What is Amarin's opinion on the VITAL clinical trial in which Lovaza failed to demonstrate cardiovascular benefit on top of statin therapy as reported in November 2018 at the annual scientific sessions of the American Heart Association?

The potential benefits of omega-3 fatty acids are broad and the science is deep. Amarin applauds all serious efforts to better understand these potential benefits and the related science, including the VITAL trial. The VITAL trial assessed the impact of vitamin D3 or omega-3 fatty acids on a range of diseases in a generally healthy population. Similar to other studies of omega-3 mixtures, in VITAL cardiovascular benefit was not demonstrated by treating patients with the prescription therapy Lovaza at 1 grams per day.[1]

This failed result in VITAL is similar to the failed result of Lovaza as studied in ASCEND and consistent with analysis of results for studies of other omega-3 mixtures. Such failed results of omega-3 mixtures are discussed in the FAQ above with respect to the ASCEND study. These failed results are differentiated from positive results of prescription Vascepa studied in the REDUCE-IT trial.

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, titled "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.[2]

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.[2]

Some of the major study differences included:

	REDUCE-IT[3]	VITAL[1]
RESULTS	Successfully met primary and key secondary endpoints	Failed to achieve primary endpoints
SPONSOR/FUNDING	Amarin	Brigham and Women's Hospital/NIH
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	Relatively healthy patients
STUDIED OMEGA-3 TREATMENTS	Vascepa 4g/day (pure EPA)	Omacor® (Lovaza®) 1g/day (mixture of EPA, DHA and other containing <50% EPA) plus Vitamin D3 2000 IU/d
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 year)
NUMBER OF PATIENTS	8,175	25,874
NUMBER OF PRIMARY EVENTS	1,606	1,214
PRIMARY ENDPOINT	Risk Reduction for CV events (composite endpoint)	Risk Reduction for CV events (composite endpoint) & cancer

[1] Manson, JE, Lee, I-Min, Mora, Samia, et al. Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. *N Engl J Med.* 2018. Epub ahead of print.

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

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 see https://www.nejm.org/doi/full/10.1056/NEJMoa1812792.