VASCEPA® (Icosapent Ethyl) Reported to Significantly Reduce Coronary Plaque in EVAPORATE Study Final Results Presented at ESC Congress 2020

August 29, 2020

Primary endpoint of slowed coronary plaque progression reported to have been met with VASCEPA

Significant coronary plaque regression of low attenuation plaque (LAP) reported with VASCEPA provides further insight to potential mechanisms of action

VASCEPA is the first and only agent studied on top of statins reported to exhibit coronary plaque regression in hypertriglyceridemic patients

DUBLIN, Ireland and BRIDGEWATER, N.J., Aug. 29, 2020 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN) today announced that the trial results from *Effect of Icosapent Ethyl on Progression of Coronary Atherosclerosis in Patients with Elevated Triglycerides on Statin Therapy: Final results of the EVAPORATE Trial* were presented at ESC Congress 2020, the annual meeting of the European Society of Cardiology, on August 29, 2020, 9:13 am CEST (Central European Summer Time) by Matthew Budoff, M.D., Director of Cardiovascular CT at The Lundquist Institute and Professor of Medicine at the David Geffen School of Medicine at UCLA, the study sponsor. VASCEPA® (icosapent ethyl) demonstrated significant, 17% regression of low attenuation plaque (LAP) volume on multidetector computed tomography (MDCT) compared with placebo over 18 months. As referenced below, these final results can be found in the concurrent publication in *European Heart Journal.*

"EVAPORATE provides important mechanistic data on coronary plaque characteristics that are potentially relevant to the overall REDUCE-IT ® results and clinical use of icosapent ethyl," commented Matthew Budoff, M.D., Director of Cardiovascular CT at The Lundquist Institute and Professor of Medicine at the David Geffen School of Medicine at UCLA. "The REDUCE-IT REVASC analysis presented at American Society for Preventive Cardiology last month reported an early coronary revascularization benefit signal with sustained statistical significance attained by 11 months. EVAPORATE is the first demonstration of imaging results with icosapent ethyl using MDCT. The coronary plaque reduction shown in EVAPORATE is consistent with the benefits of icosapent ethyl in cardiovascular event outcomes shown in REDUCE-IT, a separate study."

A total of 80 patients were enrolled in the randomized, double-blind, placebo-controlled EVAPORATE trial. Patients had to have coronary atherosclerosis as documented by MDCT (1 or more angiographic stenoses with ≥20% narrowing), be on statin therapy, and have persistently elevated triglyceride (TG) levels (mean TG at baseline was 259.1 mg/dL [+/- 78.1]). Patients underwent an interim scan at 9 months and a final scan at 18 months. The prespecified primary endpoint was a comparison of change in LAP volume at 18 months between icosapent ethyl and placebo. EVAPORATE was not powered for long-term outcomes.

The final results showed a significant reduction in the primary endpoint; icosapent ethyl reduced LAP plaque volume by 17% from baseline to the 18-month scan, whereas there was a progression of LAP plaque volume in the placebo group. There were significant differences between icosapent ethyl and placebo at study end for secondary endpoints of other types of plaque volume changes, including and sequentially total, total non-calcified, fibrofatty, and fibrous plaque volumes. All regressed in the icosapent ethyl group and progressed in the placebo group, ($p<0.01$ for all). The only secondary endpoint which did not achieve a significant difference between groups in multivariable modeling was dense calcium ($p=0.053$).

The mineral oil placebo, used for consistency with REDUCE-IT, was also analyzed against plaque changes from baseline in another placebo in a separate study. Rates of plaque changes in patients randomized to mineral oil (the placebo cohort) in the EVAPORATE study were compared with rates of plaque changes in the placebo arm of a second study that used a cellulose-based placebo. There was no difference in plaque progression between mineral oil and cellulose based placebos.[1]

"Coronary plaque regression is an important finding with VASCEPA and may explain, in part, the substantial cardiovascular benefit seen in REDUCE-IT," said Craig Granowitz, M.D., Ph.D., Amarin's senior vice president and chief medical officer. "The EVAPORATE study results potentially shed further light on how VASCEPA works to lower residual cardiovascular risk."

Limitations of this single study include a small sample size. More study is needed to demonstrate the effects of VASCEPA on coronary plaque to determine the relationship of such effects, if any, on cardiovascular risk reduction.

The presentation will be available here with a concurrent publication in *European Heart Journal*.

Financial Disclosure
Funding from Amarin was provided to the sponsor of the EVAPORATE study, The Lundquist Institute, for Dr. Matthew Budoff's work on the study.

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. VASCEPA is not yet approved and available in any other countries. Amarin, on its own or together with its commercial partners in select geographies, is pursuing additional regulatory approvals for VASCEPA in China, Europe 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.[2] In aggregate, there are more than 2.4 million major adverse cardiovascular events per year from cardiovascular disease or, on average, 1 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%.[3] 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.[4,5,6]

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.*[7] The primary results of REDUCE-IT were published in *The New England Journal of Medicine* in November 2018.[8] The total events results of REDUCE-IT were published in the *Journal of the American College of Cardiology* in March 2019.[9] 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 n (%)	Incidence Rate (per 100 patient years)	N = 4090 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 (17.2)	4.3	901 (22.0)	5.7	0.75 (0.68, 0.83)
Key secondary composite endpoint					
Cardiovascular death, myocardial infarction, stroke (3-point MACE)	459 (11.2)	2.7	606 (14.8)	3.7	0.74 (0.65, 0.83)
Other secondary endpoints					
Fatal or non-fatal myocardial infarction	250 (6.1)	1.5	355 (8.7)	2.1	0.69 (0.58, 0.81)
Emergent or urgent coronary revascularization	216 (5.3)	1.3	321 (7.8)	1.9	0.65 (0.55, 0.78)
Cardiovascular death [1]	174 (4.3)	1.0	213 (5.2)	1.2	0.80 (0.66, 0.98)
Hospitalization for unstable angina [2]	108 (2.6)	0.6	157 (3.8)	0.9	0.68 (0.53, 0.87)
Fatal or non-fatal stroke	98 (2.4)	0.6	134 (3.3)	0.8	0.72 (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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