Amarin Corporation

Multiple New VASCEPA® (Icosapent Ethyl)-Related Scientific Findings Presented at American Heart Association's Virtual Scientific Sessions 2020

November 18, 2020

Findings further support the differentiated multifactorial mechanism of action of VASCEPA and its robust clinical effectiveness in reducing major adverse cardiovascular events (MACE) in studied high-risk patients

Breadth of scientific evidence presented provides further insight into the unique, single molecule active ingredient of VASCEPA and confirms status as first-and-only prescription treatment for the at-risk population studied

Amarin to Webcast Discussion of Presented Data on November 18, 2020 at 4:30 p.m., Eastern Standard Time

DUBLIN, Ireland and BRIDGEWATER, N.J., Nov. 18, 2020 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN) supported new data, presented at American Heart Association's (AHA) Virtual Scientific Sessions 2020, held virtually from November 13 – 17, 2020, adding to the growing body of knowledge on VASCEPA® (icosapent ethyl) and its differentiated positioning in treating patients at risk for major adverse cardiovascular events (MACE). The data, from a broad group of clinicians and scientists, continues to reinforce the unique mechanistic, clinical, and pharmacoeconomic impact of VASCEPA.

"The AHA Virtual Scientific Sessions 2020 is an important opportunity for the medical community to advance its understanding of how to best address the growing impact of cardiovascular disease," said Craig Granowitz, M.D., Ph.D., Amarin's senior vice president and chief medical officer. "At Amarin, we share this passion and are pleased to provide additional insights into how VASCEPA, with its unique effects, properties, and attributes, can potentially reduce cardiovascular disease in appropriate patients."

Featured Amarin-supported data presented at AHA Virtual Scientific Sessions 2020 included:

1) **Findings regarding the unique mechanistic effects of the active ingredient in VASCEPA:**

"Eicosapentaenoic Acid, but Not Docosahexaenoic Acid or a Mixed Omega-3 Fatty Acid Supplement, Inhibits Low-density Lipoprotein Oxidation in a Time-dependent Manner" – presented on behalf of all authors by Samuel Sherratt, B.S., Elucida Research, Beverly, MA

Highlights: The purpose of the study was to compare the effects of eicosapentaenoic acid (EPA) versus docosahexaenoic acid (DHA) and a mixed omega-3 fatty acid (EPA/DHA) dietary supplement on oxidation of human low-density lipoprotein (LDL) *in vitro.*

EPA, a stable form of which is the active ingredient in icosapent ethyl, in laboratory or *in vitro* study, significantly inhibited LDL oxidation compared to a control vehicle and did so over a more sustained period of time than DHA and mixed omega-3 fatty acid. Inhibiting LDL is associated with lowering cholesterol and oxidation of LDL is associated with making LDL atherogenic. Evaluation was made based on quantifying changes in malondialdehyde (MDA), a reactive aldehyde produced by LDL oxidation.

In the study, EPA after 4 hours inhibited MDA levels by 96% compared with the control vehicle oxidation level. DHA compared with the control vehicle inhibited MDA levels at 2 hours at a level which was less pronounced than EPA and this level of antioxidant activity with DHA was lost within 4 hours. The mixed omega-3 fatty acid, which is a dietary supplement, failed to show any antioxidant activity through 4 hours. Fatty acid analysis showed that the mixed omega-3 fatty acid dietary supplement, which is widely used commercially, in addition to EPA and DHA, contained more than 30 other fatty acids, including saturated fats, that may have nullified any potential benefits.

These data support LDL antioxidant effects of EPA that were sustained over time compared with DHA, which had a transient effect, or a mixed omega-3 fatty acid dietary supplement, which had no beneficial effect at all.

"Contrasting Effects of Phospholipid Linked Eicosapentaenoic Acid (EPA) and Arachidonic Acid (AA) on Membrane Structure and Stability" – presented on behalf of all authors by Samuel Sherratt, B.S., Elucida Research, Beverly, MA

Highlights: The purpose of this *in vitro* study was to compare the separate and combined effects of phospholipid-linked EPA and AA on membrane structure. Small angle x-ray diffraction approaches compared the effects of 1-palmitoyl-2-eicosapentaenoyl-sn-glycero-3-phosphocholine (PL-EPA) and 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine (PL-AA) at a 1:20 ratio in membranes composed of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) and cholesterol (C) at a 0.3:1 C:PL ratio.

PL-EPA was shown to cause membrane stability, which may improve the signaling and function of endothelial cells. The PL-EPA effect on improving membrane stability was negatively disrupted by the presence of PL-AA. The contrasting effects of PL-EPA and PL-AA on membrane structure may contribute to differences in biological activity between these two omega-3 fatty acid molecules, EPA and AA.

"Achieved Eicosapentaenoic Acid (EPA) Levels Predicts Regression of Coronary Plaque Volumes by Coronary Computed Tomography Angiography (CCTA) in the EVAPORATE Trial" – presented on behalf of all authors by Suvasini Lakshmanan, M.D., M.S., Lundquist Institute at Harbor-UCLA Medical Center, Torrance, CA

Highlights: EVAPORATE was a randomized, double-blind, placebo-controlled trial enrolling a total of 80 patients who had to have coronary atherosclerosis as documented by multidetector computed tomography (MDCT) (1 or more angiographic stenoses with ≥20% narrowing), be on statin therapy, and have persistently elevated triglyceride (TG) levels. Patients underwent an interim scan at 9 months and a final scan at 18 months using Coronary Computed Tomography Angiography (CCTA) to evaluate the effects of icosapent ethyl as an adjunct to statins on coronary plaque volumes. The previously reported results of the prespecified primary endpoint was a 17% regression in low attenuation plaque (LAP) volume at 18 months for

icosapent ethyl relative to placebo. These results were previously presented with publication in the *European Heart Journal*.

The pre-specified secondary endpoint was the association of achieved serum EPA levels, and change in coronary plaque volumes in the pooled cohort. At 18 months, higher serum EPA levels were reported to predict regression of fibro-fatty plaque, total non-calcified plaque (TNCP), and total plaque (TP), after adjustment for age, sex, diabetes, hypertension, and baseline TG levels.

"Effect of Icosapent Ethyl on Changes in Coronary Plaque Characteristics at 9 Months in Patients With Elevated Triglycerides on Statin Therapy: Insights From EVAPORATE" – presented on behalf of all authors by Suvasini Lakshmanan, M.D., M.S., Lundquist Institute at Harbor-UCLA Medical Center, Torrance, CA

Highlights: In this analysis of the EVAPORATE trial, plaque characteristics including lipid rich necrotic core (LRNC), fibrous cap thickness, and intraplaque hemorrhage (IPH) were assessed using vascuCAP® (Elucid Bioimaging Inc., Boston, MA). A total of 60 patients had interpretable images.

Relative to placebo, patients on icosapent ethyl were reported to have decreased wall volume, LRNC, and IPH, as well as increased cap thickness, indicating a migration to more stable phenotypes. This study reported that icosapent ethyl, when added to statin therapy, is associated with reduction in vulnerable plaque, moving patients to a more stable plaque phenotype.

2) **Findings further supporting the robustness of the clinical efficacy demonstrated with VASCEPA:**

"Icosapent Ethyl Reduces Ischemic Events in Patients With Prior Coronary Artery Bypass Grafting: REDUCE-IT CABG" – presented on behalf of all authors by Subodh Verma, M.D., Ph.D., University of Toronto, Toronto, Ontario, Canada

Highlights: VASCEPA, compared with placebo, significantly reduced primary composite first and total major adverse cardiovascular events (MACE) in *post hoc* exploratory analyses of patients with a history of coronary artery bypass grafting (CABG) procedures by 24% and 36%, respectively, and key secondary composite first hard MACE, comprised of heart attacks, stroke and cardiovascular death, by 31%.

As reported in a press release dated November 13, 2020, the REDUCE-IT® CABG analysis examined 1,837 (22.5%) of the patients enrolled in REDUCE-IT, representing all patients who had undergone a prior coronary artery bypass grafting (CABG) procedure, a common form of surgical intervention to help treat coronary heart disease. Baseline characteristics were similar among patients randomized to VASCEPA versus placebo. *Post hoc* exploratory analyses of this subgroup showed that, for the composite endpoint of 5-point MACE, which was the prespecified primary endpoint for the full REDUCE-IT study cohort, time to first event was significantly reduced with VASCEPA versus placebo by 24% and total (first and subsequent) events were also reduced by 36%. For the REDUCE-IT study's key secondary composite endpoint of 3-point MACE, time to first event was reduced by 31% in the subgroup of patients with a prior CABG.

"Significant Reductions in Both Adjudicated and Investigator-Reported Ischemic Events in REDUCE-IT" – presented on behalf of all authors by Deepak L. Bhatt, M.D., M.P.H., Brigham and Women's Hospital, Boston, MA

Highlights: The REDUCE-IT ADJUDICATION analysis sought to determine whether there were any differences in the effect of icosapent ethyl whether endpoints were investigator-reported or blindly adjudicated. Icosapent ethyl significantly reduced primary and key secondary composite first MACE by 26% and 25%, respectively, as reported by the site investigators. There was a high degree of concordance between investigator-reported and adjudicated endpoints, underscoring the robustness of the cardiovascular benefits of icosapent ethyl seen in REDUCE-IT.

3) **Findings regarding the cost-effectiveness of VASCEPA:**

"Consistent Cost-effectiveness of Icosapent Ethyl Across Patient Profiles From REDUCE-IT" – presented on behalf of all authors by Zugui Zhang, Ph.D., ChristianaCare Health System, Newark, DE

Highlights: The purpose of this study was to conduct subgroup analyses of lifetime cost-effectiveness (CE) of icosapent ethyl (IPE) compared to standard care (SC) alone. The analysis used cardiovascular event reduction data demonstrated with IPE in the REDUCE-IT study and third-party data regarding the cost associated with treating such high-risk patients, including costs for treating heart attacks and strokes if they are not reduced by IPE.

Based on the results of this analysis, IPE was found to be a dominant strategy over the lifetime in 69.7% of simulations with the probability of CE at the nominal $50,000, $100,000, and $150,000 thresholds being replicated in 87.9%, 98.6%, and 99.9% of simulations, respectively. Being a dominant strategy means that not only is the therapy found to be cost-effective based on typical quality-adjusted life year (QALY) criteria but also that the therapy in most scenarios saves money for society. While the REDUCE-IT study was not powered for subgroup analysis, CE analysis was also conducted for subgroups of age, sex, diabetic status and whether they were secondary or primary prevention patients at the time of being enrolled into the REDUCE-IT study. In multiple subgroups, IPE was reported to be a dominant strategy over lifetime, in particular the subgroups of: age <65 years; male sex; subjects with diabetes; subjects without diabetes; secondary prevention cohort, TG levels ≥200 mg/dL; TG levels ≥150 mg/dL; and baseline LDL ≥70 mg/dL. In multiple subgroups IPE was found to be cost effective but did not reach the rarely achieved cost dominant threshold. In subgroups for female sex and the primary prevention cohort, IPE was found to be cost effective with an incremental cost of $16,660 or $21,890 per QALY gained, respectively, which are both well below the most stringent typical criteria for assessing cost-effectiveness of medical therapy.

In all subgroups, IPE at the cost of therapy used per the analysis per third-party reference was shown to be cost effective at a willingness-to-pay threshold of $50,000 per QALY and was a dominant treatment strategy in most subgroups.

4) **Findings further supporting the broad global need for preventive cardiovascular care:**

"Are the Results of Clinical Trials Relevant in the Real World? The Applicability of REDUCE-IT to the Fast-MI Registry" – presented on behalf of all authors by Jean Ferrières, M.D., M.Sc., Toulouse Rangueil University Hospital, Toulouse, France

Highlights: In order to evaluate the applicability of results of the REDUCE-IT cardiovascular outcomes study in a segment of the French population, the inclusion and exclusion criteria of the landmark REDUCE-IT study were applied to French patients who were admitted to coronary or intensive care units within 48 hours of symptom onset during a 1-month period (French Registry on Acute ST-elevation and non-ST-elevation Myocardial Infarction [FAST-MI], 2010 and 2015). The results support that, even in this limited registry of patients, many French patients would qualify for the inclusion criteria of REDUCE-IT in which patients treated with VASCEPA experienced significant reductions in major adverse cardiovascular events. These

results were previously presented with publication in *Clinical Lipidology*.

All analyses highlighted above were funded by Amarin.

Additional information on AHA Virtual Scientific Sessions 2020 can be found here.

Audio Webcast Information
Amarin will host an audio webcast today, November 18, 2020, at 4:30 p.m. EST to further discuss these and other VASCEPA-related findings presented during the AHA Virtual Scientific Sessions 2020. 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 877-407-8033 within the United States, 201-689-8033 from outside the United States.

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.[1] In aggregate, there are 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%.[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 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.

Amarin Contact Information

Investor Inquiries:
Investor Relations
Amarin Corporation plc
In U.S.: +1 (908) 719-1315
IR@amarincorp.com (investor inquiries)

Solebury Trout
lstern@soleburytrout.com

Media Inquiries:
Alina Kolomeyer
Communications
Amarin Corporation plc
In U.S.: +1 (908) 892-2028
PR@amarincorp.com (media inquiries)

[1] American Heart Association. Heart Disease and Stroke Statistics—2020 Update: A Report From the American Heart Association*Circulation*. 2020;141:e139–e596.

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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.

[8] Bhatt DL, Steg PG, Miller M, et al., on behalf of the REDUCE-IT Investigators. Reduction in first and total ischemic events with icosapent ethyl across baseline triglyceride tertiles. *J Am Coll Cardiol*. 2019;74:1159-1161.