What is the clinical need and scientific rationale for the REDUCE-IT study?

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Cardiovascular disease and pharmacologic intervention

According to the Centers for Disease Control and Prevention, heart disease, also known as cardiovascular disease, is the leading cause of death for both men and women in the United States. About 600,000 people die of heart disease in the United States every year–that's 1 in every 4 deaths. Even after recommended diet and exercise, and treatment with standard of care statin therapy for patients with cardiovascular disease, there remains a large unmet clinical need for further reduction in cardiovascular risk. In clinical studies, statin therapy reduces cardiovascular risk by approximately one third, thereby leaving patients with substantial residual cardiovascular risk.

Statin therapy is primarily targeted at lowering high levels of a recognized surrogate for cardiovascular risk, low-density lipoprotein cholesterol (LDL-C), known as "bad" cholesterol. Triglyceride is fat and, like cholesterol, is a type of lipid in the blood. Triglyceride is carried through the body with cholesterol, on the same lipoproteins. High triglyceride levels are associated with cardiovascular disease. Numerous national and international cardiovascular treatment guidelines and position statements recommend drug therapy to treat patients who have persistently high triglyceride levels (≥200 mg/dL and <500 mg/dL), despite statin therapy and lifestyle changes in order to lower triglycerides and non-high-density lipoprotein cholesterol (non-HDL cholesterol).[1] These clinical recommendations persist, despite the fact that scientific evidence is currently inconclusive as to whether such effects in this patient population will ultimately reduce risks associated with cardiovascular disease, such as heart attack or stroke.

Approximately 70 million adults in the United States have elevated triglyceride levels (≥150 mg/dL), with approximately 40 million of those having high triglyceride levels (≥200 mg/dL), many of whom are already on statin therapy. Similar to cholesterol management, elevated triglycerides can be a chronic condition which, if not adequately addressed through diet and exercise, can be treated with long-term therapy. Many patients with high triglycerides despite statin therapy remain undertreated. This condition is not unique to the United States with many more millions of patients with elevated triglyceride levels worldwide.

Amarin's scientific rationale for the REDUCE-IT study

The REDUCE-IT cardiovascular outcomes study is designed to determine whether high doses of Vascepa, a highly-pure EPA omega-3 prescription product, will reduce cardiovascular risk in statin-treated patients that still have elevated or high triglyceride levels.

<u>The triglyceride-lowering hypothesis</u>

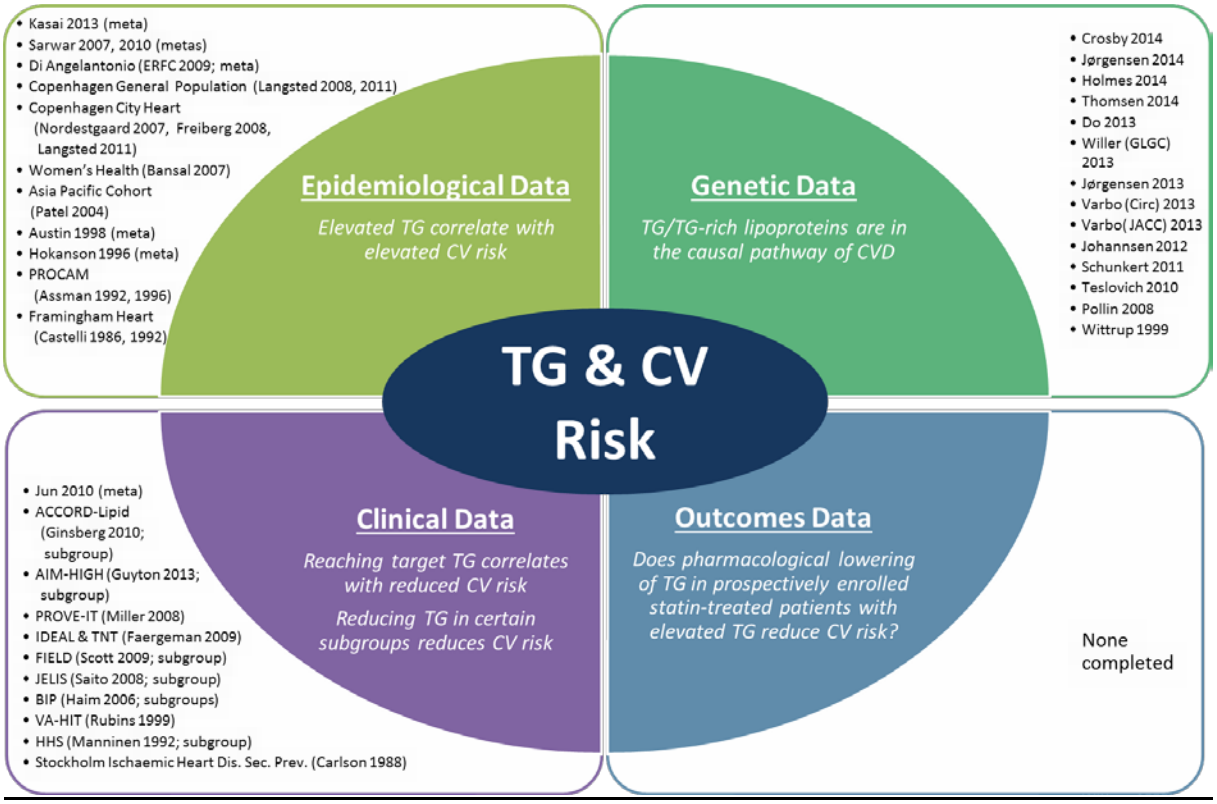
Amarin's scientific rationale for the REDUCE-IT study, which is based on the hypothesis that reduction in triglycerides will reduce cardiovascular risk in statin treated patients with persistently elevated triglyceride levels, is summarized below and illustrated in Figure 1:

- epidemiological data suggest that elevated triglyceride levels correlate with increased cardiovascular disease risk;

[1] HDL cholesterol refers to high-density lipoprotein, which is known as "good cholesterol." Non-HDL cholesterol refers to all other kinds of cholesterol.

- genetic data suggest that triglyceride and/or triglyceride-rich lipoproteins (as well as LDL-C) are independently in the causal pathway for cardiovascular disease; and
- clinical data suggest that substantial triglyceride reduction in patients with elevated baseline triglyceride levels correlates with reduced cardiovascular risk.

Figure 1: Studies supporting a correlation between triglycerides and cardiovascular disease. Each of the four quadrants below represents a category of scientific data. The outer boxes list supportive studies only. Together, the epidemiological, genetic, and clinical data suggest that triglycerides and the lipoproteins that carry them are within the causal pathway of cardiovascular disease, and that treating elevated triglycerides may result in reduced cardiovascular risk. Before the REDUCE-IT study, no outcomes study was designed to specifically address this triglyceride-lowering hypothesis. For a recent review of triglycerides and cardiovascular disease, please see Nordestgaard 2014. TG = triglyceride, CV = cardiovascular, CVD = CV disease.



The JELIS study of EPA and other omega-3 outcomes studies

The Japan EPA Lipid Intervention Study, or JELIS, is the only other cardiovascular outcomes study involving the use of a highly-pure EPA omega-3 product. JELIS showed that EPA in conjunction with statins in Japanese patients (N=18,645) reduced cardiovascular events by 19% compared to statins alone. Importantly, this result was obtained in a population in which triglycerides were in the normal range in approximately half of the patients. In addition, this study showed a 53% reduction in cardiovascular events in the EPA with statin group compared to the statin-only group within the subset of patients (N=957) who had both elevated levels of triglycerides (≥150 mg/dL) and low levels of HDL-C (<40 mg/dL). However, as previously disclosed, there are several limitations to JELIS. The patient population was exclusively Japanese, disproportionately female (69%), and statin doses were low, potentially limiting its generalizability to the intended, broader REDUCE-IT target population. It is unknown

whether the favorable effects in JELIS would have persisted if these limitations were not present or if a broader patient population had been treated with higher statin doses. Additionally, JELIS was an open-label trial, which could have influenced patient and physician behavior and reporting of symptoms, decisions regarding hospitalization, and referral of events for adjudication. Nevertheless, Amarin believes JELIS is the most relevant study when assessing the potential efficacy of EPA-only Vascepa in REDUCE-IT.

Regarding the broader category of outcome studies that have administered mixtures of omega-3 fatty acids, retrospective reviews of the effects of omega-3s on cardiovascular risk have been confounded by significant under-dosing of such therapies (low doses of omega-3s have demonstrated limited to no effect on key biomarkers) and by increases in LDL-C correlated to inclusion of the omega-3 fatty acid docosahexaenoic acid (DHA) in the composition studied. These retrospective reviews are also limited by inclusion of patients who were at relatively low risk for cardiovascular disease. The safety and tolerability profile of EPA-only Vascepa demonstrated in the MARINE and ANCHOR studies support the use of a 4 gram per day dose in the REDUCE-IT study.

Vascepa FDA regulatory review in statin-treated patients with persistently high triglycerides

Amarin's commitment to complete the REDUCE-IT study follows the previously announced third FDA denial of Amarin's appeal to reinstate the ANCHOR study special protocol assessment (SPA) agreement, which supported Amarin's application for FDA approval of Vascepa for use in statin-treated patients with persistently high triglycerides. To approve an indication based on triglyceride lowering in statin-treated patients with triglyceride levels below 500 mg/dL, FDA stated in the October 2013 Vascepa advisory committee meeting that it needs to be confident that the triglyceride lowering effects will result in cardiovascular risk reduction. As previously disclosed, failed results of cardiovascular outcomes studies of other drugs, fenofibrates in the ACCORD-Lipid study and nicotinic acid in the AIM-HIGH and HPS2-THRIVE studies, reduced FDA's confidence in the use of triglycerides as a surrogate for regulatory approval of a drug focused on cardiovascular risk reduction. In its most recent appeal denial, FDA acknowledged that Vascepa demonstrated a reduction in triglycerides over placebo in the ANCHOR study and urged Amarin to complete the REDUCE-IT cardiovascular outcomes study. However, FDA concluded that in its view the totality of scientific data and information, including its reevaluation and improved understanding of the relevant scientific knowledge since the ANCHOR trial began, does not support use of decreases in triglycerides as a validated surrogate for cardiovascular risk reduction in the proposed patient population. The supplemental new drug application filed to expand the indicated use of Vascepa to adult patients with high triglycerides (≥200 mg/dL and <500 mg/dL) who are also on statin therapy is still pending with FDA.

About the REDUCE-IT study design

REDUCE-IT (Reduction of Cardiovascular Events with EPA - Intervention Trial), is a multinational, prospective, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the effectiveness of 4 grams daily of Vascepa in reducing the prevalence of first major cardiovascular events in a high-risk patient population. The control arm of the study is comprised of patients on stable statin therapy plus placebo. The active arm of the study is comprised of patients on stable statin therapy plus Vascepa.

Patients enrolled in the REDUCE-IT study have elevated or high triglyceride levels despite statin therapy and either coronary heart disease or risk factors for coronary heart disease.

The REDUCE-IT study is designed with a composite MACE (Major Adverse Cardiovascular Event) endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina caused by myocardial ischemia. The study also includes secondary and tertiary endpoints and subgroup analyses agreed-upon with FDA.

The REDUCE-IT study, since its commencement at the end of 2011, has enrolled over 7000 patients into this event-driven trial. Amarin currently estimates that full patient enrollment in this study will be completed in 2015. The pre-specified interim analysis by the independent data monitoring committee at 60% of the targeted events is anticipated in 2016, with 100% of the targeted events currently anticipated to occur by the end of 2017 with results expected to be available in 2018. The independent data monitoring committee periodically reviews the ongoing safety results of the study.

About Vascepa® (icosapent ethyl) capsules

Vascepa® (icosapent ethyl) capsules, known in scientific literature as AMR101, is a highly-pure EPA omega-3 prescription product in a 1 gram capsule.

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.
- The effect of Vascepa on the risk for pancreatitis and cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

Important Safety Information for Vascepa

- Vascepa is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to Vascepa or any of its components and should be used with caution in patients with known hypersensitivity to fish and/or shellfish.
- The most common reported adverse reaction (incidence > 2% and greater than placebo) was arthralgia (2.3% for Vascepa, 1.0% for placebo).

FULL VASCEPA PRESCRIBING INFORMATION CAN BE FOUND AT WWW.VASCEPA.COM

Forward-looking statements

This FAQ contains forward-looking statements, including statements about the regulatory review, potential efficacy, safety and therapeutic benefits of Amarin's product candidates, Amarin's statement regarding clinical trial results, including statements about the clinical importance of certain biomarkers and potential mechanisms of action and the impact and potential impact of Vascepa on such biomarkers, cardiovascular risk reduction after statin therapy and the endpoints defined in the REDUCE-IT study. Forward-looking statements also include statements about Amarin's plans to continue the REDUCE-IT study, anticipated enrollment, event occurrence and data availability, and statements concerning its current belief in the final results of the REDUCE-IT study. These forward-looking statements are not promises or guarantees and involve substantial risks and uncertainties. Among the factors that could cause actual results to differ materially from those described or projected herein include uncertainties associated generally with research and development, clinical trials and related regulatory reviews and approvals, including the risk that historical and comparable clinical trial results may not be predictive of future REDUCE-IT study results, that regulatory reviews may impact the current design of the REDUCE-IT study and cause a change in strategic direction with respect to continuation of the study, and that changes in studied lipid biomarkers may not have clinically meaningful effect or support regulatory approvals. Other factors that could cause results to differ materially include factors that contribute to Amarin's operational cash flow, such as revenue levels from Vascepa sales, expenses related to the sale of the drug

and company operations, and Amarin's ability to protect Vascepa from generic and other competition through patent protection and other means. A further list and description of these risks, uncertainties and other risks associated with an investment in Amarin can be found in the press release issued with this FAQ and Amarin's filings with the U.S. Securities and Exchange Commission, including its most recent Quarterly Report on Form 10-Q. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. Amarin undertakes no obligation to update or revise the information contained in this press release, whether as a result of new information, future events or circumstances or otherwise.

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