What is Amarin's perspective on the results of Novartis's CANTOS study on canakinumab?

The CANTOS study results[1] announcement on August 27th 2017 serves as a reminder that, despite currently available standard of care treatments, patients with a prior heart attack and inflammatory atherosclerosis as measured by high-sensitivity C-reactive protein (hsCRP) levels of >=2mg/L, a known marker of inflammation, continue to be at an increased risk for cardiovascular disease and death.

The CANTOS study results appear to have validated the hypothesis that a long-term drug treatment focused on a specific anti-inflammatory mechanism in patients with a prior heart attack and inflammatory atherosclerosis can reduce cardiovascular events.

Amarin has reported that Vascepa® (icosapent ethyl) capsules utilized in REDUCE-IT, on top of statin therapy, was positive. Details can be found at www.amarincorp.com. The degree to which lowering markers of inflammation, as demonstrated by Vascepa, contributed to these successful outcomes study results is unknown. 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 thesis with published scientific findings based on various degrees of evidence that show that icosapent ethyl may interrupt the atherosclerotic processes (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. [1, 2, 3, 4, 5]

Amarin believes that there are other factors beyond a drug's efficacy profile that impact whether a drug becomes broadly accepted by the medical community to combat the drug-appropriate disease states. These factors include a drug's cost-effectiveness, reimbursement availability, method of administration (e.g., injectable vs. oral), and side effect profile. Vascepa has these characteristics as it is affordably priced, has broad managed care access, is dosed in capsule form, is administered orally with a favorable benefit/risk profile.

Vascepa was studied for cardiovascular event reduction in the REDUCE-IT study. The REDUCE-IT study population included both primary and secondary prevention patients. Study inclusion criteria included:

- Men or women ≥45 years of age with established cardiovascular disease or ≥50 years of age with diabetes in combination with one additional risk factor for cardiovascular disease
- Fasting triglyceride levels ≥135 mg/dL and <500 mg/dL
- LDL-cholesterol levels >40 mg/dL and ≤100 mg/dL, stable statin therapy (± ezetimibe) for ≥4 weeks prior to the LDL-cholesterol and triglyceride qualifying measurements

About VASCEPA® (icosapent ethyl) Capsules

Vascepa® (icosapent ethyl) capsules are a single-molecule prescription product in an oral capsule. The active ingredient in Vascepa is icosapent ethyl which has a unique chemical structure and clinical effect and safety profile that has not been shown for any other product. 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.

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

- 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

As with any study result, further REDUCE-IT data assessment and data release by Amarin and FDA could yield additional useful information to inform greater understanding of the trial outcome. Investors should not place undue reliance on primary data. The FDA has not reviewed and opined on a supplemental new drug application related to REDUCE-IT. FDA has thus not determined whether to approve Vascepa for use to reduce the risk of major adverse cardiovascular events in the REDUCE-IT patient population.

Further information regarding the results of the REDUCE-IT trial, including discussion of drug safety in the at-risk population studied, are available in Amarin's press release dated November 10, 2018, which can be reviewed by clicking https://investor.amarincorp.com/news-releases/news-release-details/vascepar-icosapent-ethyl-26-reduction-key-secondary-composite **and via review of published result of the REDUCE-IT study in The New England Journal of Medicine https://www.nejm.org/doi/full/10.1056/NEJMoa1812792.**

[1] 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.
[2] 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.
[3] Nelson JR, Wani O, May HT, et al. Potential benefits of eicosapentaenoic acid on atherosclerotic plaques. *Vascul Pharmacol*. 2017;91:1–9.
[4] 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.
[5] 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.

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