What is Amarin's opinion on the ASCEND clinical trial in which Lovaza failed to demonstrate cardiovascular benefit on top of statin therapy as reported in August 2018 at the annual scientific sessions of the European Society of Cardiology?

Amarin applauds all serious efforts to better understand the potential benefits 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.[1] In the past, cardiovascular outcomes trials of omega-3 mixtures have reported negligible impact on cardiovascular events.

The European Medicines Agency (EMA) determined, on March 29, 2019, that omega-3 mixture products, such as Omacor/Lovaza, are not effective at a dose of 1 gram/day (the dose studied in the VITAL and ASCEND studies and the dose at which Omacor/Lovaza was approved in various countries in Europe) in preventing further heart problems after a heart attack.[2] This determination reflects, and is consistent with, the most current understanding of cardiovascular outcomes trials of omega-3 mixtures. It also stands in sharp contrast to the unique and beneficial effects of Vascepa demonstrated in the REDUCE-IT™ cardiovascular outcomes trial. REDUCE-IT data presented on March 18, 2019 showed that Vascepa at 4 grams/day provided a statistically significant 30% risk reduction in total (first and subsequent) cardiovascular events compared to placebo in the high-risk statin-treated patient population studied.[3] This determination from the EMA supports our belief that Vascepa's pure and stable EPA drug is unique as no other omega-3 therapy has shown the benefits that Vascepa did in the REDUCE-IT trial. The uniqueness of the active ingredient in Vascepa was also reaffirmed on March 27, 2019 by the American Diabetes Association's (ADA) important updates to the *Standards of Medical Care in Diabetes for 2019*,[4] including updates related to the results of the REDUCE-IT™ cardiovascular outcomes study.[3, 5]

Also, as reported in the March 2018 *JAMA* article entitled "Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks", most of the studies included in the *JAMA* meta-analysis utilized mixed EPA and DHA omega-3 products administered daily at a low dose, and were not positive, including prescription therapy and dietary supplements.[6] Similar analysis has been conducted and published by other sources, including the Cochrane review described further below. Failed results with omega-3 mixtures on top of statin therapy were again demonstrated in the results of the VITAL study published in November 2018 in *The New England Journal of Medicine* (*NEJM*) in which Lovaza again failed to demonstrate cardiovascular benefit.

Prior to the successful results of the REDUCE-IT cardiovascular outcomes study of the prescription drug Vascepa, 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 prescription 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 *JAMA* 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."

A new systematic review of evidence on omega-3 fatty acids by Cochrane, reported in July 2018, combined the results of 79 randomized trials involving 112,059 people and assessed the effects of consuming additional omega-3 fatty acids on cardiovascular disease. The authors reported that increasing EPA and DHA intake together had little or no meaningful effect on the risk of death from any cause, which was 8.8% in people who had increased their intake of omega 3 fats, compared with 9% in people in the control groups. According to that report, which was issued prior to the REDUCE-IT trial results, taking more long chain omega-3 fatty acids primarily through supplements probably makes little or no difference to risk of cardiovascular events, coronary heart deaths, coronary heart disease events, stroke, or heart irregularities.[7]

REDUCE-IT evaluated 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. The positive results of this study were published in *NEJM* in November 2018 entitled "Cardiovascular Risk Reduction with Icosapent Ethyl in Hypertriglyceridemia." The active pharmaceutical ingredient in Vascepa, icosapent ethyl, 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.[5]

Some of the major study differences included:

	REDUCE-IT[5]	ASCEND (OMEGA-3 ARMS)[1]
RESULTS	Successfully met primary and key secondary endpoints	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 containing <50% EPA)
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	8,179	15,480
NUMBER OF PRIMARY EVENTS	1,606	1,401
PRIMARY ENDPOINT	Risk Reduction for CV events (composite endpoint)	Risk Reduction for CV events (composite endpoint) & cancer

[1] Bowman L. Effects of n-3 fatty acid supplements in diabetes mellitus. The ASCEND Study Collaborative Group. *N Engl J Med.* 2018;379(16):1540-1550.

[2] European Medicines Agency. https://www.ema.europa.eu/en/news/ema-confirms-omega-3-fatty-acid-medicines-are-not-effective-preventing-further-heart-problems-after

[3] Bhatt DL, Steg PG, Miller M, et al. Effects of Icosapent Ethyl on Total Ischemic Events: From REDUCE-IT. *J Am Coll Cardiol* 2019;73(22):2791-2802.

[4] American Diabetes Association. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2019. http://care.diabetesjournals.org/content/42/Supplement_1/S103

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

[6] 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.

[7] Abdelhamid AS, Brown TJ, Brainard JS, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2018;7:CD003177. doi: 10.1002/14651858.CD003177.pub3.

Important Cautionary Information About These Data

Recurrent event analyses for the total primary endpoint events and for the total key secondary endpoint events in REDUCE-IT as published in the *Journal of the American College of Cardiology* 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.

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