

Mineral Oil and Placebo Inertness Issue

A more detailed review of communications between the FDA and Amarin suggest bureaucratic ineptness and lack of coordination between groups within the FDA, and inappropriate data analysis.

Furthermore, the issue never should have been raised, as it had already been dealt with to the satisfaction of the FDA earlier in its review of the MARINE NDA in which a similar observation was noted with the FDA's review of Lovaza several years earlier.

The Negotiated Special Protocol Assessment (SPA)

In drafting the terms of the SPA, the FDA agreed that light mineral oil was acceptable as a placebo as long as the amount per capsule did not exceed the amounts in FDA-approved products given by the same route of administration. Each placebo capsule contained approximately 1 g of light mineral oil, which was dosed two capsules twice daily with food, or about 4 ml/day. Mineral oil has been medically used as a laxative at much higher doses of 15 – 45 ml/day. Light mineral oil, also known as light liquid paraffin (LLP), is highly refined mineral white oil and is a mixture of liquid hydrocarbons obtained from petroleum, which do not contain any functional groups (e.g., no carboxyl groups in contrast with fatty acids in vegetable oils) and are considered chemically inert with minimal systemic.

Issue Raised in FDA Briefing Book

The specific language of the FDA Briefing Book prepared in October of 2013 in relation to this matter follows:

"The FDA briefing documents raised questions about the mineral oil placebo used in the ANCHOR clinical trial intended to support the expanded approval, thereby potentially negatively impacting the control group data, and suggesting that "the treatment effects observed with [Vascepa] may be overestimated."

Amarin's sNDA Submission in February of 2013 (this is actually from the MARINE NDA) So point is if they approved the mineral oil use in MARINE and approved Vascepa in July 2013 why would the same issue be raised when reviewing the sNDA for ANCHOR.

An excerpt of Amarin's submission, which clearly indicates communication with Dr. Iffat Chowdhury of the FDA, who was involved with a preliminary review, includes the following:

"Given the increase in median TG levels in the placebo group from baseline to Week 12, Dr. Iffat Chowdhury [of the FDA] requested that the applicant submit information about the composition of the placebo capsule used in the clinical study. The placebo was composed of light mineral oil or paraffin light liquid. Data submitted by the applicant support the assertion that light mineral oil does not increase serum TG levels. Dr. Chowdhury notes in her review that similar increases in TG levels were observed in the placebo groups from the Lovaza clinical trials of hypertriglyceridemic patients."

Inappropriate Analysis

The doubt cast by the FDA was accomplished by merely suggesting that the data was so strong compared to the placebo group, that perhaps the effects of mineral oil were not as inert as previously assumed and that, just maybe mineral oil was in some way degrading the effect of the stain therapy all participants were on, thus exaggerating the data.

First reduce confidence, then, ask for vote of confidence...

A closer look at the manner in which the data was skewed by the FDA in its briefing suggests either; the FDA was "innocently incompetent" or that a sinister plot was underway to purposefully undermine the panelists' confidence in Vascepa's effectiveness. Before discussing how FDA officials accomplished this feat, consider the final voting question. The FDA asked the panel to consider their personal confidence in the performance of Vascepa to reduce cardiovascular events in an outcomes study expected to be completed in approximately four years time. Assuming the goal of the FDA was to extract a negative vote tally from the panelists, it stands to reason the FDA would have to find a way to discredit the clinical trial data, before they posed the voting question.

FDA trickery

Before the FDA could be effective at casting the "net of doubt" into the minds of the AdCom, it needed to suggest it had "stumbled" upon this possible "explanation of great efficacy" using standard methods statistical analysis. But in fact, the FDA blatantly skewed the statistical analysis and thus manipulated the conclusion. Here is how they did it.

The FDA achieved this "sleight of hand" by using a clever technique. They used "non---scale week" in the x---axis and in doing so, could now point to what now appeared to be unusual rise of triglycerides in the placebo group. Hence, they could now paint themselves as "detectives of due diligence" and unveil what the shocking revelation; "perhaps mineral oil isn't as inert as previously assumed".

An analytical faux pas or outright deception by FDA?

In a normal scientific presentation, plots of time dependent data are made on a time scale plot. The X---axis should be a time scale. But the FDA plotted the data in random manner.

The week ---6 to ---8 weeks should be for the screening period far left of the scale. But Week 11 and week 12 show the same axial space as from week 4 to week 11. Week 0 to week 4 shows same axial space as week 0 to ---1 week. By using this falsified data, the FDA "brings down the house" by displaying a graph that suggests mineral oil is doing something 'unexpected' and achieves its desired outcome; doubt of efficacy.

By skewing the representation of the data, the FDA manipulation is not visible to those unaccustomed to scrutinizing statistics and thus the FDA hid the true performance and effectiveness of Vascepa.

A detailed analysis of the FDA (manipulated) analysis

All groups prior to taking 4 gms of mineral oil, 2gms of AMR with 2 gms of mineral oil and 4 gms of AMR have showed TG increasing steadily during 6---8 weeks wash---out period. The data shows that TG for all subjects are rising steadily when all other secondary therapies are stopped.

If the mineral oil had interaction with the ineffectiveness of statin, TG at 4 weeks in Placebo group should have elevated high level of TG. The rate of change in TG as a function of time should have been accelerated. However, the plot of TG against 6 weeks of period prior to taking oil and 12 weeks with the mineral oil shows a linear function. TG is increasing linearly as a function of time until the trial ends. **The point is that mineral oil did not affect the pace of the TG rise in Placebo group. It was already there before taking 4gms of mineral oil.**

This observation, based on the data in the Briefing Document prepared by FDA, indicates that there is not any significant interaction between oil and statin to lower the effectiveness of statin toward TG. Subjects in the Placebo group show continuously increasing TG over 18 weeks period.

This observation clearly indicates that stable dose statin therapy alone is not powerful enough to control triglycerides in this population group (TG>200 mg/mL to <500 mg/mL).

The effectiveness of Vascepa for reducing TG is truly dose dependent. The group taking 2 gms of Vascepa shows TG gradually decreasing during 12 weeks of trial period. It may not have reached the full effect of Vascepa.

The group taking 4 gms of Vascepa has shown full effect on TG within 4 weeks period by reaching a pseudo equilibrium zone (a stable state) during next 8 weeks.

In conclusion, we suggest that increase in triglycerides (TG) for the Placebo group during the 12 weeks trial period is not related to interference of mineral oil in statin therapy. It is related to the effectiveness of statin therapy not powerful enough to control TG upon removing secondary treatment taken by the Placebo group prior to admitting to the Phase 3 Trial. This indicates that the population group (TG>200 mg/mL to <500 mg/mL) needs effective additional secondary treatment in addition to statin therapy to control TG. Daily dose of 4 gms of Vascepa is recommended to control TG in addition to statin for the control of TG.