



## **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  $\geq 45$  years of age with established cardiovascular disease or  $\geq 50$  years of age with diabetes in combination with one additional risk factor for cardiovascular disease were eligible for inclusion. Fasting triglyceride levels  $\geq 150$  mg/dL and  $< 500$  mg/dL were required. LDL-cholesterol levels needed to be  $> 40$  mg/dL and  $\leq 100$  mg/dL, with patients on stable statin therapy ( $\pm$  ezetimibe) for  $\geq 4$  weeks prior to the LDL-cholesterol and triglyceride qualifying measurements for randomization.

#### **Table 1. General Inclusion Criteria.**

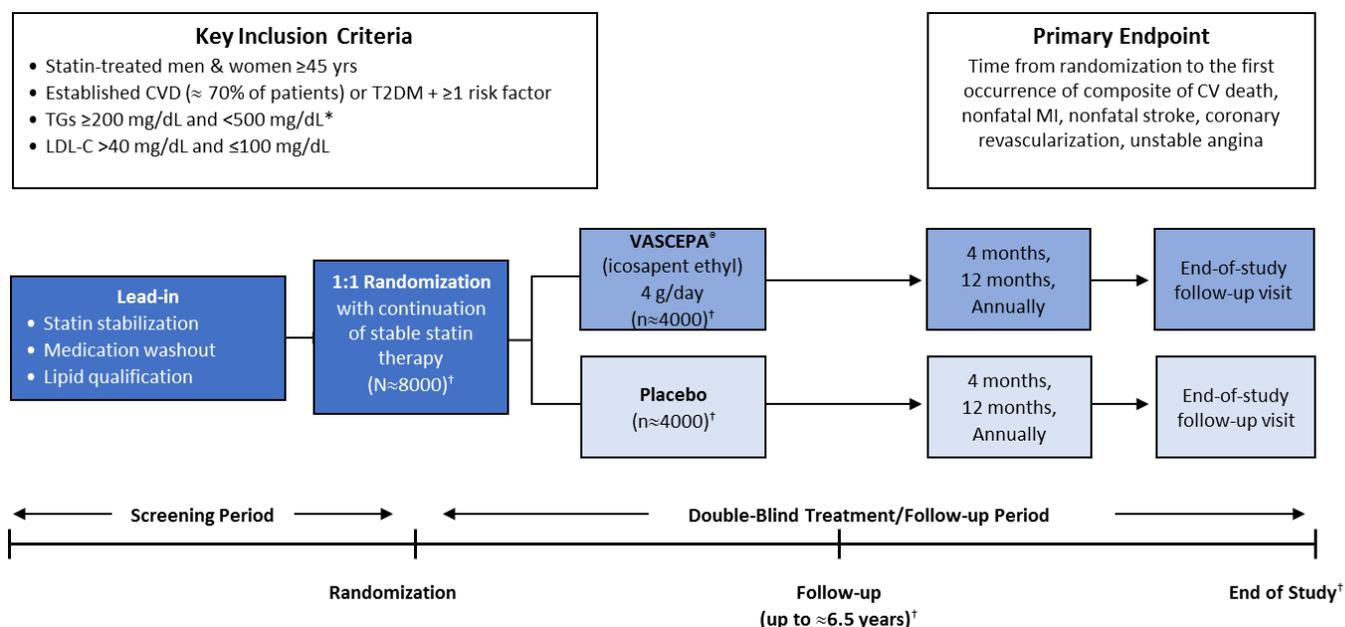
- 
1. Men or women  $\geq 45$  years of age with established CVD ) or  $\geq 50$  years of age with diabetes in combination with one additional risk factor for CVD
  2. Fasting TG levels  $\geq 150$  mg/dL and  $< 500$  mg/dL\*
  3. LDL-C  $> 40$  mg/dL and  $\leq 100$  mg/dL and on stable statin therapy ( $\pm$  ezetimibe) for  $\geq 4$  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  $\geq 150$  mg/dL to  $\geq 200$  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: CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

Click here for [Exclusion Criteria. Table 2.](#)

## REDUCE-IT Study Design



\*A study amendment (May 2013) was made, increasing the lower end of the fasting TG level from  $\geq 150$  mg/dL to  $\geq 200$  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. <sup>†</sup>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 Primary Efficacy Endpoint.

#### Primary Efficacy Endpoint<sup>1</sup>

Time from randomization to the first occurrence of the following:

Composite of the following clinical events:

- CV death
- Nonfatal MI<sup>2</sup>
- Nonfatal stroke
- Coronary revascularization
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization

<sup>1</sup>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.

<sup>2</sup>Including silent MI; electrocardiography will be performed annually for the detection of silent MI.

Acronyms: CV, cardiovascular; MI, myocardial infarction.

## 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.

[Click here for important safety information about Vascepa](#)

[Click here for full prescribing information for Vascepa](#)

## Suggested Reading

Bhatt DL, Steg PG, Brinton EA, Jacobson TA, Miller M, Tardif J-C, Ketchum SB, Doyle R 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>

**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<sub>1c</sub> >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.*