# The Vascepa sNDA... An Open Letter to Dr. Janet Woodcock, Dr. Curtis Rosebraugh and Dr. Stephen Ostroff

*AIM-HIGH, ACCORD-Lipid and HPS2-THRIVE do not support FDA's claim that high TG-lowering in the ANCHOR population will likely not result in clinical benefit.*

HOUSTON, TX, USA, February 13, 2014 /EINPresswire.com/ -- A lawyer's perspective:

Amarin's appeal of FDA's rescission of the ANCHOR SPA presents this issue: Is there sufficient evidence to support FDA's assertion that there is a substantial, new scientific issue regarding the basis (a possibility of some clinical benefit) for using Vascepa to lower high (200-499 mg/dL) triglycerides (TGs) in patients with mixed dyslipidemia? FDA reviewers offer as their evidence AIM HIGH, ACCORD-Lipid and HPS2-THRIVE, arguing those studies did not demonstrate CVD risk reduction when fibrates or niacin were used to lower TGs.

> We need to employ the best science in ways that will increase efficiency, productivity and our shared ability to find creative solutions to the challenges that confront us.
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> *Dr. Margaret A. Hamburg, FDA Commissioner*

The Citizen's Petition (CP) amply demonstrates why those studies' results do not satisfy FDA's evidentiary burden. Fibrates and niacin materially differ from Vascepa, having entirely different mechanisms of action. Further, none of the three studies was designed to show TG-lowering effects in high TG patients. Significantly, all studies' patient populations had median baseline TG levels that were normal or only borderline high, below the 200-499 mg/dL "high" range of ANCHOR. The FDA's evidence and reasoning, therefore, can hardly be characterized as sound, "scientific" or "substantial." The plainly apparent weaknesses in FDA's evidence, alone, should end the inquiry and warrant reinstatement of the SPA.

Importantly, however, the CP also demonstrates how (ironically) two of those studies, AIM HIGH and ACCORD-Lipid, actually suggest the contrary of FDA's claim, i.e., that TG-lowering drugs used in high TG patients likely do result in CVD event reduction. Subgroup analyses in AIM HIGH and ACCORD-Lipid showed patients with TGs > 200 mg/dL had 37% and 28% reduction in CVD risk, respectively. FDA reviewers ignored these results (as subgroup analyses) in their advisory committee presentation. That omission might be excusable had they not concurrently relied, unscientifically, on the same studies in arguing that TG-lowering using Vascepa is unlikely to have clinical benefit in high TG patients. But, they did so ignore, and did so rely, casting serious doubt on the scientific integrity of the

review process.

A third study, JELIS, provides additional, valuable insight. There, 18,645 Japanese patients on statin therapy were randomized to receive either statin plus Ethyl-EPA (a drug similar to Vascepa) or statin alone and were followed for 5 years for cumulative incidence of major coronary events. Subgroup analysis (n=957) of those with TG > 150 mg/dL and low HDLc (< 40 mg/dL) showed the Ethyl-EPA arm had an impressive 53% reduction in events vs. such patients on statin alone (Saito, et al Atherosclerosis, 2008; 200: 135-140). This result, also, and again contrary to FDA reviewers' theory, suggests that lowering elevated TGs (here, using a drug similar to Vascepa) significantly lowers CVD event rates.

There are not, however, just three trials (AIM-HIGH, ACCORD-Lipid and JELIS) that cumulatively support the contrary of FDA's position. There is a fourth that, until recently, may have been overlooked: The Bezafibrate Infarction Prevention (BIP) Study http://circ.ahajournals.org/content/102/1/21.full.

BIP, similar to AIM-HIGH, JELIS, and ACCORD-Lipid (again in subgroup analysis) suggests that lowering elevated TG in a TG >200 mg/dL population reduces CVD event rates.

In BIP, a double-blind trial, 3,090 patients with a previous myocardial infarction or stable angina, total cholesterol of 180-250 mg/dL, HDL-C ≤45 mg/dL, TG ≤300 mg/dL, and LDL-C ≤180 mg/dL, were randomized to receive either 400 mg of bezafibrate per day or placebo; they were followed for a mean of 6.2 years. Bezafibrate increased HDL-C by 18% and reduced TG by 21%. Both Placebo and Bezofibrate treatment group had baseline TG = 145 +/- 51 mg/dL. Frequency of the primary end point (fatal or nonfatal MI, or sudden death) was 13.6% on bezafibrate versus 15.0% on placebo (P=0.26). After 6.2 years, the reduction in the cumulative probability of the primary end point was 7.3%, (P=0.24).

Post hoc analysis was performed to determine the effect on primary end point for patients with baseline TG ≥ 200 mg/dL compared to the effect on patients with baseline TG < 200 mg/dL. Among patients with baseline TG ≥200 mg/dL (225 patients in the placebo group and 234 in the bezafibrate group), bezafibrate reduced the cumulative probability of a primary end point by 39.5% (P=0.02), whereas among patients with baseline TG <200 mg/dL (1317 patients in the placebo group and 1314 in the bezafibrate group), the reduction in the cumulative probability of an end point was insignificant. Once again, the high TG subgroup, when treated, experienced a significantly lower CVD event rate.

AIM-HIGH, ACCORD-Lipid and HPS2-THRIVE plainly do not support FDA's claim that high TG-lowering in the ANCHOR population will likely not result in clinical benefit. For that reason, alone, the SPA should be reinstated.

Four trials' (AIM-HIGH, ACCORD-Lipid, JELIS, and BIP) subgroup analyses, by contrast, consistently suggest the contrary of FDA's claim. In all four, "high" (> 150 mg/dl in JELIS) TG patients who received TG-lowering therapy experienced lower incidence of CVD events.

These data should be viewed in context with other relevant data sources regarding hypertriglyceridemia and CVD risk. Many, large epidemiologic studies have indisputably demonstrated a correlation between TG elevation and CVD risk. TG-associated CVD risk has been shown to exist in all races and both genders. Meta-analyses have shown TG elevation to be an important risk factor in both healthy subjects and those with underlying CVD risk. Most importantly, these studies have shown that increased CVD risk is proportional to the degree of TG elevation. For example, in their 2013 meta-analysis, Liu, et al concluded that every 10 mg/dL increase in TG predicts a 1.4% increase in CVD risk (Liu, et al, Lipids Health Disease, 2013).

In light of these data, major medical societies recognize the importance of TG elevation as a risk factor in CVD. The American Heart Association (AHA), American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), and American College of Cardiology (ACC) recommend treatment of patients whose TG > 200 mg/dL. If, after lifestyle modification (diet, weight loss, and exercise) efforts, TG level remains > 200 mg/dL, treatment with TG-lowering drugs should be considered, they advise.

Meanwhile, the enormous human toll and economic cost of further delay in ANCHOR approval grows. It is reasonably possible, if not likely, that CVD event reduction rates experienced by AIM-HIGH, ACCORD-Lipid, JELIS and BIP high (or > 150 mg/dL, in JELIS) TG subgroups would also occur in ANCHOR's (high TG) population if treated with TG-lowering Vascepa. If their CVD event reduction rates were applied to the approximately 36 million Americans in the ANCHOR population, the number of fatal or debilitating cardiovascular events (America's leading cause of death) those Americans will suffer would be significantly lowered, as would the resulting cost to our over-burdened health care system. Vascepa has a good safety profile, notably better than those of other TG-lowering agents. Its manufacturer, therefore, should be permitted to inform those 36 million high TG patients, and their doctors and insurers, of the ANCHOR data, and to market Vascepa for that indication. Only then will these patients, in consultation with their doctors, be able to make informed decisions whether to use Vascepa to lower their high TGs.

Sound public health policy demands swift, corrective action. Vascepa's ANCHOR SPA should be reinstated, and the ANCHOR sNDA should be approved, without further delay.

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