REDUCE-IT™ (Reduction of Cardiovascular Events With EPA – Intervention Trial) NCT01492361

REDUCE-IT is a Phase 3 international, multicenter, prospective, randomized, double-blinded, placebo-controlled, parallel-group trial of stable statin therapy plus icosapent ethyl 4 grams/day (2 grams twice daily with food) versus stable statin therapy plus placebo.

Objective

The main objective is to evaluate whether treatment with icosapent ethyl reduces ischemic events in patients at elevated cardiovascular risk concurrently treated with statins.

Rationale

Cardiovascular disease remains the leading cause of death in the United States, with the estimated costs of treating heart attacks, strokes and other cardiovascular diseases exceeding $300 billion annually. In the United States, more than 35 million patients are treated with statins for the primary and secondary prevention of atherosclerotic cardiovascular events, including myocardial infarctions (heart attacks), and stroke. Despite the demonstrated clinical benefits of lowering LDL-C with statins, significant residual cardiovascular risk remains for statin-treated patients. Vascepa is being studied in REDUCE-IT as an add-on to statin therapy to further reduce cardiovascular risk, not as a replacement for statin therapy.

Enrollment

There are 8,175 patients enrolled and the study has reached its enrollment target. Enrollment is currently closed.

Study Population - Inclusion, Exclusion Criteria

The inclusion and exclusion criteria are listed in Table 1 and Table 2, respectively. Men or women ≥45 years of age with established cardiovascular disease or ≥50 years of age with diabetes in combination with one additional risk factor for cardiovascular disease were eligible for inclusion. Fasting triglyceride levels ≥150 mg/dL and <500 mg/dL were required. LDL-cholesterol levels needed to be >40 mg/dL and ≤100 mg/dL, with patients on stable statin therapy (± ezetimibe) for ≥4 weeks prior to the LDL-cholesterol and triglyceride qualifying measurements for randomization.

Table 1. General Inclusion Criteria.

1. Men or women ≥45 years of age with established CVD (CV Risk Stratum 1; see Table 1a) *or* ≥50 years of age with diabetes in combination with one additional risk factor for CVD (CV Risk Stratum 2; see Table 1b)
2. Fasting TG levels ≥150 mg/dL and <500 mg/dL*
3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to the LDL-C and TG qualifying measurements for randomization
4. Women who are not pregnant, not breastfeeding, not planning on becoming pregnant, and using an acceptable form of birth control during the study (if of child-bearing potential)
5. Able to provide informed consent and adhere to study schedules
6. Agree to follow and maintain a physician-recommended diet during the study

*A study amendment (May 2013) was made, increasing the lower end of the fasting TG level from ≥150 mg/dL to ≥200 mg/dL to increase enrollment of patients with TG at or above 200 mg/dL; it is anticipated that mean and median qualifying triglyceride levels will be above 200 mg/dL.

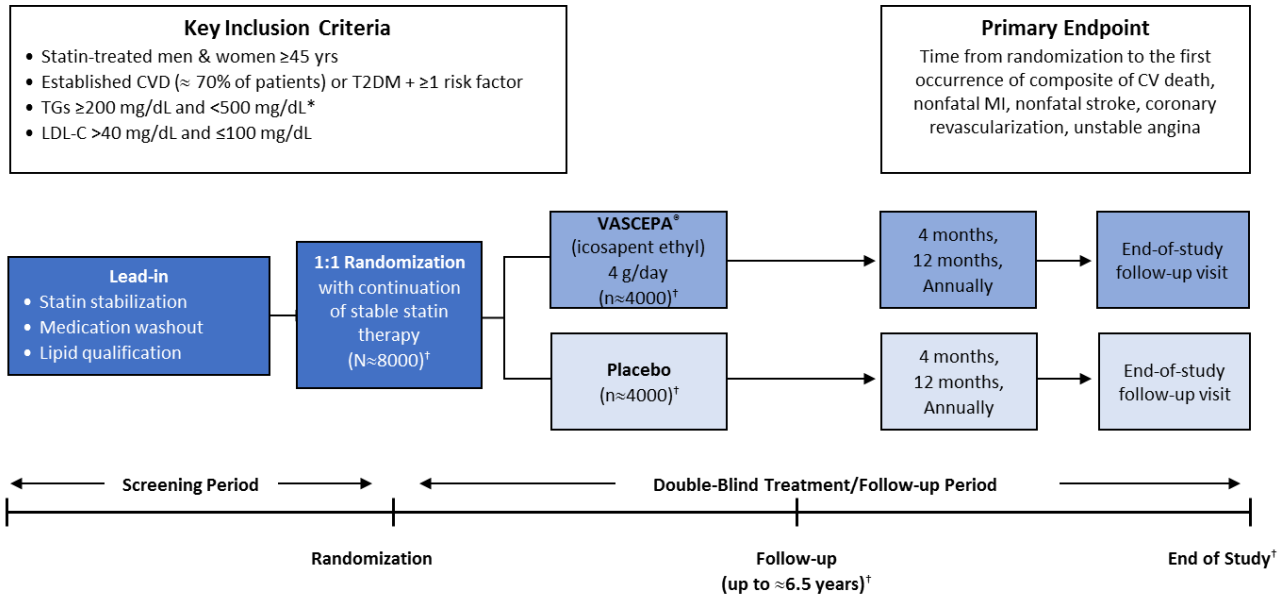
Acronyms: CV, cardiovascular; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

Table 2. Exclusion Criteria.

1. Severe (New York Heart Association [NYHA] class IV) heart failure
2. Any life-threatening disease expected to result in death within the next 2 years (other than CVD)
3. Diagnosis or laboratory evidence of active severe liver disease
4. Hemoglobin A_{1c} >10.0% at screening
5. Poorly controlled hypertension: SBP ≥200 mm Hg or DBP ≥100 mm Hg (despite antihypertensive therapy)
6. Planned coronary intervention or any noncardiac major surgical procedure
7. Known familial lipoprotein lipase deficiency (Fredrickson Type I), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type III)
8. Participation in another clinical trial involving an investigational agent within 90 days prior to screening
9. Intolerance or hypersensitivity to statin therapy
10. Known hypersensitivity to fish and/or shellfish, or ingredients of the study product or placebo
11. History of acute or chronic pancreatitis
12. Malabsorption syndrome and/or chronic diarrhea
13. Use of non-study drug-related, nonstatin, lipid-altering medications, dietary supplements, or foods during the screening period (after Visit 1) and/or plans for use during the treatment/follow-up period including:
    a. Niacin (>200 mg/d) or fibrates (unless ≥28 day washout)
    b. Any OM-3 fatty acid medications (unless ≥28 day washout)
    c. Dietary supplements containing OM-3 fatty acids (eg, flaxseed, fish, krill, or algal oils; unless ≥28 day washout)
    d. Bile acid sequestrants (unless ≥7 day washout)
    e. PCSK9 inhibitors (unless ≥90 day washout)
14. Other medications (not indicated for lipid alteration):
    a. 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
    b. Cyclophosphamide or systemic retinoids during the screening period (unless ≥28 day washout) and/or plans for use during the treatment/follow-up period
15. Known AIDS (HIV-positive patients without AIDS are allowed)
16. Requirement for peritoneal dialysis or hemodialysis for renal insufficiency or creatinine clearance <30 mL/min
17. Unexplained elevated creatine kinase concentration >5 × ULN or elevation due to known muscle disease
18. 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
19. Drug or alcohol abuse within the past 6 months, and inability/unwillingness to abstain from drug abuse and excessive alcohol consumption during the study
20. 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

Acronyms: AIDS, acquired immunodeficiency syndrome; CVD, cardiovascular disease; DBP, diastolic blood pressure; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; OM-3, omega-3; SBP, systolic blood pressure; PCSK9, proprotein convertase subtilisin/kexin type 9; TG, triglyceride; ULN, upper limit of normal.

REDUCE-IT Study Design



*A study amendment (May 2013) was made, increasing the lower end of the fasting TG level from ≥150 mg/dL to ≥200 mg/dL to increase enrollment of patients with TG at or above 200 mg/dL; it is anticipated that mean and median qualifying triglyceride levels will be above 200 mg/dL. †Final values to be known at study unblinding. Event-driven design: approximately 1612 primary efficacy events will be required during the study; study duration will vary accordingly.
Acronyms: CV, cardiovascular; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; T2DM, type 2 diabetes mellitus; TG, triglycerides.

Endpoints

Table 3. REDUCE-IT Key Efficacy Endpoints.

Primary Efficacy Endpoint[1]	Secondary Efficacy Endpoint
Time from randomization to the first occurrence of the following:	
Composite of the following clinical events: • CV death • Nonfatal MI[2] • Nonfatal stroke • Coronary revascularization • Unstable angina determined to be caused by myocardial ischemia by invasive/noninvasive testing and requiring emergent hospitalization	Key secondary endpoint: • Composite of CV death, nonfatal MI,[2] or nonfatal stroke

[1]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.
[2]Including silent MI; electrocardiography will be performed annually for the detection of silent MI.
Acronyms: CV, cardiovascular; MI, myocardial infarction.

Several other secondary, tertiary, and exploratory endpoints will be assessed. For a full listing of endpoints click here.

Contact Us

If you have any additional questions, please feel free to contact us directly at 1-855-VASCEPA (1-855-827-2372) and follow the prompts for Medical Information.

Suggested Reading

Bhatt DL, Steg PG, Brinton EA, Jacobson TA, Miller M, Tardif J-C, Ketchum SB, Doyle RT Jr, Murphy SA, Soni PN, Braeckman RA, Juliano RA, Ballantyne CM and on behalf of the REDUCE-IT Investigators. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial, *Clin Cardiol*, 2017. https://doi.org/10.1002/clc.22692

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Table 1a. Inclusion Criteria for Cardiovascular Risk Stratum 1.

Defined as men and women ≥45 years of age with one or more of the following:

1. 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 non-ST-segment elevation acute coronary syndrome (NSTE-ACS) (with objective evidence of ischemia: ST-segment deviation or biomarker positivity).
2. 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).
3. Documented peripheral arterial disease (PAD; one or more of the following primary criteria must be satisfied):
    - Ankle-brachial index (ABI) <0.9 with symptoms of intermittent claudication;
    - History of aortoiliac or peripheral arterial intervention (catheter-based or surgical).

Acronyms: ABI, Ankle-brachial index; CAD, coronary artery disease; MI, myocardial infarction; PAD, peripheral arterial disease.

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Table 1b. Inclusion Criteria for Cardiovascular Risk Stratum 2.

Defined as patients with:

1. Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication AND
2. Men and women ≥50 years of age AND
3. One of the following at Visit 1 (additional risk factor for CVD):
    - Men ≥55 years of age and Women ≥65 years of age;
    - Cigarette smoker or stopped smoking within 3 months before Visit 1;
    - Hypertension (blood pressure ≥140 mm Hg systolic OR ≥90 mm Hg 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: Creatinine clearance (CrCL) >30 and <60 mL/min;
    - Retinopathy, defined as any of the following: nonproliferative 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 Stratum 1).

Note: Patients with diabetes and CVD as defined above are eligible based on the CVD requirements and will be counted under CV Risk Stratum 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 Stratum 2.

Acronyms: ABI, Ankle-brachial index; CrCL; creatinine clearance; CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein; PAD, peripheral arterial disease; TG, triglyceride.

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Table 3a. REDUCE-IT Efficacy Endpoints.

Primary Efficacy Endpoint[1]	Secondary Efficacy Endpoints[2]	Tertiary/Exploratory Efficacy Endpoints[2]
Time from randomization to the first occurrence of the following:		
Composite of the following clinical events: • CV death • Nonfatal MI[4] • Nonfatal stroke • Coronary revascularization • Unstable angina determined to be caused by myocardial ischemia by invasive/noninvasive testing and requiring emergent hospitalization	Key secondary endpoint: • Composite of CV death, nonfatal MI,[4] or nonfatal stroke Additional individual or composite endpoints (tested in order listed): • Composite of CV death or nonfatal MI[4] • Fatal or nonfatal MI[4] • Nonelective coronary revascularization (defined as emergent or urgent) • CV death • Unstable angina determined to be caused by myocardial ischemia by invasive/noninvasive testing and requiring emergent hospitalization • Fatal and nonfatal stroke • Composite of total mortality, nonfatal MI[4], or nonfatal stroke • Total mortality	• Total CV events[3] • Primary endpoint in patient subsets: diabetes mellitus, metabolic syndrome, impaired glucose metabolism at baseline • Key secondary composite endpoint in patients with impaired glucose metabolism at baseline • Additional composite endpoints[5] • New CHF, new CHF as the primary cause of hospitalization, transient ischemic attack, amputation for PVD, and carotid revascularization • All coronary revascularizations (defined as the composite of emergent, urgent, elective, or salvage) and each subtype of coronary revascularization (emergent, urgent, elective, • and salvage) • Cardiac arrhythmias requiring hospitalization ≥24h • Cardiac arrest • Ischemic stroke, hemorrhagic stroke, and fatal or nonfatal stroke (with prior history of stroke) • New-onset type 2 diabetes or hypertension • Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, Apo B, hsCRP, hsTnT, and RLP-C[6] • Change in body weight and waist circumference

[1]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.
[2]For the secondary and tertiary endpoints that count a single event, the time from randomization to the first occurrence of this type of event will be counted for each patient. For secondary and tertiary endpoints that are composites of 2 or more types of events, the time from randomization to the first occurrence of any of the event types included in the composite will be counted for each patient.
[3]The time from randomization to occurrence of the first and all recurrent major CV events defined as CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/noninvasive testing and requiring emergent hospitalization.
[4]Including silent MI; electrocardiography will be performed annually for the detection of silent MI.[5] Composite endpoints include: Composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, cardiac arrhythmia requiring hospitalization of ≥24 hours, or cardiac arrest; Composite of CV death, nonfatal MI (including silent MI), nonelective coronary revascularizations (defined as emergent or urgent classifications), or unstable angina

determined to be caused by myocardial ischemia by invasive/noninvasive testing and requiring emergent hospitalization; Composite of CV death, nonfatal MI (including silent MI), nonelective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/noninvasive testing and requiring emergent hospitalization, nonfatal stroke, or PVD requiring intervention, such as angioplasty, bypass surgery, or aneurysm repair; and Composite of CV death, nonfatal MI (including silent MI), nonelective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/noninvasive testing and requiring emergent hospitalization, PVD requiring intervention, or cardiac arrhythmia requiring hospitalization of ≥24 hours.

[6]Assessment of the relationship between baseline biomarker values and treatment effects within the primary and key secondary composite endpoints; assessment of the effect of study drug on each marker; and assessment of the relationship between postbaseline biomarker values and treatment effects within the primary and key secondary composite endpoints by including postbaseline biomarker values (for example, at 4 months, or at 1 year) as a covariate.

Acronyms: Apo B, apolipoprotein B; CHF, coronary heart failure; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; hsTnT, high-sensitivity troponin T; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; non-HDL-C, non-high-density lipoprotein cholesterol; PVD, peripheral vascular disease; RLP-C, remnant lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; VLDL-C, very-low-density lipoprotein cholesterol.