

Amarin Corporation

Vascepa® (icosapent ethyl) 26% Reduction in Key Secondary Composite Endpoint of Cardiovascular Death, Heart Attacks and Stroke Demonstrated in REDUCE-IT™ Supports 25% Overall Reduction in Five-Point Major Adverse Cardiovascular Event Primary Composite E

November 10, 2018

Landmark Cardiovascular Risk Reduction Benefits Demonstrated in REDUCE-IT Are Largest of Any Major Cardiovascular Outcomes Study of a Drug Intended to Address Residual Cardiovascular Risk Remaining After Cholesterol Management

Cardiovascular Death Reduced by 20%
Fatal or Nonfatal Heart Attacks Reduced by 31%
Fatal or Nonfatal Stroke Reduced by 28%
Urgent or Emergent Coronary Revascularization Reduced by 35%
Hospitalization for Unstable Angina Reduced by 32%

Number Needed to Treat for Primary Composite Endpoint: 21

Patient Years of Study Support Favorable Benefit/Risk Profile in REDUCE-IT

Affordably Priced Vascepa Positions Amarin with Potential to Help Millions of Patients

Conference Call Scheduled for Today, Saturday, November 10, 2018 at 7:15 pm CT/8:15 pm ET

CHICAGO, Nov. 10, 2018 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN) announced today the primary results from the Vascepa® (icosapent ethyl) cardiovascular (CV) outcomes trial, REDUCE-IT™, following presentation of the late-breaking clinical trial results at the 2018 Scientific Sessions of the American Heart Association (AHA) in Chicago, Illinois. REDUCE-IT primary results confirmed 25% relative risk reduction (RRR) for the topline primary endpoint result with multiple robust demonstrations of efficacy, including 20% reduction in cardiovascular death.

Cardiovascular benefits appeared not to be influenced significantly by triglyceride (TG) levels at baseline (135 mg/dL to 499 mg/dL baseline range) or as achieved at one year, suggesting mechanisms at work with use of Vascepa that are independent of triglyceride reduction. Results were robust across multiple subgroups, including in patients with and without diabetes at baseline. REDUCE-IT study results were simultaneously published in *The New England Journal of Medicine* and are available at nejm.org/doi/full/10.1056/NEJMoa1812792.

REDUCE-IT was a global study of 8,179 statin-treated adults with elevated CV risk. Many patients with well-managed LDL-C remain at high risk for cardiovascular events. No therapy is currently approved to treat the residual risk in REDUCE-IT patients and no other therapy has demonstrated a 25% risk reduction on top of statin therapy in a major cardiovascular outcomes trial. REDUCE-IT studied Vascepa 4 grams/day as compared to placebo over a median follow-up time of 4.9 years.

Efficacy results for Vascepa as presented today from REDUCE-IT are as follows:

Primary endpoint achieved: **25%** relative risk reduction (RRR) (hazard ratio (HR), 0.75; 95% confidence interval CI, 0.68-0.83; $p < 0.001$) in first occurrence of major adverse CV events (MACE) in the intent-to-treat population consisting of a composite of cardiovascular death, nonfatal myocardial infarction (MI or heart attack), nonfatal stroke, coronary revascularization (procedures such as stents and by-pass) and unstable angina requiring hospitalization.

- Number needed to treat (NNT) was **21** for the first occurrence of MACE in the 5-point primary composite endpoint.
 - For perspective, NNTs for cholesterol-managing drugs atorvastatin (Lipitor®)¹ and evolocumab (Repatha®)² were reported to be 45 and 67, respectively. These drugs are not competitors with Vascepa as Vascepa is not a therapy for cholesterol (LDL-C) management nor has Vascepa been evaluated in a head-to-head study with these drugs.

Key secondary endpoint achieved: **26%** RRR (HR, 0.74; 95% CI, 0.65-0.83; $p < 0.001$) in 3-point MACE in the intent-to-treat population consisting of a composite of cardiovascular death, nonfatal heart attack and nonfatal stroke.

Additional secondary endpoints achieved: Seven secondary endpoints were achieved below the key secondary endpoint, as follows (in order of sequential statistical testing within the prespecified hierarchy):

- Cardiovascular death or nonfatal heart attack: **25%** RRR (HR, 0.75; 95% CI, 0.66-0.86; $p < 0.001$)
- Fatal or nonfatal heart attack: **31%** RRR (HR, 0.69; 95% CI, 0.58-0.81; $p < 0.001$)
- Urgent or emergent revascularization: **35%** RRR (HR, 0.65; 95% CI, 0.55-0.78; $p < 0.001$)
- Cardiovascular death: **20%** RRR (HR, 0.80; 95% CI, 0.66-0.98; $p = 0.03$)
- Hospitalization for unstable angina: **32%** RRR (HR, 0.68; 95% CI, 0.53-0.87; $p = 0.002$)
- Fatal or nonfatal stroke: **28%** RRR (HR, 0.72; 95% CI, 0.55-0.93; $p = 0.01$)
- Total mortality, nonfatal heart attack or nonfatal stroke: **23%** RRR (HR, 0.77; 95% CI, 0.69-0.86; $p < 0.001$)

The next prespecified secondary endpoint in the hierarchy, and the only such endpoint that did not achieve statistical significance, is as follows:

- Total mortality, which includes mortality from non-cardiovascular and cardiovascular events: 13% RRR (HR, 0.87; 95% CI, 0.74-1.02; p=0.09)

Baseline demographics: Patients qualified to enroll in REDUCE-IT had LDL-C between 41-100 mg/dL (median baseline LDL-C 75 mg/dL) controlled by statin therapy and various cardiovascular risk factors including persistent elevated triglycerides (TGs) between 135-499 mg/dL (median baseline 216 mg/dL) and either established cardiovascular disease (secondary prevention cohort) or age 50 or more with diabetes mellitus and at least one other CV risk factor (primary prevention cohort). Approximately 59% of the patients had diabetes at baseline and approximately 71% of the patients had established cardiovascular disease at time of enrollment.

Safety: Excluding the major adverse CV events (MACE) results described above, overall adverse event rates in REDUCE-IT were similar across the statin plus Vascepa and the statin plus placebo treatment groups. There were no significant differences between treatments in the overall rate of treatment emergent adverse events or serious adverse events leading to withdrawal of study drug. The one serious adverse event occurring at a frequency of >2% was pneumonia which occurred at a numerically higher rate in the statin plus placebo treatment group (2.9%) than in the statin plus Vascepa treatment group (2.6%). Adverse events occurring in 5% or greater of patients and more frequently with Vascepa than placebo were peripheral edema (6.5% Vascepa patients versus 5.0% placebo patients), constipation (5.4% Vascepa patients versus 3.6% placebo patients), and atrial fibrillation (5.3% Vascepa patients versus 3.9% placebo patients). There were numerically more serious adverse events related to bleeding in the statin plus Vascepa treatment group although overall rates were low with no fatal bleeding observed in either group and no significant difference in adjudicated hemorrhagic stroke or serious central nervous system or gastrointestinal bleeding events between treatments. In summary, Vascepa was well tolerated with a safety profile generally consistent with clinical experience associated with omega-3 fatty acids and current FDA-approved labeling of such products.

Subgroups and other REDUCE-IT information: Positive REDUCE-IT results were consistent across various patient subgroups, including female/male, diabetic/non-diabetic and secondary/primary prevention. At baseline, approximately 59% and 71% of the patients had diabetes and established cardiovascular disease, respectively. Approximately 71% of the patients studied were classified as Westernized with the largest cohort from the United States. Vital status was obtained for 99.8% of the patients randomized supporting robust trial results.

Differentiated result and mechanism of action: The success of REDUCE-IT is distinct from past failures to show significant benefit of other agents that lower triglyceride levels when studied on top of statin therapy, including mixtures of omega-3 fatty acids, fenofibrates, niacin and CETP inhibitors. In REDUCE-IT, the median change in triglyceride levels from baseline to year one was -18.3% (-39 mg/dL) for Vascepa and +2.2% (4.5 mg/dL) for placebo; placebo-corrected median change from baseline of -19.7% (-44.5 mg/dL; p<0.001). As expressed in *The New England Journal of Medicine* publication, at least some of the reduction in MACE demonstrated by Vascepa in REDUCE-IT is likely explained by metabolic effects other than triglyceride lowering.³

The active pharmaceutical ingredient in Vascepa has a unique molecular structure. Vascepa has demonstrated clinical effects that have not been shown for any other product. The clinical effects of Vascepa demonstrated in REDUCE-IT cannot be generalized to any other product.

Mechanisms responsible for Vascepa's effects in the REDUCE-IT study were not directly evaluated in the outcomes study. Independent of REDUCE-IT, Amarin has worked to further support the REDUCE-IT hypothesis with published scientific findings based on various degrees of evidence that show that icosapent ethyl may interrupt the atherosclerotic process (e.g., plaque formation and instability) by beneficially affecting cellular functions thought to contribute to atherosclerosis and cardiovascular events and by beneficially affecting lipid, lipoprotein and inflammation biomarkers.^{4, 5, 6, 7, 8}

Scientific presentation: Presentation of the REDUCE-IT results at AHA were made by the Global Principal Investigator and Steering Committee Chair for the study, Deepak L. Bhatt, MD, MPH, Professor of Medicine at Harvard Medical School, Executive Director of Interventional Cardiovascular Programs at Brigham and Women's Hospital Heart and Vascular Center.

Dr. Bhatt stated, "REDUCE-IT establishes a new paradigm for the prevention of important cardiovascular events in statin-treated patients at elevated risk with increased triglycerides. I believe that the results of this study may represent the most significant breakthrough in preventative cardiovascular care since the introduction of statin therapy decades ago."

Amarin perspective: Commenting on these results from Amarin:

"The robustness and consistency of these clinical results are exciting. Extensive scientific evaluation led to the design and conduct of this study; but the degree of benefit shown with Vascepa nevertheless exceeded our expectation," stated Steven Ketchum, president of research and development and chief scientific officer of Amarin. "We believe that these positive results identify an important new treatment option to help lower cardiovascular risk in appropriate patients. Cholesterol management lowers cardiovascular risk by 25-35%. REDUCE-IT suggests that the residual 65-75% cardiovascular risk beyond cholesterol management can be significantly lowered with Vascepa in studied patients. We again thank all of the patients, investigators and others involved in this landmark study."

"Amarin has spent over \$500 million developing Vascepa. We are intently focused on improving patient care. Our priorities are now shifting to educate the world regarding these results so that the pain, loss of productivity and high costs of cardiovascular events can be reduced," stated John F. Thero, president and CEO of Amarin.

Regulatory Pathway

The REDUCE-IT study was designed under a special protocol assessment agreement with the U.S. Food and Drug Administration (FDA). Amarin intends to submit an sNDA to the FDA in early 2019 seeking approval to expand the label for Vascepa based on the cardioprotective effect of Vascepa demonstrated in the REDUCE-IT study. FDA's determination of standard or priority review will be made when the sNDA is submitted. At this time, Amarin is planning for a standard review with potential approval anticipated in late 2019.

Vascepa is Affordably Priced

Vascepa is a low-cost drug. The majority of patients covered by insurance who obtain prescriptions for Vascepa pay a monthly co-pay charge of \$9.99 or less. A patient with commercial insurance can pay as little as \$9.00 for a 90-day supply prescription of Vascepa.

Commercial Expansion and Next Steps

As previously described, Amarin is in the process of increasing the number of company sales representatives promoting Vascepa to over 400 people in the United States. Amarin's plans provide for greater concentration of coverage in current sales territories and new coverage where Amarin currently does not have sales representatives. With numerous experienced applicants for these new positions, the company is well on its way towards having these new sales representatives hired and trained heading into 2019. The company is also planning to support various medical education forums covering preventative solutions in cardiovascular care. Amarin anticipates making the published results of REDUCE-IT available to healthcare professionals. Following potential label expansion, Amarin will consider other initiatives to expand Vascepa promotion including more extensive consumer promotion focused on cardiovascular risk reduction.

Financial Disclosure

Funding from Amarin was provided to Brigham and Women's Hospital for Dr. Deepak L. Bhatt's work as the REDUCE-IT study chair and global principal investigator.

Conference Call and Webcast Information

Amarin will host a conference call at 7:15 p.m. CT/ 8:15 p.m. ET, November 10, 2018 to discuss this information. The call will be accessible through the investor relations section of the company's website at www.amarincorp.com. The call can also be heard via telephone by dialing 877-407-8033. A replay of the call will be made available for a period of two weeks following the conference call. To hear a replay of the call, dial 877-481-4010 (inside the United States) or 919-882-2331 (outside the United States). A replay of the call will also be available through the company's website shortly after the call. For both dial-in numbers please use conference ID 39894.

About Amarin

Amarin Corporation plc. is a rapidly growing, innovative pharmaceutical company focused on developing therapeutics to improve cardiovascular health. Amarin's product development program leverages its extensive experience in lipid science and the potential therapeutic benefits of polyunsaturated fatty acids. Vascepa (icosapent ethyl) is Amarin's first FDA-approved drug and is available by prescription in the United States, Lebanon and the United Arab Emirates. Amarin's commercial partners are pursuing additional regulatory approvals for Vascepa in Canada, China and the Middle East. For more information about Amarin, visit www.amarincorp.com.

About Cardiovascular Disease

Worldwide, cardiovascular disease (CVD) remains the #1 killer of men and women. In the United States CVD leads to one in every three deaths – one death approximately every 38 seconds – with annual treatment cost in excess of \$500 billion.^{9, 10}

Multiple [primary and secondary prevention](#) trials have shown a significant reduction of 25% to 35% in the risk of [cardiovascular events](#) with [statin](#) therapy, leaving significant persistent residual risk despite the achievement of target LDL-C levels.⁴

Beyond the cardiovascular risk associated with LDL-C, genetic, epidemiologic, clinical and real-world data suggest that patients with elevated triglycerides (TG) (fats in the blood), and TG-rich lipoproteins, are at increased risk for cardiovascular disease.^{11, 12, 13, 14}

About VASCEPA® (icosapent ethyl) Capsules

Vascepa® (icosapent ethyl) capsules are a single-molecule prescription product consisting of the omega-3 acid commonly known as EPA in ethyl-ester form. Vascepa is not fish oil, but is derived from fish through a stringent and complex FDA-regulated manufacturing process designed to effectively eliminate impurities and isolate and protect the single molecule active ingredient from degradation. Vascepa, known in scientific literature as AMR101, has been designated a new chemical entity by the FDA. Amarin has been issued multiple patents internationally based on the unique clinical profile of Vascepa, including the drug's ability to lower triglyceride levels in relevant patient populations without raising LDL-cholesterol levels.

Indication and Usage Based on Current FDA-Approved Label (not including REDUCE-IT results)

- Vascepa (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.
- The effect of Vascepa on the risk for pancreatitis and cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

Important Safety Information for Vascepa Based on Current FDA-Approved Label (not including REDUCE-IT results) (Includes Data from Two 12-Week Studies (n=622) (MARINE and ANCHOR) of Patients with Triglycerides Values of 200 to 2000 mg/dL)

- Vascepa is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to Vascepa or any of its components.
- In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy.
- Use with caution in patients with known hypersensitivity to fish and/or shellfish.
- The most common reported adverse reaction (incidence $>2\%$ and greater than placebo) was arthralgia (2.3% for Vascepa, 1.0% for placebo). There was no reported adverse reaction $>3\%$ and greater than placebo.
- Adverse events and product complaints may be reported by calling 1-855-VASCEPA or the FDA at 1-800-FDA-1088.
- Patients receiving treatment with Vascepa and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.
- Patients should be advised to swallow Vascepa capsules whole; not to break open, crush, dissolve, or chew Vascepa.

FULL VASCEPA PRESCRIBING INFORMATION CAN BE FOUND AT WWW.VASCEPA.COM.

Vascepa has been approved for use by the United States Food and Drug Administration (FDA) as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. Nothing in this press release should be construed as promoting the use of Vascepa in any indication that has not been approved by the FDA.

Important Cautionary Information About REDUCE-IT Primary Results

Further REDUCE-IT data assessment and data release could yield additional useful information to inform greater understanding of the trial outcome. Further detailed data assessment by Amarin and regulatory authorities will continue and take several months to complete and record. The final evaluation of the totality of the efficacy and safety data from REDUCE-IT may include some or all of the following, as well as other considerations: new information affecting the degree of treatment benefit on studied endpoints; study conduct and data robustness, quality, integrity and consistency; additional safety data considerations and risk/benefit considerations; consideration of REDUCE-IT results in the context of other clinical studies.

Forward-Looking Statements

This press release contains forward-looking statements, including expectations regarding planned regulatory filings and the nature of FDA's review and related timing thereof; expectations that REDUCE-IT results could lead to a new treatment paradigm in the patient population studied; and plans for sales force, international and insurance coverage expansion. These forward-looking statements are not promises or guarantees and involve substantial risks and uncertainties. In addition, Amarin's ability to effectively commercialize Vascepa will depend in part on its ability to continue to effectively finance its business, efforts of third parties, its ability to create market demand for Vascepa through education, marketing and sales activities, to achieve market acceptance of Vascepa, to receive adequate levels of reimbursement from third-party payers, to develop and maintain a consistent source of commercial supply at a competitive price, to comply with legal and regulatory requirements in connection with the sale and promotion of Vascepa and to maintain patent protection for Vascepa. 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, clinical trials and related regulatory approvals; the risk that sales may not meet expectations and related cost may increase beyond expectations; the risk that patents may not be upheld in patent litigation and applications may not result in issued patents sufficient to protect the Vascepa franchise. 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.

Availability of Other Information About Amarin

Investors and others should note that Amarin communicates with its investors and the public using the company website (<http://www.amarincorp.com/>), the investor relations website (<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.

References

- ¹ LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; 352: 1425–35.
- ² Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713.
- ³ Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. DOI: 10.1056/NEJMoa1812792.
- ⁴ 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.
- ⁵ Borow KM, Nelson JR, Mason RP. Biologic plausibility, cellular effects, and molecular mechanisms of eicosapentaenoic acid (EPA) in atherosclerosis. *Atherosclerosis*. 2015;242(1):357-366.
- ⁶ Nelson JR, Wani O, May HT, et al. Potential benefits of eicosapentaenoic acid on atherosclerotic plaques. *Vascul Pharmacol*. 2017;91:1–9.
- ⁷ Mason RP, Dawoud H, Jacob RF, et al. Eicosapentaenoic acid improves endothelial function and nitric oxide bioavailability in a manner that is enhanced in combination with a statin. *Biomed Pharmacother*. 2018;103:1231-1237.
- ⁸ Takamura M, Kurokawa K, Ootsuji H, et al. Long-term administration of eicosapentaenoic acid improves post-myocardial infarction cardiac remodeling in mice by regulating macrophage polarization. *J Am Heart Assoc*. 2017;6(2). pii: e004560.
- ⁹ American Heart Association. 2018. Disease and Stroke Statistics-2018 Update.
- ¹⁰ American Heart Association. 2017. Cardiovascular disease: A costly burden for America projections through 2035.
- ¹¹ Budoff M. Triglycerides and triglyceride-rich lipoproteins in the causal pathway of cardiovascular disease. *Am J Cardiol*. 2016;118:138-145.
- ¹² 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.
- ¹³ Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease - New insights from epidemiology, genetics, and biology.

Circ Res. 2016;118:547-563.

¹⁴ Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet.* 2014;384:626–635.

Amarin Contact Information

Investor Relations:

Elisabeth Schwartz

Investor Relations and Corporate Communications

Amarin Corporation plc

In U.S.: +1 (908) 719-1315

investor.relations@amarincorp.com

Lee M. Stern

Trout Group

In U.S.: +1 (646) 378-2992

lstern@troutgroup.com

Media Inquiries:

Christy Maginn

Burson-Marsteller

In U.S.: +1 (646) 280-5210

Christy.Maginn@bm.com



Source: Amarin Corporation plc