Amarin Corporation

Amarin Supports Investigator-Initiated Trial at Kaiser Permanente in the U.S. to Study the Effects of VASCEPA® (icosapent ethyl) in Reducing Viral Upper Respiratory Infections, Including COVID-19 and Flu, and the Clinical Severity of Such Infections

August 7, 2020

DUBLIN, Ireland and BRIDGEWATER, N.J., Aug. 07, 2020 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN), today announced support for an investigator-initiated trial to study the effects of icosapent ethyl (VASCEPA®) (IPE) on laboratory-confirmed viral upper respiratory infection (URI) rates, clinical impact and outcomes, especially with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection which causes COVID-19, in adults with established atherosclerotic cardiovascular disease (ASCVD) who are at elevated risk of experiencing moderate to severe COVID-19.[1,2]

The trial, dubbed Prag**M**atic random**I**zed **T**rial of **I**cosapent ethyl for hi**G**h-c**A**rdiovascular risk adults in **T**he **E**ra of **CO**rona**VI**rus **D**isease 20**19** (**MITIGATE COVID-19**), is sponsored by Kaiser Permanente Northern California (KPNC), and is being led by Dr. Andrew P. Ambrosy, Associate Program Director for Research (Fellowship), Department of Cardiology, Kaiser Permanente San Francisco Medical Center, and Dr. Alan S. Go, Regional Medical Director, Clinical Trials Program and Associate Director, Cardiovascular and Metabolic Conditions Research, Division of Research, Kaiser Permanente Northern California.

MITIGATE COVID-19 will randomly assign 1500 U.S. patients aged 50 years or older with established ASCVD and no prior history of confirmed COVID-19 to receive 4 grams per day of icosapent ethyl (VASCEPA) and follow these patients for a minimum of 6 months. The co-primary study endpoints are the rate of moderate to severe laboratory-confirmed viral URI, including COVID-19 and influenza, prompting urgent care encounters, emergency department visits, or hospitalization and the worst clinical status due to a laboratory-confirmed viral URI based on an ordinal scale taking hospitalization, death, supplemental oxygen, and other clinical factors into account. A control group will consist of 15,000 adults meeting the same eligibility criteria who will be passively followed through KPNC's comprehensive and state-of-the-art electronic health record system for outcome ascertainment.

Current understanding of the biology of COVID-19 is that patients that have or are at high risk for developing ASCVD are at higher risk of death and severe effects from infection, and that the morbidity and mortality associated with COVID-19 are due both to the direct toxicity of the virus as well as the body's robust inflammatory response leading to 'cytokine storm'. [1,2,3,4] Based on data related to the mechanism of action and effects of VASCEPA, it is hypothesized that VASCEPA may play a potential beneficial role in preventing SARS-CoV-2 infection and to potentially reduce clinical severity in patients infected by the virus.[4,5,6]

The clinical effects of VASCEPA are multi-factorial. Multiple mechanisms of action associated with VASCEPA based on clinical and mechanistic studies support the rationale to test its effects in patients with or at risk for COVID-19 disease. Some of these postulated mechanisms include the following:

- Potential antiviral/antimicrobial effects[7,8]
- Fibrosis and cardiac damage mitigation in animal models[9,10]
- Anti-inflammatory effects (acute) in pulmonary/lung tissue[11,12]

"Most prior clinical trials for COVID-19 have focused on treating patients hospitalized for moderate or severe COVID-19 with experimental agents," according to Dr. Ambrosy. "**MITIGATE COVID-19** is novel in that we will study the effects of pre-treatment with IPE, an FDA-approved therapy for primary and secondary prevention with putative anti-inflammatory as well as antiviral properties, in high-risk outpatients with ASCVD on subsequent risk of viral URI-related morbidity and mortality."

Dr. Go further stated, "In my 20+ years as a health services researcher and clinical trialist, this is the first time that a large-scale study will be undertaken using a completely virtual model including patient recruitment and consent, follow-up visits, and outcome ascertainment within an ethnically-diverse, community-based population. Kaiser Permanente Northern California has been at the forefront of telehealth for delivering high-quality clinical care, especially during the current pandemic, and we are pleased to be able to adapt this innovative approach for safely and efficiently testing a potential intervention."

For more information about Amarin's COVID-19 research, please visit the COVID-19 Related Materials section on Amarin's publications page at https://investor.amarincorp.com/publications.

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. Amarin, 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.[13] In aggregate, this is 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%.[14] 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.[15,16,17]

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.*[18] The primary results of REDUCE-IT were published in *The New England Journal of Medicine* in November 2018.[19] The total events results of REDUCE-IT were published in the *Journal of the American College of Cardiology* in March 2019.[20] 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 for benefit from the study of VASCEPA in the treatment of patients with COVID-19. 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. 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:
Elisabeth Schwartz
Investor Relations
Amarin Corporation plc
In U.S.: +1 (908) 719-1315
IR@amarincorp.com (investor inquiries)

Lee M. Stern
Solebury Trout
In U.S.: +1 (646) 378-2992

lstern@soleburytrout.com

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

References

---

[1] Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020; (published online May 19.) https://doi.org/10.1016/S0140-6736(20)31189-2

[2] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054-1062.

[3] Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-1034.

[4] Panigrahy D, Gilligan MM, Huang S, et al. Inflammation resolution: a dual-pronged approach to averting cytokine storms in COVID-19? *Cancer Metastasis Rev*. 2020;1-4. doi:10.1007/s10555-020-09889-4.

[5] Morita M, Kuba K, Ichikawa A, et al. The lipid mediator protectin D1 inhibits influenza virus replication and improves severe influenza. Cell. 2013;153:112-25.

[6] Das UN. Can Bioactive Lipids Inactivate Coronavirus (COVID-19)? *Arch Med Res*. 2020;51(3):282-286.

[7] Morita M, Kuba K, Ichikawa A, et al. The lipid mediator protectin D1 inhibits influenza virus replication and improves severe influenza. *Cell.* 2013;153:112-25.

[8] Desbois, A.P. (2013). Antimicrobial Properties of Eicosapentaenoic Acid (C20:5n −3). In Marine Microbiology, S.-K. Kim (Ed.). doi:10.1002/9783527665259.ch20.

[9] Eclov JA, Qian Q, Redetzke R, et al. EPA, not DHA, prevents fibrosis in pressure overload-induced heart failure: potential role of free fatty acid receptor 4. *J Lipid Res*. 2015;56(12):2297-2308.

[10] Ito S, Sano Y, Nagasawa K, et al. Highly purified eicosapentaenoic acid ameliorates cardiac injury and adipose tissue inflammation in a rat model of metabolic syndrome. *Obes Sci Pract*. 2016;2(3):318-329.

[11] Mickleborough TD, Tecklenburg SL, Montgomery GS, Lindley MR. Eicosapentaenoic acid is more effective than docosahexaenoic acid in inhibiting proinflammatory mediator production and transcription from LPS-induced human asthmatic alveolar macrophage cells. Clin Nutrition. 2009;28:71-77.

[12] El Kebir D, Gjorstrup P, Filep JG. Resolvin E1 promotes phagocytosis-induced neutrophil apoptosis and accelerates resolution of pulmonary inflammation. Proc Natl Acad Sci U S A. 2012;109(37):14983-14988.

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

[14] 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.

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

[16] 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.

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

[18] 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.

[19] 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.

[20] 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.