

# Amarin Corporation

## VASCEPA® (Icosapent Ethyl) Reported to Impact Vulnerable Coronary Plaque Features in New Analyses of EVAPORATE Study Presented as Late-Breaking Science at ESC Preventive Cardiology 2021

April 17, 2021

*Study quantified coronary plaque changes in patients administered 4 g/day of VASCEPA® (icosapent ethyl) on top of statin therapy*

*Effect on coronary plaque stabilization reported to be significant at 9 months and sustained at 18 months*

DUBLIN, Ireland and BRIDGEWATER, N.J., April 17, 2021 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN) today announced that further analyses from the *Effect of Icosapent Ethyl on Progression of Coronary Atherosclerosis in Patients with Elevated Triglycerides on Statin Therapy: EVAPORATE Trial* were presented as Late-Breaking Science at European Society of Cardiology (ESC) Preventive Cardiology 2021, the Annual Congress of the European Association of Preventive Cardiology, on April 17, 2021, 3:50 PM CEST (Central European Summer Time) by Andrew Buckler, Founder and CTO of Elucid. As previously reported and published in the [European Heart Journal](#), VASCEPA® (icosapent ethyl) demonstrated significant, 17% regression of low attenuation plaque (LAP) volume on multidetector computed tomography (MDCT) compared with placebo over 18 months. The *Effect of Icosapent Ethyl on Changes in Coronary Plaque Morphology: EVAPORATE* analyses presented at ESC Preventive Cardiology 2021 demonstrated that with administration of 4 g/day of VASCEPA on top of statin therapy, there was an observed change in plaque stability occurring at 9 months and sustained through 18 months.

"The EVAPORATE plaque morphology study provides valuable insight into how we can utilize scientific imaging to examine the mechanisms at work that may contribute to observed clinical trial results," commented Matthew Budoff, M.D., Director of Cardiovascular CT at The Lundquist Institute and Professor of Medicine at the David Geffen School of Medicine at UCLA, the study sponsor. "The results suggest consistent benefits of icosapent ethyl on clinical cardiovascular outcomes as observed in the REDUCE-IT® cardiovascular outcomes study, and on plaque progression and plaque vulnerability as observed in EVAPORATE."

Of the 80 patients that were enrolled in the randomized, double-blind, placebo-controlled EVAPORATE trial, 55 patients had images that were able to be utilized for the histology-validated software. The EVAPORATE plaque morphology study used ElucidVivo (Elucid, Boston, MA), the first FDA-cleared analysis for specific tissue characterization using histopathologic correlates to assess plaque morphology characteristics, including Lipid Rich Necrotic Core (LRNC), fibrous cap thickness, and intraplaque hemorrhage (IPH). Whereas with placebo LRNC increased and cap thickness decreased, both indicative of moving to a less stable phenotype, with icosapent ethyl there was a measured LRNC decrease and cap thickness increase, indicative of moving to a more stable phenotype.

"Coronary plaque stabilization is an important finding with VASCEPA and may explain, in part, the substantial cardiovascular benefit seen in REDUCE-IT," said Craig Granowitz, M.D., Ph.D., Amarin's senior vice president and chief medical officer. "The EVAPORATE plaque morphology study results provide additional insight into one of the likely multifactorial effects of VASCEPA, which effects collectively have been shown or observed to lower residual cardiovascular risk."

The primary limitation of this single coronary plaque study as identified by its investigators is its small sample size. More study is needed to more fully understand the effects of VASCEPA on coronary plaque to determine the relationship, if any, of such plaque effects on cardiovascular risk reduction.

More information on ESC Preventive Cardiology 2021 can be found [here](#).

### 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.<sup>1</sup> 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%.<sup>2</sup> 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.<sup>3,4,5</sup>

### 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*.<sup>6</sup> The primary results of REDUCE-IT were published in *The New England Journal of Medicine* in November 2018.<sup>7</sup> The total events results of REDUCE-IT were published in the *Journal of the American College of Cardiology* in March 2019.<sup>8</sup> These and other publications can be found in the R&D section on the company's website at [www.amarincorp.com](http://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 ( $\geq 500$  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 VASKEPA.

#### 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 ( $\geq 150$  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 ( $\geq 500$  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)
<b>Primary composite endpoint</b>					
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)
<b>Key secondary composite endpoint</b>					
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](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 Annual Report on Form 10-K. 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](http://www.amarincorp.com)), the investor relations website ([investor.amarincorp.com](http://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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AMARIN, VASCEPA, VAZKEPA and REDUCE-IT are trademarks of Amarin Pharmaceuticals Ireland Limited. VAZKEPA is a registered trademark in Europe and other countries and regions and is pending registration in the United States.

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

<sup>2</sup> 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.

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

<sup>4</sup> 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.

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

<sup>6</sup> 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.

<sup>7</sup> Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22.

<sup>8</sup> 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.