DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Ave
Building 51
Silver Spring, MD 20993

MAR 27 2015

Robert J. Blumenthal, D.M.D.
150 W. Half Way Road #102
Buffalo Grove, IL 60089

Re: Docket No. FDA-2013-P-1612

Dear Dr. Blumenthal:

This letter responds to your citizen petition received on December 13, 2013 (Petition).[1] Your Petition requests that the Food and Drug Administration (FDA or the Agency):[2]

(1) "overturn the FDA's decision to rescind the Special Protocol Assessment [SPA] Agreement for the ANCHOR trial" conducted with Vascepa (icosapent ethyl) capsules,

(2) "conduct an independent scientific review of the three outcome trials cited by the FDA reviewing division that were asserted to reveal 'substantial scientific issue' and were given as justification for rescinding the ANCHOR SPA,"

(3) "rule that the outcome trials cited by the FDA reviewing division show that the patients with high TG [triglyceride] level (≥ 200 [milligram/deciliter (mg/dl)]) and low HDL [high-density lipoprotein]-cholesterol, the patient population covered by the ANCHOR SPA, had a reduction in cardiovascular disease (CVD) risks,"

(4) "delay the PDUFA [Prescription Drug User Fee Act] date for the ANCHOR sNDA [supplemental new drug application]," and

(5) "investigate the reviewing division for possible misconduct during the ANCHOR sNDA review process, including concern with the timely communication and conveying of key issues to the sponsor, improper processing of the briefing document, omission of key data and information related to the three trials cited by the FDA reviewer, improper and imbalanced review of the three referenced studies, improper rescinding of the ANCHOR SPA, improper handling of the FDA advisory panel meeting, and improper voting question not addressing the ANCHOR SPA."

We have carefully and thoroughly reviewed the information in your Petition. For the reasons described below, your Petition is denied.

[1] The introductory paragraph of the Petition suggests that EPA Drug Initiative submitted the Petition, though it was submitted and signed by the petitioner and not specifically EPA Drug Initiative. Petition at 1.

[2] Id. at 1-2.

I. BACKGROUND

A. Vascepa

FDA approved new drug application (NDA) 202057 for Vascepa (icosapent ethyl) capsules on July 26, 2012, as an adjunct to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dl) hypertriglyceridemia. The NDA holder for Vascepa is Amarin Pharmaceuticals Ireland Limited (Amarin). The active ingredient in Vascepa is icosapent ethyl, an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA), which is derived from fish oil. On February 21, 2013, Amarin submitted an sNDA to extend the use of Vascepa as an adjunct to diet and in combination with a statin to reduce TG, non-HDL-cholesterol, Apo B, low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and very low-density lipoprotein cholesterol (VLDL-C) in adult patients with mixed dyslipidemia and coronary heart disease (CHD) or a CHD risk equivalent (ANCHOR indication). As discussed at an October 16, 2013, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC), the new indication was supported in part by data from what is known as the ANCHOR trial.[3]

B. ANCHOR Special Protocol Assessment

A "Special Protocol Assessment agreement" (SPA agreement) is an agreement between FDA and a sponsor regarding the design of certain types of trials. Section 505(b)(5)(B) of the Federal Food, Drug, and Cosmetic (FD&C) Act[4] directs FDA to meet with sponsors for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an efficacy claim in an application submitted under section 505(b) of the FD&C Act or section 351 of the Public Health Service Act.[5] Such applications include NDAs, biological license applications (BLAs), and efficacy supplements to approved NDAs and BLAs. If a sponsor makes a reasonable written request to meet with the Agency to reach an agreement on the design and size of a clinical trial, FDA will meet with the sponsor. If an agreement is reached, the Agency will reduce the SPA agreement to writing and make it part of the administrative record.[6] A SPA agreement is generally considered binding between the division reviewing the protocol and the sponsor and may not be changed by the sponsor or FDA after the trial begins, except (1) with the written agreement of the sponsor and FDA, or (2) if the director of the reviewing division determines "that a substantial scientific issue essential to determining the safety or

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[3] See generally, October 16, 2013, EMDAC Meeting Briefing Information, at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm370984.htm. FDA has interpreted Amarin's proposed indication as describing patients similar to those enrolled in the ANCHOR study (i.e., on a stable statin dose, fasting TG ≥ 200 mg/dL and < 500 mg/dL) and, as reflected in the briefing materials and discussion at the EMDAC meeting, has referred to the proposed indication as the "ANCHOR indication."

[4] 21 U.S.C. 355(b)(5)(B).

[5] 42 U.S.C. 262.

[6] FDA, guidance for industry, "Special Protocol Assessment." The guidances referenced in this document are available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page.

effectiveness of the drug has been identified after the testing has begun."[7]

The ANCHOR trial was the subject of a 2009 SPA agreement.[8] You claim that the "ANCHOR trial fulfilled all aspects of the ANCHOR SPA and demonstrated the efficacy of Vascepa in lowering TG without raising LDL-cholesterol in patients with high TG levels."[9] You also assert that the "briefing document developed by the FDA's reviewing division for the [EMDAC meeting],[10] released several days before the meeting, raised new issues never previously conveyed to Amarin and questioned for the first time whether TG lowering in the ANCHOR population (i.e. patients with high TG level ≥ 200 and < 500 mg/dl) leads to clinical benefit."[11] You state that the "FDA reviewing division specifically referenced three recently completed outcome trials (ACCORD-Lipid,[12] AIM-HIGH[13] and HPS2-THRIVE[14] trials) as providing 'substantial scientific evidence' that Vascepa lowering of TG in patients with high TG (≥ 200 and < 500 mg/dl) would not lead to clinical benefit."[15] You maintain that, because most of the patients who participated in these three clinical trials had normal or borderline TG levels, FDA improperly extrapolated the findings associated with these patients to conclude that lowering TG levels in patients with high TG levels would not reduce their cardiovascular disease risk. You state that subgroup analyses from the three clinical trials in fact showed that patients with high TG levels "had an impressive reduction in CV risk of 28 and 37 %."[16]

You further claim that the "briefing document and FDA presentation during the [EMDAC meeting] omitted crucial information related to the three clinical trials that would support ANCHOR sNDA application and refute the FDA reviewer's assertion that TG lowering in high TG patients would not be clinically beneficial."[17] You maintain that the "voting question [at the EMDAC meeting] was convoluted and confusing, and did not cover ANCHOR SPA, . . . but asked whether a completion of an outcome trial (REDUCE-IT) was required for the ANCHOR approval."[18] You also assert that "[f]ollowing the FDA advisory panel meeting, the FDA gave

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[7] Section 505(b)(5)(C) of the FD&C Act; see also Special Protocol Assessment guidance, supra note 6, at 9-10.

[8] October 16, 2013, EMDAC Meeting FDA Briefing Document at 12, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM370985.pdf.

[9] Petition at 2, emphasis omitted.

[10] The Petition refers to the EMDAC meeting as "ADCOM."

[11] Petition at 2.

[12] The ACCORD Study Group. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. N Engl J Med 2011;362:1563-74.

[13] The AIM-HIGH Investigators. Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy. N Engl J Med 2011; 365:2255-67.

[14] The HPS2-THRIVE Collaborative Group. Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients. N Engl J Med 2014; 371:203-212.

[15] Petition at 2.

[16] Id. at 4.

[17] Id. at 2.

[18] Id. at 3.

notice, without elaboration, that the ANCHOR SPA was being rescinded because a 'scientific issue of substance,' not known at the time that the ANCHOR SPA was completed as agreed, had now come to light. The issue being that the FDA reviewing division no longer considers high serum TG concentration as a CVD risk factor."[19]

II. DISCUSSION

Your Petition states that the division reviewing Amarin's sNDA improperly rescinded the SPA agreement for the ANCHOR study.[20] You request that the Agency overturn the "decision to rescind the [SPA] Agreement for the ANCHOR trial."[21]

A. FDA Has a Specific Process For Resolving Disputes Regarding SPA Agreements

You assert that "[f]ollowing the FDA advisory panel meeting, the FDA gave notice, without elaboration, that the ANCHOR SPA was being rescinded because a 'scientific issue of substance,' not known at the time that the ANCHOR SPA was completed as agreed, had now come to light. The issue being that the FDA reviewing division no longer considers high serum TG concentration as a CVD risk factor."[22] FDA has established a specific process for resolving disputes involving SPA agreements. FDA's final guidance on Special Protocol Assessments explains the process for sponsors to resolve disagreements with FDA with respect to the SPA process. Specifically, the guidance states that if a sponsor tries to resolve a disagreement on an FDA action with the review division and is not satisfied with the division's response, then the sponsor can decide to initiate the formal dispute resolution process.[23]

The decision to dispute an FDA action with respect to a SPA agreement is made by the sponsor that entered into the SPA agreement with FDA. Therefore, your request to overturn a decision by an FDA review division regarding a SPA agreement is denied.

B. FDA Will Not Discuss the Three Outcome Trials Because They Have a Direct Bearing on an Unapproved Application

You next request the Agency to "conduct an independent scientific review of the three outcome trials cited by the FDA reviewing division that were asserted to reveal 'substantial scientific issue' and were given as justification for rescinding the ANCHOR SPA."[24] You claim that the "FDA reviewing division erred in extrapolating that these 3 outcome trials showed that [TG]

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[19] Id.

[20] Id. at 1-2.

[21] Id. at 1.

[22] Id. at 3.

[23] See Special Protocol Assessment guidance, supra note 6, at 10. See also, FDA, guidance for industry, "Formal Dispute Resolution, Appeals Above the Division Level," (Feb. 2000). This guidance is available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[24] Petition at 1.

lowering therapy would not be beneficial in patients with high TG level (≥ 200 and < 500 mg/dl), the population covered by the ANCHOR SPA."[25] Related to this request is your third requested action, which is that the Agency "rule that the outcome trials cited by the FDA reviewing division show that the patients with high TG level (≥ 200 mg/dl) and low HDL-cholesterol, the patient population covered by the ANCHOR SPA, had a reduction in [CVD] risks."[26] You claim that "[s]ub-group analyses from these trials indicate that patients with high TG and low HDL had a reduction in CVD risk of 28 and 37%."[27]

As discussed above in Sections I.A and I.B, Amarin submitted an sNDA in 2013 for the use of Vascepa for the ANCHOR indication. As reflected in the briefing information from the October 16, 2013, EMDAC meeting, the results of the three outcome trials to which you refer have a direct bearing on that sNDA. As stated above, FDA has thoroughly reviewed all of the information in your Petition. However, under applicable laws and regulations, and consistent with longstanding policy, the Agency generally does not comment publicly on information pertaining to an unapproved application; therefore, your requests are denied.

C. FDA Will Not Extend the PDUFA Goal Date for the ANCHOR sNDA

You request that the Agency "delay the PDUFA date for the ANCHOR sNDA . . . for 180 days to allow for a thorough investigation of the issues raised" in the Petition.[28] We interpret your request to "delay the PDUFA date" as a request to extend the PDUFA goal date. Under the PDUFA Reauthorization Performance Goals and Procedures (PDUFA Agreement),[29] the Agency may extend the PDUFA goal date when an applicant submits a "major amendment"[30] to its application. If an applicant submits a major amendment, the review division may choose to review the amendment. As the PDUFA Agreement states, if the review division determines that the major amendment will result in an extension of the PDUFA goal date, the review division will inform the applicant of the new planned review timeline at the time of the clock extension.[31] Because your Petition does not constitute a major amendment to an application submitted by the applicant, your request to extend the PDUFA goal date to review the issues raised in your Petition is denied.

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[25] Id.

[26] Id.

[27] Id.

[28] Id.

[29] FDA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017, available at http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf.

[30] Id. at 31-32. A major amendment may include a major new clinical safety/efficacy study report or major re-analysis of previously submitted study(ies). Such major amendments can extend the PDUFA goal date by 3 months. A major amendment to a manufacturing supplement may extend the goal date by 2 months.

[31] Id. at 12-13.

D. The Petition Provided Insufficient Justification for Investigating the Review Division

You also request that FDA "investigate the reviewing division for possible misconduct during the ANCHOR sNDA review process," including with respect to Agency communications with the sponsor and various issues related to the October 16, 2013, EMDAC meeting.[32] As a part of the review process, FDA may request outside advice from an advisory committee when the data raise challenging or novel scientific issues relating to the drug's use. After thorough review of the background materials and consideration of comments made by the applicant, FDA, and the public, the advisory committee members provide the Agency with their informed advice. FDA highly values the expertise of the independent experts on its advisory committees and considers advice obtained from the Agency's advisory committees when evaluating a marketing application; however, advisory committee votes and recommendations are not binding on the Agency.

The Agency takes seriously all comments and concerns about advisory committee proceedings and FDA personnel. FDA is committed to ensuring that the drug review and advisory committee processes are conducted professionally and in accordance with applicable statutes and regulations. Furthermore, the Agency recognizes the value of making its advisory committee proceedings transparent to the American public.

Your Petition does not provide sufficient reason for the Agency to open an investigation into these matters. Regarding the review division's handling of the ANCHOR sNDA, the Agency is committed to addressing concerns raised by sponsors, and has several mechanisms in place (for example, formal dispute resolution) that sponsors may avail themselves of during the drug development and application process. Regarding the assessment of the three outcome trials, in Section II.B., we explained that those trials have a direct bearing on an unapproved application. Under applicable laws and regulations, and consistent with longstanding Agency policy, FDA generally does not comment publicly on Agency actions regarding or information pertaining to unapproved applications.

Your claim that the FDA review division omitted key information from its briefing document for and presentation to the October 16, 2013, EMDAC meeting is without merit. You assert that 1) the briefing information and presentation should have clearly presented the primary intent and study design of the three outcome trials, 2) the composition of the enrolled patients should have been included in the presentation, and 3) certain sub-group analyses should have been presented.[33] With respect to the first, section 8.2 of the briefing document describes the study design and composition of the patients enrolled in the three outcome trials.[34] Regarding your second assertion, FDA's presentation describes the relevant baseline lipid/lipoprotein (TG, HDL-

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[32] Petition at 2.

[33] Id. at 6.

[34] October 16, 2013, EMDAC Meeting FDA Briefing Document at 77-94, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM370985.pdf.

C, and LDL-C) levels of the study populations in the three outcome trials.[35] Finally, the review division also described the subgroup analyses, including high TG/low HDL-C subgroup, for the three outcome studies and "JELIS"[36] in its briefing document.[37] Therefore, you have not provided any information that would justify opening an investigation into the way that the review division handled either the briefing document or the EMDAC meeting.

Regarding your concerns about the voting question, clarification of a voting question is a recommended procedure of the advisory committee voting process.[38] Prior to casting their votes, the EMDAC members had an opportunity to seek clarification on the voting question. Voting occurred only after the review division ensured that no additional clarification was needed on the question.[39] Accordingly, your Petition does not provide any information that would justify opening an investigation into the way that the review division handled the voting question at the EMDAC meeting.

As stated above, we have thoroughly reviewed your Petition. Because it does not provide sufficient reason for the Agency to open an investigation into the review division's handling of the ANCHOR sNDA, data associated with the three outcome trials, the EMDAC briefing document, the EMDAC meeting itself, or the voting question at the EMDAC meeting, your request to open an investigation into the review division's actions during the review process for the sNDA discussed at the meeting is denied.

III. CONCLUSION

For the reasons described above, your Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

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[35] October 16, 2013, EMDAC Meeting FDA Presentation at 31-34, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM371761.pdf.

[36] Yokoyama M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007; 369:1090-98.

[37] See supra note 34.

[38] FDA, "Guidance for FDA Advisory Committee Members and FDA Staff: Voting Procedures for Advisory Committee Meetings" (August 2008), available at http://www.fda.gov/regulatoryinformation/guidances/ucm122045.htm.

[39] October 16, 2013, EMDAC Meeting Transcript at 304, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM376102.pdf.