What is Amarin's opinion on the VITAL and ASCEND clinical trials?

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 and ASCEND trials. The VITAL trial assesses the impact of vitamin D or omega-3 fatty acids on a range of diseases in a generally healthy population, and the ASCEND trial examines the role of aspirin and/or omega-3 fatty acids in reducing the risk of cardiovascular events in people with diabetes and without diagnosed occlusive arterial disease. These studies, however, differ significantly from REDUCE-IT. They do not study the same high-risk patient population nor active compound. Nor do they appear to have the same levels of control and rigor.

Some of the major study differences include:

VITAL/ASCEND	REDUCE-IT
Treatment arm of low-dose, 1-gram per day administration	Treatment arm of 4-grams per day
DHA/EPA mixture treatment arm	100% pure, prescription EPA
Inclusion criteria do not mandate statin use	Statin-treated population with LDL <100 mg/dL as inclusion criteria
Results documented with yearly questionnaires filled out by the patients	Clinically run and monitored with periodic patient visits with clinical labs and other measurements recorded
Study designs include the use of other products, such as vitamin D and aspirin	Study designed to assess the effects of Vascepa on top of statins
Exclude high risk people with prior cardiovascular events	Specifically includes people at risk for cardiovascular disease including people with prior events
Triglyceride levels not an inclusion criteria	All patients have elevated triglycerides

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

- Dose levels are important
    - High-dose omega-3 fatty acids are likely to have a more pronounced effect on lipid measures and, we believe, outcomes, especially 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 ofclinical 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.
    - VITAL and ASCEND both use 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 VITAL, ASCEND AND REDUCE-IT will all lead to improved understandings of how the products being studied can potentially improve patient care. They are all aimed at helping the populations being studied in these trials. However, there are many differences between the VITAL and ASCEND trials and the REDUCE-IT trial, including that REDUCE-IT is focused on a large, under-treated population with cardiovascular risk. If the VITAL and ASCEND studies do not report positive results, this may be due to the relatively low-dose treatment levels or other elements related to the design and populations being studied. If the VITAL and ASCEND studies result in improved outcomes based on their relatively low-dose treatment levels, these results could provide added optimism regarding the potential magnitude of effect of 4 grams per day of Vascepa as is being studied in REDUCE-IT.

[1] Maki, Kevin C. et al., **Use of Supplemental Long-chain Omega-3 Fatty Acids and Risk for Cardiac Death: An Updated Meta-analysis and Review of Research Gaps**. Journal of Clinical Lipidology. 2017.
http://www.lipidjournal.com/article/S1933-2874(17)30395-1/fulltext