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 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.[1] In the past, studies of omega-3 mixtures have not found positive results.

As the article published in March 2018 in JAMA titled 'Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks'[2] reported, most of the studies included in this 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. Similar analysis has been conducted and published by other sources, including the Cochrane review described below. Failed results with omega-3 mixtures on top of statin therapy was again demonstrated in the results of the VITAL study published in November 2018 the 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 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.[3]

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 The New England Journal of Medicine 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.[4]

Some of the major study differences included:

	REDUCE-IT[4]	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] 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.

[3] 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.

[4] Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl in Hypertriglyceridemia. *N Engl J Med.* 2018.

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 nejm.org/doi/full/10.1056/NEJMoa1812792 and via review of published result of the REDUCE-IT study in The New England