

Amarin Corporation

U.S. Veterans with Decreased Renal Function Shown to Be at Higher Risk for Adverse Cardiovascular Events if They Have Moderately Elevated Triglyceride (TG) Levels Despite Well-Controlled Low-Density Lipoprotein (LDL)-Cholesterol

October 23, 2020

New analysis of contemporary real-world data presented at American Society of Nephrology (ASN) Kidney Week 2020

DUBLIN, Ireland and BRIDGEWATER, N.J., Oct. 23, 2020 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN) today announced the presentation of real-world evidence data at American Society of Nephrology (ASN) Kidney Week 2020, held virtually from October 22 – October 25, 2020, adding to the growing body of knowledge on the association of elevated triglyceride (TG) levels with increased cardiovascular (CV) risk independent of cholesterol management. These new analyses, conducted by the U.S. Department of Veterans Affairs and supported by Amarin, were presented in a poster presentation by Sarah Leatherman, Ph.D., U.S. Department of Veterans Affairs.

This retrospective analysis used real-world data from the U.S. Veterans Affairs Corporate Data Warehouse between 2010 and 2015. The analysis consisted of patients (N=152,266 veterans) not treated for triglyceride management who had baseline statin-controlled low-density lipoprotein (LDL)-cholesterol levels (40-100 mg/dL) and decreased renal function (eGFR <60 ml/min). Of these patients, 43,670 (29%) had elevated TG levels (150 to 499 mg/dL). This cohort of patients was compared to patients with similarly statin-controlled LDL-cholesterol and decreased renal function but with normal baseline TG levels (<150 mg/dL). Veterans within the cohort with elevated TG levels experienced higher rates of both composite and individual major adverse events cardiovascular events (non-fatal myocardial infarctions, stroke, unstable angina and coronary revascularization) than the control cohort. The overall crude and adjusted cardiovascular event rate ratios were 1.28 (95% CI 1.23,1.33) and 1.12 (95% CI 1.07,1.16), respectively. While the analysis supports the hypothesis that elevated TG levels are an independent identifier of cardiovascular risk, the analysis did not assess the extent to which lowering TG levels results in lower CV risk.

"The U.S. Department of Veterans Affairs analysis presented at ASN Kidney Week 2020 shows that veterans with decreased renal function and elevated triglycerides are at an increased risk of having a major adverse cardiovascular event, supporting the need to look at elevated triglycerides as an independent marker of cardiovascular risk, even more so in already high-risk patients like those analyzed in the study," said Craig Granowitz, M.D., Ph.D., Amarin's senior vice president and chief medical officer.

These results add further support to recent epidemiological and genetic linkage studies which have shown that elevated baseline TG levels could potentially be a factor in an increased incidence of cardiovascular events.^{1,2,3}

Notable presentations at ASN Kidney Week 2020

["Increased Residual Cardiovascular Risk in US Veterans with Moderately Elevated Baseline Triglycerides, Well-Controlled LDL Cholesterol Levels on Statins, and Decreased Renal Function"](#) – presented on behalf of all authors by Sarah Leatherman, Ph.D. – available from October 22

["Benefits of Icosapent Ethyl Across a Range of Baseline Renal Function in Patients with Established Cardiovascular Disease or Diabetes: Results of REDUCE-IT RENAL"](#) – to be presented on behalf of all authors by Arjun Majithia, M.D. – October 23, 5:00 – 7:00 pm EDT

Additional information on ASN Kidney Week 2020 can be found [here](#).

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.⁴ 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%.⁵ 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.^{6,7,8}

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*.⁹ The primary results of REDUCE-IT were published in *The New England Journal of Medicine* in November 2018.¹⁰ The total events results of REDUCE-IT were published in the *Journal of the American College of Cardiology* in March 2019.¹¹ 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 $\geq 3\%$ and $\geq 1\%$ 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 $\geq 1\%$ 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](http://www.vascepa.com) CAN BE FOUND AT [WWW.VASCEPA.COM](http://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:

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)

¹ Budoff M. Triglycerides and triglyceride-rich lipoproteins in the causal pathway of cardiovascular disease. *Am J Cardiol*. 2016;118:138-145.

² 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.

³ Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease - New insights from epidemiology, genetics, and biology. *Circ Res*. 2016;118:547-563.

⁴ American Heart Association. Heart Disease and Stroke Statistics—2020 Update: A Report From the American Heart Association. *Circulation*. 2020;141:e139–e596.

⁵ Ganda OP, Bhatt DL, Mason RP, et al. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol*.

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⁶ Budoff M. Triglycerides and triglyceride-rich lipoproteins in the causal pathway of cardiovascular disease. *Am J Cardiol.* 2016;118:138-145.

⁷ 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.

⁸ Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease - New insights from epidemiology, genetics, and biology. *Circ Res.* 2016;118:547-563.

⁹ 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.

¹⁰ 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.

¹¹ 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.