What is Amarin's opinion on the ASCEND clinical trial?

Amarin applauds all serious efforts to better understand the potential benefits and the related science of Omega-3's, including the ASCEND trial. Amarin is not surprised that Lovaza® (named Omacor in Europe), which is a prescription omega-3 mixture of EPA, DHA and other ingredients, administered at a low dose of 1 gram/day in the omega-3 arms of the ASCEND study did not find a reduction of serious vascular events in patients with diabetes and without diagnosed cardiovascular disease. In the past, studies of omega-3 mixtures have not found positive results.

As the article published in JAMA titled 'Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks'[1] reported, most of the studies included in this meta-analysis concerned mixed EPA and DHA omega-3 products administered daily at a low dose, and were not positive. The only trial conducted with a different drug and dose level was the JELIS trial, which showed a statistically significant positive result. JELIS used 1.8 grams/day of a pure EPA product in a Japanese patient population with a demonstrated relative risk reduction of 19% on top of statin therapy compared to statin therapy alone. While there are many differences between the JELIS study and studies conducted in Western populations, one difference is that approximately 4 grams/day of pure EPA is required in a Western patient population to achieve the levels of EPA in plasma achieved in the JELIS study. This is likely due to the relatively high baseline levels of EPA in plasma in Japanese patients because of their customary fish consumption. Additionally, the authors of the meta-analysis highlighted the importance of drug studies such as REDUCE-IT™, distinguishing Amarin's ongoing study of pure EPA prescription drug therapy from the studies of fish oil supplements in the meta-analysis: "Importantly, ... REDUCE-IT ... will test the effects on major vascular events of much higher doses of omega-3 FAs [fatty acids] (...4 g/d)." Further noting the distinction, the authors concluded the following: "The results of the ongoing trials are needed to assess if higher doses of omega-3 FAs (3-4 g/d) may have significant effects on risk of major vascular events."

Important differences between studies of omega-3 products is the product being studied (e.g. whether it is pure EPA or a mixture of various ingredients), dose levels and the population being evaluation. Most omega-3 products include around 10% or more of ingredients which are not omega-3 fatty acids. They typically also contain DHA which can raise LDL-cholesterol levels. EPA is a small molecule with effects which appear to differ from other omega-3s. The science of lipid management and the clinical effects of omega-3 fatty acids are complex. Furthermore, dose levels are important, as high-dose omega-3 fatty acids are likely to have a more pronounced effect on lipid and other measures and, we believe, on outcomes on top of contemporary medical therapy. We also believe that patient populations studied matter. If seeking to demonstrate adverse cardiovascular event reduction, selecting higher risk patients is believed to increase the likelihood of identifying a more pronounced result. Therefore, one cannot draw conclusions between the collection of studies included in this paper and the REDUCE-IT study. REDUCE-IT is a potential landmark study, and different than all studies to date on omega-3s.

REDUCE-IT is evaluating whether a daily four-gram dose of icosapent ethyl, an FDA-approved prescription pure EPA medication known as Vascepa®, added to statin therapy may reduce major adverse cardiovascular events and is expected to report topline results before the end of September 2018. Vascepa has not been shown to raise LDL-C, in contrast to the increase in LDL-C presented in FDA-approved labelling for the omega-3 mixtures containing DHA.

REDUCE-IT has the potential to be the right study, using the right drug in the right patients.

Some of the major study differences include:

	REDUCE-IT[3]	ASCEND (OMEGA-3 ARMS)[4]
RESULTS	Pending	Failed to achieve primary endpoints
SPONSOR/FUNDING	Amarin	Oxford University/British Heart Foundation
STUDY TYPE	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled
PATIENT POPULATION	Statin-treated patients with high CV risk, including TG 150-499 mg/dL	Patients with diabetes, without evidence of cardiovascular disease
STUDIED OMEGA-3 TREATMENTS	Vascepa 4g/day (pure EPA)	Omacor® (Lovaza®) 1g/day (mixture of EPA, DHA and other)
STATIN THERAPY	Statin use mandated for all patients	Statin use not mandated
RESULT CAPTURE	Clinically run and monitored with periodic visits to clinical sites	Self-reported (results documented with questionnaires filled out by the patients every 6 months)
NUMBER OF PATIENTS	8,175	15,480
NUMBER OF PRIMARY EVENTS	~1,612 (expected)	1,401 (actual)
PRIMARY ENDPOINT	Risk Reduction for CV events (composite endpoint)	Risk Reduction for CV events (composite endpoint) & cancer

Amarin believes that these differences in study drug, design, and execution clearly differentiate REDUCE-IT from the ASCEND clinical trial. Some of these differences include:

- Different drugs studied (pure EPA vs. mixture containing less than 50% EPA)
- Dose levels are important
    - High-dose omega-3 fatty acids are likely to have a more pronounced effect on lipid measures and, we believe, on outcomes on top of contemporary medical therapy.
    - Many past studies of low-dose, EPA/DHA mixture omega-3 fatty acids showed a negligible to modest benefit for people with cardiovascular disease on top of contemporary medical therapy.[1]
- Patient populations studied matter
    - If seeking to demonstrate cardiovascular event reduction, selecting higher risk patients is believed to increase the likelihood of identifying a more pronounced result.
- Study rigor will be considered when evaluating results
    - REDUCE-IT is being conducted using a controlled patient population and on-site recording of clinical labs and other measurements, all intended to enhance clinical precision and governance. REDUCE-IT was designed under a Special Protocol Assessment agreement with the FDA.
    - ASCEND used patient self-assessment questionnaires.

We believe that the rigorous design of the REDUCE-IT study, the at-risk populations of patients being studied and the broad clinical effects of pure, prescription EPA position the study to potentially provide a great scientific benefit towards a better understanding of how to treat millions of patients with elevated triglycerides after statin therapy and other cardiovascular risk factors.

Amarin hopes that ASCEND and REDUCE-IT will lead to improved understandings of how the products being studied can potentially improve patient care. They are aimed at helping the populations being studied in these trials. However, there are many differences between the ASCEND and the REDUCE-IT trials, including that REDUCE-IT is focused on a large, under-treated population with cardiovascular risk. An additional outcomes study, VITAL[4], utilizing Lovaza plus Vitamin D is anticipated to have results available before the end of 2018. Like ASCEND, VITAL will evaluate the impact of a prescription EPA/DHA mixture on patient outcomes and may lead to improved understandings of how to improve patient care.

[1] Aung T, Halsey J, Kromhout D, et al. Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77 917 Individuals. *JAMA Cardiol.* 2018;3(3):225–234. doi:10.1001/jamacardio.2017.5205

[2] Bhatt DL, Steg PG, Brinton EA, et al. Clin Cardiol. 2017;40(3):138-148.

[3] Bowman L. Effects of n-3 fatty acid supplements in diabetes mellitus. The ASCEND Study Collaborative Group. *N Engl J Med.* 2018.

[4] Pradhan AD, Manson JE. Update on the vitamin D and omega-3 trial (VITAL). *The Journal of steroid biochemistry and molecular biology*. 2016;155(0 0):252-256. doi:10.1016/j.jsbmb.2015.04.006.

Forward-Looking Statements

This FAQ contains forward-looking statements, including expectations for timing of completion of the REDUCE-IT study, the potential for the results of the REDUCE-IT study to be positive and expectation for timing of announcements related to REDUCE-IT results. These forward-looking statements are not promises or guarantees and involve substantial risks and uncertainties. In particular, as disclosed in its previous company filings with the U.S. Securities and Exchange Commission, completing and reporting results from cardiovascular outcomes trials such as REDUCE-IT are complex undertakings that involve substantial risks such as the complex nature of collecting and analyzing clinical data and reliance on third parties. Vascepa may not show clinically meaningful effects in REDUCE-IT or support regulatory approvals for intended uses. 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 the sale of pharmaceutical products, 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.