visit, patients will bring unused drug supplies dispensed to them earlier. From the drug supplies assigned to each patient, site personnel will administer drug while the patients are at the Research Site.

The investigator or designee must contact the IWR system or a designee of the Sponsor for the study (if no IWR system is used) when any unscheduled replacements of study medication are needed.

During the last visit during the treatment period, patients will bring the unused drug supplies for site personnel to calculate the final study medication compliance by unused capsule count.

Storage Conditions

At the Research Sites, study drugs must be stored at room temperature, 68° F. to 77° F. (20° C. to 25° C.). Do not allow storage temperature to go below 59° F. (15° C.) or above 86° F. (30° C.). Store in the original package.

Study drugs must be stored in a pharmacy or locked and secure storage facility, accessible only to those individuals authorized by the investigator to dispense the drug. The investigator or designee will keep accurate dispensing records. At the conclusion of the study, study site personnel will account for all used and unused study drug. Any unused study drug will be destroyed. The investigator agrees not to distribute study drug to any patient, except those patients participating in the study.

Efficacy Assessments

Specification of Variables and Procedures

The primary endpoint and the majority of the secondary and tertiary endpoints are based on clinical events related to CVD and mortality. All events occurring between randomization and the study end date (inclusive) must be recorded. Only adjudicated events will be included in the final analyses. Further details on the assessment of clinical events and their definitions will be found in the CEC charter.

Efficacy Endpoints

Primary Efficacy Endpoint

Time from randomization to the first occurrence of the composite of the following clinical events:

CV death,

Nonfatal MI (including silent MI; ECGs will be performed annually for the detection of silent MIs),

Nonfatal stroke,

Coronary revascularization

Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing.

The first occurrence of any of these major adverse vascular events during the follow-up period of the study will be included in the incidence.

Secondary Efficacy Endpoints

The key secondary efficacy endpoint is:

The composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or peripheral CVD requiring intervention, angioplasty, bypass surgery, or aneurysm repair.

Other secondary efficacy endpoints are as follows (to be tested in said order):

The composite of total mortality, nonfatal MI, or nonfatal stroke;

The composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, peripheral CVD requiring intervention, or cardiac arrhythmia requiring hospitalization;

The composite of death from CV causes, nonfatal MI, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;

The composite of death from CV causes or nonfatal MI;

Total mortality;

Fatal and nonfatal MI (including silent MI);

Coronary Revascularization;

Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing;

Fatal and nonfatal stroke.

For the secondary endpoints that count a single event, the first occurrence of this type of event will be counted in each patient. For secondary endpoints that are composites of two or more types of events, the first occurrence of any of the event types included in the composite will be counted in each patient.

Tertiary Efficacy Endpoints:

The second, third, fourth, and fifth major CV event of the primary composite endpoint. The type of (nonfatal) events may occur in any order.

Primary endpoint in subset of patients with diabetes mellitus;

Primary endpoint in subset of patients with metabolic syndrome;

New CHF, new CHF leading to hospitalization, transient ischemic attack, amputation for CVD and carotid revascularization;

Elective coronary revascularization and emergent coronary revascularization;

New onset diabetes;

Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP, and hsTnT: effect of baseline and on-treatment change of biomarkers on primary and key secondary endpoints;

CV mortality;

Cardiac Arrhythmias requiring hospitalization;

Cardiac Arrest;

To explore the effect of AMR101 on weight and waist circumference.

For the tertiary endpoints that count a single event, the first occurrence of this type of event will be counted in each patient. For tertiary endpoints that are composites of two or more types of events, the first occurrence of any of the event types included in the composite will be counted in each patient (except when stated otherwise, for the second, third, fourth, and fifth major CV event).

Safety Assessments

Specification of Variables and Procedures

Safety assessments will include adverse events, clinical laboratory measurements (chemistry, hematology), 12-lead ECGs, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), and physical examinations as per Study Procedures/Table 1.

A complete medical, surgical and family history will be completed at Visit 1.

All laboratory test results must be evaluated by the investigator as to their clinical significance. Any observations at physical examinations or laboratory values considered by the investigator to be clinically significant should be considered an adverse event.

Adverse Events

An adverse event is defined as any untoward medical occurrence, which does not necessarily have a causal relationship with the medication under investigation. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medication product, whether or not related to the investigational medication product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate CRF. Each adverse event is to be evaluated for duration, intensity, and causal relationship with the study medication or other factors.

Adverse events, which include clinical laboratory test variables, will be monitored from the time of informed consent until study participation is complete. Patients should be instructed to report any adverse event that they experience to the investigator. Beginning with Visit 2, investigators should assess for adverse events at each visit and record the event on the appropriate adverse event CRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate adverse event on the CRF.

Any medical condition that is present when a patient is screened or present at baseline that does not deteriorate should not be reported as an adverse event. However, medical conditions or signs or symptoms present at baseline and that change in severity or seriousness at any time during the study should be reported as an adverse event.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen will be reported as adverse events or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

The investigator will rate the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to study drug using the categories of Yes or No.

Severity:

Mild—An event that is usually transient in nature and generally not interfering with normal activities.

Moderate—An event that is sufficiently discomforting to interfere with normal activities.

Severe—An event that is incapacitating with inability to work or do usual activity or inability to work or perform normal daily activity.

Causality Assessment:

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, no relation)—The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes—The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

The temporal sequence from study medication administration

The event should occur after the study medication is given. The length of time from study medication exposure to event should be evaluated in the clinical context of the event.

Underlying, concomitant, intercurrent diseases

Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

Concomitant medication

The other medications the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

Known response pattern for this class of study medication

Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

Exposure to physical and/or mental stresses

The exposure to stress might induce adverse changes in the patient and provide a logical and better explanation for the event.

The pharmacology and pharmacokinetics of the study medication

The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study medication should be considered.

Unexpected Adverse Events—An unexpected adverse event is an adverse event either not previously reported or where the nature, seriousness, severity, or outcome is not consistent with the current Investigator's Brochure.

Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets any of the following criteria:

Results in death

Is life-threatening—Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires hospitalization or prolongation of existing hospitalization—Note: In general, hospitalization for treatment of a pre-existing condition(s) that did not worsen from baseline is not considered adverse events and should not be reported as SAEs.

Results in disability/incapacity

Is a congenital anomaly/birth defect;

Is an important medical event—Note: Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

By design of this study SAEs that are endpoint events will only be recorded for the endpoint determination and not captured as SAEs. The intention is that the endpoint events are not reported to IRBs as SAEs, unless the IRB requires that these are reported. Investigators should specifically inform their institution/IRB of this plan and confirm whether or not they want the endpoint events reported. By agreement with the US FDA, these endpoints will also not be reported to the US FDA as SAEs; rather they will be reported as endpoint events. Following adjudication if the event is determined to not meet the criteria for an event, the event will be evaluated as an SAE beginning with that day as Day 0.

Serious Adverse Event Reporting—Procedure for Investigators

Initial Reports

All SAEs occurring from the time of informed consent until 28 days following the last administration of study medication must be reported to the Sponsor or designee within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). SAEs that the investigator considers related to study medication occurring after the 28-day follow-up period will also be reported to the Sponsor or designee.

The investigator is required to submit SAE reports to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local requirements. All investigators involved in studies using the same investigational medicinal product (IMP) will receive any Suspected Unexpected Serious Adverse Reaction (SUSAR) reports for onward submission to their local IRB as required. All reports sent to investigators will be blinded.

In addition, regulatory agencies will be notified of SAEs per the requirements of the specific regulatory jurisdiction regulations and laws.

Follow-Up Reports

The investigator must continue to follow the patient until the SAE has subsided, or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies. Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., laboratory test reports, patient discharge summary, or autopsy reports) to the Sponsor or designee via fax or email.

Reporting by the Sponsor

IRBs and IECs will be informed of SUSARs according to local requirements. Cases will be unblinded for reporting purposes as required.

Exposure In Utero During Clinical Trials

If a patient becomes pregnant during the study, the investigator should report the pregnancy to the Sponsor or designee within 24 hours of being notified. The Sponsor or designee will then forward the Exposure In Utero form to the investigator for completion.

The patient should be followed by the investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the Sponsor or designee. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

Treatment Discontinuation/Patient Withdrawal

Patients may withdraw from the study at any time and for any reason. Study drug administration may also be discontinued at any time, at the discretion of the investigator. In any case, follow-up for efficacy and safety should be continued.

Reasons for Early Study Drug Discontinuation

Study drug discontinuation should be avoided as much as possible, but may be done for any of the following reasons:

Patient withdraws consent or requests early discontinuation from the study for any reason. Patients should be encouraged to continue to participate in the study for the entire duration of the study even if they choose not to take study medication any longer.

Occurrence of a clinical or laboratory adverse event, either serious or non-serious, at the discretion of the investigator. The Sponsor or designee should be notified if a patient is discontinued because of an adverse event or laboratory abnormality. It is recommended that, unless clear contraindications arise, patients be strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any interruptions of therapy should, if possible, be brief (e.g., <4 weeks) and only for clinically indicated reasons, such as adverse events. The following should be considered reason for discontinuation:

ALT>3×ULN and bilirubin>1.5×ULN

ALT>5×ULN

ALT>3×ULN and appearance or worsening of hepatitis

ALT>3×ULN persisting for >4 weeks

ALT>3×ULN and cannot be monitored weekly for 4 weeks

Any medical condition or personal circumstance that, in the opinion of the investigator, exposes the patient to risk by continuing in the study or precludes adherence to the protocol.

Sponsor discontinues the study.

A TG value that is flagged as critically high, i.e., >1000 mg/dL (11.29 mmol/L), and confirmed as critically high by a repeat measurement (new fasting blood sample) within 7 days. In this case, a patient may be discontinued from study drug (with the option to remain ODIS) and other lipid-altering medications may be (re)initiated. If the TG value is flagged as >2000 mg/dL (22.58 mmol/L) then appropriate medical action can be taken by the investigator as soon as possible.

Occurrence of an outcome event according to the judgment of the investigator is not considered a valid reason for study drug discontinuation.

Patients whose treatment with study medication is discontinued early, and have not withdrawn consent, will stay in study and will be monitored until the end of the study. Patients that continue in the study after indefinite cessation of therapy will be characterized as Off Drug In Study (ODIS). ODIS patients should be asked to return to the study site for an interim visit once the patient has been off study drug for >30 days. Procedures at this visit are consistent with those at Visit 5. If not contraindicated, patients will also have the option to restart study medication at any point once characterized as ODIS.

The reason for study drug discontinuation or interruption will be recorded on the CRF.

Follow-Up after Early Study Drug Discontinuation/Lost to Follow-Up

Patients who prematurely discontinue study drug are not to be replaced.

All randomized patients must be followed up according to the study flowchart until the study end date or death, regardless of whether they discontinue study drug prematurely or not. Any event occurring after early study drug discontinuation will be recorded up through the study end date.

In order to follow the medical status of the patients, especially when they discontinued the study, investigators are encouraged to obtain information from the patient's primary care practitioner (physician or any other medical care provider). Investigators are also requested to try as much as possible to re-contact those patients at the end of the trial to obtain at least their vital status as well as their status with respect to the primary endpoint, and thus avoid lost to follow-up for the efficacy assessment.

If patients are lost to follow-up, the CRF must be completed up to the last visit or contact.

Statistics

Analysis Populations

Randomized Population

The randomized population will include all patients who sign the informed consent form and are assigned a randomization number at Visit 2 (Day 0).

Intent-to-Treat Population

The Intent-to-Treat (ITT) population will consist of all randomized patients who take at least one dose of study drug. The ITT population is the primary analysis population. All efficacy analyses will be performed on the ITT population.

Per-Protocol Population

The per-protocol (PP) population will include all ITT patients without any major protocol deviations, and who had ≥80% compliance with study drug while on treatment (up to discontinuation for patients whose treatment is terminated early). The per-protocol efficacy analysis for CV events will be restricted to each patient's time on study drug plus 30 days thereafter.

Safety Population

All safety analyses will be conducted based on the safety population, which is defined as all randomized patients who receive at least one dose of study drug. This is the same as the ITT population.

Statistical Methods

Safety and efficacy variables will be analyzed using appropriate statistical methods to be described in detail in a separate Statistical Analysis Plan (SAP). The SAP will be finalized before study unblinding.

Patient Disposition and Demographic/Baseline Characteristics

The numbers of patients screened, the number of patients randomized per treatment group (randomized population), and the number of patients in the ITT and PP populations by treatment group will be listed.

For randomized patients who discontinued treatment with study drug, the primary reason for discontinuation will be listed and summarized by treatment group.

Summary statistics (mean, standard deviation, median, minimum and maximum) will be provided by treatment

group for demographic characteristics (e.g., age, sex, race, and ethnicity) and baseline characteristics (e.g., body weight, height, and body mass index) in the ITT and PP populations.

Demographic data and baseline characteristics will be compared among treatment groups for the ITT and PP population. Differences in demographic and baseline characteristics will be tested using a chi-square test (for categorical variables) or a 1-way analysis of variance model with treatment as a factor (for continuous variables). The p-values will be used as descriptive statistics, primarily as an assessment of the adequacy of randomization.

Study Medication Exposure and Compliance

The final compliance to study drug will be calculated as the percent of doses taken relative to doses scheduled to be taken. Overall percent compliance will be calculated per patient in the ITT and PP populations and summarized by treatment group using summary statistics (n, mean, standard deviation, median, minimum, and maximum).

Concomitant Therapies

Concomitant medication/therapy verbatim terms will be coded using the latest version of the World Health Organization Drug Dictionary. The numbers and percentages of patients in each treatment group taking concomitant medications will be summarized by anatomic and therapeutic chemical classification and preferred term.

Analysis of Efficacy

For efficacy endpoints including CV events, only adjudicated events will be included in the final statistical analyses.

Summary Statistics

Summary statistics (n, mean, standard deviation, median, minimum, and maximum) for the baseline and post-baseline measurements, the percent changes, or changes from baseline will be presented by treatment group and by visit for all efficacy variables to be analyzed. The summary statistics will include changes in body weight and body mass index from baseline by treatment group and by visit.

Primary Endpoint

The primary efficacy endpoint is the time from randomization to the first occurrence of any component of the composite of the following clinical events:

CV death,

Nonfatal MI (including silent MI),

Nonfatal stroke,

Coronary revascularization,

Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing.

The analysis of the primary efficacy endpoint will be performed using the log-rank test comparing the 2 treatment groups (AMR101 and placebo) and including the stratification factor "CV risk category", use of ezetimibe and geographical region (Westernized, Eastern European, and Asia Pacific countries) (each as recorded in the IWR at the time of enrollment) as covariates. Treatment difference will be tested at alpha level of 0.0476 accounting for one interim efficacy analysis. The hazard ratio for treatment group (AMR101 vs. placebo) from a Cox proportional hazard model that includes the stratification factor will also be reported, along with the associated 95% confidence interval. Kaplan-Meier estimates from randomization to the time to the primary efficacy endpoint will be plotted.

The size and direction of the treatment effects of the individual components of the composite endpoint and their relative contribution to the composite endpoint will be determined as well.

Secondary Endpoints

The statistical analyses of the secondary endpoints will be analyzed by the same log-rank test specified above for the primary efficacy endpoint. Treatment differences will be tested at alpha level of 0.05 using a sequential procedure for controlling type 1 error starting with the key secondary variable. The remaining secondary variables will be tested in the order specified in Section 9.2.2. Estimates of the hazard ratios from the Cox proportional hazard model and the associated 95% confidence intervals will also be provided. Kaplan-Meier estimates from randomization the time to the secondary efficacy endpoints will be plotted.

Tertiary Endpoints

For event rates, the statistical analyses of the tertiary endpoints will be similar to the analysis of the secondary efficacy endpoints. All tertiary analyses will be conducted for the ITT population. No adjustments for multiple testing will be made.

For measurements of lipids, lipoproteins and inflammatory markers the change from baseline will be analyzed in the units of each marker, and the percent change from baseline. Since these biomarkers are typically not normally distributed, the Wilcoxon rank-sum test will be used for treatment comparisons of the percent change from baseline, and medians and quartiles will be provided for each treatment group. The medians of the differences between the treatment groups and 95% confidence intervals will be estimated with the Hodges-Lehmann method.

New onset diabetes is defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period (i.e. patients with no history of diabetes at randomization).

For purposes of this study, a diagnosis of diabetes is made based on the observation of:

1. $HbA_{1c} \geq 6.5\%$. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay. In the absence of unequivocal hyperglycemia, $HbA_{1c} > 6.5\%$ should be confirmed by repeat testing.

OR

2. Fasting plasma glucose (FPG)≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hr. In the absence of unequivocal hyperglycemia, FPG≥126 mg/dL (7.0 mmol/L) should be confirmed by repeat testing.

OR

3. 2-hr plasma glucose≥200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. In the absence of unequivocal hyperglycemia, 2-hr plasma glucose≥200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT) should be confirmed by repeat testing.

OR

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose≥200 mg/dL (11.1 mmol/L).

Exploratory Subgroup Analyses

Subgroup analyses of the primary and key secondary endpoints (as defined in the Statistical Analysis Plan) will be performed. All subgroup analyses will be conducted for the ITT population. No adjustments for multiple testing will be made.

Log-rank tests, treatment effects and the associated 95% confidence intervals for the primary and key secondary efficacy endpoints within each subgroup will be provided using the Cox proportional hazard model with treatment

(AMR101 or placebo), and stratification as a factor (with the exception of the subgroup analyses of those subgroup variables related to the stratification factors, i.e., CV risk category that will not have stratification as a factor).

Subgroups including, but not limited to the following, will be explored. A complete list will be prospectively defined in the Statistical Analysis Plan.

Demographics:

Gender,

age (<65 yr and ≥65 yr),

race (white and nonwhite, or any other subset with at least 10% of the total number of patients),

geography (western vs. non-western)

Disease Parameters:

CV risk category,

the presence/absence of diabetes at baseline,

renal impairment

Treatment Parameters:

by statin intensity (statin type and regimen),

relevant concomitant medications,

Baseline Lipid and Lipoprotein Parameters:

LDL-C (by tertile),

HDL-C (by tertile),

TG (by tertile),

TG≥150 mg/dL,

TG≥200 mg/dL and TG<200 mg/dL, combined highest tertile for TG and lowest tertile for HDL-C,

hs-CRP (≤3 mg/L and >3 mg/L),

Apo B (by tertile),

non-HDL-C (by tertile)

The consistency of the treatment effects in subgroups will be assessed for the primary and key secondary efficacy endpoints. For each subgroup variable, a Cox proportional hazard model with terms for treatment, stratification factors (with the exception of those subgroup variables related to the stratification factors, i.e., CV risk category), subgroup, and treatment-by-subgroup interaction will be performed. The main treatment effect will not be tested with this model. P-values for testing the interaction terms will be provided.

Interim Efficacy Analysis

One interim analysis will be performed for the primary efficacy endpoint using best available data (adjudicated events and site reported endpoints) based on data when approximately 60% of the total number of primary endpoint events is reached. The interim analysis will be based on a group sequential design that includes early stopping rules for benefit while preserving the overall Type I error rate (O'Brien-Fleming). This allows for interim analysis and preserves the overall Type I error probability of α=0.05 for the primary endpoint.

Approximately 1612 primary efficacy endpoint events are planned to be observed during the trial, based on sample size calculation assumptions. Therefore, the interim analysis will occur after at least 967 primary efficacy endpoint events have been observed. According to this boundary, the critical p-value at the interim analysis has to be p≤0.0076, resulting in the final evaluation p-value of 0.0476.

The interim results of the study will be monitored by an independent DMC. The analyses will be performed by the independent statistical group unblinded to the treatment assignment. The results will be reported only to the DMC. The unblinded information will not be released to sponsor under any circumstance before the completion of the study. Specific statistical guidelines for data monitoring will be discussed and formalized in a separate Interim Statistical Analysis Plan and DMC Charter.

Analysis of Safety

All analyses of safety will be conducted on the safety population, which is defined as all randomized patients who receive at least one dose of study drug. The safety assessment will be based on the frequency of adverse events, physical exams, vital signs and safety laboratory tests.

Adverse events with new onset during the study between the initiation of study drug and 30 days after the last dose of study drug for each patient will be considered treatment-emergent (TEAEs). This will include any AE with onset prior to initiation of study drug and increased severity after the treatment initiation.

Treatment-emergent adverse events will be summarized by system organ class and preferred term, and by treatment. This will include overall incidence rates (regardless of severity and relationship to study drug), and incidence rates for moderate or severe adverse events. A summary of SAEs and adverse events leading to early discontinuation from the study will be presented through data listings.

Safety laboratory tests and vital signs will be summarized by post-treatment change from baseline for each of the parameters using descriptive statistics by treatment group. Those patients with significant laboratory abnormalities will be identified in data listings. Additional safety parameters will be summarized in data listings.

Sample Size Determination

Sample size estimation is based on the assumption that the primary composite endpoint (time from randomization to the first occurrence of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina requiring hospitalization) would be relatively reduced by 15%, from an event rate by 4 years of 23.6% in the placebo group to 20.5% in the AMR101 group. It is expected that a minimum of 1612 primary efficacy endpoint events will be required during the study. A total of approximately 6990 patients are needed to be able to detect this difference at 4.76% significance level (because of the interim analysis described in Section 12.2.4.6) and with 90% power, assuming an 18-month enrollment period and a median follow-up of 4 years. The current sample size calculation is based on an estimated placebo yearly event rate of 5.9% (23.6% over 4 years). To protect against the possibility that the actual placebo event rate is lower than estimated, an extra 1000 patients will be enrolled (approximately 7990 patients in total). By adding the extra 1000 patients, the event rate in the placebo group could be 5.2% per year (20.8% over 4 years) without having to modify the other sample size assumptions.

Since this is an events-driven trial, the 'sample size' is the number of events rather than the number of patients. The number of events that occur depends primarily on three factors: how many patients are enrolled, the combined group event rate, and how long the patients are followed. Because of the difficulty in predicting the combined event rate, the sponsor will monitor that event rate as the trial progresses. If the combined event rate is less than anticipated, either increasing the number of patients, extending the length of follow-up, or a balance of adjusting both factors may be necessary to achieve the sample size of 1612 events.

Before completing the enrollment phase of the trial, i.e. approximately 3- to 6-months prior to the projected enrollment of the 7990th patient, the actual event rate based on pooled, blinded accumulation of primary efficacy endpoint events will be calculated and plotted. If those analyses suggest the number of patients with at least 1 adjudicated, primary event (and appropriately accounting for patients with potential primary events for which the adjudication process is then incomplete) is consistent with projections,

then the study could continue toward the protocol-specified target enrollment of 7990 patients. However, if the number of such events appears less than, and inconsistent with projections, the Sponsor will consider (under blinded conditions) re-calculating the number of patients needed to achieve the target number of events within the desired timeline or extend the follow-up period. If the projected increase in number of patients is ≤25% of the original 7990 target population, the Sponsor may, with documented approval of both the REDUCE-IT Steering Committee (SC) and the Data Monitoring Committee (DMC), extend enrollment to the revised target number without need for an additional protocol amendment. Under those conditions, all principal investigators, ethics committees, and regulatory authorities associated with the protocol will be promptly notified of the action. Should the projected increase in number of patients be more than 25% above the original 7990 target (i.e. more than 1998 additional patients) a formal protocol amendment will be initiated.

If the number of patients to be studied is increased, the enrollment phase will be extended to allow enrollment of the additional patients.

At completion of study enrollment, the actual number of patients randomized may vary from the target number (either original or revised) as a result of the inherent lag between the date the last patient started screening and the date the last patient was randomized.

Monitoring, Data Management, and Record Keeping

Data Management

Data Handling

Data will be recorded at the site on CRFs. All entries on a CRF are ultimately the responsibility of the Investigator, who is expected to review each form for completeness and accuracy before signing. A CRF must be completed for each randomized patient. The CRFs and source documents must be made available to the Sponsor and/or its designee.

Record Keeping

The Investigator must maintain all documents and records, originals or certified copies of original records, relating to the conduct of this trial, and necessary for the evaluation and reconstruction of the clinical trial. This documentation includes, but is not limited to protocol, CRFs, AE reports, patient source data (including records of patients, patient visit logs, clinical observations and findings), correspondence with health authorities and IRB, consent forms, inventory of study product, Investigator's curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures, and laboratory director curriculum vitae.

The Investigator and affiliated institution should maintain the trial documents as required by the applicable regulations. The Investigator and affiliated institution should take measures to prevent accidental or premature destruction of documents. Clinical trial documents must be kept in the clinical site's archives indefinitely, unless written authorization is obtained from the Sponsor.

Direct Access to Source Data/Documents

The investigator and research institution agree that the Sponsor, their representatives and designees, the IRB or IEC, and representatives from worldwide regulatory agencies will have the right, both during and after the clinical trial, to review and inspect pertinent medical records related to the clinical trial.

Quality Control and Quality Assurance

The Sponsor and/or its designee(s) will perform quality control and quality assurance checks of all clinical trials that it sponsors. Before the enrollment of any patient in this study, the Sponsor or its designee will review with the investigator and site personnel the following documents: protocol, Investigator's Brochure, CRFs and procedures for their completion, the informed consent process, and the procedure for reporting SAEs. Site visits will be performed by the Sponsor and/or its designees. During these visits, information recorded on the CRFs will be verified against source documents and requests for clarification or correction may be made. After the CRF data is entered by the site, the Sponsor or designee will review for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical trial. If necessary, requests for clarification or correction will be sent to investigators.

By signing the protocol, the Sponsor agrees directly or through its designee(s) to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice (GCP), International Conference on Harmonization (ICH) and other applicable regulations.

Completion of Study

The end of the study will be at the time of the last patient-last visit of the follow-up period of the study. The IRB and IEC will be notified about the end of the study according to country-specific regulatory requirements.

TABLE 1

SCHEDULE OF PROCEDURES

	Screening								
	Up to 42 days before Day 0	If a Visit 1.1 takes place, Visit 1 may occur up to 60 days before Day 0 [2]	Follow-Up (FU) [13]						
Study Day			0	120 ± 10	360 ± 10	720 ± 10	1080 ± 10	1440 ± 10	1800 + 30
Months of FU			0	4	12	24	36	48	60
Years of FU			0	0.33	1	2	3	4	5
Visit #	1	1.1	2	3	4	5	6	7	LV [14]

TABLE 1-continued

SCHEDULE OF PROCEDURES

	Screening		Follow-Up (FU) [13]						
Study Day	Up to 42 days before Day 0	If a Visit 1.1 takes place, Visit 1 may occur up to 60 days before Day 0 [2]	0 0	120 ± 10	360 ± 10	720 ± 10	1080 ± 10	1440 ± 10	1800 + 30
Study Procedures:									
Informed Consent	X								
Medical, Surgical & Family History	X								
Demographics	X								
Evaluate inclusion/ exclusion criteria	X [1]	X [3]	X						
Physical Examination			X	X	X	X	X	X	X
Weight, Height [4]	X		X	X	X	X	X	X	X
Vital Signs [5]	X	X	X	X	X	X	X	X	X
Waist Circumference			X			X			X
12-Lead ECG	X		X		X	X	X	X	X
Urine pregnancy test [6]	X		X						
Concomitant Meds	X	X	X	X	X	X	X	X	X
Randomization			X						
Dosing at the Research Site [7]			X	X	X	X	X	X	
Efficacy events				X	X	X	X	X	X
AE Evaluations			X	X	X	X	X	X	X
Compliance Check [8]				X	X	X	X	X	X
Chemistry and hematology [9]	X	X [3]	X	X	X	X	X	X	X
Fasting lipid profile [10]	X	X [3]	X	X	X	X	X	X	X
Genetic testing [11]			X						
Biomarkers: hs-CRP, apo B, hsTNT			X			X			X
Fasting blood sample for archiving [12]			X		X	X	X	X	X

What is claimed is:

1. A method of reducing risk of cardiovascular death in a subject with established cardiovascular disease, the method comprising administering to said subject about 4 g of ethyl icosapentate per day for a period effective to reduce risk of cardiovascular death in the subject.

2. The method of claim **1**, wherein the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL and a fasting baseline LDL-C level of about 40 mg/dL to about 100 mg/dL.

3. The method of claim **1**, wherein the ethyl icosapentate is present in a pharmaceutical composition and the ethyl icosapentate comprises at least about 96 wt. % of all omega-3 fatty acids in the pharmaceutical composition.

4. The method of claim **3**, wherein about 1 g of the pharmaceutical composition is present in each of 4 capsules.

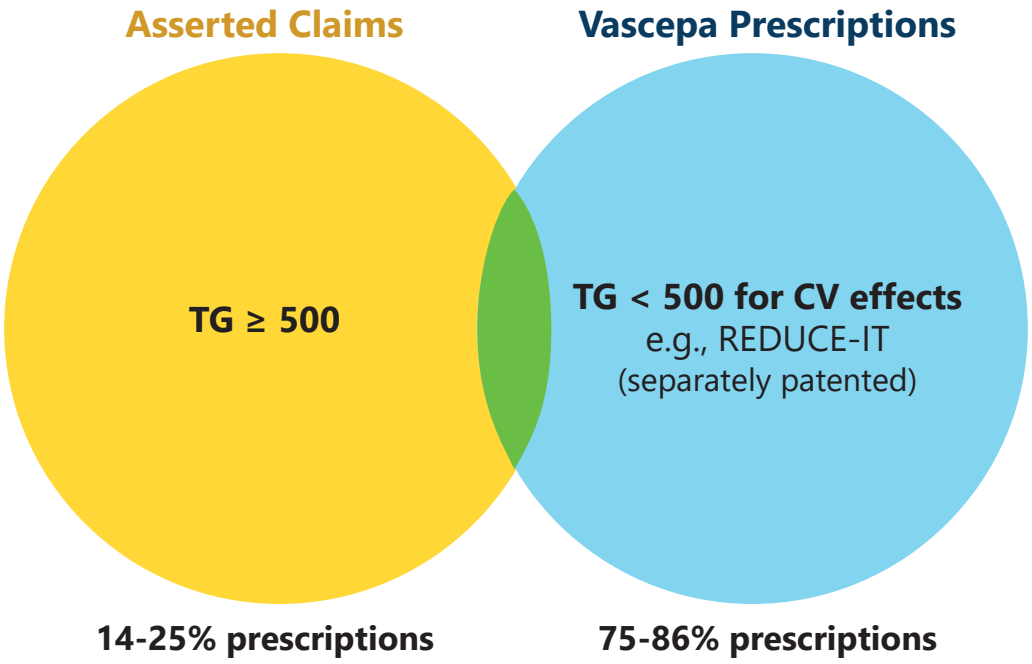
5. The method of claim **1**, wherein said period ends at least 2 years after initial administration of the ethyl icosapentate to the subject.

6. The method of claim **1**, wherein the subject is on statin therapy.

7. The method of claim **1**, wherein the subject has a triglyceride level of at least 135 mg/dL and is on statin therapy.

* * * * *

Secondary Considerations (e.g., REDUCE-IT, Commercial Success) Lack A Nexus To The Claims



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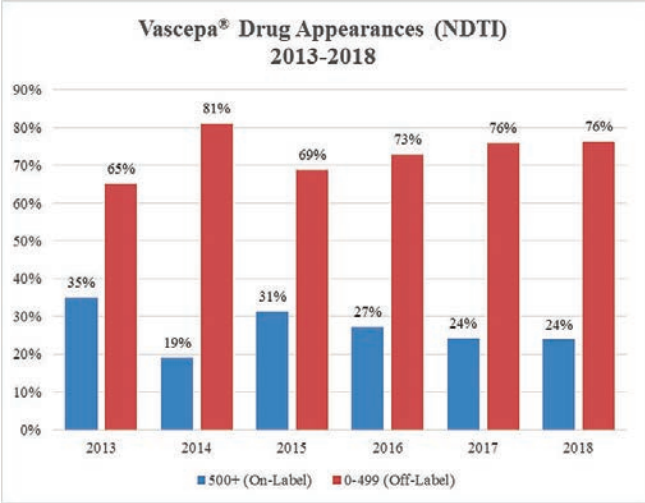
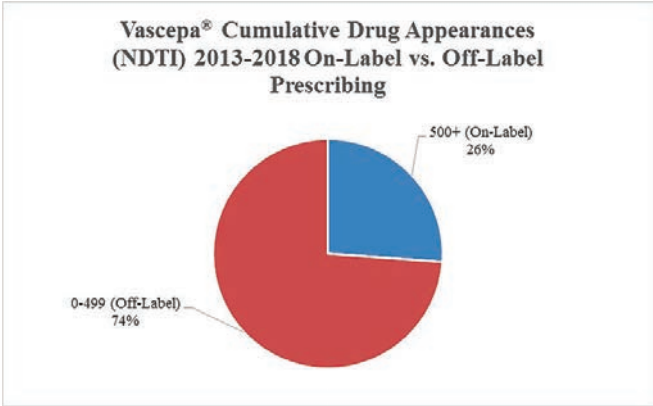
DDX1.36

Vascepa® Cumulative Drug Appearances





HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LOVAZA safely and effectively. See full prescribing information for LOVAZA.

LOVAZA (omega-3-acid ethyl esters capsules), for oral use
Initial U.S. Approval: 2004

----------INDICATIONS AND USAGE----------
LOVAZA is a combination of ethyl esters of omega 3 fatty acids, principally eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia (HTG). (1)

Limitations of Use:
- The effect of LOVAZA on the risk for pancreatitis has not been determined. (1)
- The effect of LOVAZA on cardiovascular mortality and morbidity has not been determined. (1)

----------DOSAGE AND ADMINISTRATION----------
- The daily dose of LOVAZA is 4 grams per day taken as a single 4-gram dose (4 capsules) or as two 2-gram doses (2 capsules given twice daily). (2)
- Patients should be advised to swallow LOVAZA capsules whole. Do not break open, crush, dissolve, or chew LOVAZA. (2)

---------- DOSAGE FORMS AND STRENGTHS----------
Capsules: 1 gram (3)

----------CONTRAINDICATIONS ----------
LOVAZA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to LOVAZA or any of its components. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy. (5.1)
- LOVAZA may increase levels of low-density lipoprotein (LDL). Monitor LDL levels periodically during therapy. (5.1)
- Use with caution in patients with known hypersensitivity to fish and/or shellfish. (5.2)
- There is a possible association between LOVAZA and more frequent recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation, particularly within the first months of initiating therapy. (5.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence >3% and greater than placebo) were eructation, dyspepsia, and taste perversion. (6)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------
Omega-3-acids may prolong bleeding time. Patients taking LOVAZA and an anticoagulant or other drug affecting coagulation (e.g., anti-platelet agents) should be monitored periodically. (7.1)

---------- USE IN SPECIFIC POPULATIONS----------
Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 4/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LOVAZA (omega-3-acid ethyl esters) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (greater than or equal to 500 mg per dL) hypertriglyceridemia (HTG).

Usage Considerations: Patients should be placed on an appropriate lipid-lowering diet before receiving LOVAZA and should continue this diet during treatment with LOVAZA.

Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting therapy with LOVAZA. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid

abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Limitations of Use:

The effect of LOVAZA on the risk for pancreatitis has not been determined.

The effect of LOVAZA on cardiovascular mortality and morbidity has not been determined.

2 DOSAGE AND ADMINISTRATION

- Assess triglyceride levels carefully before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, medications) of high triglyceride levels and manage as appropriate *[see Indications and Usage (1)]*.
- Patients should be placed on an appropriate lipid-lowering diet before receiving LOVAZA, and should continue this diet during treatment with LOVAZA. In clinical studies, LOVAZA was administered with meals.

The daily dose of LOVAZA is 4 grams per day. The daily dose may be taken as a single 4-gram dose (4 capsules) or as two 2-gram doses (2 capsules given twice daily).

Patients should be advised to swallow LOVAZA capsules whole. Do not break open, crush, dissolve, or chew LOVAZA.

3 DOSAGE FORMS AND STRENGTHS

LOVAZA (omega-3-acid ethyl esters) capsules are supplied as 1-gram transparent, soft-gelatin capsules filled with light-yellow oil and bearing the designation "GS FH2".

4 CONTRAINDICATIONS

LOVAZA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to LOVAZA or any of its components.

5 WARNINGS AND PRECAUTIONS

5.1 Monitoring: Laboratory Tests

In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored periodically during therapy with LOVAZA. In some patients, increases in ALT levels without a concurrent increase in AST levels were observed.

In some patients, LOVAZA increases low-density lipoprotein cholesterol (LDL-C) levels. LDL-C levels should be monitored periodically during therapy with LOVAZA.

Laboratory studies should be performed periodically to measure the patient's TG levels during therapy with LOVAZA.

5.2 Fish Allergy

LOVAZA contains ethyl esters of omega-3 fatty acids (EPA and DHA) obtained from the oil of several fish sources. It is not known whether patients with allergies to fish and/or shellfish, are at increased risk of an allergic reaction to LOVAZA. LOVAZA should be used with caution in patients with known hypersensitivity to fish and/or shellfish.

5.3 Recurrent Atrial Fibrillation (AF) or Flutter

In a double-blind, placebo-controlled trial of 663 subjects with symptomatic paroxysmal AF (n = 542) or persistent AF (n = 121), recurrent AF or flutter was observed in subjects randomized to LOVAZA who received 8 grams per day for 7 days and 4 grams per day thereafter for 23 weeks at a higher rate relative to placebo. Subjects in this trial had median baseline triglycerides of 127 mg per dL, had no substantial structural heart disease, were taking no anti-arrhythmic therapy (rate control permitted), and were in normal sinus rhythm at baseline.

At 24 weeks, in the paroxysmal AF stratum, there were 129 (47%) first recurrent symptomatic AF or flutter events on placebo and 141 (53%) on LOVAZA (primary endpoint, HR 1.19; 95% CI: 0.93, 1.35). In the persistent AF stratum, there were 19 (35%) events on placebo and 34 (52%) events on LOVAZA (HR 1.63; 95% CI: 0.91, 2.18). For both strata combined, the HR was 1.25; 95% CI: 1.00, 1.40. Although the clinical significance of these results is uncertain, there is a possible association between LOVAZA and more frequent recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation, particularly within the first 2 to 3 months of initiating therapy.

LOVAZA is not indicated for the treatment of AF or flutter.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions reported in at least 3% of subjects treated with LOVAZA and at a greater rate than placebo based on pooled data across 23 clinical trials are listed in Table 1.

Table 1. Adverse Reactions Occurring at Incidence ≥3% and Greater than Placebo in Clinical Trials of LOVAZA

Adverse Reaction[a]	LOVAZA (n = 655)		Placebo (n = 370)	
	n	%	n	%
Eructation	29	4	5	1
Dyspepsia	22	3	6	2
Taste perversion	27	4	1	<1

[a] Trials included subjects with HTG and severe HTG.

Additional adverse reactions from clinical trials are listed below:

Digestive System

Constipation, gastrointestinal disorder, and vomiting.

Metabolic and Nutritional Disorders

Increased ALT and increased AST.

Skin

Pruritus and rash.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the events described below have been identified during post-approval use of LOVAZA. Because these events are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or to always establish a causal relationship to drug exposure.

The following events have been reported: anaphylactic reaction, hemorrhagic diathesis, urticaria.

7 DRUG INTERACTIONS

7.1 Anticoagulants or Other Drugs Affecting Coagulation

Some trials with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these trials has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical trials have not been done to thoroughly examine the effect of LOVAZA and concomitant anticoagulants. Patients receiving treatment with LOVAZA and an anticoagulant or other drug affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. It is unknown whether LOVAZA can cause fetal harm when administered to a pregnant woman or

can affect reproductive capacity. LOVAZA should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

Animal Data

Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 grams per day based on a body surface area comparison.

In female rats given oral gavage doses of 100, 600, and 2,000 mg per kg per day beginning 2 weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high-dose group (5 times human systemic exposure following an oral dose of 4 grams per day based on body surface area comparison).

In pregnant rats given oral gavage doses of 1,000, 3,000, and 6,000 mg per kg per day from gestation Day 6 through 15, no adverse effects were observed (14 times human systemic exposure following an oral dose of 4 grams per day based on a body surface area comparison).

In pregnant rats given oral gavage doses of 100, 600, and 2,000 mg per kg per day from gestation Day 14 through lactation Day 21, no adverse effects were seen at 2,000 mg per kg per day (5 times the human systemic exposure following an oral dose of 4 grams per day based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal Day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3,000 mg per kg per day (7 times the human systemic exposure following an oral dose of 4 grams per day based on a body surface area comparison).

In pregnant rabbits given oral gavage doses of 375, 750, and 1,500 mg per kg per day from gestation Day 7 through 19, no findings were observed in the fetuses in groups given 375 mg per kg per day (2 times human systemic exposure following an oral dose of 4 grams per day based on a body surface area comparison). However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 grams per day based on a body surface area comparison).

8.3 Nursing Mothers

Studies with omega-3-acid ethyl esters have demonstrated excretion in human milk. The effect of this excretion on the infant of a nursing mother is unknown; caution should be exercised when LOVAZA is administered to a nursing mother. An animal study in lactating rats given oral gavage ^{14}C-ethyl EPA demonstrated that drug levels were 6 to 14 times higher in milk than in plasma.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

A limited number of subjects older than 65 years were enrolled in the clinical trials of LOVAZA. Safety and efficacy findings in subjects older than 60 years did not appear to differ from those of subjects younger than 60 years.

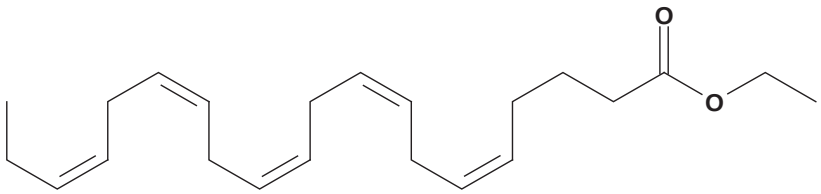
9 DRUG ABUSE AND DEPENDENCE

LOVAZA does not have any known drug abuse or withdrawal effects.

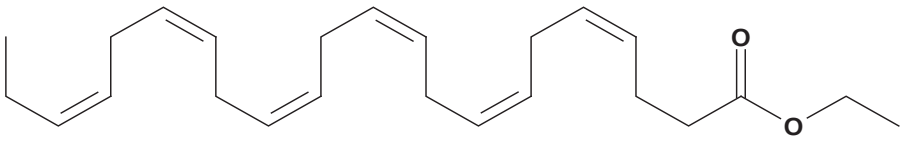
11 DESCRIPTION

LOVAZA, a lipid-regulating agent, is supplied as a liquid-filled gel capsule for oral administration. Each 1-gram capsule of LOVAZA contains at least 900 mg of the ethyl esters of omega-3 fatty acids sourced from fish oils. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA — approximately 465 mg) and docosahexaenoic acid (DHA — approximately 375 mg).

The empirical formula of EPA ethyl ester is $C_{22}H_{34}O_2$, and the molecular weight of EPA ethyl ester is 330.51. The structural formula of EPA ethyl ester is:



The empirical formula of DHA ethyl ester is $C_{24}H_{36}O_2$, and the molecular weight of DHA ethyl ester is 356.55. The structural formula of DHA ethyl ester is:



LOVAZA capsules also contain the following inactive ingredients: 4 mg α-tocopherol (in a carrier of soybean oil), and gelatin, glycerol, and purified water (components of the capsule shell).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of LOVAZA is not completely understood. Potential mechanisms of action include inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal β-oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. LOVAZA may reduce the synthesis of triglycerides in the liver

because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.

12.3 Pharmacokinetics

Absorption

In healthy volunteers and in subjects with hypertriglyceridemia, EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters (LOVAZA) induced significant dose-dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters.

Specific Populations

Age: Uptake of EPA and DHA into serum phospholipids in subjects treated with LOVAZA was independent of age (younger than 49 years versus 49 years and older).

Male and Female Patients: Females tended to have more uptake of EPA into serum phospholipids than males. The clinical significance of this is unknown.

Pediatric Patients: Pharmacokinetics of LOVAZA have not been studied.

Patients with Renal or Hepatic Impairment: LOVAZA has not been studied in patients with renal or hepatic impairment.

Drug Interaction Studies

Simvastatin: In a 14-day trial of 24 healthy adult subjects, daily coadministration of simvastatin 80 mg with LOVAZA 4 grams did not affect the extent (AUC) or rate (C_{max}) of exposure to simvastatin or the major active metabolite, beta-hydroxy simvastatin, at steady state.

Atorvastatin: In a 14-day trial of 50 healthy adult subjects, daily coadministration of atorvastatin 80 mg with LOVAZA 4 grams did not affect AUC or C_{max} of exposure to atorvastatin, 2-hydroxyatorvastatin, or 4-hydroxyatorvastatin at steady state.

Rosuvastatin: In a 14-day trial of 48 healthy adult subjects, daily coadministration of rosuvastatin 40 mg with LOVAZA 4 grams did not affect AUC or C_{max} of exposure to rosuvastatin at steady state.

In vitro studies using human liver microsomes indicated that clinically significant cytochrome P450-mediated inhibition by EPA/DHA combinations are not expected in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a rat carcinogenicity study with oral gavage doses of 100, 600, and 2,000 mg per kg per day, males were treated with omega-3-acid ethyl esters for 101 weeks and females for 89 weeks without an increased incidence of tumors (up to 5 times human systemic exposures following an

oral dose of 4 grams per day based on a body surface area comparison). Standard lifetime carcinogenicity bioassays were not conducted in mice.

Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or human lymphocytes. Omega-3-acid ethyl esters were negative in the in vivo mouse micronucleus assay.

In a rat fertility study with oral gavage doses of 100, 600, and 2,000 mg per kg per day, males were treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and throughout mating, gestation, and lactation. No adverse effect on fertility was observed at 2,000 mg per kg per day (5 times human systemic exposure following an oral dose of 4 grams per day based on a body surface area comparison).

14 CLINICAL STUDIES

14.1 Severe Hypertriglyceridemia

The effects of LOVAZA 4 grams per day were assessed in 2 randomized, placebo-controlled, double-blind, parallel-group trials of 84 adult subjects (42 on LOVAZA, 42 on placebo) with very high triglyceride levels. Subjects whose baseline triglyceride levels were between 500 and 2,000 mg per dL were enrolled in these 2 trials of 6 and 16 weeks' duration. The median triglyceride and LDL-C levels in these subjects were 792 mg per dL and 100 mg per dL, respectively. Median high-density lipoprotein cholesterol (HDL-C) level was 23.0 mg per dL.

The changes in the major lipoprotein lipid parameters for the groups receiving LOVAZA or placebo are shown in Table 2.

Table 2. Median Baseline and Percent Change from Baseline in Lipid Parameters in Subjects with Severe Hypertriglyceridemia (≥500 mg per dL)

	LOVAZA n = 42		Placebo n = 42		
Parameter	**BL**	**% Change**	**BL**	**% Change**	**Difference**
TG	816	-44.9	788	+6.7	-51.6
Non-HDL-C	271	-13.8	292	-3.6	-10.2
TC	296	-9.7	314	-1.7	-8.0
VLDL-C	175	-41.7	175	-0.9	-40.8
HDL-C	22	+9.1	24	0.0	+9.1
LDL-C	89	+44.5	108	-4.8	+49.3

BL = Baseline (mg per dL); % Change = Median Percent Change from Baseline; Difference = LOVAZA Median % Change – Placebo Median % Change. VLDL-C = Very-low-density lipoprotein (VLDL) cholesterol.

LOVAZA 4 grams per day reduced median TG, VLDL-C, and non-HDL-C levels and increased median HDL-C from baseline relative to placebo. Treatment with LOVAZA to reduce very high TG levels may result in elevations in LDL-C and non-HDL-C in some individuals. Patients should be monitored to ensure that the LDL-C level does not increase excessively.

The effect of LOVAZA on the risk of pancreatitis has not been determined.

The effect of LOVAZA on cardiovascular mortality and morbidity has not been determined.

16 HOW SUPPLIED/STORAGE AND HANDLING

LOVAZA (omega-3-acid ethyl esters) capsules are supplied as 1-gram, transparent, soft-gelatin capsules filled with light-yellow oil and bearing the designation "GS FH2".

Bottles of 120: NDC 0173-0884-08.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Information for Patients

- LOVAZA should be used with caution in patients with known sensitivity or allergy to fish and/or shellfish *[see Warnings and Precautions (5.2)]*.
- Advise patients that use of lipid-regulating agents does not reduce the importance of adhering to diet *[see Dosage and Administration (2)]*.
- Advise patients not to alter LOVAZA capsules in any way and to ingest intact capsules only *[see Dosage and Administration (2)]*.

- Instruct patients to take LOVAZA as prescribed. If a dose is missed, advise patients to take it as soon as they remember. However, if they miss one day of LOVAZA, they should not double the dose when they take it.

Manufactured for:

GlaxoSmithKline
Research Triangle Park, NC 27709

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LVZ:XXPI

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION
LOVAZA (LO-VA-ZA)
(omega-3-acid ethyl esters capsules)

What is LOVAZA?

LOVAZA is a prescription medicine used along with a low-fat and low-cholesterol diet to lower very high triglyceride (fat) levels in adults.

It is not known if LOVAZA changes your risk of having inflammation of your pancreas (pancreatitis).

It is not known if LOVAZA prevents you from having a heart attack or stroke.

It is not known if LOVAZA is safe and effective in children.

Who should not take LOVAZA?

Do not take LOVAZA if you are allergic to omega-3-acid ethyl esters or any of the ingredients in LOVAZA. See the end of this leaflet for a complete list of ingredients in LOVAZA.

Before taking LOVAZA, tell your healthcare provider about all of your medical conditions, including if you:

- have diabetes.
- have a low thyroid problem (hypothyroidism).
- have a liver problem.
- have a pancreas problem.
- have a certain heart rhythm problem called atrial fibrillation or flutter.
- are allergic to fish or shellfish. It is not known if people who are allergic to fish or shellfish are also allergic to LOVAZA.
- are pregnant or plan to become pregnant. It is not known if LOVAZA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. LOVAZA can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take LOVAZA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

LOVAZA can interact with certain other medicines that you are taking. Using LOVAZA with medicines that affect blood clotting (anticoagulants or blood thinners) may cause serious side effects.

How should I take LOVAZA?

- Take LOVAZA exactly as your healthcare provider tells you to take it.
- You should not take more than 4 capsules of LOVAZA each day. Either take all 4 capsules at one time or 2 capsules two times a day.
- Do not change your dose or stop LOVAZA without talking to your healthcare provider.
- Take LOVAZA with food.
- Take LOVAZA capsules whole. Do not break, open, crush, dissolve, or chew LOVAZA capsules before swallowing. If you cannot swallow LOVAZA capsules whole, tell your healthcare provider. You may need a different medicine.
- If you miss a dose of LOVAZA, take the missed dose as soon as you remember. If you miss one day

of LOVAZA, **do not** double your dose the next time you take it.

- Your healthcare provider may start you on a cholesterol-lowering diet before giving you LOVAZA. Stay on this diet while taking LOVAZA.
- Your healthcare provider should do blood tests to check your triglyceride, bad cholesterol (LDL-C), and liver function (ALT and AST) levels while you take LOVAZA.

What are the possible side effects of LOVAZA?

LOVAZA may cause serious side effects, including:

- **changes in certain blood tests.** LOVAZA may cause an increase in the results of blood tests used to check your liver function and your bad cholesterol levels.
- **increased risk of a heart rhythm problem in people who have a heart rhythm problem.** LOVAZA may cause an increase in the frequency of a heart rhythm problem (atrial fibrillation or flutter), especially in the first few months of taking LOVAZA, if you already have a heart rhythm problem.

The most common side effects of LOVAZA include:

- burping
- upset stomach
- a change in your sense of taste

These are not all the possible side effects of LOVAZA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LOVAZA?

- Store LOVAZA at room temperature between 68°F to 77°F (20°C to 25°C).
- **Do not** freeze LOVAZA.
- Safely throw away medicine that is out of date or no longer needed.

Keep LOVAZA and all medicines out of the reach of children.

General information about the safe and effective use of LOVAZA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LOVAZA for a condition for which it was not prescribed. Do not give LOVAZA to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about LOVAZA that is written for health professionals.

What are the ingredients in LOVAZA?

Active Ingredient: omega-3-acid ethyl esters, mostly EPA and DHA

Inactive Ingredients: alpha-tocopherol (in soybean oil), gelatin, glycerol, purified water.

Manufactured for:

GlaxoSmithKline

Research Triangle Park, NC 27709

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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 4/2019

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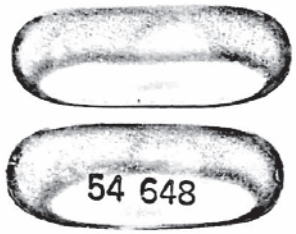
Icosapent Ethyl Capsules



Generic Name: Icosapent Ethyl Capsules
Therapeutic Category: Hypertriglyceridemia
Rating: AB
Storage + Safety: Store at 20° to 25°C (68° to 77°F). See USP Controlled Room Temperature.

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Hikma's generic version is indicated for fewer than all approved indications of the Reference Listed Drug.

Product Image	NDC Number	Strength	Unit Size	Package Quantity	Downloads
	0054-0508-23	1 gram	120 Capsules Per Bottle		(https://dailymed.nlm setid=e3d38d1d-fbe7-413d-849a- 675e7dfb8b0a&audie (/~/media/Files/wws Ethyl Capsules - SDS.ashx)

PI Package Insert

MS DS Material Safety Data Sheet

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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.)

From Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston (D.L.B.); FACT (French Alliance for Cardiovascular Trials), Département Hospitalo-Universitaire FIRE (Fibrose, Inflammation, and Remodeling), Assistance Publique–Hôpitaux de Paris, Hôpital Bichat, Université Paris-Diderot, INSERM Unité 1148, Paris (P.G.S.); National Heart and Lung Institute, Imperial College, Royal Brompton Hospital, London (P.G.S.); the Department of Medicine, University of Maryland School of Medicine, Baltimore (M.M.); the Utah Lipid Center, Salt Lake City (E.A.B.); the Office of Health Promotion and Disease Prevention, Department of Medicine, Emory University School of Medicine, Atlanta (T.A.J.); Amarin Pharma, Bedminster, NJ (S.B.K., R.T.D.J., R.A.J., L.J., C.G.); Montreal Heart Institute, Université de Montréal, Montreal (J.-C.T.); and the Department of Medicine, Baylor College of Medicine, and the Center for Cardiovascular Disease Prevention, Methodist DeBakey Heart and Vascular Center, Houston (C.M.B.). Address reprint requests to Dr. Bhatt at Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, 75 Francis St., Boston, MA 02115, or at dlbhattmd@post.harvard.edu.

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

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A Quick Take is available at NEJM.org

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

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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

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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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LDL cholesterol level was 75.0 mg per deciliter (1.94 mmol per liter), the median high-density lipoprotein cholesterol level was 40.0 mg per deciliter (1.03 mmol per liter), and the median triglyceride level was 216.0 mg per deciliter (2.44 mmol per liter).[22]

FOLLOW-UP AND EFFECTS ON LIPIDS

The median duration of follow-up was 4.9 years (maximum, 6.2 years). The median change in triglyceride level from baseline to 1 year was a decrease of 18.3% (–39.0 mg per deciliter [–0.44 mmol per liter]) in the icosapent ethyl group and an increase of 2.2% (4.5 mg per deciliter [0.05 mmol per liter]) in the placebo group; the median reduction from baseline (as estimated with the use of the Hodges–Lehmann approach) was 19.7% greater in the icosapent ethyl group than in the placebo group (a 44.5 mg per deciliter [0.50 mmol per liter] greater reduction; P<0.001). The median change in LDL cholesterol level from baseline was an increase of 3.1% (2.0 mg per deciliter [0.05 mmol per liter]) in the icosapent ethyl group and an increase of 10.2% (7.0 mg per deciliter [0.18 mmol per liter]) in the placebo group — a 6.6% (5.0 mg per deciliter [0.13 mmol per liter]) lower increase with icosapent ethyl than with placebo (P<0.001). The results with respect to levels of EPA and lipid, lipoprotein, and inflammatory biomarkers are provided in Table S4 in the Supplementary Appendix.

CLINICAL END POINTS

A total of 1606 adjudicated primary end-point events occurred. 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), an absolute between-group difference of 4.8 percentage points (95% CI, 3.1 to 6.5); the number needed to treat to avoid one primary end-point event was 21 (95% CI, 15 to 33) over a median follow-up of 4.9 years.[23,24] The event curves based on a Kaplan–Meier analysis of the primary efficacy end point are provided in Figure 1A. The results of time-to-event analyses of each component of the primary end point are provided in Figure S3 in the Supplementary Appendix. A key secondary efficacy end-point event (Fig. 1B) occurred in 11.2% of the patients in the icosapent ethyl group, as compared with 14.8% of the patients in the placebo group (hazard ratio, 0.74; 95% CI, 0.65 to 0.83; P<0.001), corresponding to an absolute between-group difference of 3.6 percentage points (95% CI, 2.1 to 5.0); the number needed to treat to avoid one key secondary end-

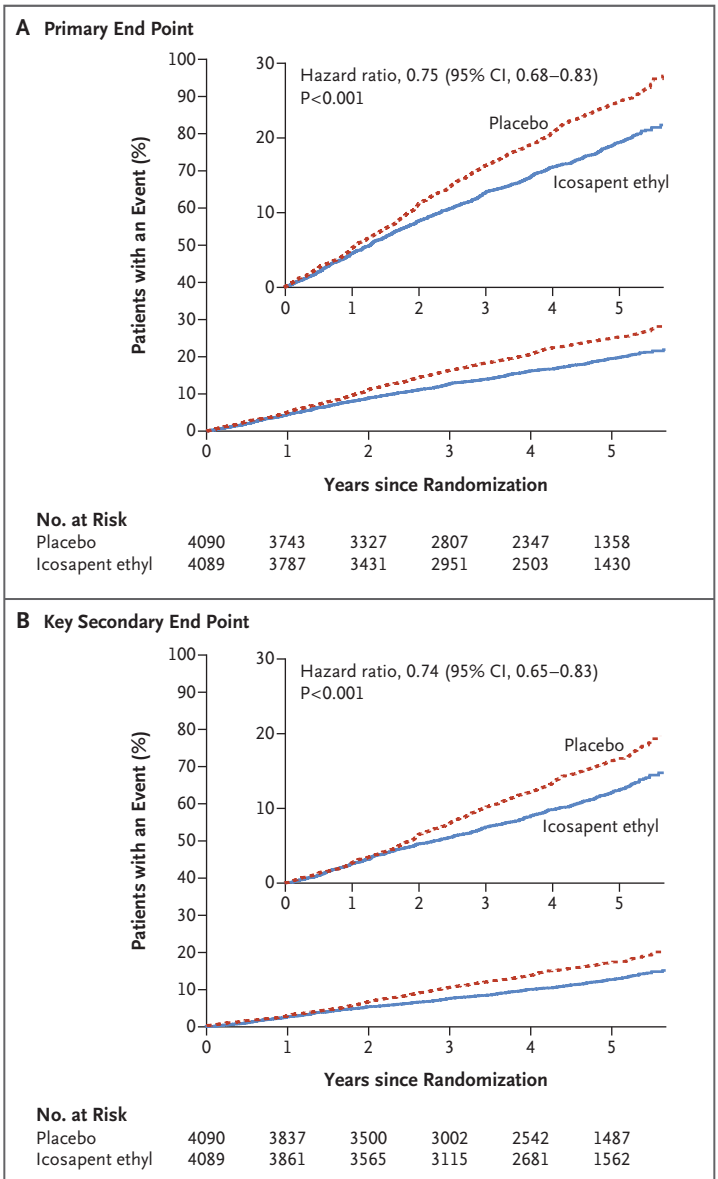

Figure 1. Cumulative Incidence of Cardiovascular Events.

Panel A shows the Kaplan–Meier event curves for the primary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in the icosapent ethyl group and the placebo group, in a time-to-event analysis. Panel B shows the Kaplan–Meier event curves for the key secondary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the two trial groups, in a time-to-event analysis. In each panel, the inset shows the same data on an expanded y axis. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

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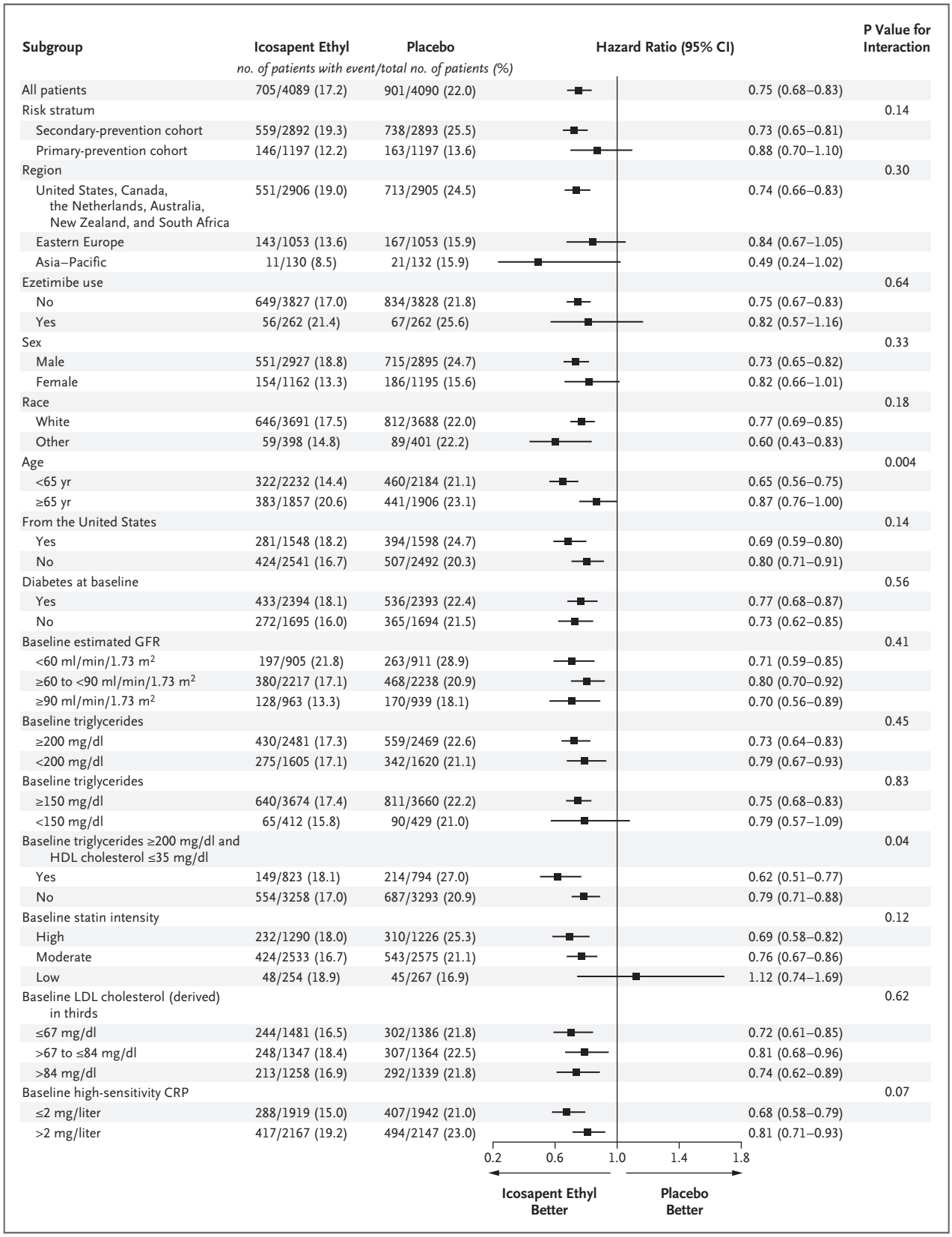

Subgroup	Icosapent Ethyl	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
All patients	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68–0.83)	
Risk stratum				0.14
Secondary-prevention cohort	559/2892 (19.3)	738/2893 (25.5)	0.73 (0.65–0.81)	
Primary-prevention cohort	146/1197 (12.2)	163/1197 (13.6)	0.88 (0.70–1.10)	
Region				0.30
United States, Canada, the Netherlands, Australia, New Zealand, and South Africa	551/2906 (19.0)	713/2905 (24.5)	0.74 (0.66–0.83)	
Eastern Europe	143/1053 (13.6)	167/1053 (15.9)	0.84 (0.67–1.05)	
Asia–Pacific	11/130 (8.5)	21/132 (15.9)	0.49 (0.24–1.02)	
Ezetimibe use				0.64
No	649/3827 (17.0)	834/3828 (21.8)	0.75 (0.67–0.83)	
Yes	56/262 (21.4)	67/262 (25.6)	0.82 (0.57–1.16)	
Sex				0.33
Male	551/2927 (18.8)	715/2895 (24.7)	0.73 (0.65–0.82)	
Female	154/1162 (13.3)	186/1195 (15.6)	0.82 (0.66–1.01)	
Race				0.18
White	646/3691 (17.5)	812/3688 (22.0)	0.77 (0.69–0.85)	
Other	59/398 (14.8)	89/401 (22.2)	0.60 (0.43–0.83)	
Age				0.004
<65 yr	322/2232 (14.4)	460/2184 (21.1)	0.65 (0.56–0.75)	
≥65 yr	383/1857 (20.6)	441/1906 (23.1)	0.87 (0.76–1.00)	
From the United States				0.14
Yes	281/1548 (18.2)	394/1598 (24.7)	0.69 (0.59–0.80)	
No	424/2541 (16.7)	507/2492 (20.3)	0.80 (0.71–0.91)	
Diabetes at baseline				0.56
Yes	433/2394 (18.1)	536/2393 (22.4)	0.77 (0.68–0.87)	
No	272/1695 (16.0)	365/1694 (21.5)	0.73 (0.62–0.85)	
Baseline estimated GFR				0.41
<60 ml/min/1.73 m^2	197/905 (21.8)	263/911 (28.9)	0.71 (0.59–0.85)	
≥60 to <90 ml/min/1.73 m^2	380/2217 (17.1)	468/2238 (20.9)	0.80 (0.70–0.92)	
≥90 ml/min/1.73 m^2	128/963 (13.3)	170/939 (18.1)	0.70 (0.56–0.89)	
Baseline triglycerides				0.45
≥200 mg/dl	430/2481 (17.3)	559/2469 (22.6)	0.73 (0.64–0.83)	
<200 mg/dl	275/1605 (17.1)	342/1620 (21.1)	0.79 (0.67–0.93)	
Baseline triglycerides				0.83
≥150 mg/dl	640/3674 (17.4)	811/3660 (22.2)	0.75 (0.68–0.83)	
<150 mg/dl	65/412 (15.8)	90/429 (21.0)	0.79 (0.57–1.09)	
Baseline triglycerides ≥200 mg/dl and HDL cholesterol ≤35 mg/dl				0.04
Yes	149/823 (18.1)	214/794 (27.0)	0.62 (0.51–0.77)	
No	554/3258 (17.0)	687/3293 (20.9)	0.79 (0.71–0.88)	
Baseline statin intensity				0.12
High	232/1290 (18.0)	310/1226 (25.3)	0.69 (0.58–0.82)	
Moderate	424/2533 (16.7)	543/2575 (21.1)	0.76 (0.67–0.86)	
Low	48/254 (18.9)	45/267 (16.9)	1.12 (0.74–1.69)	
Baseline LDL cholesterol (derived) in thirds				0.62
≤67 mg/dl	244/1481 (16.5)	302/1386 (21.8)	0.72 (0.61–0.85)	
>67 to ≤84 mg/dl	248/1347 (18.4)	307/1364 (22.5)	0.81 (0.68–0.96)	
>84 mg/dl	213/1258 (16.9)	292/1339 (21.8)	0.74 (0.62–0.89)	
Baseline high-sensitivity CRP				0.07
≤2 mg/liter	288/1919 (15.0)	407/1942 (21.0)	0.68 (0.58–0.79)	
>2 mg/liter	417/2167 (19.2)	494/2147 (23.0)	0.81 (0.71–0.93)	

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Figure 2 (facing page). Primary Efficacy Composite End Point in Selected Prespecified Subgroups.

Shown are the hazard ratios and 95% confidence intervals for the primary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, as assessed in a time-to-event analysis, in selected prespecified subgroups of the intention-to-treat population (all patients who underwent randomization). The confidence intervals shown for the subgroup analyses have not been adjusted for multiple testing, and inferences drawn from the intervals may not be reproducible. Race was reported by the investigators. Eastern European region includes Poland, Romania, Russia, and Ukraine, and Asia–Pacific region includes India. 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. CRP denotes C-reactive protein, GFR glomerular filtration rate, HDL high-density lipoprotein, and LDL low-density lipoprotein. The LDL cholesterol value obtained by means of preparative ultracentrifugation was used. If the preparative ultracentrifugation value was missing, the LDL cholesterol value measured by another method was used in the following order of priority: the nonmissing value obtained by means of direct measurements of LDL cholesterol, the value derived with the use of the Friedewald equation, and the value derived with the use of the calculation published by Johns Hopkins University investigators.[22]

point event was 28 (95% CI, 20 to 47) over a median follow-up 4.9 years.[23,24]

The rates of the primary and key secondary efficacy end points in selected prespecified subgroups are provided in Figures 2 and 3; the findings show a consistent benefit with icosapent ethyl. Baseline triglyceride levels (≥150 vs. <150 mg per deciliter or ≥200 or <200 mg per deciliter) had no influence on the primary or key secondary efficacy end points (Figs. 2 and 3). The attainment of triglyceride levels of 150 mg per deciliter or higher or below 150 mg per deciliter at 1 year after randomization also had no influence on the efficacy of icosapent ethyl as compared with placebo with respect to the primary or key secondary efficacy end point (Fig. S4 in the Supplementary Appendix). In a post hoc analysis, we found no substantial difference in the benefit of icosapent ethyl as compared with placebo with respect to the primary end point according to whether the patients who received placebo had an increase in LDL cholesterol levels at 1 year or had no change or a decrease in LDL cholesterol levels.

In the prespecified hierarchical testing of end points (Fig. 4), the rates of all individual and composite ischemic end points (except for death from any cause — the last secondary end point in the hierarchy) 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). The rate of death from any cause was 6.7% in the icosapent ethyl group and 7.6% in the placebo group (hazard ratio, 0.87; 95% CI, 0.74 to 1.02). The results for selected prespecified tertiary end points, which were not adjusted for multiple comparisons, are provided in Table S3 in the Supplementary Appendix. Among these results, the rates of adjudicated sudden cardiac death were 1.5% in the icosapent ethyl group and 2.1% in the placebo group (hazard ratio, 0.69; 95% CI, 0.50 to 0.96), and the rates of cardiac arrest were 0.5% and 1.0%, respectively (hazard ratio, 0.52; 95% CI, 0.31 to 0.86).

SAFETY AND ADVERSE EVENTS

The overall rates of adverse events that occurred while the patients were in the trial and the rates of serious adverse events leading to discontinuation of the trial drug or placebo did not differ significantly between the trial groups (Table S5 in the Supplementary Appendix). The only serious adverse event that occurred at a frequency of at least 2% was pneumonia (2.6% in the icosapent ethyl group and 2.9% in the placebo group, P=0.42). Adverse events that occurred in at least 5% of patients are reported in Table S6 in the Supplementary Appendix. The rate of atrial fibrillation was significantly higher in the icosapent ethyl group than in the placebo group (5.3% vs. 3.9%), as was the rate of peripheral edema (6.5% vs. 5.0%), but the rate of anemia was significantly lower in the icosapent ethyl group than in the placebo group (4.7% vs. 5.8%), as were the rates of diarrhea (9.0% vs. 11.1%) and gastrointestinal adverse events (33.0% vs. 35.1%) (Table S7 in the Supplementary Appendix). The rate of the prespecified adjudicated tertiary end point of heart failure did not differ significantly between the icosapent ethyl group and the placebo group (4.1% and 4.3%, respectively). The rate of the prespecified adjudicated tertiary end point of hospitalization for atrial fibrillation or flutter was significantly higher in the icosapent ethyl group than in the placebo group (3.1% vs. 2.1%, P=0.004). The overall rates of serious adverse bleeding

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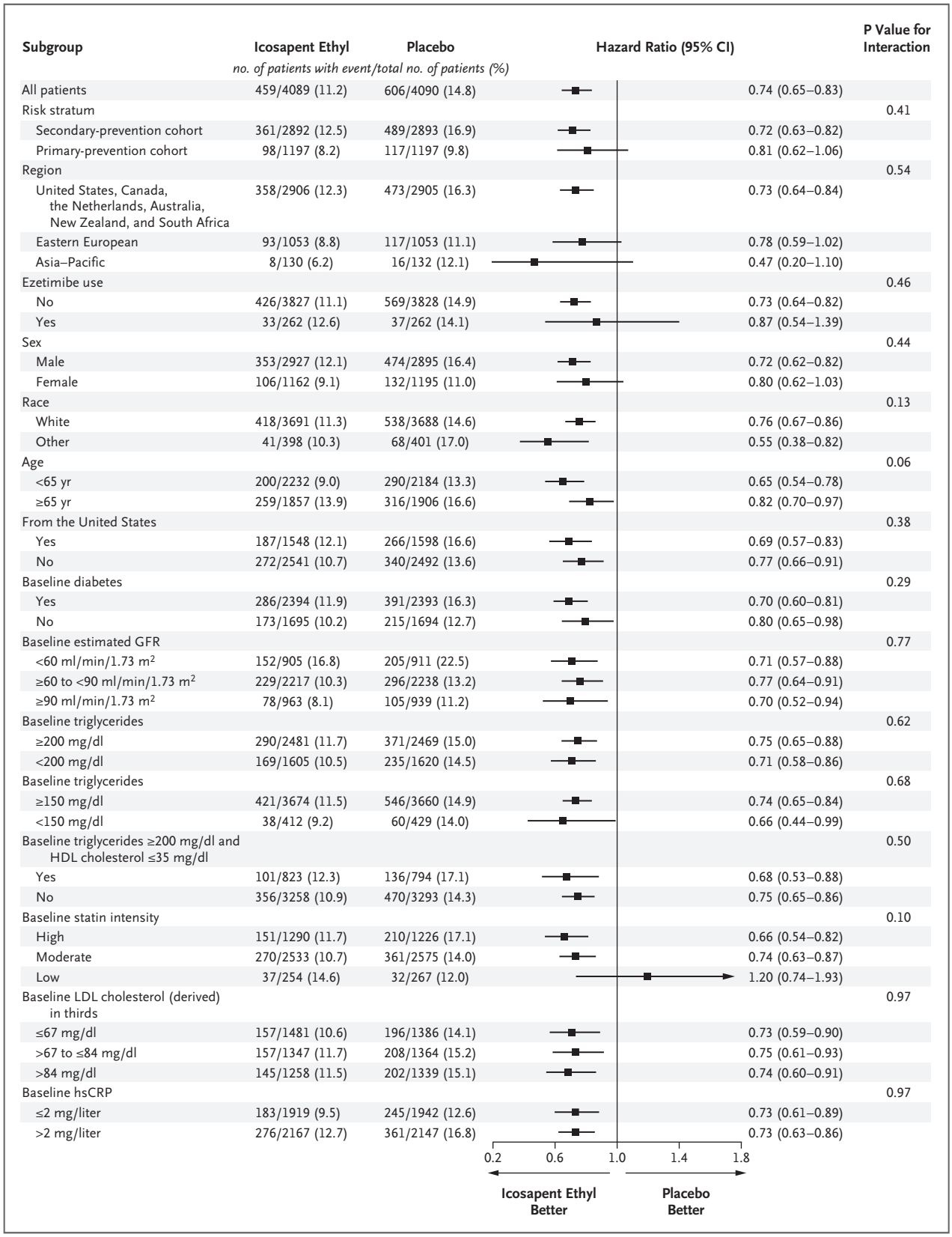

Subgroup	Icosapent Ethyl	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
All patients	459/4089 (11.2)	606/4090 (14.8)	0.74 (0.65–0.83)	
Risk stratum				0.41
Secondary-prevention cohort	361/2892 (12.5)	489/2893 (16.9)	0.72 (0.63–0.82)	
Primary-prevention cohort	98/1197 (8.2)	117/1197 (9.8)	0.81 (0.62–1.06)	
Region				0.54
United States, Canada, the Netherlands, Australia, New Zealand, and South Africa	358/2906 (12.3)	473/2905 (16.3)	0.73 (0.64–0.84)	
Eastern European	93/1053 (8.8)	117/1053 (11.1)	0.78 (0.59–1.02)	
Asia–Pacific	8/130 (6.2)	16/132 (12.1)	0.47 (0.20–1.10)	
Ezetimibe use				0.46
No	426/3827 (11.1)	569/3828 (14.9)	0.73 (0.64–0.82)	
Yes	33/262 (12.6)	37/262 (14.1)	0.87 (0.54–1.39)	
Sex				0.44
Male	353/2927 (12.1)	474/2895 (16.4)	0.72 (0.62–0.82)	
Female	106/1162 (9.1)	132/1195 (11.0)	0.80 (0.62–1.03)	
Race				0.13
White	418/3691 (11.3)	538/3688 (14.6)	0.76 (0.67–0.86)	
Other	41/398 (10.3)	68/401 (17.0)	0.55 (0.38–0.82)	
Age				0.06
<65 yr	200/2232 (9.0)	290/2184 (13.3)	0.65 (0.54–0.78)	
≥65 yr	259/1857 (13.9)	316/1906 (16.6)	0.82 (0.70–0.97)	
From the United States				0.38
Yes	187/1548 (12.1)	266/1598 (16.6)	0.69 (0.57–0.83)	
No	272/2541 (10.7)	340/2492 (13.6)	0.77 (0.66–0.91)	
Baseline diabetes				0.29
Yes	286/2394 (11.9)	391/2393 (16.3)	0.70 (0.60–0.81)	
No	173/1695 (10.2)	215/1694 (12.7)	0.80 (0.65–0.98)	
Baseline estimated GFR				0.77
<60 ml/min/1.73 m^2	152/905 (16.8)	205/911 (22.5)	0.71 (0.57–0.88)	
≥60 to <90 ml/min/1.73 m^2	229/2217 (10.3)	296/2238 (13.2)	0.77 (0.64–0.91)	
≥90 ml/min/1.73 m^2	78/963 (8.1)	105/939 (11.2)	0.70 (0.52–0.94)	
Baseline triglycerides				0.62
≥200 mg/dl	290/2481 (11.7)	371/2469 (15.0)	0.75 (0.65–0.88)	
<200 mg/dl	169/1605 (10.5)	235/1620 (14.5)	0.71 (0.58–0.86)	
Baseline triglycerides				0.68
≥150 mg/dl	421/3674 (11.5)	546/3660 (14.9)	0.74 (0.65–0.84)	
<150 mg/dl	38/412 (9.2)	60/429 (14.0)	0.66 (0.44–0.99)	
Baseline triglycerides ≥200 mg/dl and HDL cholesterol ≤35 mg/dl				0.50
Yes	101/823 (12.3)	136/794 (17.1)	0.68 (0.53–0.88)	
No	356/3258 (10.9)	470/3293 (14.3)	0.75 (0.65–0.86)	
Baseline statin intensity				0.10
High	151/1290 (11.7)	210/1226 (17.1)	0.66 (0.54–0.82)	
Moderate	270/2533 (10.7)	361/2575 (14.0)	0.74 (0.63–0.87)	
Low	37/254 (14.6)	32/267 (12.0)	1.20 (0.74–1.93)	
Baseline LDL cholesterol (derived) in thirds				0.97
≤67 mg/dl	157/1481 (10.6)	196/1386 (14.1)	0.73 (0.59–0.90)	
>67 to ≤84 mg/dl	157/1347 (11.7)	208/1364 (15.2)	0.75 (0.61–0.93)	
>84 mg/dl	145/1258 (11.5)	202/1339 (15.1)	0.74 (0.60–0.91)	
Baseline hsCRP				0.97
≤2 mg/liter	183/1919 (9.5)	245/1942 (12.6)	0.73 (0.61–0.89)	
>2 mg/liter	276/2167 (12.7)	361/2147 (16.8)	0.73 (0.63–0.86)	

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Figure 3 (facing page). Key Secondary Efficacy Composite End Point in Selected Prespecified Subgroups.

Shown are the hazard ratios and 95% confidence intervals for the key secondary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, as assessed in a time-to-event analysis, in selected prespecified subgroups of the intention-to-treat population. The confidence intervals shown for the subgroup analyses have not been adjusted for multiple testing, and inferences drawn from the intervals may not be reproducible.

events that occurred while the patients were in the trial were 2.7% in the icosapent ethyl group and 2.1% in the placebo group (P=0.06), although there were no fatal bleeding events in either group; there were no significant differences between the icosapent ethyl group and the placebo group in the rates of adjudicated hemorrhagic stroke (0.3% vs. 0.2%, P=0.55), serious central nervous system bleeding (0.3% vs. 0.2%, P=0.42), or gastrointestinal bleeding (1.5% vs. 1.1%, P=0.15) (Table S8 in the Supplementary Appendix).

DISCUSSION

In REDUCE-IT, the risk of the primary composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, assessed in a time-to-event analysis, was significantly lower, by 25%, among the patients who received 2 g of icosapent ethyl twice daily than among those who received placebo, corresponding to an absolute between-group difference of 4.8 percentage points in the rate of the end point and a number needed to treat of 21. The risk of the key secondary composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis was also significantly lower, by 26%, in the icosapent ethyl group than in the placebo group, corresponding to an absolute between-group difference of 3.6 percentage points in the rate of the end point and a number needed to treat of 28. Prespecified hierarchical testing of other secondary end points revealed that the risks of a variety of fatal and nonfatal ischemic events were lower in the icosapent ethyl group than in the placebo group, including a 20% lower risk of cardiovascular death. The benefits were observed against a background of appropriate statin use among patients who had a median LDL cholesterol level of 75.0 mg per deciliter at baseline.

The overall rates of adverse events were similar in the trial groups. Serious adverse events related to bleeding occurred in more patients in the icosapent ethyl group than in the placebo group, although the overall rates were low; there were no fatal bleeding events in either group, and the rates of adjudicated hemorrhagic stroke, serious central nervous system bleeding, and serious gastrointestinal bleeding were not significantly higher in the icosapent ethyl group than in the placebo group. The rate of hospitalization for atrial fibrillation or flutter was significantly higher in the icosapent ethyl group than in the placebo group, although the rates were low. The rates of adverse events and serious adverse events leading to discontinuation of trial drug were similar in the two groups.

The results of REDUCE-IT stand apart from the negative findings of several contemporary trials of other agents that also lower triglyceride levels, including other n–3 fatty acids, extended-release niacin, fenofibrate, and cholesteryl ester transfer protein inhibitors.[10-13] It is not known whether the lack of benefit from n–3 fatty acids in previous trials may be attributable to the low dose or to the low ratio of EPA to docosahexaenoic acid (DHA).[12,13] Both the formulation (a highly purified and stable EPA ethyl ester) and dose (total daily dose of 4 g) used in REDUCE-IT were different from those in previous outcome trials of n–3 fatty acids. JELIS, which compared a combination of statin therapy and pure EPA with statin therapy alone, showed that the risk of ischemic events was significantly lower in the group that received the combination treatment than in the group that received statin therapy alone.[14] Although the dose of EPA administered in JELIS (1.8 g daily) was lower than the EPA-equivalent dose used in REDUCE-IT (4 g daily), it resulted in a plasma EPA level (170 μg per milliliter in a Japanese population) similar to that attained in a previous 12-week lipid study in which a total daily dose of 4 g of icosapent ethyl was used in a Western population (183 μg per milliliter)[25,26] and similar to that attained in the current trial. However, unlike the current trial, JELIS included an open-label design without a placebo group, used a low-intensity statin, and was conducted in a single country; patients also had higher levels of LDL cholesterol at baseline (182 mg per

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End Point	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary composite	705 (17.2)	901 (22.0)	0.75 (0.68–0.83)	<0.001
Key secondary composite	459 (11.2)	606 (14.8)	0.74 (0.65–0.83)	<0.001
Cardiovascular death or nonfatal myocardial infarction	392 (9.6)	507 (12.4)	0.75 (0.66–0.86)	<0.001
Fatal or nonfatal myocardial infarction	250 (6.1)	355 (8.7)	0.69 (0.58–0.81)	<0.001
Urgent or emergency revascularization	216 (5.3)	321 (7.8)	0.65 (0.55–0.78)	<0.001
Cardiovascular death	174 (4.3)	213 (5.2)	0.80 (0.66–0.98)	0.03
Hospitalization for unstable angina	108 (2.6)	157 (3.8)	0.68 (0.53–0.87)	0.002
Fatal or nonfatal stroke	98 (2.4)	134 (3.3)	0.72 (0.55–0.93)	0.01
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	549 (13.4)	690 (16.9)	0.77 (0.69–0.86)	<0.001
Death from any cause	274 (6.7)	310 (7.6)	0.87 (0.74–1.02)	—

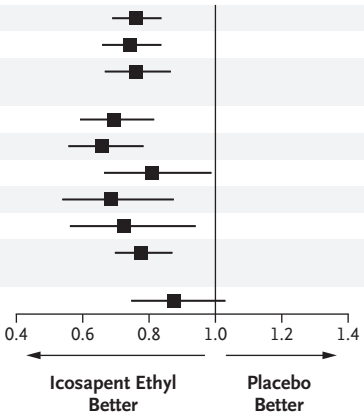

Figure 4. Hierarchical Testing of End Points.

Shown is the prespecified plan for hierarchical testing of end points. The rates of all end points up to death from any cause were significantly lower in the icosapent ethyl group than in the placebo group.

deciliter [4.71 mmol per liter] before initiation of statin therapy) and lower baseline triglyceride values (151 mg per deciliter [1.70 mmol per liter]) than the patients in REDUCE-IT.

Metabolic data provide evidence that icosapent ethyl–based formulations do not raise LDL cholesterol levels, whereas DHA-based formulations do.[27] The results of the current trial should not be generalized to other n–3 fatty acid preparations — in particular, dietary-supplement preparations of n–3 fatty acid mixtures, which are variable and unregulated and which have not been shown to have clinical benefit.

A triglyceride level of 150 mg per deciliter or higher was an initial inclusion criterion in REDUCE-IT (although the required level was subsequently changed to ≥200 mg per deciliter); however, owing to allowance for variability in these levels, 10.3% of enrolled patients had triglyceride levels lower than 150 mg per deciliter at baseline. The observed cardiovascular benefits were similar across baseline levels of triglycerides (<150, ≥150 to <200, and ≥200 mg per deciliter). In addition, the significantly lower risk of major adverse cardiovascular events with icosapent ethyl than with placebo appeared to occur irrespective of the attained triglyceride level at 1 year (≥150 or <150 mg per deciliter), which suggests that the cardiovascular risk reduction was not associated with attainment of a more normal triglyceride level. These observations suggest that at least some of the effect of icosapent ethyl that resulted in a lower risk of ischemic events than that with placebo may be explained by metabolic effects other than a reduction of triglyceride levels.[28]

Mechanisms responsible for the benefit of icosapent ethyl observed in REDUCE-IT are currently not known. The timing of the divergence of the Kaplan–Meier event curves suggests a delayed onset of benefit, which may reflect the time that is needed for a benefit from a reduction in triglyceride levels to be realized or may indicate that other mechanisms are involved. The modestly higher rate of bleeding events with icosapent ethyl suggests that there may be an antithrombotic mechanism of action. However, it is unlikely that an antithrombotic effect would reduce the rate of elective revascularization. Also, if the full explanation involved an antiplatelet or anticoagulant effect, one might expect a large increase in the rate of major bleeding events, which was not observed.[29] It is possible that membrane-stabilizing effects could explain part of the benefit.[20,21,30] Stabilization or regression of coronary plaque (or both) may also play a part.[19,31] Our observation of lower rates of cardiac arrest and sudden cardiac death with icosapent ethyl than with placebo in the current trial might support that mechanism, although these findings should be viewed as exploratory. It is also possible that the difference in high-sensitivity C-reactive protein level observed in REDUCE-IT may contribute to the benefit; the Canakinumab Antiinflam-

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matory Thrombosis Outcome Study (CANTOS) showed a significant reduction in the risk of ischemic events with treatment targeted at inflammation.[32-35] Blood samples obtained during REDUCE-IT have been banked for biomarker and genetic analyses that may provide more information regarding mechanisms of action.

Ongoing trials of moderate-to-high doses of pure EPA ethyl ester will provide further information on the effects of these agents.[10,36] These trials include the Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy–Statin and EPA (RESPECT-EPA; UMIN Clinical Trials Registry number, UMIN000012069), a secondary prevention outcomes trial involving statin-treated patients in Japan, and the Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy (EVAPORATE; ClinicalTrials.gov number, NCT02926027), which is examining changes in coronary plaque over 9 to 18 months.

Our trial has certain limitations. First, at the time the trial was designed, there was relatively little use of ezetimibe or data supporting its use.[37] However, subgroup analyses do not suggest a differential benefit for patients taking ezetimibe. Similarly, proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors were not available for the majority of the patients in the trial.[38] Second, if mineral oil in the placebo affected statin absorption in some patients, this might have contributed to differences in outcomes between the groups. However, the relatively small differences in LDL cholesterol levels between the groups would not be likely to explain the 25% lower risk observed with icosapent ethyl, and a post hoc analysis suggested a similar lower risk regardless of whether there was an increase in LDL cholesterol level among the patients in the placebo group. Although JELIS was designed as an open-label study that did not use a mineral oil placebo, it showed a 19% lower risk of ischemic events with statin therapy plus EPA than with statin therapy alone.

In conclusion, among patients with elevated triglyceride levels who were receiving statin therapy, the risk of major ischemic events, including cardiovascular death, was significantly lower with 2 g of icosapent ethyl twice daily (total daily dose, 4 g) than with placebo.

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