Amarin Corporation

# VASCEPA® (icosapent ethyl) Shows Significant Cardiovascular Risk Reduction in People with Diabetes in Prespecified and Post Hoc Subgroup Analyses of Landmark REDUCE-IT® Study

June 15, 2020

*Primary composite first and total major adverse cardiovascular event (MACE) reductions of 23% each shown with VASCEPA in prespecified tertiary and post hoc exploratory analyses of the subgroup of people with diabetes*

*Key secondary composite first and total MACE reductions of 30% and 29%, respectively, shown with VASCEPA in prespecified tertiary and post hoc exploratory subgroup analyses*

*Reductions also observed in post hoc exploratory analyses of other composite endpoints, in people with diabetes, and in people with established cardiovascular disease with or without diabetes at baseline*

DUBLIN, Ireland and BRIDGEWATER, N.J., June 15, 2020 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN) today announced that data from the REDUCE-IT® study presented during the 80th Scientific Sessions of the American Diabetes Association by Deepak L. Bhatt, M.D., M.P.H., Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, showed that administration of 4 g/day of VASCEPA® (icosapent ethyl) resulted in significant 23% reductions in both first and total primary composite major adverse cardiovascular events (5-point MACE) in people with diabetes. Reductions of 30% and 29% were observed in both first and total hard (3-point) MACE, the key secondary composite endpoint, respectively. The late-breaking presentation, titled "Substantial Cardiovascular Benefit from Icosapent Ethyl in Patients with Diabetes: REDUCE-IT DIABETES" was heard on June 13, 2020 at 10:00 am CST.

The leading cause of morbidity and mortality in type 2 diabetes mellitus continues to be cardiovascular disease, especially in those patients who already have established atherosclerotic cardiovascular disease (ASCVD).[1] Above normal blood levels of triglycerides (TG) are common in patients with diabetes,[2,3] and have been associated with increased ASCVD (30% and 23% higher risk for non-fatal myocardial infarction (MI) and stroke, respectively) in this patient population, despite statin therapy.[4]

Many of the world's leading diabetes and cardiovascular disease professional societies, including the American Diabetes Association (ADA) and the American Heart Association (AHA), are working to educate patients and clinicians on the urgent need to identify and manage risk with appropriate therapies. The AHA Scientific Statement on *Clinical Management of Stable Coronary Artery Disease in Patients with Type 2 Diabetes Mellitus*, published in April of this year, states that "icosapent ethyl is the first non–LDL (low-density lipoprotein)-focused lipid therapy to demonstrate cardiovascular benefit and should be considered first-line therapy for patients with T2DM (type 2 diabetes mellitus) and CAD (coronary artery disease) whose triglycerides remain elevated (>135 mg/dL) despite maximally tolerated statin and lifestyle changes."[1]

"People with diabetes are at markedly increased risk of cardiovascular disease, and that intersection has become a target for research and a focus for clinical care," commented Dr. Deepak L. Bhatt, M.D., M.P.H., Executive Director of Interventional Cardiovascular Programs at Brigham and Women's Hospital Heart & Vascular Center and Professor of Medicine at Harvard Medical School, and senior author of the REDUCE-IT DIABETES analyses. "In these analyses, we see the substantial impact that icosapent ethyl could have on reducing cardiovascular risks and complications from diabetes."

The prespecified tertiary and *post hoc* exploratory analyses from the REDUCE-IT study showed that, for the primary composite endpoint of 5-point MACE, time to first event was significantly reduced with VASCEPA versus placebo by 23% ($p<0.0001$) and total (first and subsequent) events were also reduced by 23% ($p=0.0003$) in the subgroup of people with diabetes. For the key secondary composite endpoint of 3-point MACE, time to first event was reduced by 30% ($p<0.0001$) and total events were reduced by 29% ($p<0.0001$) in the subgroup of people with diabetes. Observed reductions in MACE were supported by further *post hoc* exploratory analyses of the data across cardiovascular risk category and diabetes status at baseline.

"The REDUCE-IT DIABETES subgroup analyses further our understanding of the potential for VASCEPA to benefit people with diabetes," said Steven Ketchum, Ph.D., senior vice president and president, research & development and chief scientific officer, Amarin. "The data in our analyses shows consistent outcomes across the at-risk population and supports that VASCEPA can help reduce the already significant burden of cardiovascular disease in people with diabetes."

These REDUCE-IT analyses suggest benefits with VASCEPA that are incremental to those of statin and other therapies with known cardiovascular benefit, including anti-diabetic medications that were well-utilized across people with diabetes, approximately half of whom were taking two or more anti-diabetic therapies.

REDUCE-IT was not specifically powered to examine patient subgroups, therefore p-values presented for these diabetes analyses are nominal and exploratory with no adjustment for multiple comparisons. In addition, while the cardiovascular risk categories of established cardiovascular disease or diabetes plus additional risks were stratification factors, the presence or absence of diabetes in patients with established cardiovascular disease was not. These REDUCE-IT DIABETES results include both prespecified tertiary and *post hoc* exploratory analyses. Nonetheless, results from these time to first and total events analyses consistently suggest benefit across the various endpoints and recurrent event statistical models. Together, the REDUCE-IT DIABETES first and total events results support the robustness and consistency of the clinical benefit of VASCEPA therapy beyond current standards of medical management in reducing cardiovascular events in patients with diabetes.

Slides from the presentation will be made available on www.acc.org.

**Financial Disclosure**

Funding from Amarin was provided to Brigham and Women's Hospital for Dr. Deepak L. Bhatt's work as the REDUCE-IT study chair and global

principal investigator.

**About Amarin**

Amarin Corporation plc is a rapidly growing, innovative pharmaceutical company focused on developing and commercializing therapeutics to cost-effectively improve cardiovascular health. Amarin's lead product, VASCEPA® (icosapent ethyl), is available by prescription in the United States, Canada, Lebanon and the United Arab Emirates. Amarin, together with its commercial partners in select geographies, is pursuing additional regulatory approvals for VASCEPA in China, the European Union and the Middle East. For more information about Amarin, visit www.amarincorp.com.

**About Cardiovascular Risk**

The number of deaths in the United States attributed to cardiovascular disease continues to rise. There are 605,000 new and 200,000 recurrent heart attacks per year (approximately 1 every 40 seconds), in the United States. Stroke rates are 795,000 per year (approximately 1 every 40 seconds), accounting for 1 of every 19 U.S. deaths. Cardiovascular disease results in 859,000 deaths per year in the United States.[5] In aggregate, this is more than 2.4 million major adverse cardiovascular events per year from cardiovascular disease or, on average, one every 13 seconds in the United States alone.

Controlling bad cholesterol, also known as LDL-C, is one way to reduce a patient's risk for cardiovascular events, such as heart attack, stroke or death. However, even with the achievement of target LDL-C levels, millions of patients still have significant and persistent risk of cardiovascular events, especially those patients with elevated triglycerides. Statin therapy has been shown to control LDL-C, thereby reducing the risk of cardiovascular events by 25-35%.[6] Significant cardiovascular risk remains after statin therapy. People with elevated triglycerides have 35% more cardiovascular events compared to people with normal (in range) triglycerides taking statins.[7,8,9]

**About REDUCE-IT®**

REDUCE-IT was a global cardiovascular outcomes study designed to evaluate the effect of VASCEPA in adult patients with LDL-C controlled to between 41-100 mg/dL (median baseline 75 mg/dL) by statin therapy and various cardiovascular risk factors including persistent elevated triglycerides between 135-499 mg/dL (median baseline 216 mg/dL) and either established cardiovascular disease (secondary prevention cohort) or diabetes mellitus and at least one other cardiovascular risk factor (primary prevention cohort).

REDUCE-IT, conducted over seven years and completed in 2018, followed 8,179 patients at over 400 clinical sites in 11 countries with the largest number of sites located within the United States. REDUCE-IT was conducted based on a special protocol assessment agreement with FDA. The design of the REDUCE-IT study was published in March 2017 in *Clinical Cardiology.*[10] The primary results of REDUCE-IT were published in *The New England Journal of Medicine* in November 2018.[11] The total events results of REDUCE-IT were published in the *Journal of the American College of Cardiology* in March 2019.[12] These and other publications can be found in the R&D section on the company's website at www.amarincorp.com.

**About VASCEPA® (icosapent ethyl) Capsules**

VASCEPA (icosapent ethyl) capsules are the first-and-only prescription treatment approved by the FDA comprised solely of the active ingredient, icosapent ethyl (IPE), a unique form of eicosapentaenoic acid. VASCEPA was initially launched in the United States in 2013 based on the drug's initial FDA approved indication for use as an adjunct therapy to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia. Since launch, VASCEPA has been prescribed over eight million times. VASCEPA is covered by most major medical insurance plans. The new, cardiovascular risk indication for VASCEPA was approved by the FDA in December 2019.

Indications and Limitation of Use

VASCEPA 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 two 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.

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

Important Safety Information

- VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components.
- VASCEPA was associated with an increased risk (3% vs 2%) 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.
- It is not known whether patients with allergies to fish and/or shellfish are at an increased risk of an allergic reaction to VASCEPA. Patients with such allergies should discontinue VASCEPA if any reactions occur.
- VASCEPA was associated with an increased risk (12% vs 10%) 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.
- Common adverse reactions in the cardiovascular outcomes trial (incidence ≥3% and ≥1% more frequent than placebo):

musculoskeletal pain (4% vs 3%), peripheral edema (7% vs 5%), constipation (5% vs 4%), gout (4% vs 3%), and atrial fibrillation (5% vs 4%).

- Common adverse reactions in the hypertriglyceridemia trials (incidence ≥1% more frequent than placebo): arthralgia (2% vs 1%) and oropharyngeal pain (1% vs 0.3%).
- Adverse events may be reported by calling 1-855-VASCEPA or the FDA at 1-800-FDA-1088.
- Patients receiving VASCEPA and concomitant anticoagulants and/or anti-platelet agents should be monitored for bleeding.

Key clinical effects of VASCEPA on major adverse cardiovascular events are included in the Clinical Studies section of the prescribing information for VASCEPA, as set forth below:

**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<br>n (%) | Incidence Rate (per 100 patient years) | N = 4090<br>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<br>(17.2) | 4.3 | 901<br>(22.0) | 5.7 | 0.75<br>(0.68, 0.83) |
| **Key secondary composite endpoint** | | | | | |
| Cardiovascular death, myocardial infarction, stroke (3-point MACE) | 459<br>(11.2) | 2.7 | 606<br>(14.8) | 3.7 | 0.74<br>(0.65, 0.83) |
| **Other secondary endpoints** | | | | | |
| Fatal or non-fatal myocardial infarction | 250<br>(6.1) | 1.5 | 355<br>(8.7) | 2.1 | 0.69<br>(0.58, 0.81) |
| Emergent or urgent coronary revascularization | 216<br>(5.3) | 1.3 | 321<br>(7.8) | 1.9 | 0.65<br>(0.55, 0.78) |
| Cardiovascular death [1] | 174<br>(4.3) | 1.0 | 213<br>(5.2) | 1.2 | 0.80<br>(0.66, 0.98) |
| Hospitalization for unstable angina [2] | 108<br>(2.6) | 0.6 | 157<br>(3.8) | 0.9 | 0.68<br>(0.53, 0.87) |
| Fatal or non-fatal stroke | 98<br>(2.4) | 0.6 | 134<br>(3.3) | 0.8 | 0.72<br>(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.

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

**Forward-Looking Statements**

This press release contains forward-looking statements, including statements regarding the potential impact of VASCEPA in various clinical uses. 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 and clinical trials such as further clinical evaluations failing to confirm earlier findings. 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. Amarin's forward-looking statements do not reflect the potential impact of significant transactions the company may enter into, such as mergers, acquisitions, dispositions, joint ventures or any material agreements that Amarin may enter into, amend or terminate.

**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), the investor relations website (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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