What is Amarin's perspective on the use of mineral oil in its clinical trials and the variability commonly observed in blood-based lipid values in clinical trials of statin-stabilized patients (updated November 23, 2018)?

Overview

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. Each of the three Vascepa clinical trials was conducted under a special protocol agreement, or SPA, with FDA in which FDA agreed to the use of mineral oil 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 and safety for the indication studied.

Consistent with conclusions from two prior FDA reviews of Vascepa clinical trials, no strong evidence for biological activity of the mineral oil placebo was found by the REDUCE-IT cardiovascular outcomes trial independent Data Monitoring Committee, or DMC. The DMC was requested by FDA to examine unblinded data on an ongoing basis over a period of several years and to specifically look for a signal of biological activity from the mineral oil placebo. The DMC noted variation in LDL-C measurements in both study arms, and considered whether or not a small physiological effect of mineral oil was possible. However, the DMC concluded that it was not possible to determine if the LDL-C increase in the placebo arm was due to the mineral oil or other factors. Increased lipid parameter levels have been observed in multiple clinical trials similar to REDUCE-IT. It is, in fact, generally understood that variability in blood-based lipid, lipoprotein and inflammation values is a common occurrence in clinical studies of statin-stabilized patients, and many long-term studies of statin-stabilized patients have observed increases in biomarkers with time, including LDL-C. Factors cited as potentially contributing to this circumstance include decreased drug and lifestyle regimen compliance, physiological compensation for drug-induced lipid changes, regression to the mean, intraindividual variability, lab variability, genetics, metabolic state, disease state, age, and season. The DMC examined whether variation in the placebo arm might have affected outcomes, found no such effect, and concluded that the small LDL-C change was not likely to explain the observed benefit of Vascepa over placebo.

Finally, a *post hoc* analysis covered in *The New England Journal of Medicine* publication of REDUCE-IT results concludes that LDL-C changes observed at one year for REDUCE-IT patients within the placebo arm did not alter outcomes. The analysis shows there was no significant difference in event rates within the primary or key secondary endpoints for patients in the placebo arm that had an increase in LDL-C as compared to those with no change or a decrease in LDL-C.

Variability in Lipid Measurements Observed in Long-term Clinical Studies of Statin-stabilized Patients

Variability in blood-based lipid values is a common occurrence in clinical studies of statin-stabilized patients. For patients with elevated triglycerides, such as those enrolled in the MARINE, ANCHOR, and REDUCE-IT studies, a greater likelihood of variability within an individual's lipid measurements (including

LDL-C), or intraindividual variability, has been reported. For example, investigators from the AFCAPS/TexCAPS study found that approximately 10% of patients failed study screening due to an LDL-C intraindividual variability of greater than 15%.[1] The average LDL-C variability for these patients ranged from approximately 23 to 29%, and they tended to have elevated triglycerides and a higher prevalence of familial coronary heart disease compared to patients with less variable LDL-C.

In fact, intraindividual variability in lipid measurements has been studied for many years, and, using LDL-C as an example, variability in healthy adults tends to range from approximately 2 to 12%.[2,3,4,5,6,7,8] LDL- C variability can also be influenced by a number of generic factors, including patient level influences, such as drug regimen and dietary compliance, genetics, metabolic state, disease state, age, and season, and lab level influences such as collection procedures, sample processing, and assay methods.[9,10,11,12,13,14,15,16,17,18] In addition, much more significant fluctuations, on a magnitude of several fold increases, can result from within a single patient,[19,20,21,22,23]and as noted above, these variations can be of even greater magnitude in patients with elevated triglyceride levels.

Importantly, increased lipid levels have been observed in multiple clinical trials. An upward drift in LDL-C (and other lipid) levels has been commonly (although not always) observed in statin-stabilized patients across numerous studies within varying patient populations, and many have estimated LDL-C increases of at least 6% and ranging up to more than 30%.[24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40] These LDL-C increases despite statin stabilization have been postulated to be due to a number of possible factors as set forth above. Such factors include a decrease in patient drug and life style compliance with time,[41] physiological compensation mechanisms whereby the body attempts to counteract a statin- induced decrease in cholesterol (known as, physiological escape phenomenon),[42] regression to the mean (particularly in studies with low baseline LDL-C),[43] and increased intraindividual variability with time.[44]

The Examination of Placebo from the MARINE Study FDA Review

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 (Note: AMR101 research code identifier for Vascepa that is used within clinical studies):

> "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."

The Examination of Placebo from the ANCHOR Study FDA review

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.

In the April 27, 2015 complete response letter from FDA issued in connection with the Amarin supplemental new drug application related to the ANCHOR study, there was no suggestion by FDA of an issue with the mineral oil placebo being biologically active or interfering with the statin-treated patient population in the ANCHOR study.

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 to healthcare professionals of ANCHOR data related to the mineral oil placebo.

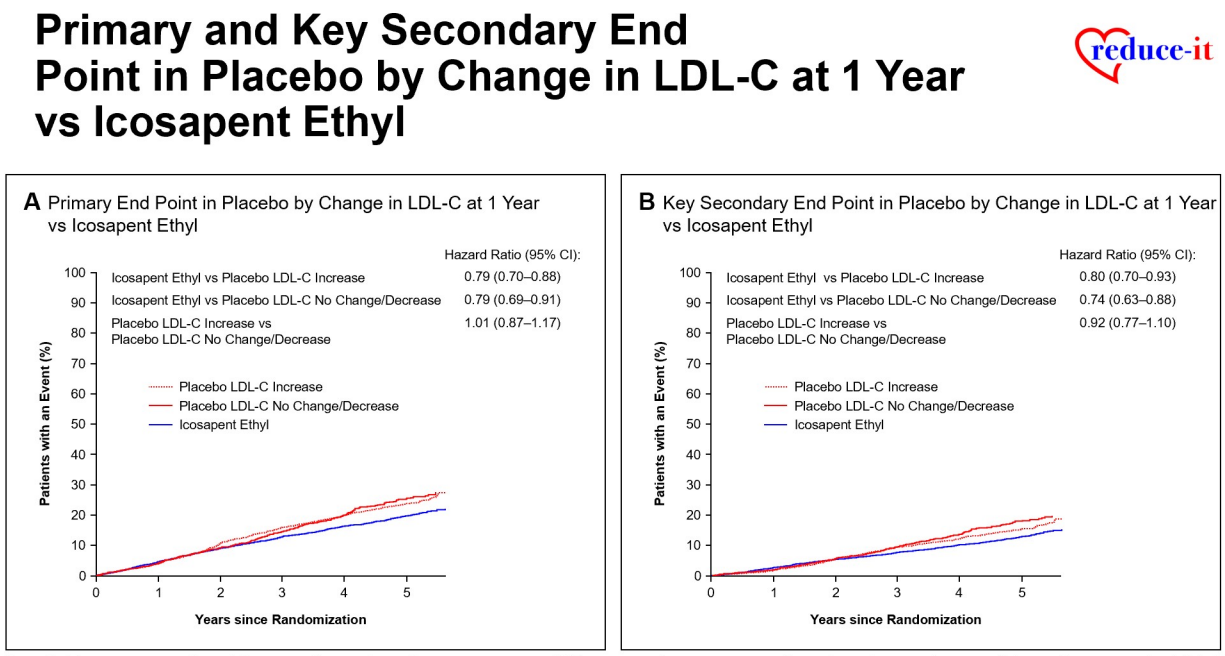
The Examination of Placebo in the REDUCE-IT Study

Early 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. Over several years, 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, Amarin announced an amendment to the 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,[45] 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% (**-5.0mg/dL**; p < 0.001) at one year. 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 likely explain the 25% risk reduction observed with VASCEPA, and *post hoc* analyses suggested similar results for the primary and key secondary endpoints regardless of whether there was an increase in LDL-C level among the patients in the placebo group. *See* Figures A and B (Vascepa is referred to as icosapent ethyl in these figures).

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.

Within the data presented in the above figures, patient-by-patient differences in LDL-C levels from baseline to Year 1 included some patients with increases, some patients with decreases and others with no change in both the Vascepa arm and the placebo arm of the REDUCE-IT study. If mineral oil affected statin absorption significantly, it is reasonable to expect that such effect might be evident in all patients on placebo (i.e., if mineral oil had a definitive effect one would expect LDL-C increases would be *consistently* observed among patients in the placebo arm) rather than the observed mixed results that include many patients with LDL-C decreases or lack of change in LDL-C.

Other Cardiovascular Benefits Observed with Eicosapentaenoic Acid (EPA) Independent of Mineral Oil Use

Although open label, the Japan EPA Lipid Intervention Study (JELIS) previously demonstrated a 19% risk reduction with a high concentration EPA product (an ethyl EPA preparation similar to icosapent ethyl) without a placebo.[46] JELIS provides supportive but not conclusive data that EPA drug therapy could

reduce major coronary events. JELIS included 18,645 patients with hypercholesterolemia in Japan, and it showed that patients receiving a highly purified EPA drug product plus a statin had 19% fewer major coronary events after a mean of 4.6 years than those taking only a statin.

Patients treated with EPA and statin in JELIS achieved triglyceride levels that were only 5% lower, on average, than those achieved among patients treated with statin alone; however, the reduction in cardiovascular risk in the primary endpoint analysis was 19%. Likewise, within the primary and secondary prevention sub-analyses, triglyceride levels were lowered only 5% on average in the EPA plus statin group compared with the statin alone group; however, the relative risk reduction was as follows:

- 53% in the primary prevention population with elevated triglyceride and low HDL-C levels[47]
- 23% in the secondary prevention population with established coronary artery disease[48]

Again, no placebo was used in JELIS.

In connection with FDA regulatory review of Vascepa, JELIS results led Amarin to request that FDA consider whether the cardioprotective effects of EPA observed in JELIS were due not to a single mode of action, such as triglyceride lowering, but rather to multiple mechanisms working together. In regulatory dialogue with Amarin, FDA did not disagree with this possibility.

Also in Japan, the CHERRY study showed that EPA added to high dose statin doubled plaque regression vs. high dose statin therapy alone.[49]

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."

The observation that at least some of the effect of icosapent ethyl that resulted in a lower risk of ischemic events may be explained by metabolic effects other than a reduction of triglyceride levels is consistent with prior interpretations of JELIS.

REDUCE-IT was designed as a cardiovascular outcomes study, and as such, 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 triglyceride reduction, anti-thrombotic effects, antiplatelet or anticoagulant effects, membrane-stabilizing effects, effects on stabilization and/or regression of coronary plaque and inflammation reduction. Each of these potential mechanisms were

supported by earlier stage mechanistic and other studies cited in *The New England Journal of Medicine* publication of REDUCE-IT results. Independent of REDUCE-IT, Amarin has worked for years 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.[50,51,52,53,54]

More information on how Vascepa might work to lower cardiovascular risk is available here: https://investor.amarincorp.com/static-files/eaf1ff2e-e014-4180-880b-058278dffb06.

Conclusion

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, agreed that the results of REDUCE-IT support the study conclusions 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 *The New England Journal of Medicine*.

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

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