

Amarin Corporation

Additional Real-World Data Show a Significant Risk Increase in Cardiovascular Events in People with Elevated Triglyceride Levels

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BEDMINSTER, N.J. and DUBLIN, Ireland, March 18, 2019 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN), a pharmaceutical company focused on improving cardiovascular health, announced today that real-world data reported by the U.S. Veteran's Administration supports that patients with elevated triglyceride (TG) levels, despite statin therapy, had a significant 19% relative risk increase in a composite of cardiovascular events during a follow-up period of up to five years. These findings are consistent with previous observational, real-world, epidemiological, and genetic data that have consistently found an association between elevated TG levels and major adverse cardiovascular events.

These findings, in a poster titled, "*Increased Residual Cardiovascular Risk in US Veterans with Moderately-Elevated Baseline Triglycerides and Well-Controlled LDL-C Levels on Statins*," were presented at the American College of Cardiology's (ACC) 68th Annual Scientific Session today, March 18, 2019 in New Orleans, LA.

This research examined over 400,000 veterans, 30% of whom had elevated triglyceride levels. The data reported that those with elevated TG levels (150-500 mg/dL) showed a statistically significant 19% relative increase in cardiovascular (CV) events comprised of nonfatal heart attack, nonfatal stroke, unstable angina, and coronary revascularization despite well-controlled LDL-C on statin therapy with adjustment for other CV risk factors when compared with veterans whose baseline TG was <150 mg/dL. Cardiovascular death was not included as an endpoint for this analysis as the data was not readily available in this database.

This poster was authored by Sarah Leatherman, Ryan E. Ferguson, Isabelle R. Weir, Cynthia Hau, Craig B. Granowitz, Kelly Harrington, Sephy Philip, Peter P. Toth, Deepak L. Bhatt, and William E. Boden.

"These data highlight the high rate of cardiovascular events in people with elevated triglyceride levels," said Craig B. Granowitz, M.D., Ph.D., senior vice president and chief medical officer of Amarin. "Real-world data continues to support that elevated triglycerides are a marker of cardiovascular risk, separate from management of LDL-C and other risk factors."

In a separate presentation today at the ACC 68th Annual Scientific Session, additional data was reported from the Amarin cardiovascular outcomes study of Vascepa, the REDUCE-IT study, which demonstrated that Vascepa lowers both primary major adverse cardiovascular events (MACE) and recurrent MACE in patients with elevated TG levels (≥ 135 mg/dL) and other cardiovascular risk factors¹. While lowering TG levels alone have not been demonstrated to lower cardiovascular risk, the REDUCE-IT study demonstrated that in patients with high levels of cardiovascular risk despite statin therapy, as identified by having elevated triglyceride levels and other risk factors, Vascepa significantly lowered the first occurrence of primary MACE by 25% and primary plus recurrent MACE by 30%, each compared to placebo. This benefit appears to derive from the multifactorial effects of Vascepa, a portion of which appear to be related to lowering TG levels with the balance of the effects likely explained by other effects of Vascepa as separately evaluated. As summarized below, in REDUCE-IT, 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.

Amarin Investor/Analyst Conference Call

Amarin plans to webcast live a physician panel discussion for investors and analysts today at 4:00 p.m. CT / 5:00 p.m. ET. During the panel discussion leading physicians are anticipated to review data pertaining to Vascepa presented at ACC's 68th Annual Scientific Session, including the presentation today in the late-breaker session regarding additional data from the REDUCE-IT cardiovascular outcomes study. The panel discussion may also cover data from the above described poster and from other posters presented at ACC.

This physician panel discussion will commence at the time shown above and will be accessible via webcast through the investor relations section of the company's website at www.amarincorp.com. The panel discussion can also be heard via telephone by dialing 877-407-8033. A replay of the panel discussion will be made available for a period of two weeks following the webcast. 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 panel discussion will also be available through the company's website shortly after the webcast. For both dial-in numbers please use conference ID 44518.

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 polyunsaturated fatty acids and lipid science. 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 REDUCE-IT

REDUCE-IT², an 8,179-patient cardiovascular outcomes study, was completed in 2018. REDUCE-IT was a multinational cardiovascular outcomes study that evaluated the effect of prescription pure EPA therapy as an add-on to statins in patients with high cardiovascular risk who, despite stable statin therapy, had elevated triglyceride levels (at least 135 mg/dL). A large portion of the male and female patients enrolled in this outcomes study were diagnosed with type 2 diabetes.

More information on the REDUCE-IT study results can be found at 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.^{3, 4}

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.⁵

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.^{6, 7, 8, 9}

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.

Important Safety Information for Vascepa based on REDUCE-IT, as previously reported in *The New England Journal of Medicine*¹ publication of the primary results of the REDUCE-IT study:

- Excluding the major adverse cardiovascular 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.
- There was no serious adverse event (SAE) occurring at a frequency of $>2\%$ which occurred at a numerically higher rate in the statin plus Vascepa treatment group than in the statin plus placebo treatment group.
- Adverse events (AEs) 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), although there was no increase in the rate of heart failure in Vascepa patients
 - constipation (5.4% Vascepa patients versus 3.6% placebo patients), although mineral oil, as used as placebo, is known to lower constipation, and
 - atrial fibrillation (5.3% Vascepa patients versus 3.9% placebo patients), although there were reductions in rates of cardiac arrest, sudden death and myocardial infarctions observed in Vascepa patients
- There were numerically more SAEs 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.

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. FDA has not reviewed and opined on a supplemental new drug application related to REDUCE-IT. FDA has not reviewed the information herein or determined whether to approve Vascepa for use to reduce the risk of MACE. 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 These Data

Recurrent event analyses for the total primary endpoint events and for the total key secondary endpoint in REDUCE-IT as published in the *Journal of the American College of Cardiology*¹ were conducted using a series of statistical models. These analyses were tertiary or exploratory endpoints; most of the models used were prespecified and one was post hoc. Each recurrent event statistical model has inherent strengths and weaknesses, with no single model considered definitive or outperforming the other models, and this is an evolving field of science. Nonetheless, results from the total primary and total key secondary endpoint events analyses are consistent across the various recurrent event statistical models and are also consistent with the original primary and secondary endpoint results. Together, the REDUCE-IT recurrent event analyses and the original primary and key secondary endpoint analyses support the robustness of the clinical benefit of Vascepa therapy in reducing cardiovascular risk.

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 statements related to cardiovascular risk in patient groups based on data presented. 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 data of this type, research and development, clinical trials and related regulatory approvals. A list and description of uncertainties and 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.

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 Bhatt DL, Steg PG, Miller M, et al. Effects of Icosapent Ethyl on Total Ischemic Events – Further Insights from REDUCE-IT. *J Am Coll Cardiol* 2019. epub ahead of print.

<http://www.onlinejacc.org/content/early/2019/03/01/j.jacc.2019.02.032>

² Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med* 2019;380:11-22.

³ American Heart Association. 2018. Disease and Stroke Statistics-2018 Update.

⁴ American Heart Association. 2017. Cardiovascular disease: A costly burden for America projections through 2035.

⁵ 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.

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

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