What is Amarin's opinion on the ASCEND and VITAL clinical trials in which Lovaza® failed to demonstrate cardiovascular benefit on top of statin therapy?

Amarin applauds all serious efforts to better understand the potential benefits of omega-3's, including the ASCEND and VITAL trials. Amarin was 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 and VITAL studies, did not show a cardiovascular risk reduction benefit. This is consistent with prior cardiovascular outcomes trials of omega-3 mixtures that have reported negligible impact, if any, on lowering the occurrence of adverse cardiovascular events.[1]

In the ASCEND study, the omega-3 arms did not show a reduction of serious vascular events in the population studied, which was patients with diabetes and without established cardiovascular disease.[2]

In the VITAL study, the omega-3 arm, which used 1 gram/day of Lovaza, also did not show a cardiovascular benefit in the population studied which was a generally healthy population.[3]

The European Medicines Agency (EMA) determined, on March 29, 2019, that omega-3 mixture products, such as Omacor/Lovaza, are not effective in preventing further heart problems after a heart attack.[4] This determination reflects, and is consistent with, the most current understanding of cardiovascular outcomes trials of omega-3 mixtures. Such assessment was made factoring in available clinical data for Omacor/Lovaza following the VITAL and ASCEND studies, in which patients were dosed at 1 gram/day, the dose at which Omacor/Lovaza was previously approved in various countries in Europe.

The clinical results of omega-3 mixtures, such as Omacor/Lovaza stand in sharp contrast to the unique and beneficial effects of VASCEPA® (icosapent ethyl) capsules demonstrated in the REDUCE-IT® cardiovascular outcomes trial. REDUCE-IT showed that VASCEPA at 4 grams/day provided a statistically significant 30% relative risk reduction in total (first and subsequent) cardiovascular events compared to placebo in the high-risk statin-treated patient population studied.[5] 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 has been reaffirmed by the many medical societies that have recognized VASCEPA and REDUCE-IT in their guidelines. More information on these medical societies can be found in this FAQ.

Also, as reported in the March 2018 *JAMA* article titled, "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.[1] Similar analysis has been conducted and published by other sources, including the Cochrane review described further below.

A systematic review of evidence on omega-3 fatty acids by Cochrane, reported in early 2020, combined the results of 86 randomized trials involving 162,796 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, death from cardiovascular causes, on cardiovascular events, stroke, or arrhythmia.[6]

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 online in *NEJM* in November 2018 and titled, "Cardiovascular Risk Reduction with Icosapent Ethyl in Hypertriglyceridemia."[7] The active pharmaceutical ingredient in VASCEPA, icosapent ethyl, has a unique and stable 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.

Some of the major study differences included:

	REDUCE-IT[5,7]	ASCEND (OMEGA-3 ARMS)[1]	VITAL[2]
RESULTS	Successfully met primary and key secondary endpoints	Failed to achieve primary endpoints	Failed to achieve primary endpoints
SPONSOR/FUNDING	Amarin	Oxford University/British Heart Foundation	Brigham and Women's Hospital/NIH
STUDY TYPE	Randomized, double-blind, placebo-controlled	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	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)	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	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)	Self-reported (results documented with questionnaires filled out by the patients every year)
NUMBER OF PATIENTS	8,179	15,480	25,874
NUMBER OF PRIMARY EVENTS	1,606	1,401	1,214
PRIMARY ENDPOINT	Risk Reduction for CV events (composite endpoint)	Risk Reduction for CV events (composite endpoint) & cancer	Risk Reduction for CV events (composite endpoint) & cancer

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[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.
[2] 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.
[3] 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.* 2019;380(1):23-32.

[4] 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

[5] 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.

[6] Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, Deane KHO, Summerbell CD, Worthington HV, Song F,Hooper L. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* 2020, Issue 3. Art. No.: CD003177. DOI: 10.1002/14651858.CD003177.pub5.

[7] Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med.* 2019;380(1):11-22.