REDUCE-IT Exploratory Post Hoc Biomarker Sub-Analysis Shows Relatively Small Changes in Inflammatory Markers Between Icosapent Ethyl and Placebo

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-- Sub-Analysis Findings Support Prior Analyses that Eicosapentaenoic Acid (EPA) Level is The Major Determinant of Benefit in REDUCE-IT --

DUBLIN, Ireland and BRIDGEWATER, N.J., June 30, 2022 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN) today announced an exploratory post hoc sub-analysis of REDUCE-IT serum samples that found statin-treated patients allocated to icosapent ethyl (IPE) had limited differences in certain lipid and inflammatory biomarkers compared with statin-treated patients allocated to mineral oil placebo. These findings are consistent with prior reported data and support previous analyses that demonstrated the majority of benefit from IPE was from achieved eicosapentaenoic acid (EPA) levels in REDUCE-IT. This sub-analysis was published online today in the journal *Circulation*.

In the landmark REDUCE-IT cardiovascular outcomes study, IPE achieved 25 percent relative risk reduction of major adverse cardiovascular events (MACE, 5-point composite endpoint: cardiovascular death, non-fatal heart attack, non-fatal stroke, coronary revascularization, or unstable angina). This also included relative risk reductions of 31 percent, 28 percent and 20 percent in heart attacks, strokes and cardiovascular deaths, respectively. As previously presented, the only marker that seems to have strong association with reductions in MACE from the REDUCE-IT study is serum EPA levels; these data were previously presented at the American College of Cardiology Scientific Sessions in 2020.[i]

“Regardless of biomarker pathway, effects were small on an absolute scale for both icosapent ethyl and for placebo, and changes in values were mostly below the limits of quantification in this exploratory sub-analysis,” said Deepak L. Bhatt, M.D., M.P.H., Executive Director of Interventional Cardiovascular Programs at Brigham and Women’s Hospital and Professor of Medicine at Harvard Medical School, principal investigator of REDUCE-IT and co-author of the biomarker sub-analysis. “While the mechanisms of action contributing to the reduction of cardiovascular events with icosapent ethyl are not completely understood and are likely multi-factorial, previous studies have clearly demonstrated the anti-inflammatory effects of EPA. The current analysis of REDUCE-IT finds a difference in inflammatory markers between icosapent ethyl and placebo, however, the absolute magnitude of these differences is too small to explain the substantial reduction in clinical events seen in the REDUCE-IT trial, which is most likely due to the approximate 400% increase in EPA levels.”

Additionally, clinical studies suggest that IPE may be contributing to plaque reduction, regression and stabilization in patients with coronary artery disease.[ii,iii,iv] Additional studies are needed to further elucidate any effects on plaque characteristics. A prior randomized, cardiovascular outcomes trial of EPA versus standard of care demonstrated that EPA provided a 19% cardiovascular risk reduction in patients with normal triglyceride levels and only lowered triglyceride levels by 5%, suggesting that the effects of EPA go beyond triglyceride lowering.[v]

“While exploratory biomarker sub-analyses are interesting scientifically, what is most clear and important clinically are the cardiovascular outcomes results seen in the REDUCE-IT trial overall,” said Nabil Abadir, MB. CH.B., Chief Medical Officer, Amarin. “As we know, the REDUCE-IT trial demonstrated the clear risk reduction benefits of icosapent ethyl in reducing cardiovascular events among patients most at risk for cardiovascular disease, especially those with prior cardiovascular events such as heart attack or coronary revascularization procedures.”

Added Dr. Abadir, “The landmark REDUCE-IT trial and its clinical outcomes underpin the international regulatory approvals of VASCEPA®/VAZKEPA® as well as the more than 25 clinical treatment guidelines, consensus statements and scientific statements from medical societies or journals around the globe that have been updated recommending the use of icosapent ethyl in appropriate at-risk patients. Based on the results of REDUCE-IT, regulatory agencies granted approval of IPE for ASCVD risk reduction for millions of high-risk patients with characteristics like those enrolled and followed in the study.”

This REDUCE-IT post hoc biomarker sub-analysis was funded by Amarin under a research grant.

About Amarin
Amarin is an innovative pharmaceutical company leading a new paradigm in cardiovascular disease management. From our foundation in scientific research to our focus on clinical trials, and now our commercial expansion, we are evolving and growing rapidly. Amarin has offices in Bridgewater, New Jersey in the United States, Dublin in Ireland, Zug in Switzerland, and other countries in Europe as well as commercial partners and suppliers around the world. We are committed to increasing the scientific understanding of the cardiovascular risk that persists beyond traditional therapies and advancing the treatment of that risk.

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.[vi] The primary results of REDUCE-IT were published in *The New England Journal of Medicine* in November 2018.[vii] The total events results of REDUCE-IT were published in the *Journal of the American College of Cardiology* in March 2019.[viii] These and other publications can be found in the Science section on the company’s website at www.amarincorp.com.

About VASCEPA® (icosapent ethyl) Capsules
VASCEPA (icosapent ethyl) capsules are the first prescription treatment approved by the U.S. Food and Drug Administration (FDA) comprised solely of the active ingredient, icosapent ethyl (IPE), a unique form of eicosapentaenoic acid. VASCEPA was launched in the United States in January 2020

as the first and only drug approved by the U.S. FDA for treatment of the studied high-risk patients with persistent cardiovascular risk after statin therapy. 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 more than 18 million times. VASCEPA is covered by most major medical insurance plans. In addition to the United States, icosapent ethyl is approved and sold in Canada, Germany, Lebanon and the United Arab Emirates. In Europe, in March 2021 marketing authorization was granted to icosapent ethyl in the European Union for the reduction of risk of cardiovascular events in patients at high cardiovascular risk, under the brand name VAZKEPA.

Indications and Limitation of Use (in the United States)
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.

FULL U.S. FDA-APPROVED VASCEPA PRESCRIBING INFORMATION CAN BE FOUND AT WWW.VASCEPA.COM.

Forward-Looking Statements

This press release contains forward-looking statements which are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, including statements regarding the potential for VASCEPA (marketed as VAZKEPA in Europe), as well as the potential role that IPE may have in influencing inflammatory biomarkers and plaque reduction. These forward-looking statements are not promises or guarantees and involve substantial risks and uncertainties. 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 Amarin's annual report on Form 10-K for the full year ended 2021. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date they are made. Amarin undertakes no obligation to update or revise the information contained in its forward-looking statements, 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) and the investor relations website (investor.amarincorp.com), including but not limited to investor presentations, 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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