What is Amarin's perspective on the use of mineral oil in its clinical trials?

All information below has been previously disclosed other than Figures A and B.

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.

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 us to promote the results of the ANCHOR study, FDA did not dispute the veracity of the ANCHOR trial data or seek to require that we include any qualification in our promotion of ANCHOR data related to the mineral oil placebo.

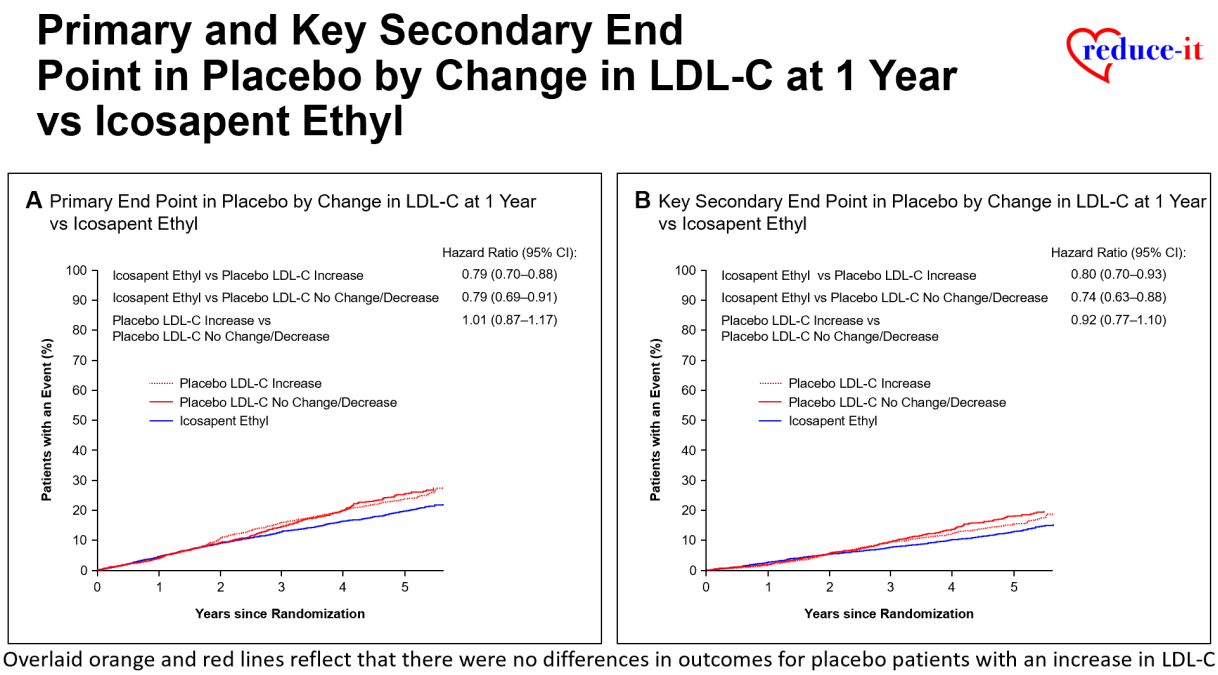
REDUCE-IT

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



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.

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.