What is Amarin's perspective on the use of mineral oil in its clinical trials (updated November 12, 2018)?

A placebo comprised of light liquid paraffin oil, or mineral oil, was used in the MARINE, ANCHOR and REDUCE-IT clinical trials of Vascepa. Mineral oil was selected as the appropriate placebo to mimic the color and consistency of Vascepa.

No strong evidence for biological activity of mineral oil was identified

- in connection with FDA approval of Vascepa in July 2012 based on the MARINE phase 3 clinical trial,
- in connection with FDA review of the ANCHOR phase 3 clinical trial or
- after several years of quarterly review by the Data Monitoring Committee, or DMC, for REDUCE-IT cardiovascular outcomes trial after FDA requested the DMC to periodically review unblinded lipid data to monitor for signals that the placebo might not be inert.

Each of the three Vascepa clinical trials, MARINE, ANCHOR and REDUCE-IT, was conducted under a special protocol, or SPA, agreement with FDA in which mineral oil was agreed with FDA as an acceptable placebo. A SPA is an evaluation by the FDA of a protocol with the goal of reaching an agreement that the trial protocol design, clinical endpoints, and statistical analyses are acceptable to support regulatory approval of the drug product candidate with respect to effectiveness for the indication studied.

MARINE

FDA approval of Vascepa in 2012 was based primarily on efficacy data from the MARINE trial. As part of this approval, Amarin submitted to FDA data from both the MARINE and ANCHOR trials for consistency of results and review of safety data. Consideration of external data regarding characteristics of mineral oil was also assessed by FDA before FDA's approval. An overview of FDA assessment of MARINE clinical data was provided by FDA as follows in connection with FDA review of ANCHOR data:

> "During the review of the MARINE data, the Division noted that several lipid parameters (including TG) increased from baseline to week 12 in the placebo group, treated with mineral oil. The available literature regarding potential effects of mineral oil was considered. Similar increases in TG levels observed in the placebo groups from the Lovaza (omega-3 EE) clinical trials of hypertriglyceridemic patients were noted, and these trials did not use a mineral oil placebo. Because no strong evidence for biological activity of mineral oil was identified, ultimately it was concluded that the between-group differences likely provided the most appropriate descriptions of the treatment effect of AMR101 and that whatever factor(s) led to the within-group changes over time in the placebo group were likely randomly distributed to all treatment groups. Taken together, along with the statistical robustness in primary and sensitivity analyses of AMR101 4g/day on TG lowering, the Division concluded that AMR101 4g/day is an effective TG-lowering agent for patients with severe hypertriglyceridemia. AMR101 was approved for the following treatment indication on July 26, 2012: Treatment of Severe Hypertriglyceridemia VASCEPA™ (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia."

ANCHOR

During the October 16, 2013 public advisory committee meeting held by FDA as part of its review of our ANCHOR sNDA, a discussion was held regarding observed, nominally statistically significant changes in the placebo group from baseline of certain lipid parameters in an adverse direction, while on background statin therapy. Nevertheless, the discussion raised questions about the possibility that the mineral oil placebo in the ANCHOR trial (and then at use in the REDUCE-IT trial) might not be biologically inert and might be viewed as artificially exaggerating the clinical effect of Vascepa when measured against placebo in the ANCHOR trial. It was ultimately concluded that the between-group differences likely provided the most appropriate descriptions of the treatment effect of Vascepa and that whatever factor(s) led to the within-group changes over time in the placebo group were likely randomly distributed to all treatment groups.

From May 2015 through March 2016, in connection with the First Amendment litigation with FDA and the related settlement agreement that allowed Amarin to promote the results of the ANCHOR study, FDA did not dispute the veracity of the ANCHOR trial data or seek to require that Amarin include any qualification in our promotion of ANCHOR data related to the mineral oil placebo.

REDUCE-IT

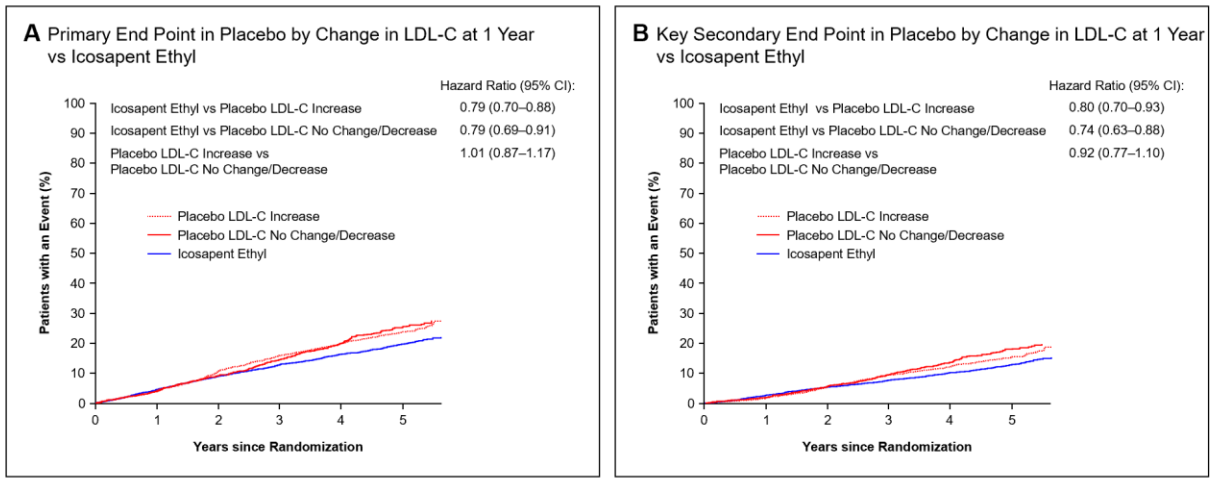
Early on in the course of the REDUCE-IT trial, FDA directed the DMC for REDUCE-IT to periodically review unblinded lipid data to monitor for signals that the placebo might not be inert. After each such quarterly unblinded safety analysis and review meeting, the DMC recommended to continue the REDUCE-IT study as planned. Each of these DMC recommendations was shared with FDA.

In August 2016, we announced an amendment to our REDUCE-IT SPA agreement with FDA that reaffirmed FDA concurrence on key elements of the study. In this amended REDUCE-IT SPA agreement, FDA agreed that, based on the information submitted to the agency, the critical elements of the revised REDUCE-IT protocol and analysis plans adequately address the objectives necessary to support a regulatory submission.

As published within the main presentation of the REDUCE-IT results (Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2018.), at baseline, the median LDL-C was 75.0 mg/dL. The median change in LDL-C was 3.1% (+2.0 mg/dL) for VASCEPA and 10.2% (+7.0 mg/dL) for the mineral oil placebo arm; placebo-corrected median change from baseline of -6.6% (**-5.0 mg/dL**; $p < 0.001$). If mineral oil in the placebo might have affected statin absorption in some patients, this might have contributed to differences in outcomes between the groups. However, the relatively small differences in LDL-C levels between groups would not be likely to explain the 25% risk reduction observed with VASCEPA, and a *post hoc* analysis suggested a similar lower risk regardless of whether there was an increase in LDL-C level among the patients in the placebo group. *See* Figures A and B.

Figures A and B

Primary and Key Secondary End Point in Placebo by Change in LDL-C at 1 Year vs Icosapent Ethyl



Overlaid orange and red lines reflect that there were no differences in outcomes for placebo patients with an increase in LDL-C

Data supporting statement in Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Although open label, Japan EPA Lipid Intervention Study (JELIS) previously demonstrated a 19% risk reduction without a mineral oil placebo.

Potential Mechanisms of Action

As noted in *The New England Journal of Medicine*:

> "The observed cardiovascular benefits were similar across baseline levels of triglycerides (<150, ≥150 to <200, and ≥200 mg per deciliter). In addition, the significantly lower risk of major adverse cardiovascular events with icosapent ethyl than with placebo appeared to occur irrespective of the attained triglyceride level at 1 year (≥150 or <150 mg per deciliter), which suggests that the cardiovascular risk reduction was not associated with attainment of a more normal triglyceride level. These observations suggest that at least some of the effect of icosapent ethyl that resulted in a lower risk of ischemic events than that with placebo may be explained by metabolic effects other than a reduction of triglyceride levels."

Determining the mechanisms responsible for the benefit shown in REDUCE-IT were not the focus of REDUCE-IT. As summarized from the primary results of REDUCE-IT in *The New England Journal of Medicine*, potential Vascepa mechanisms of action at work in REDUCE-IT may include TG reduction, anti-thrombotic effects, antiplatelet or anticoagulant effects, membrane-stabilizing effects, effects on stabilization and/or regression of coronary plaque and inflammation reduction, each as supported by earlier stage mechanistic studies. 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 inflammatory biomarkers.[1,2,3,4,5]

Summary

The use of mineral oil placebo in REDUCE-IT cannot explain the significant 25% risk reduction in the study, even if one assumes the placebo was not fully inert. The independent Data Monitoring Committee review throughout the almost seven-year study and reviewers at *The New England Journal of Medicine*, after careful review of relevant data, concluded that the results of the REDUCE-IT study reflect that VASCEPA significantly lowered the risk of ischemic events, including cardiovascular death. Amarin stands behind these results as presented at The American Heart Association and published in NEJM.

Amarin looks forward to the results of this landmark study being used to help many at-risk patients.

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1 Ganda OP, Bhatt DL, Mason RP, et al. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. J Am Coll Cardiol. 2018;72(3):330-343.

2 Borow KM, Nelson JR, Mason RP. Biologic plausibility, cellular effects, and molecular mechanisms of eicosapentaenoic acid (EPA) in atherosclerosis. Atherosclerosis. 2015;242(1):357-366.

3 Nelson JR, Wani O, May HT, et al. Potential benefits of eicosapentaenoic acid on atherosclerotic plaques. Vascul Pharmacol. 2017;91:1–9.

4 Mason RP, Dawoud H, Jacob RF, et al. Eicosapentaenoic acid improves endothelial function and nitric oxide bioavailability in a manner that is enhanced in combination with a statin. Biomed Pharmacother. 2018;103:1231-1237.

5 Takamura M, Kurokawa K, Ootsuji H, et al. Long-term administration of eicosapentaenoic acid improves post-myocardial infarction cardiac remodeling in mice by regulating macrophage polarization. J Am Heart Assoc. 2017;6(2). pii: e004560.