Further Insights into Mechanism of Action of Icosapent Ethyl and Its Unique Form of Eicosapentaenoic Acid (EPA) Presented at the European Atherosclerosis Society (EAS) Congress 2021

June 2, 2021

Studies support potentially important anti-inflammatory, protein modulation, and cell function effects of icosapent ethyl as known by the brand name VASCEPA® in much of the world and as VAZKEPA in Europe

DUBLIN, Ireland and BRIDGEWATER, N.J., June 02, 2021 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN) today announced the presentation of further insights into various potential mechanisms of action of icosapent ethyl and differences in biological actions of the unique form of eicosapentaenoic acid (EPA) in icosapent ethyl from other mediators in a number of experimental systems that mimic various aspects of arterial atherosclerotic plaque initiation and progression. These data were presented at European Atherosclerosis Society (EAS) Congress 2021, held virtually from May 30 – June 2, 2021, and are based on research and analyses supported by Amarin. These data and analyses build on previously presented clinical, epidemiological and genetic findings, including cardiovascular outcomes study results.

"The story of the unique multifactorial mechanism of action of icosapent ethyl continues to unfold as we elucidate further insights into how this agent, a unique form of eicosapentaenoic acid, impacts cellular processes and protein expression," said Craig Granowitz, M.D., Ph.D., Amarin's senior vice president and chief medical officer. "The consistency of results from basic science seen in these and previous presentations to translational studies to clinical outcomes is incredibly powerful. It is an elegant articulation of the broad elements that support the unique cardiovascular risk reduction impact of icosapent ethyl."

EAS Congress 2021 presentations were as follows:

- "EICOSAPENTAENOIC ACID MODULATES ENDOTHELIAL FUNCTION AND INFLAMMATORY PROTEIN EXPRESSION FROM PULMONARY AND VASCULAR TISSUES FOLLOWING CYTOKINE CHALLENGE" – presented on behalf of all authors by R. Preston Mason, Ph.D., Brigham and Women's Hospital, Boston, MA

Highlights: EPA significantly modulated >50 proteins coordinately in pulmonary or vascular endothelial cells (ECs) following interleukin-6 (IL-6) exposure. These included seven proteins related to neutrophil degranulation and cytokine signaling, and five proteins linked to EC function and inflammation. In human umbilical vein ECs (HUVECs), treatment with eicosapentaenoic acid (EPA) also significantly increased nitric oxide (NO) release by 13% relative to IL-6 alone. EPA favorably modulated expression of EC proteins associated with inflammation and improved NO bioavailability during IL-6 exposure. These studies support favorable anti-inflammatory effects of EPA on ECs in multiple vascular beds that may contribute to reduced CV risk.

- "EICOSAPENTAENOIC ACID REDUCES CYTOKINE-INDUCED EXPRESSION OF MULTIPLE PROTEINS RELATED TO PLATELET ACTIVATION AND AGGREGATION IN PULMONARY AND VASCULAR ENDOTHELIUM" – presented on behalf of all authors by R. Preston Mason, Ph.D., Brigham and Women's Hospital, Boston, MA

Highlights: EPA significantly downregulated a total of 36 proteins involved in platelet activation, signaling, aggregation, in EC following IL-6 exposure. Platelet endothelial cell adhesion molecule (PECAM) was the only common protein that EPA significantly downregulated in both HUVECs and PECs. In PECs, EPA significantly modulated 26 other proteins related to platelet activation, including amyloid-beta precursor protein and thrombin receptor, while in HUVECs there were 9 other proteins modulated related to platelet activation, including superoxide dismutase. EPA significantly reduced expression of PECAM in ECs from different tissues, as well as other proteins associated with platelet activity. These findings suggest potential novel antithrombotic mechanisms for EPA that may contribute to reduced ischemic events.

- "EICOSAPENTAENOIC ACID INCREASES OMEGA-3 FATTY ACID CONTENT AND REDUCES INFLAMMATORY PROTEIN LEVELS IN PULMONARY ENDOTHELIAL CELLS DURING IL-6 EXPOSURE" – presented on behalf of all authors by R. Preston Mason, Ph.D., Brigham and Women's Hospital, Boston, MA

Highlights: Pretreatment of pulmonary ECs (PECs) with EPA decreased production of more than 60 proteins after IL-6 stimulation including angiotensin converting enzyme (ACE) and ICAM-1. These changes correlated with increases in cellular content of EPA, docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) levels after EPA pretreatment. EPA also significantly reduced levels of palmitic acid (PA), while levels of linoleic acid (LA) and arachidonic acid (AA) did not change. EPA significantly reduced expression of proteins associated with vasoconstriction and inflammation that correlated with increased omega-3 fatty acids and lower PA. These findings indicate a novel effect of EPA with implications for vascular and pulmonary function.

- "EICOSAPENTAENOIC ACID REDUCED LEVELS OF ANGIOTENSIN CONVERTING ENZYME AND CAVEOLIN-1 IN PULMONARY ENDOTHELIAL CELLS FOLLOWING CYTOKINE TREATMENT" – presented on behalf of all authors by R. Preston Mason, Ph.D., Brigham and Women's Hospital, Boston, MA

Highlights: Pulmonary ECs treated with EPA following IL-6 exposure showed significant changes in expression of >400 proteins including those that mediate inflammation and vasodilation. EPA significantly downregulated caveolin-1, an inhibitor on NOS, and increased levels of heat shock protein-90 (Hsp90) compared to IL-6. EPA significantly reduced expression of additional proteins linked to NOS inhibition and as well as ACE and

endothelin-converting enzyme-1 (ECE-1) levels. EPA favorably modulated expression of proteins associated with NOS activation and vasoconstriction following IL-6 exposure, including ACE and ECE-1. These studies support a novel effect of EPA on pulmonary ECs that may contribute to reduced CV disease progression.

- "EICOSAPENTAENOIC ACID INHIBITS LIPOPOLYSACCHARIDE (LPS)-INDUCED MACROPHAGE ACTIVATION IN A MANNER THAT IS ENHANCED WITH COLCHICINE" – presented on behalf of all authors by R. Preston Mason, Ph.D., Brigham and Women's Hospital, Boston, MA

Highlights: Treatment with LPS increased nitrite production by 465%. EPA treatment reduced nitrite production in a significant, dose-dependent manner by 40-77% at 10-40 µM, respectively, compared to LPS-alone. EPA at the lowest concentration tested produced an effect similar to diclofenac, which reduced nitrite levels by 40%. Colchicine treatment reduced nitrite production significantly only at the highest concentration at 35%. The combination of EPA and colchicine (each at 10µM) reduced nitrite release, and therefore macrophage activation, in an additive manner by 70%, that significantly exceeded their separate effects. The ability of EPA and colchicine to reduce macrophage activity may contribute to limiting inflammation that participates in cardiovascular diseases.

All analyses highlighted above were funded by Amarin.

Additional REDUCE-IT® and icosapent ethyl-related topics presented at EAS Congress 2021 can be found here. For investors, additional scientific data regarding icosapent ethyl, including data pertaining to clinical results and mechanisms of action, can be found in the publications section of the company's website.

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.

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

Solebury Trout
amarinir@troutgroup.com

Media Inquiries:
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.

[2] Ganda OP, Bhatt DL, Mason RP, et al. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol.* 2018;72(3):330-343.

[3] Budoff M. Triglycerides and triglyceride-rich lipoproteins in the causal pathway of cardiovascular disease. *Am J Cardiol*. 2016;118:138-145.

[4] Toth PP, Granowitz C, Hull M, et al. High triglycerides are associated with increased cardiovascular events, medical costs, and resource use: A real-world administrative claims analysis of statin-treated patients with high residual cardiovascular risk. *J Am Heart Assoc.* 2018;7(15):e008740.

[5] Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease - New insights from epidemiology, genetics, and biology. *Circ Res.* 2016;118:547-563.

[6] Bhatt DL, Steg PG, Brinton E, et al., on behalf of the REDUCE-IT Investigators. Rationale and Design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol*. 2017;40:138-148.

[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.