

What is Amarin’s perspective on the editorial in *NEJM* commenting on the primary publication of REDUCE-IT results in *NEJM* (Bhatt et al. 2018)?

Amarin is grateful for the continued scientific and academic examination of the landmark REDUCE-IT cardiovascular outcomes study. Amarin is likewise grateful to the editorial authors for their contribution to ongoing dialogue examining where REDUCE-IT results and Vascepa® (icosapent ethyl) capsules fit within the body of evidence on successful cardiovascular risk reduction drug interventions. We agree that REDUCE-IT has shown a substantial benefit with respect to major adverse cardiovascular events.

Major advances in cardiovascular outcomes from studies like REDUCE-IT disrupt the status quo and pave new paths forward to help patients in need. Major advances like REDUCE-IT also motivate the medical community to search for ways to fit the result into the mosaic of prior successful studies like JELIS and CANTOS and their associated mechanisms of action and to also distinguish results from what the authors of the editorial refer to as the “parade of failed cardiovascular outcome trials of fish oils,” such as ASCEND, VITAL and others. It is important for the medical community to understand related science on icosapent ethyl and REDUCE-IT better. We believe this will lead to increased Vascepa use.

The editorial makes progress in aiding understanding of REDUCE-IT results and how Vascepa works. We note some coverage in the editorial did not fully present important information, which can lead to misleading conclusions. For example, discussion of issues related to the placebo used in REDUCE-IT is covered more completely here: <https://investor.amarincorp.com/static-files/5967c222-7ed6-46bc-b17b-ac8930554534>. Also, there was no increase in log hsCRP from baseline in the placebo arm and the between-group change showed a 22.5% reduction at Year 2 that was driven by Vascepa therapy (for more information, see <https://amarincorp.gcs-web.com/static-files/97e31858-1936-43da-80ea-2f78bb7e7260>). In addition, determining the mechanisms responsible for the benefit shown in REDUCE-IT was not the focus of REDUCE-IT. Not fully covered in the editorial are the multiple published scientific findings from data independent of REDUCE-IT that show based on various degrees of evidence how icosapent ethyl might work to interrupt the atherosclerotic processes. More information is available here: <https://investor.amarincorp.com/static-files/eaf1ff2e-e014-4180-880b-058278dff06>.

We appreciate that the authors of the editorial disclose that both are actively involved in the STRENGTH trial for a potentially competitive therapy to Vascepa. One of the authors discloses that he is a member of the Executive Committee for STRENGTH and the other author, who works at the same medical institution, discloses that he is an investigator in the STRENGTH trial. Amarin hopes, for the benefit of science and increased awareness of patient care options, that the STRENGTH study succeeds. However, given the broad support for the REDUCE-IT trial results that we are hearing from the vast majority of physicians, we are surprised that physicians with such meaningful conflicts of interest were published in the editorial.

The global principal investigator and lead author of the primary *NEJM* REDUCE-IT publication plans to respond to any resulting letters to the editor through the recognized process. We expect that will result in a response publication in *NEJM* which, based on the schedule of *NEJM*, we anticipate seeing sometime in the first half of 2019. In the interim, we hope you find this information helpful.