New REDUCE-IT® Analyses Show VASCEPA®/VAZKEPA® (Icosapent Ethyl) Benefit in High-Risk Cardiovascular Disease Patient Subgroups

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-- Findings Presented on VASCEPA/VAZKEPA Utility in REDUCE-IT Patient Subgroups by Baseline High/Low Lp(a), LDL-C Levels --

-- Lp(a) Results Published Simultaneously in the Journal of the American College of Cardiology (JACC) –

DUBLIN, Ireland and BRIDGEWATER, N.J., April 06, 2024 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN) today highlighted two data presentations at ACC.24 describing the effects of VASCEPA®/VAZKEPA® (icosapent ethyl) on reducing MACE (Major Adverse Cardiovascular Events) in patients with baseline high or low Lipoprotein(a) [Lp(a)] levels, as well as reducing the risk of cardiovascular (CV) events in patients irrespective of baseline LDL-C level. The REDUCE-IT analysis results relating Lp(a) concentrations with CV risk were also published online today in the Journal of the American College of Cardiology (JACC).

“These new findings provide additional important evidence about the clinical utility of VASCEPA/VAZKEPA and further demonstrate its value in reducing cardiovascular events in at-risk patients in key subgroups,” said Nabil Abadir, MB. CH.B., Chief Medical Officer and Head of Global Medical Affairs, Amarin. “At Amarin, we’re focused on the continuous generation of science to further advance the medical community’s understanding of the role and value of VASCEPA/VAZKEPA in reducing cardiovascular events in at-risk patients globally, and we are proud to add to the body of research that further demonstrates our commitment to value creation.”

The subgroup analyses and their key findings are outlined below:

Icosapent Ethyl Reduces MACE in Patients with Elevated Triglycerides and High or Low Lipoprotein(a) Concentrations: A REDUCE-IT Subanalysis

High Lp(a) concentrations are associated with increased CV event risk, even when LDL-C levels are well-managed. There are no treatments currently approved to reduce residual CV risk on top of contemporary medical therapy in patients with high Lp(a) levels.

In this post hoc analysis of REDUCE-IT, the relationship between continuous baseline Lp(a) concentration and risk of MACE was analyzed in models that also accounted for baseline LDL-C, baseline triglycerides (TG), and double-blind treatment.

REDUCE-IT participants were randomized to receive either 2g twice daily of icosapent ethyl (IPE) or matching placebo and followed for a median 4.9 years. In this subanalysis, there were 7,026 REDUCE-IT patients with baseline Lp(a) data and a median Lp(a) value of 11.6 (Q1-Q3: 5.0-37.4) mg/dL. Results showed that baseline Lp(a) had a strong and significant relationship with MACE irrespective of baseline LDL-C, baseline TGs, and treatment assignment, and that the benefit of IPE was consistent across Lp(a) concentrations. Importantly, the treatment benefit of IPE was evident across subgroups with both high (≥50 mg/dL) and low (<50 mg/dL) Lp(a) concentrations. Specifically, for first MACE, the relative IPE treatment effects for Lp(a) ≥50 mg/dL and <50 mg/dL were HR 0.79 (95% CI 0.64-0.97; P=0.0248) and HR 0.75 (95% CI 0.66-0.84; P<0.0001), respectively. Absolute risk reductions at 5 years with IPE were 6.5% and 5.7% for Lp(a) ≥50 mg/dL and <50 mg/dL, respectively.[1]

Limitations include that participants in REDUCE-IT were not selected on the basis of their baseline Lp(a) concentration and that not all REDUCE-IT patients had available baseline Lp(a) data.

“In this analysis, IPE showed a clear clinical benefit for patients with both high and low Lp(a) levels. IPE provided a relative risk reduction of 21% among patients with an Lp(a) level of ≥50 mg/dL and 25% for those patients with an Lp(a) level of <50 mg/dL,” said Dr. Michael Szarek, professor, Division of Cardiology, University of Colorado School of Medicine and a faculty member at CPC Clinical Research. “These findings are important, as high baseline Lp(a) concentrations are a predictor for MACE, and this analysis reinforces IPE’s clinical benefit in these at-risk patient sub-populations.”

The analysis and its findings were published simultaneously online in JACC.

Efficacy of Icosapent Ethyl for Reducing Cardiovascular Outcomes by Baseline Low Density Lipoprotein Cholesterol Level

Elevated low-density lipoprotein cholesterol (LDL-C) is a well-established major CV risk factor supported by clinical evidence showing decreased atherosclerotic disease events when LDL-C is therapeutically lowered. Recent international guidelines recommend lowering LDL-C to <55 mg/dL in those patients who are at very high risk for a future CV event.

In this post hoc analysis, investigators explored REDUCE-IT data to determine if IPE reduces CV outcomes among high-risk CV patients irrespective of baseline LDL-C. Patients were stratified by LDL-C <55 vs ≥55 mg/dL. The primary outcome was a composite of CV death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina.

Among statin-treated REDUCE-IT patients with baseline LDL-C data, 1,058 (12.9%) had LDL-C <55 mg/dL and 7,117 (87.1 %) had LDL-C ≥55 mg/dL. The primary outcome rate among patients with LDL-C <55 mg/dL was 16.2% in the IPE group and 22.8% in the placebo group, HR 0.66 (95% CI 0.50-0.87; P=0.003). Findings were consistent in the LDL-C ≥55 mg/dL subgroup, with rates of 17.4% in the IPE group and 21.9% in the placebo group, HR 0.76 (95% CI 0.69-0.85; P<0.0001). No significant interaction by baseline LDL-C was observed.

Limitations are that randomization was not stratified by baseline LDL-C, however, baseline characteristics were similar among the two baseline LDL-C subgroups. REDUCE-IT patients were on statin therapy, but with low rates or unavailability of other lipid therapies such as ezetimibe, proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, or small interfering RNA (siRNA) therapies.

"As we know, LDL-C is a well-established major CV risk factor. These data are important and show that among adults with increased CV risk and elevated TGs, icosapent ethyl clearly reduced the rate of CV outcomes irrespective of baseline LDL-C, including in those with very well controlled LDL-C <55 mg/dL," said Deepak L. Bhatt, MD, MPH, MBA, Director of Mount Sinai Fuster Heart Hospital.

All analyses highlighted above were funded by Amarin. Dr. Deepak L. Bhatt served as the principal investigator for REDUCE-IT and his institution received research funding from Amarin.

About Amarin
Amarin is an innovative pharmaceutical company leading a new paradigm in cardiovascular disease management. We are committed to increasing the scientific understanding of the cardiovascular risk that persists beyond traditional therapies and advancing the treatment of that risk for patients worldwide. 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.

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.[2] The primary results of REDUCE-IT were published in The New England Journal of Medicine in November 2018.[3] The total events results of REDUCE-IT were published in the Journal of the American College of Cardiology in March 2019.[4] These and other publications can be found in the R&D section on the company's website at **www.amarincorp.com**.

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

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 VASCEPA®/VAZKEPA® (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 drug approved by the U.S. FDA for treatment of the studied high-risk patients with persistent cardiovascular risk despite being on 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 twenty million times. VASCEPA is covered by most major medical insurance plans. In addition to the United States, VASCEPA is approved and

sold in Canada, China, 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. In April 2021 marketing authorization for VAZKEPA (icosapent ethyl) was granted in Great Britain (applying to England, Scotland and Wales). VAZKEPA (icosapent ethyl) is currently approved and sold in Europe in Sweden, Denmark, Finland, Austria, the UK, Spain and the Netherlands.

United States
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.

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

Europe

For further information about the Summary of Product Characteristics (SmPC) for VAZKEPA® in Europe, please click here.

Globally, prescribing information varies; refer to the individual country product label for complete information.

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 beliefs about the potential for VASCEPA (marketed as VAZKEPA in Europe); beliefs about icosapent ethyl (IPE)'s role concerning appropriate patients suffering from cardiovascular disease (CVD) and potential population health impact, as well as general beliefs about the safety and effectiveness of VASCEPA. 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 2023. 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 communicates with its investors and the public using the company website (www.amarincorp.com) and the investor relations website (amarincorp.com/investor-relations), including but not limited to investor presentations and 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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