

# Amarin Corporation

## Amarin Provides Overview on Growing Global Attention on REDUCE-IT™ Results and Cardiovascular Risk Management Beyond Cholesterol Management

August 27, 2019

- **Multiple Papers and Presentations Highlight REDUCE-IT and Vascepa®**
- **Potential Mechanisms of Action of Vascepa Becoming Better Understood**
- **American Heart Association References REDUCE-IT in Scientific Advisory**

BEDMINSTER, N.J. and DUBLIN, Ireland, Aug. 27, 2019 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN), a pharmaceutical company focused on improving cardiovascular health, today provided an update on the growing interest in information on Amarin's REDUCE-IT™ study and the potential for use of Vascepa® (icosapent ethyl) in studied patients at risk for a cardiovascular event. Cardiovascular disease (CVD) is worldwide the #1 killer of men and women.<sup>1,2</sup> REDUCE-IT studied the effects of Vascepa on the reduction of major adverse cardiovascular events in a high-risk patient population. The study results are currently under regulatory review in the United States and Canada.

### Publications Increasingly Highlight REDUCE-IT and Vascepa

Publications and other scientific discussions have been appearing globally with increasing regularity regarding the large unmet need to treat residual risk in CVD after standard of care statin therapy and the opportunity to potentially improve patient care in the studied high-risk patient population. New examples are now observed multiple times in most weeks. Many of these examples are supported by sources unaffiliated with Amarin. And, while many of the authors are U.S. based, an increasing number of examples are from Europe and Asia. Recent examples include:

- *ANMCO Position paper: New perspectives on the role of n-3 polyunsaturated fatty acids in cardiovascular prevention*<sup>3</sup>
- *Considerations for Treating with Icosapent Ethyl*<sup>4</sup>
- *Predicting Risk for Incident Heart Failure with Omega-3 Fatty Acids: From MESA*<sup>5</sup>
- *Strategies to Overcome Residual Risk During Statins Era*<sup>6</sup>
- *Optimal Non-invasive Strategies to Reduce Recurrent Atherosclerotic Cardiovascular Disease Risk*<sup>7</sup>
- *Cardiovascular, electrophysiologic, and hematologic effects of omega-3 fatty acids beyond reducing hypertriglyceridemia: as it pertains to the recently published REDUCE-IT trial*<sup>8</sup>
- *Rounding the corner on residual risk: Implications of REDUCE-IT for omega-3 polyunsaturated fatty acids treatment in secondary prevention of atherosclerotic cardiovascular disease*<sup>9</sup>
- *Risk of Total Events with Icosapent Ethyl: Can We Reduce It?*<sup>10</sup>
- *Major Randomized Clinical Trials in Cardiovascular Disease Prevention Presented at the 2019 American College of Cardiology Annual Scientific Session*<sup>11</sup>
- *Targeting RNA to lower triglycerides: long strides from short molecules*<sup>12</sup>
- *Fish Oil and Cardiometabolic Diseases: Recent Updates and Controversies*<sup>13</sup>

These publications demonstrate increasing interest in REDUCE-IT results and are referenced here for the convenience of Amarin's investors.

### Potential Mechanisms of Action of Vascepa

In recent years there have been multiple publications exploring the multifactorial effects associated with Vascepa and its unique active ingredient, as well as the importance of that ingredient remaining stable (e.g., free from oxidation) and the importance of adequate dosing in at-risk patients. These publications are summarized on Amarin's website at [www.amarincorp.com](http://www.amarincorp.com).

While these publications have been of interest to certain researchers and healthcare professionals, the recently posted oral presentation of research from Dr. Preston Mason has been gathering increasing attention in the investment community. This presentation, part of a continuing medical education (CME) program titled, *Biologic Basis of EPA to Reduce Atherosclerosis Burden*<sup>14</sup> can be seen at: <https://reachmd.com/programs/video-library/biologic-basis-epa-reduce-atherosclerosis-burden/10541/>. The CME is intended for research and healthcare professionals and was supported by an unrestricted educational grant from Amarin. It presents an overview of certain, but not all, biological and mechanistic workings associated with eicosapentaenoic acid (EPA) and the differences studied between EPA and various other agents that also have favorable effects on lipid parameters such as triglycerides (TGs), including docosahexaenoic acid (DHA).

Mechanisms responsible for the benefits shown in REDUCE-IT were not the focal point of the REDUCE-IT study design. Potential mechanisms include TG reduction, antithrombotic effects, antiplatelet or anticoagulant effects, effects on stabilization and/or regression of coronary plaque and inflammation reduction. More study is needed to determine to what extent, if any, these effects or others may be responsible for the CV risk reduction benefits demonstrated with use of Vascepa in REDUCE-IT.

### Medical Society Updates

The American Heart Association (AHA) issued a scientific advisory on August 19, 2019 titled, *Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association*<sup>15</sup>. This advisory recognizes that elevated triglycerides may be a causal factor for CVD and that dietary supplements are not recommended, nor FDA approved, to treat medical conditions. Vascepa is the only drug

listed in this advisory that, in addition to lowering TGs, has an associated CVD outcomes study that showed CVD risk reduction. REDUCE-IT studied whether the collective multifactorial effects associated with *Vascepa* could lower cardiovascular events such as heart attacks, stroke and death. REDUCE-IT met its primary endpoint and multiple secondary endpoints but was not designed to demonstrate that lowering TG levels would lower CV risk in the patient population studied.

Earlier this year, the American Diabetes Association® (ADA) issued important updates to its *Standards of Medical Care in Diabetes for 2019 (Standards of Care)*<sup>16</sup>, including updates related to the results of the REDUCE-IT cardiovascular outcomes study. These updates included recommendations based on the results of REDUCE-IT<sup>17,18</sup> in both primary and secondary prevention populations and resulted in a revision to the Living Standards of Care to now include the recommendation that icosapent ethyl "...be considered for patients with diabetes and atherosclerotic cardiovascular disease (ASCVD) or other cardiac risk factors on a statin with controlled low-density cholesterol (LDL-C), but with elevated triglycerides (135-499) to reduce cardiovascular risk."

#### **Comment from Amarin's President and CEO**

"We appreciate the growing attention to *Vascepa*. We believe REDUCE-IT was a well-designed and well-conducted study from which the results were robust. REDUCE-IT results have been extensively and repeatedly examined and presented globally in scientific congresses and publications. We appreciate that the medical community has been scrutinizing these results and is increasingly acting on how best to apply them to improve patient care," commented John Thero, president and chief executive officer of Amarin. "For many years, medical professionals have sought a proven therapy to help prevent cardiovascular events beyond the current standards of care. Many millions of people worldwide could potentially benefit from *Vascepa* as a cost-effective therapy. Amarin looks forward to further examination of REDUCE-IT results at the planned FDA advisory committee meeting scheduled for November 14, 2019 as a pathway to what we believe will be an approval of expanded labeling for *Vascepa* based on REDUCE-IT results."

#### **About Amarin**

Amarin Corporation plc. is a rapidly growing, innovative pharmaceutical company focused on developing therapeutics to improve cardiovascular health. Amarin's product development program leverages its extensive experience in polyunsaturated fatty acids and lipid science. *Vascepa* (icosapent ethyl) is Amarin's first FDA-approved drug and is available by prescription in the United States, Lebanon and the United Arab Emirates. Amarin's commercial partners are pursuing additional regulatory approvals for *Vascepa* in Canada, China and the Middle East. For more information about Amarin, visit [www.amarincorp.com](http://www.amarincorp.com).

#### **About REDUCE-IT™**

REDUCE-IT<sup>17</sup> was an 8,179-patient multinational cardiovascular outcomes study completed in 2018. REDUCE-IT evaluated the effect of prescription pure EPA therapy as an add-on to statins in patients with high cardiovascular risk who, despite stable statin therapy, had elevated triglyceride levels (at least 135 mg/dL). A large portion of the male and female patients enrolled in this outcomes study were diagnosed with type 2 diabetes.

More information on the REDUCE-IT study results can be found at [www.amarincorp.com](http://www.amarincorp.com).

#### **About Cardiovascular Disease**

Worldwide, cardiovascular disease (CVD) remains the #1 killer of men and women. In the United States CVD leads to one in every three deaths – one death approximately every 38 seconds – with annual treatment cost in excess of \$500 billion.<sup>1,2</sup>

Multiple primary and secondary prevention trials have shown a significant reduction of 25% to 35% in the risk of cardiovascular events with statin therapy, leaving significant persistent residual risk despite the achievement of target LDL-C levels.<sup>19</sup>

Beyond the cardiovascular risk associated with LDL-C, genetic, epidemiologic, clinical and real-world data suggest that patients with elevated triglycerides (TG) (fats in the blood), and TG-rich lipoproteins, are at increased risk for cardiovascular disease.<sup>20-23</sup>

#### **About *Vascepa*® (icosapent ethyl) Capsules**

*Vascepa* (icosapent ethyl) capsules are a single-molecule prescription product consisting of the omega-3 acid commonly known as EPA in ethyl-ester form. *Vascepa* is not fish oil, but is derived from fish through a stringent and complex FDA-regulated manufacturing process designed to effectively eliminate impurities and isolate and protect the single molecule active ingredient from degradation. *Vascepa*, known in scientific literature as AMR101, has been designated a new chemical entity by the FDA. Amarin has been issued multiple patents internationally based on the unique clinical profile of *Vascepa*, including the drug's ability to lower triglyceride levels in relevant patient populations without raising LDL-cholesterol levels.

#### Indication and Usage Based on Current FDA-Approved Label (not including REDUCE-IT results)

- *Vascepa* (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe ( $\geq 500$  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* Based on Current FDA-Approved Label (not including REDUCE-IT results) (Includes Data from Two 12-Week Studies (n=622) (MARINE and ANCHOR) of Patients with Triglycerides Values of 200 to 2000 mg/dL)

- *Vascepa* is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to *Vascepa* or any of its components.
- In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy.
- Use 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). There was no reported adverse reaction >3% and greater than placebo.
- Adverse events and product complaints may be reported by calling 1-855-VASCEPA or the FDA at 1-800-FDA-1088.
- Patients receiving treatment with *Vascepa* and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.
- Patients should be advised to swallow *Vascepa* capsules whole; not to break open, crush, dissolve, or chew *Vascepa*.

**FULL VASCEPA PRESCRIBING INFORMATION CAN BE FOUND AT [WWW.VASCEPA.COM](http://WWW.VASCEPA.COM).**

Important Safety Information for *Vascepa* based on REDUCE-IT, as previously reported in The New England Journal of Medicine<sup>1</sup> publication of the primary results of the REDUCE-IT study:

- Excluding the major adverse cardiovascular events (MACE) results described above, overall adverse event rates in REDUCE-IT were similar across the statin plus *Vascepa* and the statin plus placebo treatment groups.
- There were no significant differences between treatments in the overall rate of treatment emergent adverse events or serious adverse events leading to withdrawal of study drug.
- There was no serious adverse event (SAE) occurring at a frequency of >2% which occurred at a numerically higher rate in the statin plus *Vascepa* treatment group than in the statin plus placebo treatment group.
- Adverse events (AEs) occurring in 5% or greater of patients and more frequently with *Vascepa* than placebo were:
  - peripheral edema (6.5% *Vascepa* patients versus 5.0% placebo patients), although there was no increase in the rate of heart failure in *Vascepa* patients
  - constipation (5.4% *Vascepa* patients versus 3.6% placebo patients), although mineral oil, as used as placebo, is known to lower constipation, and
  - atrial fibrillation (5.3% *Vascepa* patients versus 3.9% placebo patients), although there were reductions in rates of cardiac arrest, sudden death and myocardial infarctions observed in *Vascepa* patients
- There were numerically more SAEs related to bleeding in the statin plus *Vascepa* treatment group although overall rates were low with no fatal bleeding observed in either group and no significant difference in adjudicated hemorrhagic stroke or serious central nervous system or gastrointestinal bleeding events between treatments.
- In summary, *Vascepa* was well tolerated with a safety profile generally consistent with clinical experience associated with omega-3 fatty acids and current FDA-approved labeling of such products.

*Vascepa* has been approved for use by the United States Food and Drug Administration (FDA) as an adjunct to diet to reduce triglyceride levels in adult patients with severe ( $\geq 500$  mg/dL) hypertriglyceridemia. FDA has not yet opined on a supplemental new drug application related to REDUCE-IT. FDA has not reviewed the information herein or determined whether to approve *Vascepa* for use to reduce the risk of MACE. Nothing in this press release should be construed as promoting the use of *Vascepa* in any indication that has not been approved by the FDA.

#### **Important Cautionary Information About These Data**

Further REDUCE-IT data assessment and data release could yield additional useful information to inform greater understanding of the trial outcome. For example, detailed data assessment by regulatory authorities, such as the FDA and Health Canada, will continue and take several months to complete and announce. The FDA advisory committee process and the final evaluation by regulatory authorities of the totality of efficacy and safety data from REDUCE-IT may include some or all of the following, as well as other considerations: new information or analyses affecting the degree of treatment benefit on studied endpoints; study conduct and data robustness, quality, integrity and consistency; additional safety data considerations and risk/benefit considerations; and consideration of REDUCE-IT results in the context of other clinical studies. Because regulatory reviews are typically fluid and not definitive interactions between sponsor and agency on individual elements of an application and related information, Amarin does not plan to update investors on ongoing communications with regulatory authorities. Amarin plans to announce the final outcome of such regulatory reviews when appropriate.

#### **Forward-Looking Statements**

This press release contains forward-looking statements, including statements about anticipated regulatory review of the REDUCE-IT sNDA and the outcome of such review and the potential of *Vascepa* to improve patient care in millions of diseased patients. 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 the following: uncertainties associated generally with research and development, clinical trials and related regulatory reviews and approvals; the risk that data interpretations or other information from third parties, the regulatory review process, regulatory authorities and in connection with an advisory committee could be made public that are negative or may delay approval or limit *Vascepa's* marketability; the risk that special protocol assessment (SPA) agreements with the FDA are not a guarantee that FDA will approve a product candidate; the risk associated with the FDA's rescinding the REDUCE-IT SPA agreement; the risk related to FDA advisory committee meetings; and the risk that the FDA may not complete its review of the REDUCE-IT sNDA within the timing expected. A further list and description of these risks, uncertainties and other risks associated with an investment in Amarin can be found in 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.

#### **Availability of Other Information About Amarin**

Investors and others should note that Amarin communicates with its investors and the public using the company website ([www.amarincorp.com](http://www.amarincorp.com)), the investor relations website ([investor.amarincorp.com](http://investor.amarincorp.com)), including but not limited to investor presentations and investor FAQs, Securities and Exchange Commission filings, press releases, public conference calls and webcasts. The information that Amarin posts on these channels and websites could

be deemed to be material information. As a result, Amarin encourages investors, the media, and others interested in Amarin to review the information that is posted on these channels, including the investor relations website, on a regular basis. This list of channels may be updated from time to time on Amarin's investor relations website and may include social media channels. The contents of Amarin's website or these channels, or any other website that may be accessed from its website or these channels, shall not be deemed incorporated by reference in any filing under the Securities Act of 1933.

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