



DEC 13 2019

Steven Giardino  
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Re: Docket No. FDA-2019-P-3424

Dear Mr. Giardino:

This letter responds to a citizen petition (Petition) submitted by Medical Research Collaborative, LLC (MRC or Petitioner) received on July 16, 2019. The drug at issue is Vascepa (icosapent ethyl) capsules (new drug application (NDA) 202057). Amarin Pharma Inc. (Amarin), the NDA holder for Vascepa, submitted supplement 35 (sNDA-35 or supplement) to the Vascepa NDA for approval of a cardiovascular risk-reduction claim. The primary basis for approval of this claim is the Reduction of Cardiovascular Events with EPA — Intervention Trial (REDUCE-IT). Vascepa's supplement was the subject of the November 14, 2019, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC).<sup>1</sup>

MRC is predominantly concerned about the use of mineral oil as the placebo in REDUCE-IT because MRC believes that mineral oil interferes with the absorption of coadministered cardiovascular drugs. Specifically, MRC requests that the Food and Drug Administration (FDA, the Agency, we) take the following actions:<sup>2</sup>

- Delay approval of sNDA-35 for Vascepa, “until such time as reliable data are presented to the [Agency] from multiple clinical drug interaction studies, proving that concomitant dosing of mineral oil with cardiac medications does not attenuate the absorption/efficacy of the latter.”
- Ask that the drug-drug interaction (DDI) studies be conducted to “mimic the actual dosing patterns of subjects in the placebo group of REDUCE-IT, by requiring that the sponsor use the services of a third-party organization to poll such participants if living, and family members if deceased, to ascertain the most common dosing pattern of such subjects . . . so that drug-drug interaction studies can be designed to accurately reflect what actually occurred in the trial, not just what was recommended . . . ”

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<sup>1</sup> See FDA notice, “Endocrinologic and Metabolic Drugs Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments” (84 FR 48152, September 9, 2019), Docket No. FDA-2019-N-3936, available at <https://www.govinfo.gov/content/pkg/FR-2019-09-12/pdf/2019-19770.pdf>.

<sup>2</sup> Petition at 1-2.

- If the DDI studies “present compelling evidence the REDUCE-IT trial design, which utilized what appears to be a placebo that is not inert and may attenuate the efficacy of concomitant cardiac medications, was faulty to answer the central question of the study (i.e. ‘Does dosing with 4 [gram (g)/day (d)] icosapent ethyl reduce the risk of [atherosclerotic cardiovascular disease (ASCVD)] in subjects with elevated triglyceride levels who are also at increased risk of a cardiac event?’),” then rescind the special protocol assessment (SPA) agreement for the REDUCE-IT trial and issue a complete response letter for Vascepa’s supplement, “requesting reliable efficacy data from a new cardiovascular outcomes trial (CVOT) designed with a truly inert placebo before expanding the label for Vascepa to include patients with elevated triglycerides (~135 [milligrams (mg)/deciliter (dL)] – 499 mg/dL) and at increased risk of ASCVD.”
- “[P]lace a clinical hold on the EVAPORATE trial . . . in which the same 4 g/d mineral oil dose as in REDUCE-IT is currently being administered to [the] placebo group subjects, who are on similar background therapies and of similar ASCVD risk as the REDUCE-IT trial subjects, and any other trials that utilize mineral oil placebo where concomitant therapies might also be attenuated, until such time as mineral oil is proven harmless in this regard, as such subjects could be exposed to immediate and serious harm.”
- Add a warning to the labeling “of all largely undigestible, synthetic fats or fat-substitutes for sale in the US that are for internal use (i.e. mineral oil), or are a main ingredient in such products for consumption (i.e. olestra), mentioning the possibility that synthetic or semi-synthetic, poorly digested lipids may interfere with the absorption of orally administered drugs — unless and until the results of numerous DDI studies exonerate these specific oils in this regard.”

We have carefully considered the assertions raised in the Petition, as well as your comment.<sup>3</sup> For the reasons described below, the Petition is denied.

## I. FACTUAL BACKGROUND

FDA approved 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 ( $\geq 500$  mg/dL) hypertriglyceridemia. The active ingredient in Vascepa is icosapent ethyl, an ethyl ester of eicosapentaenoic acid (EPA), which is derived from fish oil. Vascepa is de-esterified during the absorption process, and the active metabolite EPA is absorbed in the small intestine and enters the systemic circulation mainly via the thoracic duct lymphatic system. According to Vascepa’s

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<sup>3</sup> See Docket No. FDA-2019-P-3156-0006 (Comment). This comment was submitted to a different docket (Docket No. FDA-2019-P-3156) because, according to MRC, it was unable to post the Comment to the correct (i.e., Petition) docket. While our response to petitions do not ordinarily include comments that are not in the correct docket, in this instance we have, as a matter of discretion and for the sake of completeness, reviewed and address the assertions raised in the Comment.

prescribing information, the recommended dose is 4 g/d (2 g twice daily) of icosapent ethyl.<sup>4</sup>

Vascepa (or AMR101, the alphanumeric descriptor used in the clinical trials) was initially approved for the severe hypertriglyceridemia indication with support from the MARINE trial (Study AMR-01-01-0016), a 12-week, randomized, placebo-controlled, double-blind trial of 224 adult patients with severe hypertriglyceridemia (TG between 500 and 2000 mg/dL), randomized 1:1 to AMR101 or mineral oil placebo.<sup>5</sup> Patients with severe hypertriglyceridemia are at increased risk of acute pancreatitis. In this trial, AMR101 decreased TG by 33 percent versus mineral oil placebo.

Amarin also conducted the ANCHOR trial (Study AMR-01-01-0017), a 12-week, randomized, placebo-controlled, double-blind trial of adult patients with persistent high fasting TG levels ( $\geq 200$  mg/dL and  $< 500$  mg/dL), despite statin treatment to low-density lipoprotein cholesterol (LDL-C) goal.<sup>6</sup> FDA does not consider lowering TG levels to be a surrogate endpoint for reducing the risk of cardiovascular disease (CVD).

To support the approval of a cardiovascular (CV) risk-reduction claim, Amarin conducted a CVOT called REDUCE-IT.<sup>7</sup> The main objective of REDUCE-IT was to evaluate the clinical benefit of AMR101 when added to optimized background statin therapy in patients at high risk for CVD. The trial was a randomized, double-blind, placebo-controlled, multi-center, multinational trial of 8,179 patients, randomly assigned 1:1 to either 4 g/d of AMR101 or mineral oil placebo. The primary endpoint was a composite of CV death, nonfatal myocardial infarction (including silent myocardial infarction), nonfatal stroke, coronary revascularization, and unstable angina requiring hospitalization. Patients were statin-treated men and women either with established CVD or with diabetes mellitus and one or more risk factors for CVD. Eligible patients had LDL-C between 40 and 100 mg/dL and TG  $\geq 200$  mg/dL but  $< 500$  mg/dL.

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<sup>4</sup> Vascepa Prescribing Information, Section 2 Dosage and Administration, available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/202057s019lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202057s019lbl.pdf).

<sup>5</sup> Mineral oil, or liquid paraffin, is a light mixture of higher alkanes from a mineral source, which is only minimally absorbed in human gastrointestinal (GI) tract, and thus is used as a lubricant laxative. Because of its chemical property, mineral oil can be a good solvent for many lipophilic compounds, and thus conceivably can function as a vector to reduce the absorption and facilitate the excretion of mineral oil-dissolved lipophilic compounds from the GI tract.

<sup>6</sup> The ANCHOR trial was the subject of the October 16, 2013, EMDAC meeting. Background information and briefing documents are available at: <https://wayback.archive-it.org/7993/20170404151814/> <https://www.fda.gov/AdvisoryCommittees/Calendar/ucm365571.htm>.

<sup>7</sup> November 14, 2019, FDA Briefing Document (Briefing Document) at 3, available at: <https://www.fda.gov/media/132477/download>.

## II. STATUTORY AND REGULATORY BACKGROUND

### A. New Drug Applications

The Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations require that a sponsor seeking to market a new drug submit an NDA to FDA for review.<sup>8</sup> To be approved, an NDA submitted under section 505(b) of the FD&C Act must, among other things, be supported by investigations showing the drug product to be safe and effective for its intended use(s).<sup>9</sup> Section 505(c)(1)(A) of the FD&C Act states that FDA will “approve the application if [FDA] . . . finds that none of the grounds for denying approval specified in [section 505(d) of the FD&C Act] applies.” Section 505(d) of the FD&C Act and FDA’s regulation in 21 CFR 314.125(b) include grounds for refusing to approve an application. For example, FDA will refuse to approve an application if adequate tests do not show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. FDA will also refuse to approve an application if the applicant fails to provide substantial evidence of effectiveness. As stated in section 505(d) of the FD&C Act, “substantial evidence” means:

. . . evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

Efficacy endpoints are measures intended to reflect the effects of a drug. They include assessment of clinical events (e.g., mortality, stroke, pulmonary exacerbation, venous thromboembolism); patient symptoms (e.g., pain, dyspnea, depression); measures of function (e.g., ability to walk or exercise); or a surrogate of these events or symptoms.<sup>10</sup> Demonstrating statistical significance on clinical trial endpoints alone, however, is insufficient. An applicant must also show that the drug provides a therapeutic, or clinically meaningful, benefit.<sup>11</sup>

In analyzing whether a drug meets the standard for approval, FDA conducts a benefit-risk assessment. That assessment “takes into account the extensive evidence of safety and effectiveness submitted by a sponsor . . . as well as many other factors affecting the benefit-risk assessment . . . This assessment inevitably involves both quantitative analyses and a subjective

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<sup>8</sup> Section 505(a) of the FD&C Act (21 U.S.C. 355(a)) and 21 CFR part 314.

<sup>9</sup> Section 505(b)(1) of the FD&C Act.

<sup>10</sup> See, e.g., draft guidance for industry Multiple Endpoints in Clinical Trials (January 2017), at 2. When final, this guidance will represent FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

<sup>11</sup> See, e.g., *Warner Lambert Co. v. Heckler*, 787 F.2d 147 (3d Cir. 1986). See also, FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998).

qualitative weighing of evidence.”<sup>12</sup> Key considerations of benefit “[i]nclude the results of the clinical trials and the clinical meaning of primary and secondary endpoints, as well as appropriate analyses of subpopulations.”<sup>13</sup> Key considerations of risk “[i]nclude the adequacy of the safety database, the severity and reversibility of adverse events, and the potential for sub-optimal management in the post-market setting that may be of concern.”<sup>14</sup>

## B. Investigational New Drug Applications and Clinical Hold

A sponsor must submit an investigational new drug application (IND) to FDA before conducting a clinical investigation in which a new drug is administered to humans.<sup>15</sup> An IND is the mechanism through which a sponsor requests an exemption from the legal requirement that FDA authorization must be obtained before interstate shipment and administration of any new drug product. Each proposed clinical trial is reviewed by a local institutional review board (IRB).<sup>16</sup> If approved by an IRB, a clinical investigation can begin after the IND goes into effect, which is defined as either 30 days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold under § 312.42 (21 CFR 312.42), or earlier upon notification by FDA.<sup>17</sup>

There are a few exemptions from the typical IND requirements. For example, a clinical investigation of a marketed drug is exempt from the IND requirements if *all* of the following criteria for an exemption in 21 CFR 312.2(b) are met:<sup>18</sup>

- The drug product is lawfully marketed in the United States.
- The investigation is intended neither to be reported to FDA as a well-controlled study in support of a new indication nor used to support any other significant change in the labeling of the drug.

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<sup>12</sup> See *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision Making, Draft PDUFA V Implementation Plan—February 2013, Fiscal Years 2013-2017*, at 6, available at <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf>.

<sup>13</sup> Id.

<sup>14</sup> Id.

<sup>15</sup> See 21 CFR 312.20(a).

<sup>16</sup> The IRB is a panel of scientists and non-scientists in hospitals and research institutions that oversees clinical research. IRBs approve clinical trial protocols, which describe the type of people who may participate in the clinical trial; the schedule of tests and procedures; the medications and dosages to be studied; the length of the study; the study’s objectives; and other details. IRBs make sure that the study is acceptable, that participants have given consent and are fully informed of the risks, and that researchers take appropriate steps to protect patients from harm. See “The FDA’s Drug Review Process: Ensuring Drugs Are Safe and Effective” web page, available at <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm>.

<sup>17</sup> See 21 CFR 312.40(b).

<sup>18</sup> See FDA’s guidance for clinical investigators, sponsors, and IRBs, *Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND* (September 2013).

- For a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product.
- The investigation complies with the IRB review requirements (21 CFR part 56) and with the informed consent requirements (21 CFR part 50).
- The investigation is not intended to promote or to commercialize the drug product.

FDA's IND regulations provide that FDA can place on clinical hold studies involving drug (and biological) products conducted under an IND.<sup>19</sup> Generally, a clinical hold is an order issued by FDA to the sponsor of an IND to delay a proposed clinical investigation or to suspend an ongoing clinical investigation. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and given the investigational drug; patients already in the study are expected to be taken off therapy involving the investigational drug unless treatment continuation is specifically permitted by FDA in the interest of patient safety. The regulation identifies certain grounds upon which FDA can impose a clinical hold, such as that human subjects are or would be exposed to an unreasonable and significant risk of illness or injury.<sup>20</sup>

### C. Special Protocol Assessment Agreement

A 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 FD&C Act<sup>21</sup> 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.<sup>22</sup> 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.<sup>23</sup> 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

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<sup>19</sup> See, generally, 21 CFR 312.42.

<sup>20</sup> § 312.42(b).

<sup>21</sup> 21 U.S.C. 355(b)(5)(B).

<sup>22</sup> 42 U.S.C. 262.

<sup>23</sup> FDA guidance for industry, *Special Protocol Assessment* (April 2018).

of the reviewing division determines “that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.”<sup>24</sup>

As stated in FDA’s guidance for industry on *Special Protocol Assessment*,<sup>25</sup> a substantial scientific issue essential to determining the safety or efficacy of a product may include (but is not limited to):

- Identification of data that would call into question the clinical relevance of previously agreed-upon efficacy endpoints.
- Identification of safety concerns related to the product or its pharmacological class.
- Paradigm shifts in disease diagnosis or management recognized by the scientific community and FDA.
- The relevant data, assumptions, or information provided by the sponsor in the SPA submission are found to be false statements or misstatements, or are found to omit relevant facts, such that the clinical relevance of critical components of trial design is called into question, or appropriate safety monitoring and human subject protection are affected.

#### **D. Warnings in Drug Labeling and Food Labeling**

The Agency has the authority to ensure that labeling provides truthful and nonmisleading information to consumers. Under section 502 of the FD&C Act, a drug is deemed misbranded if its labeling is false or misleading in any particular; similarly, under section 403(a)(1), a food is misbranded if its labeling is false or misleading in any particular. Section 201(n) states that in determining whether labeling is misleading, FDA shall take into account not only representations made about the product, but also the extent to which the labeling fails to reveal facts material in light of such representations made or suggested in the labeling or material with respect to consequences which may result from use of the article to which the labeling relates under the conditions of use prescribed in the labeling or under such conditions of use as are customary or usual.<sup>26</sup> The omission of certain material facts from the label or labeling of a drug or food (or any other FDA-regulated product) causes the product to be misbranded.

Subpart B of 21 CFR part 201 sets forth labeling requirements for prescription drug products, including those related to content and format. For products described in § 201.56(b)(1), FDA regulations at § 201.57 apply. Section 201.57(c)(6) states that the WARNINGS AND PRECAUTIONS section of a prescription drug’s full prescribing information must describe clinically significant adverse reactions, and other potential safety hazards (including those

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<sup>24</sup> Section 505(b)(5)(C) of the FD&C Act; see also Special Protocol Assessment guidance at 9-10.

<sup>25</sup> Special Protocol Assessment guidance at 15-16.

<sup>26</sup> See also 21 CFR 1.21, FDA’s regulation on failure to reveal material facts.

resulting from drug/drug interactions). Labeling must be revised to include a warning about a clinically significant hazard when there is reasonable evidence of a causal association of such an adverse event with the drug.<sup>27</sup>

### III. DISCUSSION

Petitioner's primary concern is with Amarin's use of mineral oil as the placebo in clinical trials, particularly in REDUCE-IT. MRC asserts that mineral oil is not inert, and that it results in decreased absorption and efficacy of ASCVD drugs. Petitioner further claims that in REDUCE-IT, use of mineral oil resulted in increased CV risk in the placebo group, and that this increased risk contributed substantially to the observed treatment difference between Vascepa and placebo. MRC thus questions the comparative risk reduction between Vascepa and placebo observed in REDUCE-IT. Petitioner presents scientific information, from Amarin's clinical trials as well as published literature, to support this assertion and has several requests concerning Amarin's studies and mineral oil.

First, Petitioner requests that FDA delay approval of Vascepa's supplement until DDI studies are conducted to evaluate the effect of mineral oil on the absorption of ASCVD drugs. MRC requests that such DDI studies should "mimic the actual dosing patterns of subjects in the placebo group of REDUCE-IT, by requiring that the sponsor use the services of a third-party organization to poll" subjects (or family members if the subject is deceased) about their use patterns so that the DDI studies can be designed to accurately reflect what occurred in REDUCE-IT.<sup>28</sup>

If the results of the DDI studies demonstrate mineral oil is not inert and may attenuate the efficacy of coadministered ASCVD drugs (such as statins), Petitioner requests that FDA rescind the SPA agreement for REDUCE-IT and issue a complete response letter for the Vascepa supplement requesting a new CVOT be conducted using an "inert" placebo before approving Vascepa for the CV risk-reduction claim. MRC also requests that FDA place on clinical hold the EVAPORATE trial and any other trial in which mineral oil is used as a placebo. Finally, Petitioner requests that a warning be added to "the label of all largely undigestible, synthetic fats or fat-substitutes for sale in the US that are for internal use (i.e. mineral oil), or are a main ingredient in such products for consumption . . . mentioning the possibility that synthetic or semi-synthetic, poorly digested lipids may interfere with the absorption of orally administered drugs — unless and until the results of numerous DDI studies exonerate these specific oils in this regard."<sup>29</sup>

For the reasons explained below, Petitioner's requests are denied.

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<sup>27</sup> § 201.57(c)(6) & (7). See also, FDA guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format Guidance* (October 2011), p. 3-5.

<sup>28</sup> Petition at 1.

<sup>29</sup> Petition at 2.

**A. Data Suggest That Any Potential Impact of Mineral Oil Interaction with ASCVD Drugs Did Not Meaningfully Affect the Magnitude of Vascepa's Positive Treatment-Benefit Compared to Placebo.**

The Petition contains numerous scientific assertions that purportedly support Petitioner's position that mineral oil is not biologically inert and causes decreased absorption of drugs used in the treatment of ASCVD. Petitioner analyzes data on certain biomarkers (e.g., LDL-C and high-sensitivity C-reactive protein (hs-CRP)) and certain events (e.g., bleeding, atrial fibrillation, peripheral edema, and anemia) from REDUCE-IT to corroborate its claim that mineral oil interferes with the absorption of coadministered drugs (particularly statins), thereby resulting in increased CV risk for subjects in the placebo group. MRC also asserts there are published reports suggesting "direct evidence" that mineral oil inhibits the absorption of ASCVD drugs.<sup>30</sup> Accordingly, Petitioner insists the treatment benefits of Vascepa compared to mineral oil placebo observed in REDUCE-IT are overstated.

MRC asserts that, according to its calculations based on the changes observed in LDL-C levels between the treatment groups, the effect of mineral oil could have inhibited statin dose in the placebo group by 3-fold. Petitioner states that if subjects in the placebo group in REDUCE-IT had significantly lower levels of their statin medication absorbed as a result of concurrent dosing of mineral oil, then a more appropriate comparison is not the relative risk between groups with lower versus higher LDL-C levels, but rather "between two groups of predominantly [coronary heart disease (CHD)] patients administered lower versus higher intensity statins, with the resultant differential effects on atherogenic markers, inflammation, atherosclerotic plaque, and ultimately, ASCVD risk."<sup>31</sup>

The Petition then focuses on clinical studies and information supporting the increased prevalence of ASCVD events in patients with elevated hs-CRP levels.<sup>32</sup> MRC states that data from these studies "demonstrate" that hs-CRP is a risk factor for CV events that is "independent and additive" to LDL-C. MRC states that hs-CRP levels in REDUCE-IT were reduced in the Vascepa arm, from 2.2 mg/L at baseline to 1.8 mg/liter (L) at Year 2 (13.9 percent reduction), and increased in the mineral oil placebo arm, from 2.1 mg/L at baseline to 2.8 mg/L at Year 2 (32.3 percent increase) ( $p<0.001$ ). Petitioner contends that the reduction in hs-CRP levels for the AMR101 group "may be explainable as regression to the mean, as one of the potential additional risk factors listed in the inclusion criteria for primary prevention subjects was a hs-CRP level  $> 3.0 \text{ mg/L}$ ."<sup>33</sup> MRC then asserts that the study "preferentially selected for those with acutely elevated as well as chronically elevated CRP levels in its primary prevention segment (~30 percent of all subjects)," and that the hs-CRP values in both groups would be expected "to lower

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<sup>30</sup> Petition at 32-44.

<sup>31</sup> Petition at 8.

<sup>32</sup> Petition at 9.

<sup>33</sup> Petition at 14. MRC also states that other studies testing 4 g/d of icosapent ethyl in subjects for 12 weeks after a stabilization period (largely controlling for regression to the mean), hs-CRP levels had only slightly decreased from baseline.

somewhat as inflammatory markers returned to normal in those with a temporary elevation.”<sup>34</sup> MRC claims the “sharp increase” in hs-CRP levels for the mineral oil placebo group was observed early and was maintained until the end of the study, which MRC claims had a significant impact on the placebo group’s ASCVD risk.<sup>35</sup>

Because statins have been shown to decrease hs-CRP levels, MRC speculates that the variance in hs-CRP levels between the Vascepa and placebo groups is attributable to the decreased absorption of statins in the placebo group. It seems that Petitioner applies the findings from a different study<sup>36</sup> to suggest that the relative risk reduction (RRR) in major coronary events for Vascepa is closer to 13.8 percent in REDUCE-IT, rather than the observed 25 percent RRR, to account for possible mineral oil interference with statin absorption.<sup>37</sup> Next, Petitioner suggests that FDA’s analyses should focus on subjects in the mineral oil placebo group that had an event and determine whether biomarker levels in these subjects were more elevated compared to those in the placebo group who did not have an event.<sup>38</sup>

Petitioner further asserts that the absorption of other ASCVD drugs (such as antithrombotics and antihypertensives) could also be inhibited by mineral oil. MRC states that in REDUCE-IT, “there was a borderline significant increase in bleeding events” in the Vascepa arm compared to placebo (111 versus 85 events, p=0.06).<sup>39</sup> MRC includes statements from various sources that suggest Vascepa has no apparent effect on bleeding time, a measure of platelet function, and does not significantly affect the anticoagulation parameters of warfarin.<sup>40</sup> The observed increase in bleeding events for the Vascepa arm, according to Petitioner, thus is likely caused by decreased absorption of antithrombotic drugs (e.g., aspirin, clopidogrel, ticagrelor) in the placebo arm because of mineral oil. MRC then contends that the 28 percent RRR in stroke and the 31 percent RRR in myocardial infarction observed for the Vascepa arm in REDUCE-IT could be related to the decreased absorption of antithrombotic drugs as these products are effective against both stroke and myocardial infarction in acute coronary syndrome patients.<sup>41</sup>

Next the Petition describes several studies suggesting “negative trends” in EPA supplementation and stroke incidence, which MRC asserts could be related to the increased incidence of atrial

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<sup>34</sup> Petition at 14.

<sup>35</sup> Petition at 15.

<sup>36</sup> The Treating to New Targets (TNT) Investigators, Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. N Engl J Med 2005; 352:1425-1435.

<sup>37</sup> Petition at 18. MRC claims that in the TNT study (see footnote 36), there was a 1.6 percent RRR in CV events for every 1 percent decrease in LDL-C. Using this ratio, Petitioner estimates that the 7 percent difference in LDL-C between the Vascepa and placebo arms implies an 11.2 percent increased risk of CV events in the placebo arm. Petitioner then subtracted the 11.2 percent increased risk from the observed 25 percent RRR in REDUCE-IT to obtain the value of 13.8 percent.

<sup>38</sup> Petition at 18-19.

<sup>39</sup> Petition at 19.

<sup>40</sup> Petition at 19-20.

<sup>41</sup> Petition at 20.

fibrillation associated with EPA.<sup>42</sup> MRC then references data from REDUCE-IT, which showed a significant increase in atrial fibrillation in the Vascepa arm compared to placebo (215 versus 159 events, p=0.003).<sup>43</sup> Because there is a causal relationship between atrial fibrillation and stroke, Petitioner contends that the 28 percent reduction in nonfatal stroke seen in REDUCE-IT for the Vascepa arm is unexpected and could possibly be explained by mineral oil inhibiting the effectiveness of antithrombotics.<sup>44</sup>

Petitioner next focuses on the effect of mineral oil on the absorption of calcium channel blockers (amlodipine, felodipine, and nifedipine), a class of drugs that can cause peripheral edema.<sup>45</sup> The Petition cites studies which suggest that omega-3 fatty acids do not cause fluid retention.<sup>46</sup> MRC theorizes that if mineral oil lowered the absorption of this class of drugs, then one would expect greater incidence of peripheral edema in the Vascepa arm. Petitioner claims that in REDUCE-IT, there was a statistically significant increase in the incidence of edema in the Vascepa arm compared to placebo (267 versus 203 events, p=0.002), which, according to MRC, confirms its theory that mineral oil interacted with the absorption of calcium channel blockers. Petitioner additionally asserts that mineral oil could have decreased absorption of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers resulting in angioedema.<sup>47</sup>

Petitioner next claims that any noted reductions in blood pressure (BP) observed in the Vascepa arm “relate only to their relative increases [compared to] placebo group subjects,” resulting from decreased absorption of antihypertensives in that group.<sup>48</sup> MRC then claims that there was a significant increase in anemia, which is a risk factor for ASCVD events, in the placebo group, which may be explained if mineral oil interacted with iron supplementation or iron-containing food.<sup>49</sup> MRC also contends that mineral oil may have affected the absorption of Vitamin D, which “may also have played a role in increased risk in those with a deficiency.”<sup>50</sup>

MRC then asserts that if mineral oil had an effect on absorption of coadministered drugs, then there would be “a lesser adverse impact in primary prevention subjects, and greater impact in secondary prevention subjects” in the placebo group, and then explains that the primary prevention subjects in REDUCE-IT showed a lower risk reduction with Vascepa (HR 0.88) compared to the secondary prevention subjects (HR 0.73). Petitioner then compares treatment outcomes across various groups (region (Eastern Europe versus United States), age (>65 years of

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<sup>42</sup> Petition at 20-21.

<sup>43</sup> Petition at 21.

<sup>44</sup> Petition at 21.

<sup>45</sup> Petition at 21.

<sup>46</sup> Petition at 22.

<sup>47</sup> Petition at 21, although Petitioner states that it is unclear if angioedema events were included in adverse events of peripheral edema.

<sup>48</sup> Petition at 22.

<sup>49</sup> Petition at 22-23.

<sup>50</sup> Petition at 23.

age versus <65 years of age), gender (women versus men)) to suggest that co-administered drugs were inhibited in the mineral oil placebo group.<sup>51</sup> It also claims that the 5-year ASCVD event rate in REDUCE-IT's placebo group seems disproportionately high compared to other trials.

Petitioner then notes that “[t]he elevation of all atherogenic and inflammatory markers measured in [the mineral oil] placebo group in the REDUCE-IT trial was previously observed to a similar degree in a separate study — the ANCHOR trial, also sponsored by Amarin Corp.”<sup>52</sup> Petitioner evaluates the biomarker levels in subjects from REDUCE-IT and ANCHOR, and compares them to the results observed in MARINE, Amarin’s clinical trial in subjects with severe ( $\geq 500$  mg/dL) hypertriglyceridemia, 25 percent of whom were on background statin therapy. MRC concludes that the direction of the changes in the biomarkers (such as hs-CRP and LDL-C) between the Vascepa and placebo arms in the trials further suggests that mineral oil inhibited the efficacy of concomitant therapies in REDUCE-IT’s placebo group.<sup>53</sup>

FDA Response:

Because Petitioner’s requests are premised on mineral oil’s interaction with the absorption of statins and other ASCVD drugs, which purportedly could result in increased CV risk in the placebo group and seemingly could exaggerate the treatment benefit of Vascepa, we address that assertion first in this response.<sup>54</sup>

Vascepa is a fish oil-derived product containing icosapent ethyl, which is highly purified ethyl ester of EPA. Most other fish oil supplements and FDA-approved, fish oil-derived drug products contain a mixture of primarily EPA and docosahexaenoic acid (DHA) in various forms, including naturally occurring triglycerides, free fatty acids, ethyl esters, carboxylic acids, re-esterified triglycerides, and phospholipids.<sup>55</sup> Following favorable results from early open-label trials,<sup>56</sup> subsequent clinical trials have shown inconsistent effects of fish oil-derived products on

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<sup>51</sup> Petition at 25.

<sup>52</sup> Petition at 27.

<sup>53</sup> Petition at 30-32.

<sup>54</sup> Petitioner criticizes Amarin’s analysis on the possible interaction of mineral oil placebo on drug absorption. See Petition at 15-16 and 66-80. We also questioned the methodology of Amarin’s analyses, and thus we conducted different analyses to estimate the effect of the increase of LDL-C in placebo on outcomes. Because FDA conducted its own analysis as described here and in the Briefing Document, which formed FDA’s basis of approval for Vascepa’s supplement, FDA will not address the validity of Amarin’s analyses and Petitioner’s assertions regarding those analyses.

<sup>55</sup> National Institutes of Health, Omega-3 Fatty Acids: Fact Sheet for Health Care Professionals, available at <https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional/>.

<sup>56</sup> See, e.g., GISSI-Prevenzione Investigators. Dietary Supplementation with N-3 Polyunsaturated Fatty Acids and Vitamin E After Myocardial Infarction: Results of the GISSI-Prevenzione Trial. Lancet 1999;354: 447-455 (GISSI-P). Yokoyama M et al. Effects of Eicosapentaenoic Acid on Major Coronary Events in Hypercholesterolemic Patients (JELIS): A Randomized Open-Label, Blinded Endpoint Analysis. Lancet 2007;369:1090-1098.

CV outcomes.<sup>57</sup> As stated in the FDA's briefing document for the November 14, 2019, EMDAC meeting (Briefing Document),<sup>58</sup> a recent meta-analysis of 10 randomized clinical trials concluded that randomization to trial arms with omega-3 fatty acid supplementation for a mean of 4.4 years had no significant effect on major vascular events,<sup>59</sup> including no benefit in any high-risk subgroups such as patients with prior vascular disease.<sup>60</sup>

An important caveat is that most of the published clinical trials evaluated products containing mixtures of EPA and DHA (as opposed to EPA alone), and all evaluated doses of EPA much lower than that studied in REDUCE-IT (4 g/d of icosapent ethyl). FDA agrees that the findings described in the studies on the effect of EPA on CV disease (such as GISSI-P and JELIS<sup>61</sup>) may not be directly relevant to Vascepa's supplement seeking approval of a CV risk-reduction claim. Although these studies may be supportive, Amarin could not rely on these studies for approval of a CV risk-reduction claim for Vascepa.

Therefore, Amarin conducted REDUCE-IT, the CVOT to support approval of Vascepa for a CV risk-reduction indication. FDA's analysis of the study results, including exploratory analyses on the possible impact of LDL-C and hs-CRP increases in the placebo arm on CV outcomes, and evaluation of the possibility of mineral oil interference with the absorption of statins and certain other ASCVD drugs, were discussed publicly at the November 14, 2019, EMDAC meeting. Relevant findings presented at the meeting that are responsive to MRC's claims are described below.

### *1. Results of REDUCE-IT*

As described in the Briefing Document, FDA found that compared to mineral oil placebo, Vascepa reduced the risk of the primary composite endpoint by 25 percent (hazard ratio (HR) = 0.752 [95% confidence intervals (CI): 0.682 to 0.830]; p<0.001).<sup>62</sup> Vascepa also reduced the risk of the key secondary endpoint, the time from randomization to the first occurrence of the composite of CV death, nonfatal myocardial infarction, or nonfatal stroke (HR = 0.735 [95% CI: 0.651 to 0.830; p=0.0000006]).

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<sup>57</sup> See e.g., ORIGIN Trial Investigators. N-3 Fatty Acids and Cardiovascular Outcomes in Patients with Dysglycemia. *N Engl J Med* 2012; 367:309-318. The Risk and Prevention Study Collaborative Group. N-3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors. *N Engl J Med* 2013;368:1800-1808.

<sup>58</sup> Briefing Document at 15.

<sup>59</sup> Aung, T. Associations of Omega-3 Fatty Acid Supplement Use with Cardiovascular Disease Risks - Meta-Analysis of 10 Trials Involving 77,917 Individuals. *JAMA Cardiol* 2018;3:225-233.

<sup>60</sup> In addition to the Aung study cited in footnote 59, several other meta-analyses of clinical trials evaluating omega-3 fatty acids and CV events failed to confirm a CV benefit from EPA and DHA supplementation. See e.g., Kwak SM et al. Efficacy of Omega-3 Fatty Acid Supplements (Eicosapentaenoic Acid and Docosahexaenoic Acid) in the Secondary Prevention of Cardiovascular Disease. *Arch Intern Med* 2012;172:686-694. Kotwal S et al. Omega 3 Fatty Acids and Cardiovascular Outcomes: Systematic Review and Meta-Analysis. *Circ Cardiovasc Qual Outcomes* 2012;5:808-818.

<sup>61</sup> See footnote 56 for the references to the GISSI-P and JELIS studies.

<sup>62</sup> Briefing Document at 15.

The Agency determined that Vascepa reduced the risk of individual components of the primary endpoint and secondary composite endpoints, such as fatal or nonfatal MI, fatal or nonfatal stroke, and 3-point MACE plus all-cause mortality.<sup>63</sup> All results were statistically significant per the pre-specified testing plan, except for the final endpoint in the hierarchy, all-cause mortality. FDA found that the results of the primary endpoint were consistent across multiple subgroups, including demographic characteristics (such as age, sex, race, and region); baseline characteristics (such as diabetes mellitus and baseline statin intensity); biomarkers (such as TG and hs-CRP levels); and the two CV risk categories.<sup>64,65</sup> Petitioner claims that outcomes across certain demographics were different, which could suggest mineral oil interference with co-administered drugs. FDA disagrees with Petitioner's characterization of the subgroup analyses in REDUCE-IT. MRC's analysis faces the problem of multiplicity or multiple comparisons. A fundamental concern with multiple comparisons performed without an appropriate, pre-specified testing strategy is that the chance of a spurious finding substantially increases with increasing numbers of comparisons performed. Considering the large number of subgroups evaluated in REDUCE-IT, there was very little heterogeneity overall, except mainly in groups comprising small samples (e.g., low-intensity statin). These findings of heterogeneity of treatment effect could very likely arise from random variation.

Focusing on one demographic, although the estimate of the HR was lower in men than women (greater effect in men), there was no qualitative difference (results favored AMR101 for both groups) and the 95 percent confidence intervals overlapped.<sup>66</sup> Furthermore, any comparison would be confounded by the fact that substantially more men were enrolled in the trial (71.2 percent men versus 28.8 percent women) and women were more likely to be in CV Risk Category 2 (high risk for CVD, i.e., the primary prevention group) compared to CV Risk Category 1 (established CVD patients, i.e., the secondary prevention group). Thus, drawing any conclusion based on-treatment outcomes among men and women, particularly that mineral oil inhibited the efficacy of concomitant therapies, would be unfounded.

FDA found that certain lipid and inflammatory biomarkers related to CV risk increased in the mineral oil placebo arm.<sup>67</sup> LDL-C increased about 7-10 mg/dL (10-13 percent) from baseline in placebo arm at Year 1, with the range of this value depending on the assay (Ultracentrifugation, Direct) or calculation method (Friedewald, Hopkins) used. High-sensitivity C-reactive protein increased by 0.47 mg/L (32 percent) from baseline in placebo arm at Year 2. We observed a

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<sup>63</sup> Briefing Document at 13.

<sup>64</sup> Briefing Document at 13 and 46-47.

<sup>65</sup> Key inclusion criteria for REDUCE-IT include that subjects must have had established CVD (CV Risk Category 1) or were at high risk for CVD (CV Risk Category 2). CV Risk Category 1 was defined as subjects  $\geq 45$  years of age with one or more of the following: documented coronary artery disease (CAD), documented cerebrovascular or carotid disease, or documented peripheral arterial disease. CV Risk Category 2 was defined as subjects with diabetes mellitus requiring treatment with medication, men and women  $\geq 50$  years of age, and one or more additional risk as defined in the protocol. See Briefing Document at 18-19 for more information.

<sup>66</sup> Briefing Document at 46.

<sup>67</sup> Briefing Document at 4, 13, and 49.

similar pattern in the mineral oil placebo arm of ANCHOR in a similar population of subjects (adults at increased risk for CVD on moderate- and high-intensity statin therapy).<sup>68</sup> LDL-C (ultracentrifugation) increased from baseline to Week 12 in the mineral oil placebo group in ANCHOR by 8.8 percent, but not in Amarin’s MARINE trial (-3 percent change from baseline). Nearly all the subjects in both REDUCE-IT and ANCHOR were on background statin treatment, while only about 25 percent of subjects in MARINE were on background statin treatment. Comparatively, subjects in the Vascepa arms experienced less fluctuation in LDL-C levels in Amarin’s three studies (-4.5 percent, 1.5 percent, and 2.8 percent change from baseline in MARINE, ANCHOR, and REDUCE-IT, respectively).

FDA agrees with Petitioner that these data on the placebo arm are atypical and may suggest a potential interference with statin absorption by the coadministration of mineral oil, which could potentially alter the observed treatment benefit of Vascepa. Accordingly, FDA conducted exploratory analyses to evaluate whether an interference by mineral oil on statin absorption meaningfully changed the magnitude of Vascepa’s treatment effect over placebo, and surveyed published literature to find any clinically meaningful effect of mineral oil on drug absorption.

## 2. *Effect of Mineral Oil on Drug Absorption*

At least since 1948, FDA has recognized a possible interaction of drugs containing mineral oil and fat-soluble vitamins, such as vitamins A, D, and K.<sup>69</sup> FDA has thus required manufacturers, packers, and distributors of mineral oil-containing drugs for internal use to add a warning to the drug’s labeling based on research suggesting that oral intake of mineral oil interfered with the absorption from the digestive track of provitamin A and lipophilic vitamins A, D, and K, which could interfere with the use of calcium and phosphorus, resulting in consumers being exposed to deficiency diseases. The following warning is suggested for the labeling of drugs intended for internal use that contain mineral oil: “Caution: To be taken only at bedtime. Do not use at any other time or administer to infants, except upon the advice of a physician.”

In our research of published studies since 1948, we found one well-documented study from 1952 on mineral oil’s interference with the absorption of vitamin A/beta-carotene (the precursor of vitamin A).<sup>70</sup> This well-controlled study investigated the effect of a 4-week ingestion of mineral oil on the absorption of food-sourced beta-carotene from a controlled diet in adults. Interference with beta-carotene absorption by mineral oil was found to be dose-dependent (2.5 milliliters (mL), 5 mL, and 10 mL of mineral oil per meal reduced mean plasma beta-carotene by 16 percent, 33 percent, and 42 percent, respectively) and meal-dependent (30 mL mineral oil at

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<sup>68</sup> Briefing Document at 4 and 58.

<sup>69</sup> FDA, “Notice to manufacturers, packers, and distributors of drugs for internal use which contain mineral oil” (13 FR 1406, March 18, 1948). The regulation is now codified in 21 CFR 201.302.

<sup>70</sup> Steigmann, F. Critical Levels of Mineral Oil Affecting the Absorption of Vitamin A. *Gastroenterology* 1952;20:587-594. See also Briefing Document at 57.

bedtime had little effect whereas 30 mL at the noon-time meal reduced mean plasma carotene concentration by 28 percent).<sup>71</sup>

Petitioner's claim of "direct evidence" of mineral oil inhibiting drug absorption is centered on a thesis that studied the issue in rats.<sup>72</sup> That thesis showed mineral oil interfered with the absorption of a model compound (DDT), a very lipophilic compound. Petitioner also cited some observations about the effect of mineral oil on the absorption of different lipophilic vitamins (A, D, E, and K). Both DDT and these vitamins, however, are more lipophilic than statins. Therefore, Petitioner's cited study is considered indirect evidence, as opposed to direct evidence, and is not dispositive of Petitioner's assertions concerning the interaction of mineral oil on ASCVD drugs, particularly statins.

Whether mineral oil affects statin absorption has not been formally tested to FDA's knowledge. Because statins are less lipophilic than beta-carotene and other lipophilic vitamins, we would expect any interaction between mineral oil and statins to be less than what has been reported in the literature for those compounds. Moreover, if mineral oil placebo and statins are taken separately, any interaction would be expected to be minimal. If they are coadministered, however, then a potential interaction between statins and mineral oil cannot be excluded.

FDA also agrees with Petitioner that data from REDUCE-IT, ANCHOR, and MARINE, which used the same mineral oil product as the placebo, could suggest an interaction between mineral oil and statins.<sup>73</sup>

FDA found a greater LDL-C increase from baseline was observed in subjects in the low-intensity statin group (12.2 percent) than in the moderate-intensity statin group (11.3 percent and high-intensity statin group (10.0 percent) in the placebo arm from REDUCE-IT. Notably, the same trend was not observed in the AMR101 group.<sup>74</sup> This pattern could be explained by a potential interference with statin absorption by mineral oil given the established dose-response characteristics of statins on LDL-C reduction.

The dose-response relationship of atorvastatin, simvastatin, rosuvastatin, and pravastatin (used in approximately 99 percent of the subjects) on LDL-C reduction follows a typical  $E_{max}$ <sup>75</sup>

<sup>71</sup> As presented at the November 14, 2019, EMDAC meeting, beta-carotene absorption decreased by 16 percent in subjects taking 2.5 mL of mineral oil three times daily with meal. The clinical meaning of this reduction is unclear. We note that in REDUCE-IT, subjects in the placebo group were instructed to take 2 g (or 2.5 mL) of mineral oil twice daily with a meal. Because subjects in REDUCE-IT took a lower daily amount of mineral oil and had at least one meal without mineral oil, and beta-carotene is more lipophilic than vitamins A, D, and K, we would expect the absorption of vitamins A, D, and K to decrease by less than 16 percent. See FDA's Clinical Pharmacology Review presentation by Yunzhao Ren, available at: <https://www.fda.gov/media/132767/download>.

<sup>72</sup> Petition at 32-39, citing Palin, KJ. Effect of Oils on Drug Absorption. Ph.D. thesis, University of Nottingham, 1981.

<sup>73</sup> Briefing Document at 58; Petition at 27-32.

<sup>74</sup> Briefing Document at 58-60.

<sup>75</sup> The  $E_{max}$  model is a nonlinear model frequently used in dose-response analyses.

pharmacological trend – that the reduction rate of LDL-C from baseline is steeper at the lower dose range than the higher dose range.<sup>76</sup> In addition, these statins' systemic exposure (area under the curve (AUC)) generally follows a reasonably linear pharmacokinetic profile within the range of therapeutic doses. This indicates that if there is any interference by mineral oil, then the interference should also be linear (consistent percentage decrease of statin AUC by mineral oil across the therapeutic dose range). In this context, a similar percentage reduction of statin AUC would result in steeper increase of LDL-C from baseline at lower doses than at higher doses. This trend was in fact observed in the placebo group of REDUCE-IT. Thus, FDA cannot rule out the possibility that mineral oil (at least to some extent) interfered with statin absorption in REDUCE-IT.<sup>77</sup>

### 3. *FDA's Exploratory Analyses on LDL-C Levels*

Consequently, FDA explored the impact of the increase that LDL-C levels and other biomarkers had on CVD outcomes. LDL-C was analyzed because it is thought to be the most clinically meaningful biomarker for an exploratory analysis to estimate CVD risk. The Agency determined that an appropriate post hoc approach to assess the impact of the increase in LDL-C on CV outcomes in the placebo group is to introduce LDL-C as a continuous covariate in the stratified Cox proportional hazards model<sup>78</sup> for the primary endpoint, assuming that the increase in LDL-C levels in the placebo group was completely contributed by mineral oil's interference with statin absorption. FDA chose Year 1 LDL-C results by the Hopkins method<sup>79</sup> representing a worst-case scenario.

FDA publicly explained its concerns on the possible interaction of mineral oil with ASCVD drugs at the November 14, 2019, EMDAC meeting. FDA's exploratory analysis, which is described in the Briefing Document, addresses FDA's (and Petitioner's) concerns on whether mineral oil's interference with statin absorption alters the direction of Vascepa's treatment effect. Through the exploratory analysis, FDA determined that the LDL-C (Hopkins) absolute value and change from baseline had only a marginal effect on the primary endpoint.<sup>80</sup> The estimated hazard ratio per unit LDL-C value suggests that the approximately 10 mg/dL (12 percent) difference in LDL-C (Hopkins) between the placebo and Vascepa arms from baseline would increase the risk of CV outcomes by 3.1 percent in the placebo arm of the REDUCE-IT trial.<sup>81</sup>

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<sup>76</sup> Briefing Document at 59-60.

<sup>77</sup> FDA also was not able to estimate the magnitude of the increase in LDL-C levels or other biomarkers that could be attributed to an interaction with mineral oil.

<sup>78</sup> The Cox proportional hazards model is a statistical model commonly used in medical research for investigating the association between the survival time of patients and one or more predictor variables (i.e., covariates).

<sup>79</sup> As explained in the Briefing Document at 53, the reasons for selecting the Hopkins method are (1) it was calculated for every subject at all timepoints when lipid data was available; and (2) it represents the greatest post-baseline difference between treatment groups (median Year 1 change from baseline was -1.1 mg/dL and 9.3 mg/dL for AMR101 group and placebo group, respectively) among the various methods to estimate LDL-C.

<sup>80</sup> Briefing Document at 53-54, 61-62.

<sup>81</sup> At the November 14, 2019, EMDAC meeting, FDA explained that the median LDL-C (Hopkins) increased 7.3 mg/dL from baseline in placebo group and decreased 1.6 mg/dL from baseline in AMR101 group on Day 120; that

This small increase in risk does not change Vascepa's overall treatment direction and does not meaningfully alter the magnitude of Vascepa's treatment effect.

4. *FDA's Exploratory Analysis on hs-CRP*

As discussed in the Briefing Document,<sup>82</sup> most subjects in REDUCE-IT had hs-CRP measured only at baseline and on Day 720 (Year 2). Because hs-CRP levels vary considerably depending on many factors (such as if the subject had an event immediately after measuring the value), especially at the lower range,<sup>83</sup> it is unclear whether the results from an exploratory analysis will provide clinically meaningful information. Nonetheless, FDA introduced hs-CRP baseline values, Year 2 values, and percentage change from baseline to Year 2 values as continuous covariates in an exploratory analysis (similar to the LDL-C exploratory analysis) for the primary endpoint.

These data show that hs-CRP absolute values, but not percentage change from baseline, are statistically significant covariates for the hazard ratio on the time to the primary endpoint. The risk of CV outcomes increases by 1.4 percent and 0.5 percent for every 1.0 mg/L increase of hs-CRP absolute value at baseline and at Year 2, respectively. The estimated hazard ratio per unit hs-CRP value suggests that the approximately 0.65 mg/L (50 percent) difference in hs-CRP between arms from baseline would increase the risk of CV outcomes by less than 0.3 percent in the placebo arm of REDUCE-IT.<sup>84</sup>

We disagree with MRC's assertion that an increase in hs-CRP was observed early on. REDUCE-IT was not designed to evaluate changes in hs-CRP (it was collected at baseline, Year 2, and Last Visit), and it is not known when, before Year 2, changes in hs-CRP may have occurred. Thus, it cannot be determined whether the observed changes in hs-CRP are caused by factors such as intercurrent events (e.g., CV events, infections) or random variation. In any event, FDA's exploratory analysis suggests that changes in hs-CRP levels would have limited effect on CV risk.

FDA also disagrees with MRC's claim that the reduction in hs-CRP levels from baseline in the Vascepa group may be explainable as regression to the mean. Elevated hs-CRP was not an inclusion criterion of subjects in CV Risk Cohort 1 (subjects with established CVD, accounting for 70 percent of enrolled subjects); hs-CRP level >3.0 mg/L is listed as one of nine possible risk factors for inclusion in CV Risk Category 2 (subjects with diabetes without established CVD) of the study (about 30 percent of enrolled subjects). Most subjects qualified for CV Risk Category

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the approximately 9 mg/dL difference between groups is estimated to increase CV risk by 3.0 percent in placebo group. See FDA's Clinical Pharmacology Review presentation by Yunzhao Ren.

<sup>82</sup> Briefing Document at 54-55.

<sup>83</sup> Bogaty, P. Time Variability of C-Reactive Protein: Implications for Clinical Risk Stratification. PLoS One 2013, available at <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0060759>. Koc, M. Variation in High-Sensitivity C-Reactive Protein Levels Over 24 Hours in Patients with Stable Coronary Artery Disease. Tex Heart Inst J 2010;37:42-48.

<sup>84</sup> Briefing Document at 54-55.

2 because of the presence of other risk factors, such as age or hypertension. Subjects who enrolled in REDUCE-IT did not necessarily have hs-CRP level >3.0 mg/L, as reflected by their median baseline values (2.2 mg/L at baseline). Thus, because hs-CRP levels were not elevated at baseline, it is unlikely that subjects would experience substantial regression to the mean.

##### 5. *FDA's Exploratory Analysis on Bleeding Events*

As Petitioner observes, a higher proportion of subjects in the Vascepa arm experienced a bleeding event compared to subjects in the placebo arm.<sup>85</sup> Potential bleeding risk has been recognized with omega-3 fatty acids,<sup>86</sup> so it was not entirely unexpected that subjects in the Vascepa arm experienced an increased incidence of bleeding events. Since its original approval, Vascepa's prescribing information has contained a drug interaction statement with anticoagulant and antiplatelet medications given the potential prolongation of bleeding time reported for omega-3 fatty acids.<sup>87</sup>

Excluding hemorrhagic strokes (which were adjudicated events), in REDUCE-IT, approximately 12 percent of subjects in the Vascepa arm and 10 percent of subjects in the mineral oil placebo arm reported a bleeding event.<sup>88</sup> The number of bleeding events was greater in the subset of subjects taking antithrombotic medications (including both antiplatelet and anticoagulant medications) versus those who were not taking such medications. This finding could be explained by several factors, including a direct effect of Vascepa on an increased bleeding risk in subjects who are already at higher risk, interaction between Vascepa and antithrombotic agents leading to increased risk, inhibitory interaction between placebo and antithrombotic drugs leading to decreased bleeding in the placebo arm, or a chance finding in a large clinical study.<sup>89</sup> But we note that the small number of events and the relatively smaller number of subjects in the subgroup of subjects not taking antithrombotic medications at baseline limit any comparison between the subjects taking antithrombotics versus those who were not on these drugs.

FDA disagrees with Petitioner's assertion that the increased bleeding rate in the Vascepa arm is attributable to decreased absorption of antithrombotics in the placebo arm, resulting in decreased bleeding events in that arm. Because of the pharmacologic profile of the two most frequently used antiplatelet agents (aspirin and clopidogrel), we would not expect the reduced absorption of either of these products by mineral oil, if there is any, to account for a difference in bleeding events between arms.<sup>90</sup> Aspirin has a flat dose-response curve for its antiplatelet effects over a range of daily doses from 50 mg to 1500 mg, while clopidogrel has a wide, flat exposure-

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<sup>85</sup> Briefing Document at 67-75; Comment at 8-14.

<sup>86</sup> See e.g., see footnote 56 for the JELIS study reference.

<sup>87</sup> Vascepa Prescribing Information, Section 7.1. Anticoagulants.

<sup>88</sup> Based on this observation, FDA is adding a new warning to Vascepa's labeling on Bleeding.

<sup>89</sup> Briefing Document at 70.

<sup>90</sup> Briefing Document at 71.

response (stable over a 4- to 5-fold range of exposures).<sup>91</sup> Therefore, a potential interaction between aspirin and mineral oil or between clopidogrel and mineral oil would be expected to have negligible effects on clinical antiplatelet activity of either drug. Regarding warfarin, because it is monitored and adjusted to achieve International Normalized Ratio (INR) within a target range, we would expect that any reduction in warfarin's effect by mineral oil to be addressed with dose-adjustments to achieve the appropriate effect in REDUCE-IT.<sup>92</sup>

To investigate whether the difference in bleeding events could have been related to an interaction between mineral oil placebo and a specific antithrombotic agent, FDA analyzed bleeding events by specific background therapy. As presented in the Briefing Document, Table 1 summarizes bleeding events in REDUCE-IT by baseline antithrombotic therapy, regardless of concomitant antithrombotic therapy (i.e., subjects could have been on more than one antithrombotic, such as aspirin and warfarin).<sup>93</sup> There were more bleeding events in the AMR101 arm compared to placebo for the three most commonly used antithrombotics — aspirin, clopidogrel, and warfarin — and the relative increase in bleeding events between AMR101 and placebo was similar, regardless of background therapy. The consistent trend of increased bleeding with AMR101 suggests that any possible interaction between mineral oil and any one of the three most commonly used antithrombotics, if there is any, had negligible effects on clinical antiplatelet activity. Although individual trends for other antithrombotics (ticagrelor, prasugrel, dipyridamole, and non-vitamin K antagonist oral anticoagulants) were variable (some favored placebo and some favored AMR101), low-event rates and a low proportion of patients taking any single agent limit any interpretation of these data.

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<sup>91</sup> Briefing Document at 71.

<sup>92</sup> Briefing Document at 72.

<sup>93</sup> Briefing Document at 73.

**Table 1: Subjects with Bleeding Events by Concomitant Baseline Oral Antithrombotic Therapy, Regardless of Background Therapy, Safety Population**

Item	Antithrombotic therapy (at baseline)	Patients with bleeding / at risk (%)	
		AMR101 N (%)	Placebo N(%)
	All randomized patients	482/4089 (11.8)	404/4090 (9.9)
A	No antithrombotic	45/582 (7.7)	42/596 (7.0)
B	Aspirin	369/3095 (11.9)	301/3082 (9.8)
C	Clopidogrel	122/847 (14.4)	80/817 (9.8)
D	Warfarin	69/327 (21.1)	57/332 (17.1)
E	Ticagrelor	3/59 (5.1)	7/57 (12.2)
F	Prasugrel	8/50 (16.0)	12/62 (19.3)
G	Dipyridamole	7/43 (16.2)	6/42 (14.2)
H	Dabigatran	7/27 (25.9)	4/26 (15.4)
I	Rivaroxaban	5/20 (25.0)	1/21 (4.5)
J	Apixaban	0/6	2/7 (28.5)
K	Ticlopidine	1/2 (50.0)	0/0 (0.0)
L	Phenindione	0/2	0/1

B includes: ACETYLSALICYLIC ACID, ACETYLSALICYLATE CALCIUM, CARBASALATE, CARBASALATE CALCIUM, ASCAL BRISPER CARDIO-NEURO, PAYNOCIL, ASPIMAG (Aspirin/Magnesium), MAGNYL (Aspirin/Magnesium), AXANUM (Aspirin and Esomeprazole), ASASANTIN (Aspirin and Dipyridamole), CLOGNIL PLUS (Aspirin and Clopidogrel), NEFAZAN COMPUESTO (Aspirin and Clopidogrel)  
C includes CLOPIDOGREL BISULFATE, CLOPIDOGREL, CLOPIDOGREL BESYLATE, NEFAZAN COMPUESTO, CLOGNIL PLUS  
D includes: WARFARIN, ACENOCOUMAROL, PHENPROCOUMON  
F includes: PRASUGREL, PRASUGREL HYDROCHLORIDE  
G includes DIPYRIDAMOLE, ASASANTIN  
H includes DABIGATRAN ETEXILATE MESILATE, DABIGATRAN ETEXILATE, DABIGATRAN

#### 6. *FDA's Analysis on Atrial Fibrillation, Atrial Flutter and Other Cardiac Arrhythmias*

Petitioner asserts that EPA is associated with higher incidence of atrial fibrillation. As described in the Briefing Document,<sup>94</sup> there was an increased risk of adjudicated events of atrial fibrillation or atrial flutter events resulting in hospitalization, or prolongation of hospitalization  $\geq 24$  hours in the Vascepa arm compared to the placebo arm. The incidence of atrial fibrillation/flutter was greater among subjects with a self-reported history of atrial fibrillation or atrial flutter, though the incidence of serious treatment-emergent atrial fibrillation/flutter adverse events reported in the safety database were similar between arms.<sup>95</sup> The observed increase in atrial fibrillation or atrial flutter, however, had minimal effect on stroke, as adjudicated stroke events (a component of the primary efficacy endpoint) favored Vascepa. Petitioner contends that the 28 percent reduction in nonfatal stroke seen in REDUCE-IT for the Vascepa arm could possibly be explained by mineral oil inhibiting absorption of antithrombotics. But as discussed above, FDA

<sup>94</sup> Briefing Document at 75-80.

<sup>95</sup> Briefing Document at 80.

found that a potential interaction between mineral oil and antithrombotic drugs would have negligible effects on clinical antiplatelet activity. Furthermore, it is not scientifically reasonable to draw definitive conclusions about stroke (or any other endpoint) in REDUCE-IT based on cross-study comparisons that investigated different study populations, products, and doses (as discussed further below in Section III.A.8). Moreover, to FDA's knowledge, there were no reported imbalances in atrial arrhythmias in the trials cited by Petitioner that might explain the difference in stroke events between the treatment arms in REDUCE-IT.

7. *FDA's Analyses on Anemia, Vitamin D Levels, Peripheral Edema, and Blood Pressure*

MRC asserts that subjects with borderline anemia may have experienced anemia if mineral oil interacted with iron supplementation, and that anemia is associated with increased ASCVD events.<sup>96</sup> In REDUCE-IT, anemia was reported as an adverse event in n=191 (4.7 percent) of subjects on Vascepa and n=236 (5.8 percent) of subjects on placebo.<sup>97</sup> For Treatment Emergent Adverse Events (TEAEs) by MedDRA High Level Term, anemia was reported in 219 subjects in the AMR101 arm (5.4 percent) and 257 subjects in the placebo arm (6.3 percent).<sup>98</sup> The incidences of serious anemia were similar between treatment arms (0.5 percent [22 subjects] and 0.5 percent [20 subjects] in Vascepa and placebo, respectively).<sup>99</sup> The clinical significance of the small difference in subjects reporting an adverse event of anemia is uncertain and not necessarily indicative of mineral oil interference with iron supplement absorption.

Petitioner referenced a review article of observational studies describing an association between low vitamin D levels and increased prevalence of CVD.<sup>100</sup> However, vitamin D levels were not measured in REDUCE-IT, so it is unknown whether any subjects in either arm experienced changes in vitamin D levels or developed vitamin D deficiency. Furthermore, associations between established CVD and vitamin D levels cannot be used to make inferences about the incidence of CV events among subjects in the two arms of REDUCE-IT.

FDA also disagrees with MRC's claim that the small imbalance in subjects experiencing peripheral edema implies decreased absorption of any class of medication. In REDUCE-IT, more subjects on Vascepa reported the term "edema, peripheral" than placebo (6.5 percent versus 5.0 percent, respectively).<sup>101</sup> A variety of clinical conditions, however, are associated with the development of edema. Angioedema associated with ACE inhibitors is an acute, idiosyncratic, allergic reaction that typically causes swelling of the mouth and face, and is not relevant to the finding of increased peripheral edema in REDUCE-IT. Moreover, although some

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<sup>96</sup> Petition at 22.

<sup>97</sup> Briefing Document at 83-84.

<sup>98</sup> Briefing Document at 85.

<sup>99</sup> Briefing Document at 64.

<sup>100</sup> Petition at 23, citing Lee PC, Kini AS, Ahsan C, et al. Anemia Is an Independent Predictor of Mortality After Percutaneous Coronary Intervention. J Amer Coll Cardiology 2004; 44(3):541-546.

<sup>101</sup> Briefing Document at 86.

antihypertensive medications, notably calcium channel blockers, cause peripheral edema, other antihypertensives, such as diuretics, reduce edema. Thus, it is not possible to make an inference about absorption of calcium channel blockers or other cardiac medications based on this isolated finding (a small imbalance in subjects experiencing edema).

FDA also disagrees with Petitioner's assertion that any decrease in blood pressure in the Vascepa group "relate[s] only to [the] relative increases in placebo group subjects."<sup>102</sup> If mineral oil decreased the absorption of antihypertensives in subjects on placebo, we would expect an effect on blood pressure (BP) control. In REDUCE-IT, mean BP changed minimally over time in both treatment arms, and the between-arm difference was small.<sup>103</sup> There was no clear difference between treatment arms in the proportion of subjects experiencing clinically significant increases in blood pressure.

#### **8.     *Weaknesses in Petitioner's Assumptions and Conclusions***

In general, the assertions made throughout the Petition to support MRC's position that mineral oil interacts with ASCVD drugs are premised on inapplicable cross-study comparisons, misleading assumptions, and erroneous conclusions. A drawback generally with cross-study comparisons, which largely forms the bases of Petitioner's hypotheses, is that the inclusion criteria, drugs evaluated, doses administered, background therapy, and trial designs vary among the studies; thus, the ability to compare these published studies to a randomized, controlled study (such as REDUCE-IT) and draw a conclusion is inherently limited. As part of our review process, FDA examined the recent CV outcomes trials in published literature.<sup>104</sup> We found that the populations in these published studies were not comparable to REDUCE-IT because of important differences in patient characteristics, such as the type of qualifying event among patients with established CVD (recent acute coronary syndrome versus chronic established CVD); the proportion of enrolled patients with or without established CVD; the proportion of patients with diabetes mellitus; baseline body mass index (BMI); baseline lipid values; and baseline statin use and statin intensity. In general, the event rate in REDUCE-IT was higher than that of studies with a lower proportion of patients with diabetes and lower baseline BMI (such as

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<sup>102</sup> Petition at 22.

<sup>103</sup> Briefing Document at 94-97. At Day 120, systolic BP increased 0.9 millimeters of mercury (mmHg) from baseline in the placebo arm and decreased 0.5 mmHg from baseline in subjects treated with Vascepa. The between-arm difference in systolic BP was 1.5 mmHg at Year 1 and decreased thereafter. At the final visit, the between-arm difference in systolic BP was 0.6 mmHg (higher in placebo). Differences between arms in diastolic BP were smaller in magnitude. Diastolic BP was 0.6 mmHg higher in placebo compared to AMR101 at Day 120, and the between-arm difference decreased thereafter. The difference was 0.3 mmHg (higher in placebo) at the final visit, with absolute reductions in diastolic BP at the final visit in both treatment arms.

<sup>104</sup> See, e.g., The FOURIER Steering Committee and Investigators, Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017; 376:1713-1722. The ODYSSEY OUTCOMES Committees and Investigators, Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* 2018; 379:2097-2107. The LEADER Steering Committee on behalf of the LEADER Trial Investigators, Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016; 375:311-322. The SAVOR-TIMI 53 Steering Committee and Investigators, Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. *N Engl J Med* 2013; 369:1317-1326.

CANTOS<sup>105</sup>), but lower than the event rate in studies with a higher proportion of patients with diabetes and established CVD.<sup>106</sup>

One example of MRC's improper cross-study comparison is its reference to the ASCEND Omega-3 trial for the proposition that omega-3 fatty acids showed no benefit for stroke compared to placebo.<sup>107</sup> This trial evaluated omega 3-fatty acids (840 mg daily) versus placebo in diabetic patients ≥40 years of age without known CVD. Given the different treatments, dosing, and patient population studied, however, the findings from the ASCEND Omega-3 trial are not relevant to the findings in REDUCE-IT. Another instance of inappropriate comparison is Petitioner's reference to analyses of atrial fibrillation and stroke from observational studies of fish consumption or omega-3 fatty acid supplement consumption.<sup>108</sup> These studies cannot be used to make inferences about the rates of stroke in randomized controlled trials that did not demonstrate imbalances in atrial fibrillation or atrial flutter.

Petitioner also references trials, such as CANTOS<sup>109</sup> and JUPITER,<sup>110</sup> to support the proposition that subjects in the Vascepa group should experience a regression to the mean with respect to their hs-CRP levels. But in both of these published trials, hs-CRP was a major inclusion criterion and median baseline hs-CRP values were greater than 4.0 mg/L, nearly double the baseline level in REDUCE-IT. Similar inadequate inferences about various CVD outcomes based on flawed cross-study comparisons are present throughout the Petition.<sup>111</sup>

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<sup>105</sup> The CANTOS Trial Group, Antinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med* 2017; 377:1119-1131; see also footnote 104 for references to the FOURIER and ODYSSEY OUTCOMES studies.

<sup>106</sup> See, e.g., footnote 104 for references to the LEADER and SAVOR-TIMI 53 studies.

<sup>107</sup> The ASCEND Study Collaborative Group, A Study of Cardiovascular Events in Diabetes – ASCEND Omega-3, available at <https://www.acc.org/latest-in-cardiology/clinical-trials/2018/08/25/02/19/ascend-omega-3>.

<sup>108</sup> Petition at 20-21.

<sup>109</sup> See footnote 105.

<sup>110</sup> Ridker PM, et al, Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein, *N Engl J Med* 2008; 359:2195-2207.

<sup>111</sup> Another example is Petitioner's claim that in two separate studies testing 4 g/d icosapent ethyl in subjects for 12 weeks after extensive stabilization period (purportedly controlling for regression to the mean), hs-CRP levels had only decreased insignificantly by 3-4 percent (Petition at 14). Petitioner cited the FDA clinical review for the MARINE trial, in which hs-CRP changes from baseline were variable. The median change from baseline was -0.1 mg/L, 0.4 mg/L, and 0.5 mg/L in the 4-gram Vascepa, 2-gram Vascepa, and placebo arm, respectively. It is unclear whether changes in hs-CRP in patients following 12 weeks of treatment are comparable or relevant to hs-CRP changes following 2 years of therapy. In the second reference, MRC cites data on the effects of omega-3 fatty acid supplementation on C-reactive protein in patients with muscle loss or impaired physical function because of age or chronic illness. The doses of EPA in these studies ranged from 900 mg to 2800 mg EPA daily, in some cases in a mixture with DHA, and not 4 g/d of icosapent ethyl as MRC claims. Buote SA et al. Update on the Impact of Omega 3 Fatty Acids on Inflammation, Insulin Resistance and Sarcopenia: A Review. *Int J Mol Sci.* 2018;19(1): pii: E218. doi: 10.3390/ijms19010218, available at <https://www.mdpi.com/1422-0067/19/1/218>. These data from different patient populations and different doses of EPA (especially when combined with DHA) cannot be extrapolated to the population studied in REDUCE-IT.

MRC also misleadingly references a published study to support the contention that liquid paraffin (i.e., mineral oil)

The Petition also contains numerous erroneous assumptions and conclusions, particularly with respect to LDL-C and hs-CRP biomarkers, to infer that Vascepa's observed treatment benefit is overstated. For example, MRC's approach in calculating CVD risk reduction based on statin treatment is inherently flawed.<sup>112</sup> Petitioner uses data regarding incremental percentage change (decrease) in LDL-C with increases in statin dose from no-treatment baseline to infer LDL-C percentage increases from baseline following a decrease from stabilized high-intensity statin therapy to a lower dose of statin. This approach is misleading because percentage change from baseline values is entirely dependent on the definition of baseline. In the examples MRC uses to support its position, the two baseline values (no-treatment versus stabilized baseline on-treatment) are not equal. However, using the appropriate baseline value radically changes Petitioner's conclusion.

For example, in the atorvastatin meta-analysis cited in the Petition,<sup>113</sup> an increase in dose from 10 mg daily (moderate-intensity) to 80 mg daily (high-intensity) resulted in additional LDL-C lowering from 37.1 percent to 51.7 percent from baseline (i.e., no treatment), otherwise described by MRC as a 14.6 percent additional decrease in LDL-C for a 4-fold increase in statin dose. Under these circumstances, a patient with baseline LDL-C of 200 mg/dL would be expected to experience a decrease of 74 mg/dL (37.1 percent) from baseline (to 126 mg/dL) with 10 mg daily of atorvastatin, and a decrease of 103 mg/dL (51.7 percent) from baseline (to 97 mg/dL) with 80 mg daily of atorvastatin.

But it does not follow that a patient with a stabilized LDL-C level on 80 mg of atorvastatin (i.e., on-treatment baseline) would experience a 14.6 percent increase in LDL-C with a reduction in dose from 80 mg daily to 10 mg daily. The percentage increase from on-treatment baseline would be considerably higher when using the appropriate baseline value. Once stabilized on 80 mg atorvastatin, the patient now would have a new, on-treatment baseline value of 97 mg/dL. If the atorvastatin dose was reduced from baseline, the patient would be expected to experience an LDL-C increase of approximately 29.9 percent (from 97 mg/dL to 126 mg/dL) with a dose reduction to 10 mg.

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decreases the absorption of warfarin. Petition at 20, citing Loes E Visser, Fernie J A Penning-van Beest, J H P Wilson, et al. Overanticoagulation associated with combined use of lactulose and acenocoumarol or phenprocoumon. Br J Clin Pharmacol. 2004; 57(4):522–524. The study was designed to evaluate overanticoagulation associated with the warfarin derivatives acenocoumarol and phenprocoumon from decreased absorption of Vitamin K with various laxatives, including liquid paraffin. The dose of the laxatives was not clearly specified, and subjects were not randomized to laxative treatment. The primary endpoint was the incidence of international normalized ratio (INR)  $\geq 6.0$ . The adjusted relative risk between liquid paraffin and no laxative was 0.7, with a wide confidence interval (95% CI: 0.1, 5.5). Petitioner described this finding as a 30 percent decreased risk in the absorption of warfarin, but because the confidence interval includes 1.0, the study did not demonstrate a difference between liquid paraffin and no laxative. Even if there had been a difference, a reduction in events of overanticoagulation would not imply decreased absorption of the anticoagulants.

<sup>112</sup> Petition at 3-8.

<sup>113</sup> Petition at 4, citing Adams SP, et al., Atorvastatin for Lowering Lipids. Cochrane Database of Systemic Reviews. 2015.

The observed difference in LDL-C between arms in REDUCE-IT represents a much smaller difference than the expected magnitude of difference with a change in intensity of statin therapy based on the atorvastatin data. The appropriate baseline in REDUCE-IT is the stabilized, on-treatment baseline LDL-C. The theoretical no-treatment, LDL-C baseline (the LDL-C value of enrolled subjects if they were not on statin treatment) is unknown.

Using appropriate baseline LDL-C values, clinical trial data support the estimated dose-response relationship in the example above in the context of an outcomes trial in which patients were not naïve to therapy at baseline. In the TNT study<sup>114</sup> cited by MRC and described in the atorvastatin prescribing information, subjects stabilized on atorvastatin 10 mg daily for 8 weeks (open-label) and subsequently randomized to atorvastatin 80 mg daily experienced a 24 mg/dL (24 percent decrease) in LDL-C versus control patients who remained on atorvastatin 10 mg daily relative to the baseline LDL-C level (98 mg/dL) at randomization. If one were to describe the LDL-C level in the low intensity group relative to the stabilized LDL-C value in the high-intensity group as reference (to estimate the effect of a reduction in dose from 80 mg daily to 10 mg daily), the mean LDL-C level in the 10 mg arm (101 mg/dL) was 31 percent higher at the final visit than the LDL-C in the 80 mg arm (77 mg/dL). Petitioner used the no-treatment baseline (152 mg/dL) as the reference for percentage reductions from baseline, resulting in smaller values for percentage change from baseline, which makes the statin dose-response relationship appear flatter than reported. Crucially for the purposes of this response, this inappropriate dose-response relationship is then used to support a finding that mineral oil exerts a much larger interference with statin absorption (a purported 3-fold) than would be the case if the proper dose-response curve were to be used.

Furthermore, we disagree with MRC's premise that higher-intensity statins do not produce greater risk reduction than lower-intensity statins in primary prevention. Evidence from multiple statin clinical trials and meta-analyses demonstrate that LDL-lowering with statins reduces the risk of CV events across a broad range of baseline LDL-C levels and populations, including primary and secondary prevention.<sup>115</sup> Relative risk reduction is proportional to the magnitude of LDL-C lowering, regardless of baseline risk or prior clinical events. Although the estimates of the hazard ratios (HRs) cited are correct, we disagree with Petitioner's characterization of the "robust size" of CV Risk Category 2 (primary prevention subgroup). The trial was not sufficiently powered to demonstrate an effect in this population, and the wide 95 percent CI in this subgroup (0.700, 1.095) reflects the uncertainty of the estimate of the HR. We note that the 95 percent CI includes the estimate of the HR for the CV Risk Category 1 (secondary prevention subgroup).

Regarding hs-CRP, FDA disagrees with Petitioner's post hoc analyses of various trials to suggest that baseline hs-CRP values above certain thresholds confer additional CV risk that is

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<sup>114</sup> See footnote 36.

<sup>115</sup> The Cholesterol Treatment Trialists' (CTT) Collaboration, Efficacy and Safety of More Intensive Lowering of LDL Cholesterol: A Meta-Analysis of Data from 170,000 Participants in 26 Randomised Trials. Lancet. 2010 Nov 13;376(9753):1670-81.

independent and additive of LDL-C.<sup>116</sup> Whether or not the hypothesis is correct, limited data from statin trials, including the JUPITER trial on rosuvastatin cited in the Petition,<sup>117</sup> indicate that statins affect both LDL-C and hs-CRP levels. In JUPITER, reduction in LDL-C with atorvastatin was associated with reduction in hs-CRP in a population selected for elevated hs-CRP at baseline. It is not possible to distinguish the relative contributions of lowering either hs-CRP or LDL-C levels to rosuvastatin's effect on CV risk reduction.

We also disagree with MRC's proposal to evaluate a post hoc subgroup analysis of biomarker changes only in subjects in the mineral oil group who experienced events to make inferences about the effect of mineral oil on statin absorption.<sup>118</sup> It would be a flawed analysis to estimate the effect of LDL-C on CV risk of the population by ignoring subjects who had an increase in LDL-C but did not experience an event. Such an analysis would be biased and challenging to interpret because the proposed subgroup is defined by a post-randomization variable (a clinical event), and the variable is known to affect the results of those biomarkers. It is expected that subjects in the trial who experienced an event would behave differently than subjects who did not experience an event. Thus, the more appropriate analysis is to evaluate the population as a whole.

Furthermore, biomarker evaluations have important limitations. Laboratory collections shortly after an event might not be interpretable. For example, immediately following MI, patients experience rapid decreases in LDL-C and other lipid parameters, while hs-CRP typically increases. Adjustment of lipid-lowering and other medication in the days or weeks after an event might further affect biomarker values. Biomarker measurements temporally separated from the event might be not reflective of values if they had collected closer to the time of the event. For example, a single hs-CRP measurement at Year 2 might not be informative if the clinical event occurred in Year 5. Data from the last available timepoint before a clinical event might be more meaningful for an individual patient in certain circumstances, but collecting data at different timepoints for different patients would introduce bias into analyses of that population. For instance, laboratory collections later in the study (e.g., Year 4 or 5) would be more likely to be influenced by post-randomization events such as study drug discontinuation or change in statin dose than laboratory collections earlier in the study. Thus, MRC's proposal to conduct post hoc analysis of certain biomarkers in placebo arm subjects who experienced an event is inherently flawed.

In summary, Petitioner relies on flawed cross-study comparisons and distorted assumptions to claim that Vascepa's treatment benefit observed in REDUCE-IT is exaggerated. Based on our review of the literature cited in the Petition and FDA's analyses, we conclude that any potential interference with the absorption of ASCVD drugs by mineral oil had limited impact on the magnitude of Vascepa's positive treatment effect.

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<sup>116</sup> Petition at 9-14; Comment at 5-6 and 15-16.

<sup>117</sup> Ridker PM, et al, Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein, N Engl J Med 2008; 359:2195-2207.

<sup>118</sup> Petition at 18-19.

**B. FDA Will Not Delay Approval of Vascepa's Supplement Until DDI Studies on Mineral Oil's Interaction with ASCVD Drugs Are Conducted.**

Petitioner requests that FDA delay approval of Vascepa's supplement until data from DDI studies proving that concomitant use of mineral oil and ASCVD drugs does not attenuate the absorption or efficacy of the latter. It also asks that such DDI studies mimic the dosing patterns of subjects in the mineral oil placebo group in REDUCE-IT, "by requiring that the sponsor use the services of a third-party organization to poll" the subjects (or their family members if the subjects are deceased) to ascertain the most common dosing pattern so that the DDI studies are designed to reflect how subjects in REDUCE-IT took the placebo.

FDA Response:

Although dedicated DDI studies could address any scientific concern on the potential interference with drug absorption by mineral oil, FDA does not consider that DDI studies evaluating mineral oil and ASCVD drugs are necessary before approval of Vascepa's supplement. As explained above, FDA determined that any potential impact of mineral oil placebo on statin absorption was limited and on antithrombotic and antihypertensive absorption was negligible. To our knowledge, there are no anti-ischemic agents with known effects on CV outcomes; thus, any theoretical effects of mineral oil on absorption of oral anti-ischemic agents are irrelevant. Even if DDI studies were conducted and they demonstrated an interaction between mineral oil and one or more statins, it still would not be possible to determine the effect that the interaction would have had on the outcomes in REDUCE-IT beyond the observed LDL-C results and the estimates from FDA's exploratory analyses, which showed that Vascepa demonstrated a significant treatment benefit even when accounting for the difference in LDL-C levels between arms.

MRC's second request about polling subjects (or family members) is moot because we will not require DDI studies on mineral oil before the approval of Vascepa's supplement. FDA also does not believe this polling would accurately capture the required information to help design DDI studies that MRC proposes. Various conditions (with or without food, taken together with statin or separately) could be selected empirically to design DDI studies.

**C. FDA Will Not Rescind the SPA Agreement For REDUCE-IT or Issue a Complete Response Letter for Vascepa's Supplement Requiring a New CVOT Before Approval of the Cardiovascular Risk-Reduction Indication.**

If the DDI studies suggest that mineral oil is not inert and may interfere with the efficacy of ASCVD drugs, Petitioner requests that FDA rescind the SPA agreement for REDUCE-IT and issue a complete response letter for Vascepa's supplement requesting a new CVOT be conducted using an "inert" placebo prior to Vascepa's approval for the CV risk-reduction claim.

FDA Response:

Petitioner has failed to demonstrate that the SPA rescission standard has been satisfied. A study's design and results are review issues that would affect FDA's approval decision on a

pending application. As discussed above, we determined that any possible interference of mineral oil on ASCVD drugs, and statins in particular, would not meaningfully affect the magnitude of the treatment effect for Vascepa. Furthermore, a SPA agreement is binding between FDA's division reviewing the protocol and the sponsor. The agreement may be rescinded if the director of the reviewing division determines "that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after testing has begun."<sup>119</sup> In guidance, the Agency identified instances when FDA may rescind a SPA, such as whether the sponsor presented false statements or omitted relevant facts in the SPA submission such that the clinical relevance of crucial components of the trial design is called into question.<sup>120</sup> Here, the Agency has determined that none of the grounds for rescinding the SPA agreement for REDUCE-IT are present. Relatedly, FDA will not issue a complete response letter for the supplement and require Amarin to conduct a new CVOT solely because mineral oil was used as the placebo in REDUCE-IT.

**D. FDA Will Not Place on Clinical Hold Any Ongoing Trials Under an IND Solely Because Mineral Oil Is Used as the Placebo.**

Petitioner requests that FDA place the EVAPORATE trial on clinical hold, as well as any other trial in which mineral oil is used as a placebo.

**FDA Response:**

FDA's clinical hold regulation states that a clinical hold may apply to one or more investigations covered by an IND.<sup>121</sup> However, we have no record that the EVAPORATE trial, a phase 4 study, is being conducted under an IND.<sup>122</sup>

Regarding Petitioner's request to place on clinical hold any other clinical study in which mineral oil is used as a placebo, we have determined there are no grounds upon which to impose an across-the-board clinical hold to all trials where mineral oil is being used as the placebo. FDA places a trial on clinical hold when, for example, human subjects are or would be exposed to an unreasonable and significant risk of illness or injury.<sup>123</sup> As stated in the Briefing Document,<sup>124</sup> the most frequent serious adverse events were generally balanced between the Vascepa and mineral oil placebo groups and consistent with expected events for the patient population. Trial data from REDUCE-IT also indicate that there were no meaningful differences between study arms in discontinuations caused by adverse events.<sup>125</sup> Furthermore, as stated above, FDA found

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<sup>119</sup> Section 505(b)(5)(C) of the FD&C Act; Special Protocol Assessment guidance at 9-10.

<sup>120</sup> Special Protocol Assessment guidance at 15-16.

<sup>121</sup> § 312.42(a).

<sup>122</sup> Information on the EVAPORATE trial is available at: <https://clinicaltrials.gov/ct2/show/NCT02926027>. We also note that trial is not being conducted by Amarin; the sponsor of the study is Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center.

<sup>123</sup> § 312.42(b)(1)(i).

<sup>124</sup> Briefing Document at 64.

<sup>125</sup> Briefing Document at 66-67.

that any potential impact of mineral oil on the interference with ASCVD drug absorption was limited. Whether a clinical hold is warranted depends on the potential risks to subjects in any individual trial and should be evaluated independently. Thus, the Agency will not place on clinical hold at this time any clinical trial solely because mineral oil is used as the placebo.

**E. No New Warnings Will Be Added to the Labeling of All Largely Undigestible, Synthetic Fats or Fat Substitutes (Including Mineral Oil Products) Concerning Potential Absorption of Orally Administered Drugs.**

Petitioner finally recommends that a warning be required on the labeling

of all largely undigestible, synthetic fats or fat-substitutes for sale in the US that are for internal use (i.e. mineral oil), or are a main ingredient in such products for consumption (i.e. olestra), mentioning the possibility that synthetic or semi-synthetic, poorly digested lipids may interfere with the absorption of orally administered drugs – unless and until the results of numerous DDI studies exonerate these specific oils in this regard.<sup>126</sup>

**FDA Response:**

The Agency has required warnings to the labeling of FDA-regulated products in cases where information is necessary to ensure that consumers are aware of special health risks associated with the consumption of a particular product. MRC does not include any specific information to support its claim to apply to “all largely undigestible, synthetic fats or fat-substitutes” except for information specific to mineral oil. We note that FDA has almost 40 regulations governing the safe use of mineral oil as a component of human and animal drugs, as well as direct and indirect food additives.<sup>127</sup> There are no data before the Agency at this time suggesting that FDA should issue regulations requiring Petitioner’s requested warning be added to the labeling of these products. When such data become available, we will consider whether compelling inclusion of such warning would be appropriate.

**F. MRC’s Additional Claims and Assertions.**

As a matter of discretion, we also address two additional issues presented in the Petition, even though there are no specific requests relating to these issues. First, MRC raised concerns regarding the medical doctors that served on Amarin’s Data Monitoring Committee (DMC) for REDUCE-IT.<sup>128</sup> FDA reviewed the profiles of the DMC members and did not identify any concerns with the composition, which comprised two cardiologists and two statisticians. Because REDUCE-IT is a CVOT seeking a CV risk-reduction claim, it was appropriate for the composition of the DMC to include cardiologists and statisticians. Furthermore, as stated in the Petition, FDA requested the DMC to review unblinded data to monitor for signals that mineral

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<sup>126</sup> Petition at 2.

<sup>127</sup> See, e.g., 21 CFR 347.10 Skin Protectant Active Ingredients; 21 CFR 172.878, White Mineral Oil (regarding use as a food additive permitted for direct addition to food for human consumption).

<sup>128</sup> Petition at 52-55.

oil placebo may affect statin absorption.<sup>129</sup> The DMC reviewed the data and did not find any significant adverse events from mineral oil placebo or evidence that mineral oil significantly affected statin absorption. Thus, the DMC did not recommend halting the conduct of REDUCE-IT. The Agency found that the DMC was independent and performed its duties by monitoring unblinded safety data for all subjects in the trial.<sup>130</sup>

MRC also purports that “Vascepa can cause organ damage,” and then describes possible liver damage stemming from consuming fatty-acid ethyl esters, particularly in combination with alcohol.<sup>131</sup> Although there are no specific requests concerning this purported claim, FDA concludes that Vascepa’s current prescribing information adequately describes potential risk to patients with hepatic impairment and no other safety signals were identified to suggest organ damage caused by Vascepa. Vascepa’s prescribing information contains the following warning: “In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored periodically during therapy with VASCEPA.”<sup>132</sup>

Elevations of ALT and AST above the normal range may occur in both patients and healthy individuals because of a variety of causes and are not diagnostic of liver damage, especially in the case of mild elevations above the normal range. Contrary to MRC’s assertion, such elevations above baseline (less than 3-times the upper limit of normal (ULN)) are not necessarily significant or indicative of liver damage.<sup>133</sup>

In REDUCE-IT, median AST and ALT decreased slightly from baseline in both study arms from baseline to final visit, and the proportion of subjects experiencing elevations greater than 3-times ULN was numerically smaller in the AMR101 arm than in placebo.<sup>134</sup> We therefore conclude that based on current available information from published literature and Amarin’s REDUCE-IT, there was no signal of liver damage in subjects using Vascepa. We further conclude that Vascepa’s current prescribing information adequately addresses patients with hepatic impairment.<sup>135</sup>

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<sup>129</sup> Petition at 45-46. aa

<sup>130</sup> Briefing Document at 16.

<sup>131</sup> Briefing Document at 55-66.

<sup>132</sup> Vascepa Prescribing Information, Section 5.1 Warnings, Monitoring: Laboratory Tests.

<sup>133</sup> See generally, FDA guidance for industry *Drug-Induced Liver Injury: Premarketing Clinical Evaluation* (July 2009). Severe elevations in ALT and AST, especially levels greater than 10- to 15-times ULN, may be associated with liver toxicity in certain circumstances. Liver toxicity is typically accompanied by elevations in serum bilirubin. Severe toxicity may be accompanied by evidence of liver dysfunction, such as jaundice, coagulopathy, or encephalopathy.

<sup>134</sup> Briefing Document at 90-91.

<sup>135</sup> FDA disagrees with MRC’s assertion that the JELIS study suggests that EPA can cause liver damage. See footnote 56 for the JELIS study. According to the published report on the JELIS study, there was an incidence of 0.4 percent (n=38) increase in glutamic oxaloacetic transaminase (GOT) in the placebo arm and 0.6 percent (n=59) increase in GOT in the EPA arm. The report does not indicate the level of increase, such as >ULN or >3 times ULN, but presumably these are elevations above normal, because it was not otherwise specified. The clinical

MRC also cites data on Epanova (another fish oil-derived, approved drug product), suggesting that the incidence of elevations of ALT were “similar” between treatment and placebo arms in preregistration clinical trials.<sup>136</sup> However, it is not clear whether this finding represents a different safety profile than Vascepa (see above where we state that the proportion of subjects experiencing elevations greater than 3-times ULN was smaller in the Vascepa arm compared to placebo). Moreover, Epanova’s prescribing information<sup>137</sup> contains the same warning concerning patients with hepatic impairment as Vascepa’s prescribing information.

Finally, regarding MRC’s concerns on organ damage generally, subjects in REDUCE-IT were followed for a median time period of 4.9 years, during which it would be expected that safety signals on organ damage could appear. But in REDUCE-IT, there were no apparent safety signals that suggest organ damage following treatment with Vascepa.<sup>138</sup> Thus, FDA finds Petitioner has failed to support its claim that Vascepa can cause organ damage.

#### IV. CONCLUSION

FDA does not disagree with Petitioner that mineral oil may interfere with the absorption of certain orally administered drugs, such as statins. The Agency’s analysis, however, reveals that any potential interaction between mineral oil and ASCVD drugs, even assuming that such an interaction existed in REDUCE-IT, would not have meaningfully altered the magnitude of Vascepa’s treatment effect. Accordingly, for the reasons described above, the Petition is denied.

Sincerely,



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

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significance of this data is uncertain. Nonetheless, the report did not report imbalances in elevations of any other liver parameters (such as AST, ALT, or bilirubin) or liver-related adverse events (such as cholestasis or jaundice) between EPA and placebo, and did not describe any events of liver toxicity in the discussion of safety. The totality of the information suggests that there was no evidence of hepatic injury in the trial. This reference is yet another example of Petitioner’s misleading characterization of a published study to support its theory on Vascepa’s risks.

<sup>136</sup> Petition at 66.

<sup>137</sup> Epanova Prescribing Information, Section 5.1 Warnings, Monitoring: Laboratory Tests, available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/205060s003lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205060s003lbl.pdf).

<sup>138</sup> Briefing Document at 64-66 and 81-85, demonstrating that there were no notable imbalances in treatment emergent adverse events between the Vascepa and placebo arms.