Latest analysis shows VASCEPA® (icosapent ethyl) significantly lowered the risk of potentially fatal cardiovascular events in patients with prior percutaneous coronary intervention

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A new post hoc sub-analysis of the landmark REDUCE-IT Study, published in the Journal of the American Heart Association (JAHA), found VASCEPA® significantly reduced the risk of cardiovascular death, strokes, heart attacks, coronary revascularization, and unstable angina by 34% in patients with a history of percutaneous coronary intervention (PCI).[1]

Icosapent ethyl resulted in robust absolute risk reductions of 8.5% and 5.4% and numbers needed to treat (NNT) of 12 and 19, respectively, for the primary and key secondary composite endpoints.[1]

DUBLIN, Ireland and BRIDGEWATER, N.J., March 10, 2022 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN) today announced the publication of new REDUCE-IT data analysis that helps support the clinical benefits of icosapent ethyl (IPE) for patients who have received a percutaneous coronary intervention (PCI) and are at high risk for experiencing a stroke, heart attack, or fatal cardiovascular (CV) event.[1]

Percutaneous coronary interventions (also known as coronary angioplasty, which can include stent insertion) are medical procedures used to open coronary arteries, the main blood vessels supplying the heart, that are narrowed or blocked by a build-up of atherosclerotic plaque.[2] The heart needs a constant supply of oxygenated blood to function effectively; if the coronary arteries become narrowed and restricted, this can lead to serious heart health complications such as angina or a heart attack.[3]

The REDUCE-IT Prior PCI study was a post hoc sub-analysis published in the Journal of the American Heart Association (JAHA). This publication furthers the clinical evidence base for icosapent ethyl treatment in patients with prior PCI at risk of a recurrent CV event.

There were 3,408 patients who had undergone a prior PCI (41.7% of the initial REDUCE-IT study population). The median time after PCI for these patients was 2.9 years. Baseline characteristics were similar among patients randomised to icosapent ethyl versus placebo. Of those patients with prior PCI included in the sub-analysis receiving standard of care treatment only, 37.6% experienced a major CV event (cardiovascular death, myocardial infarction, stroke, coronary revascularization, or unstable angina requiring hospitalization), compared with 25.6% of patients receiving icosapent ethyl.[1]

In patients with a history of PCI, icosapent ethyl treatment versus placebo reduced the first primary composite endpoint of CV death, non-fatal myocardial infarction (MI) (heart attack), non-fatal stroke, coronary revascularization, or unstable angina, by 34% (absolute risk reduction of 8.5%, HR 0.66; 95% CI, 0.58-0.76; p<0.001); number needed to treat (NNT) =12) and the total events (first and subsequent) by 39% (RR 0.61; 95% CI, 0.52-0.72; p<0.001).[1]

Icosapent ethyl also led to a 34% reduction in the key secondary composite endpoint of CV death, non-fatal MI, or non-fatal stroke versus placebo (absolute risk reduction 5.4%, HR 0.66; 95% CI, 0.56-0.79, p<0.001; NNT=19). The sub-analysis also showed that icosapent ethyl treatment led to a 40% risk reduction of repeat coronary revascularization versus placebo (absolute risk reduction 7.7%, HR 0.60; 95% CI, 0.51-0.70; p<0.001) in patients who have previously undergone PCI.[1]

Safety findings in the REDUCE-IT Prior PCI subgroup were consistent with the full study cohort.[1]

The REDUCE-IT study enrolled 8,179 patients for a median of 4.9 years, who were all receiving a stable dose of a statin for at least 4 weeks. All patients had controlled low-density lipoprotein cholesterol (LDL-C), elevated triglyceride levels, and were either 45 years of age or older, with established cardiovascular disease (CVD), or were 50 years of age or older, with diabetes and other cardiovascular risk factors.[4]

It is important to note that the exploratory nature limited this post hoc analysis. Other limitations noted by the authors include that REDUCE-IT was not powered for sub-group analyses and all P values should be considered hypothesis-generating.

Commenting on the paper's findings, Dr Deepak L. Bhatt, M.D., M.P.H., Executive Director of Interventional Cardiovascular Programs at Brigham and Women's Hospital and Professor of Medicine at Harvard Medical School, principal investigator of REDUCE-IT and senior author of the REDUCE-IT Prior PCI analyses, said:

"This analysis from REDUCE-IT highlights the benefits of icosapent ethyl in patients with elevated triglycerides and a history of prior PCI, a commonly performed procedure. The findings of benefit in at-risk patients with prior PCI are consistent with previously published coronary revascularization data demonstrating reductions in first and total coronary revascularization events of 34% and

36%, respectively, in the overall REDUCE-IT population."[5]

Dr. Bhatt continued, "Patients on standard of care treatment who nevertheless have elevated triglycerides are at high-risk for recurrent CV events. Icosapent ethyl has the potential to benefit a large proportion of these patients, including those with a history of prior PCI."[1]

There is evidence suggesting that patients who have a prior PCI are at a heightened risk of subsequent CV events compared with other patients with CV risk factors.[1] In recent years, efforts to improve stent design, LDL-C, inflammation, and platelet activity have reduced repeat events among patients who undergo coronary stenting.[1]

Yet, many patients still experience recurrent events, especially those with diabetes mellitus and elevated triglycerides.[1] This suggests there may be a need for additional treatments and interventions to reduce this remaining risk.

Karim Mikhail, Amarin's president and chief executive officer, commented, "We continue to gain new insights into the important role that IPE can play in helping patients with CVD; especially for those most vulnerable to a serious or fatal event. This latest analysis showed that IPE lowered the risk of heart attack, stroke or cardiovascular death for patients with a prior PCI -- offering additional evidence that our product can be a vital contributor in reducing harm and deaths from cardiovascular disease around the world."

The REDUCE-IT PCI subgroup analysis was funded by Amarin. Dr. Bhatt receives research funding from Amarin that goes to Brigham and Women's Hospital.

Release References

1. Peterson BE, Bhatt DL, Steg PG, et al. Treatment with Icosapent Ethyl to Reduce Ischemic Events in Patients with Prior Percutaneous Coronary Intervention - Insights from REDUCE-IT PCI. Originally published 9 Mar 2022 https://doi.org/10.1161/JAHA.121.022937, J Am Heart Assoc. 2022;0:e022937
2. https://www.nhlbi.nih.gov/health-topics/percutaneous-coronary-intervention
3. NHS UK. Coronary angioplasty and stent insertion https://www.nhs.uk/conditions/coronary-angioplasty/ Accessed March 2022.
4. 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.
5. Peterson BE, Bhatt DL, Steg PG, et al. Reduction in Revascularization With Icosapent Ethyl: Insights From REDUCE-IT Revascularization Analyses. Circulation. 2021;143(1):33-44.

About Amarin

Amarin is an innovative pharmaceutical company leading a new paradigm in cardiovascular disease management. From our foundation in scientific research 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, Zug in Switzerland, and other countries in Europe as well as commercial partners and suppliers around the world. We are committed to increasing the scientific understanding of the cardiovascular risk that persists beyond traditional therapies and advancing the treatment of that risk.

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[i] 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%.[ii] 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.[iii,iv,v]

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.[vi] The primary results of REDUCE-IT were published in *The New England Journal of Medicine* in November 2018.[vii] The total events results of REDUCE-IT were published in the *Journal of the American College of Cardiology* in March 2019.[viii] 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 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 (≥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 VAZKEPA.

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 (≥ 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:

FULL U.S. FDA-APPROVED VASCEPA PRESCRIBING INFORMATION CAN BE FOUND AT WWW.VASCEPA.COM.

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.					

Forward-Looking Statements

This press release contains forward-looking statements which are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, including beliefs about the potential for VASCEPA (marketed as VAZKEPA in Europe); beliefs about icosapent ethyl (IPE)'s role concerning patients suffering from cardiovascular disease (CVD) and impacts on the risk of heart attack, stroke or cardiovascular death for patients with a prior percutaneous coronary intervention (PCI) and general beliefs about the safety and effectiveness of VASCEPA. These forward-looking statements are not promises or guarantees and involve substantial risks and uncertainties. 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 Amarin's annual report on Form 10-K for the full year ended 2021. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date they are made. Amarin undertakes no obligation to update or revise the information contained in its forward-looking statements, 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 communicates with its investors and the public using the company website (www.amarincorp.com) and the investor relations website (investor.amarincorp.com), including but not limited to investor presentations and 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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About Section References

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

[ii] 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.

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

[iv] 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.

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

[vi] 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.

[vii] 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.

[viii] 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.