Amarin Corporation

Amarin Highlights Multiple Scientific Findings for VASCEPA® (Icosapent Ethyl) and Its Unique Active Ingredient at the American College of Cardiology's 70th Annual Scientific Session

May 17, 2021

REDUCE-IT® patients experienced substantial cardiovascular (CV) risk reduction with icosapent ethyl regardless of the presence or degree of dyslipidemia, as defined by various high TG plus low HDL-C levels

Patients randomized to VASCEPA in EVAPORATE trial, in analyses of percent atheroma volume (PAV), had 55% lower coronary total plaque (TP) PAV and 61% lower coronary total non-calcified plaque (TNCP) PAV, compared with placebo

Amarin to Webcast Discussion of Data Presented at ACC.21 Today, Monday, May 17, 2021 at 4:30 p.m., Eastern Time

DUBLIN, Ireland and BRIDGEWATER, N.J., May 17, 2021 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN) today announced the presentation of important VASCEPA® (icosapent ethyl) and its unique active ingredient-related scientific findings at ACC.21, the American College of Cardiology's 70th Annual Scientific Session, held virtually from May 15 – 17, 2021, from a variety of academic collaborators based on research and analyses supported by Amarin.

"Cardiovascular disease continues to be the leading cause of death worldwide, with the economic and societal burden increasing each year," said Steven Ketchum, Ph.D., senior vice president, president of research & development, and chief scientific officer, Amarin. "As we strive to ease the strain on patients, their families, and healthcare systems around the world, we must continuously focus on the value that innovative therapies such as icosapent ethyl might offer at-risk patients. While we are proud that the clinical efficacy and safety of icosapent ethyl has been thoroughly reviewed and approved by regulatory authorities in the United States, Canada, and Europe as the only proven therapy for its indicated use in reducing cardiovascular risk, we are hopeful that our continued support of robust scientific presentation of the clinical effects and unique multifactorial mechanisms of action of icosapent ethyl will lead to a greater understanding and usage of this important product to help appropriate at-risk patients."

These presentations were on the following topics:

REDUCE-IT® Clinical Data:

- "ICOSAPENT ETHYL REDUCES ISCHEMIC EVENTS IN PATIENTS WITH HIGH TRIGLYCERIDES AND LOW HIGH-DENSITY LIPOPROTEIN CHOLESTEROL LEVELS: REDUCE-IT HIGH TG/LOW HDL-C ANALYSES" – presented on behalf of all authors by Xiaowen Wang, M.D., Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, MA

Highlights: Prespecified and *post hoc* analyses were conducted of first and total primary and key secondary endpoint events in REDUCE-IT patients with dyslipidemia, defined by the REDUCE-IT prespecified analysis levels of TG ≥200 and HDL-C ≤35 mg/dL, *post hoc* guideline-informed levels of TG ≥150 mg/dL and HDL-C <40/50 mg/dL (men/women), or *post hoc* STRENGTH inclusion criteria-informed levels of TG ≥180 and HDL-C <42/47 mg/dL (men/women). Compared with placebo, icosapent ethyl 4g/day significantly reduced first and total primary and key secondary endpoint events by approximately 30% to 40% in patients with dyslipidemia. Similar relative risk reductions were generally observed regardless of elevated TG, low HDL-C, or the combination thereof, suggesting that patients with or without dyslipidemia experience substantial cardiovascular (CV) risk reduction with icosapent ethyl therapy.

- "REDUCTION IN HEART FAILURE WITH ICOSAPENT ETHYL: INSIGHTS FROM REDUCE-IT HF" – presented on behalf of all authors by Deepak L. Bhatt, M.D., M.P.H., Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, MA (as described in a separate press release dated May 15, 2021 on Amarin's website)

Highlights: The REDUCE-IT HF analyses examined the effects of icosapent ethyl on the incidence of new heart failure by achieved on-treatment serum EPA levels in REDUCE-IT patients. New heart failure and new heart failure requiring hospitalization were prespecified tertiary endpoints and were not significant in the overall patient population. *Post hoc* analyses were conducted based on estimated average on-treatment EPA levels in patients in the icosapent ethyl group with available EPA measurements, as compared to patients in the placebo group with available EPA measurements; these analyses showed that new heart failure and new heart failure requiring hospitalization may be reduced in patients who achieve serum EPA levels higher than approximately 150 µg/mL, though this needs to be tested prospectively.

EVAPORATE and Imaging:

- "EFFECT OF ICOSAPENT ETHYL ON PERCENT ATHEROMA VOLUME IN PATIENTS WITH ELEVATED TRIGLYCERIDES ON STATIN THERAPY: INSIGHTS FROM THE EVAPORATE TRIAL" – presented on behalf of all authors by Suvasini Lakshmanan, M.D., M.S., The Lundquist Institute at Harbor-UCLA Medical Center, Torrance, CA

Highlights: The EVAPORATE trial sought to examine the anti-atherosclerotic effects of icosapent ethyl (IPE) (4g/day) as an adjunct to statins in patients with residually elevated triglycerides on serial Coronary Computed Tomography Angiography (CCTA) over 18 months. Percent atheroma volume (PAV) is identified as a robust prognostic marker of whole-heart atherosclerotic plaque characterization with CCTA. Sixty-eight patients (54% male, age 57.4± 9.2 years) who completed 18-month follow-up and with interpretable images were included in the coronary plaque analysis that revealed that those on IPE have 55% lower total plaque (TP) PAV and 61% lower total non-calcified plaque (TNCP) PAV, compared with placebo ($p<0.01$). IPE demonstrated significant reductions in coronary plaque burden on CCTA compared with placebo over 18 months. EVAPORATE provides

crucial mechanistic insights on whole-heart atherosclerotic plaque burden that may explain the clinical benefits of IPE in REDUCE-IT.

- "ASSOCIATION OF BASELINE CORONARY PLAQUE BURDEN AND FRACTIONAL FLOW RESERVE DERIVED FROM CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY (CCTA) IN THE EVAPORATE TRIAL" – presented on behalf of all authors by Suvasini Lakshmanan, M.D., M.S., The Lundquist Institute at Harbor-UCLA Medical Center, Torrance, CA

Highlights: Atherosclerotic plaque burden and characteristics may affect vessel specific coronary physiology in high-risk patients. Forty-nine patients (49% female; age 57.2 ± 9.2 years) with interpretable images for Fractional Flow Reserve Computed Tomography (FFRCT) were included. Multivariable analyses revealed that fibrous, fibro-fatty, total non-calcified plaque, and total plaque volumes were independently associated with impaired mean distal FFRCT ($p < 0.05$) at baseline, associated with abnormal vessel specific hyperemic physiology as characterized by FFRCT in an asymptomatic cohort of high-risk patients enrolled in EVAPORATE.

Mechanism of Action Insights:

- "EICOSAPENTAENOIC ACID (EPA) INCREASES HEME OXYGENASE-1 EXPRESSION IN ENDOTHELIAL CELLS UNDER CONDITIONS OF INFLAMMATION UNLIKE DOCOSAHEXAENOIC ACID (DHA)" – presented on behalf of all authors by R. Preston Mason, Ph.D., Brigham and Women's Hospital, Boston, MA

Highlights: Inducible heme oxygenase-1 (HO-1) catalyzes the degradation of heme into biliverdin, carbon monoxide and ferrous iron. These HO-1 products have potent antioxidant, vasodilatory and anti-inflammatory actions. Expression of HO-1 has been linked to nitric oxide (NO) bioavailability; a process influenced by the omega-3 fatty acid EPA. Endothelial cells (ECs) pretreated with EPA and DHA significantly down-/up-regulated expression of select proteins, compared with IL-6 alone. Only EPA upregulated inducible HO-1 by 150% ($p = 0.02$) and only EPA significantly increased NO release by 13% ($p = 0.04$) from these cells. These beneficial effects of EPA were not reproduced by DHA and may contribute to preserved vascular EC function and reduced CV risk as demonstrated in large outcome trials.

- "PLATELET ENDOTHELIAL CELL ADHESION MOLECULE-1 (PECAM-1) AND NITROXIDATIVE STRESS REDUCED BY EICOSAPENTAENOIC ACID (EPA) DURING CYTOKINE EXPOSURE IN ENDOTHELIAL CELLS" – presented on behalf of all authors by R. Preston Mason, Ph.D., Brigham and Women's Hospital, Boston, MA

Highlights: Platelet endothelial cell adhesion molecule-1 (PECAM-1) is widely expressed in multiple tissues, including vascular endothelial cells (ECs). In addition to its adhesive actions, PECAM-1 modulates diverse functions such as platelet activation, thrombosis, responses to shear stress and leukocyte migration. Cells pretreated with EPA and arachidonic acid (AA) significantly changed the expression of certain proteins, compared with IL-6 alone. Only EPA caused a pronounced decrease in PECAM-1 by 120% ($p = 0.024$) and only EPA significantly decreased $ONOO^-$ release by 17% ($p = 0.045$) relative to IL-6 alone from the ECs, unlike AA. These anti-inflammatory effects of EPA in vascular endothelium were not reproduced by AA and may contribute to its CV benefits at pharmacologic levels in clinical trials.

Epidemiological Findings:

- "GLOBAL CARDIOVASCULAR RISK ASSESSMENT IMPROVES RISK STRATIFICATION FOR MAJOR ADVERSE CARDIAC EVENTS ACROSS A WIDE RANGE OF TRIGLYCERIDE LEVELS IN STATIN-TREATED INDIVIDUALS: INSIGHTS FROM THE KP REACH STUDY" – presented on behalf of all authors by Andrew P. Ambrosy, M.D., Kaiser Permanente San Francisco Medical Center, San Francisco, CA

Highlights: The prognostic value of a global assessment of atherosclerotic cardiovascular disease (ASCVD) risk beyond triglyceride (TG) levels in statin-treated individuals has not been previously reported. KP REACH included all statin-treated adults at Kaiser Permanente Northern California between 2010-2017 with known ASCVD, a low-density lipoprotein cholesterol (LDL-C) of 41-100 mg/dL, and an available TG measurement. The Kaiser Permanente ASCVD Risk Estimator (KPARE) and ACC/AHA pooled cohort equation (PCE) were used to estimate 10-year ASCVD risk. Among 97,832 statin-treated individuals with prior ASCVD, the median (25^{th}-75^{th}) TG level was 116 (84-164) mg/dL. The overall rate of subsequent major adverse cardiovascular events (MACE) was 22 per 100 person-years. KPARE and the ACC/AHA PCE estimated 10-year ASCVD risk was significantly associated with MACE over the entire range of available TG measurements (all $p<0.001$). Adults treated for secondary prevention with a well-controlled LDL-C remain at high risk for recurrent ischemic events and a global assessment of ASCVD risk further improves risk stratification for MACE across a broad spectrum of TG levels.

All analyses highlighted above were funded by Amarin.

Brigham and Women's Hospital receives research funding from Amarin for Dr. Bhatt's work as the REDUCE-IT study Chair.

Additional REDUCE-IT® and icosapent ethyl (EPA)-related topics presented at ACC.21 can be found here.

Audio Webcast Information
Amarin will host an audio webcast today, Monday, May 17, 2021, at 4:30 p.m. ET to further discuss these and other VASCEPA-related findings presented during ACC.21, with replay available for a period of 14 days. The discussion will include various clinicians and scientists and will be moderated by Amarin's chief medical officer, Craig Granowitz, M.D., Ph.D. To listen please register here, listen live on the investor relations section of the company's website at www.amarincorp.com, or via telephone by dialing 877-545-0320 within the United States, 973-528-0016 from outside the United States. A replay of the call will be made available for a period of two weeks following the conference call. To hear a replay of the call, dial 877-481-4010 within the United States, 919-882-2331, PIN: 41266. Any opinions or views expressed by the clinicians and scientists on the audio webcast are theirs alone. They have neither been scripted nor previewed by Amarin. While Amarin respects the scientific opinions of these clinicians and scientists, Amarin takes no responsibility for those opinions. Rather, this audio webcast is intended to provide summaries of recently presented scientific data for consideration by Amarin's investors.

About Amarin

Amarin is an innovative pharmaceutical company leading a new paradigm in cardiovascular disease management. From our scientific research foundation 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, and Zug in Switzerland as well as commercial partners and suppliers around the world. We are committed to rethinking cardiovascular risk through the advancement of scientific understanding of the impact on society of significant residual risk that exists beyond traditional therapies, such as statins for cholesterol management.

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.[1] 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%.[2] 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. [3,4,5]

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.*[6] The primary results of REDUCE-IT were published in *The New England Journal of Medicine* in November 2018.[7] The total events results of REDUCE-IT were published in the *Journal of the American College of Cardiology* in March 2019.[8] 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 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 over ten million times. VASCEPA is covered by most major medical insurance plans. In addition to the United States, VASCEPA is approved and sold in Canada, 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.

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 U.S. FDA-APPROVED 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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[7] Bhatt DL, Steg PG, Miller M, et al., on behalf of the REDUCE-IT Investigators. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med*. 2019;380:11-22.

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