Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
November 14, 2019

Location: The FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland.

Topic: The committee discussed supplemental new drug application 202057/S-035, for VASCEPA (icosapent ethyl) capsules for oral administration, sponsored by Amarin Pharma Inc., for the following proposed indication: to reduce the risk of cardiovascular events, as an adjunct to statin therapy in adult patients with elevated triglycerides levels (135 mg/dL or greater) and other risk factors for cardiovascular disease, based on the results of a clinical study entitled "A Study of AMR101 to Evaluate Its Ability to Reduce Cardiovascular Events in High Risk Patients With Hypertriglyceridemia and on Statin. The Primary Objective is to Evaluate the Effect of 4 g/Day AMR101 for Preventing the Occurrence of a First Major Cardiovascular Event. (REDUCE-IT)" (available at: https://clinicaltrials.gov/ct2/show/NCT01492361).

These summary minutes for the November 14, 2019 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on December 20, 2019.

I certify that I attended the November 14, 2019 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Jay R. Fajiculay, PharmD
Acting Designated Federal Officer, EMDAC

/s/
Kenneth D. Burman, MD
Chairperson, EMDAC

Final Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
November 14, 2019

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on November 14, 2019, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Amarin Pharma, Inc. The meeting was called to order by Kenneth D. Burman, MD (Chairperson). The conflict of interest statement was read into the record by Jay R. Fajiculay, PharmD (Acting Designated Federal Officer). There were approximately 275 people in attendance. There were 23 Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committee discussed supplemental new drug application 202057/S-035, for VASCEPA (icosapent ethyl) capsules for oral administration, sponsored by Amarin Pharma Inc., for the following proposed indication: to reduce the risk of cardiovascular events, as an adjunct to statin therapy in adult patients with elevated triglycerides levels (135 mg/dL or greater) and other risk factors for cardiovascular disease, based on the results of a clinical study entitled "A Study of AMR101 to Evaluate Its Ability to Reduce Cardiovascular Events in High Risk Patients With Hypertriglyceridemia and on Statin. The Primary Objective is to Evaluate the Effect of 4 g/Day AMR101 for Preventing the Occurrence of a First Major Cardiovascular Event. (REDUCE-IT)" (available at: https://clinicaltrials.gov/ct2/show/NCT01492361).

Attendance:

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting): Kenneth D. Burman, MD (Chairperson); Elizabeth Chrischilles, PhD, MS; James de Lemos, MD; Susan S. Ellenberg, PhD; Marvin A. Konstam, MD; Cecilia C. Low Wang, MD; Anna McCollister-Slipp (Consumer Representative); Connie Newman, MD; Thomas J. Weber, MD; Jack A. Yanovski, MD, PhD

Endocrinologic and Metabolic Drugs Advisory Committee Members Not Present (Voting): Michael Blaha, MD, MPH

Endocrinologic and Metabolic Drugs Advisory Committee Member Present (Non-Voting): Gary Meininger, MD (Industry Representative)

Temporary Members (Voting): Erica Brittain, PhD; Walter K. Kraft, MD; Martha Nason, PhD; Thomas L. Ortel, MD, PhD; Philip Posner, PhD (Patient Representative; *via phone*); Peter W. F. Wilson, MD

FDA Participants (Non-Voting): Lisa Yanoff, MD; John Sharretts, MD; Iffat Nasrin Chowdhury, MD; Roberto Crackel, PhD; Yunzhao Ren, MD, PhD

Acting Designated Federal Officer (Non-Voting): Jay R. Fajiculay, PharmD

Open Public Hearing Speakers: Seth Baum, MD (*statement read by Eliot Brinton, MD*); Alberico Catapano (University of Milano; *statement read by Eliot Brinton, MD*); Stephanie Fox-Rawlings, PhD (National Center for Health Research); David B. Shirley (Affordable Veterinary Care); Sudhir Bansal, MD; Ronald D'Agostino, DO; Antonio Gotto Jr., MD (*statement read by Eliot Brinton, MD*); Eliot Brinton, MD; R. Preston Mason, PhD, MBA; Kari Uusinarkaus, MD; Mark Pollner; Henry Kinsun Lui, MD; Joyce L. Ross, MSN, CRNP; Taylor Kelly (Aimed Alliance); Edward Goodman; Anna Norton, MS (DiabetesSisters); William S. Weintraub, MD (MedStar Washington Hospital Center; MedStar Health); William Schatzman; John M. Clymer (National Forum for Heart Disease & Stroke Prevention); Matthew Budoff, MD; Steven Edelman, MD (Taking Control Of Your Diabetes; *statement read by Robyn Sembera*); Andrea Baer (Mended Hearts, INC); Neil Sheth, MD

The agenda was as follows:

Call to Order and Introduction of Committee	**Kenneth D. Burman, MD** Chairperson, EMDAC
Conflict of Interest Statement	**Jay Fajiculay, PharmD** Designated Federal Officer (Acting), EMDAC
FDA Introductory Remarks	**John Sharretts, MD** Deputy Director (Acting) Division of Metabolism and Endocrinology Products (DMEP) Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Amarin Pharma Inc.**
Introduction	**Rebecca Juliano, PhD** Senior Vice President Clinical Research and Development Amarin Pharma Inc.
Medical Need	**Michael Miller, MD** Professor of Cardiovascular Medicine, Epidemiology & Public Health Director, Center for Preventative Cardiology University of Maryland School of Medicine
REDUCE-IT Clinical Efficacy and Safety Data	**Deepak L. Bhatt, MD, MPH** Executive Director of Interventional Cardiovascular Programs, Professor Brigham and Women's Hospital Harvard Medical School

APPLICANT PRESENTATIONS (CONT.)

Clinical Perspectives	**Ann Marie Navar, MD, PhD** Assistant Professor of Cardiology Duke University School of Medicine Duke Clinical Research Institute
Closing Remarks	**Rebecca Juliano, PhD**
Clarifying Questions to Applicant	

BREAK

FDA PRESENTATIONS

Introduction and Clinical Review	**Iffat Nasrin Chowdhury, MD** Medical Officer DMEP, ODE-II, OND, CDER, FDA
Statistical Review of Efficacy	**Roberto Crackel, PhD** Statistical Reviewer Division of Biometrics II Office of Biostatistics Office of Translational Sciences (OTS), CDER FDA
Clinical Pharmacology Review	**Yunzhao Ren, MD, PhD** Clinical Pharmacology Reviewer Division of Clinical Pharmacology II Office of Clinical Pharmacology, OTS, CDER, FDA
Additional Statistical Analysis and Conclusions	**Roberto Crackel, PhD**
Clinical Review of Safety	**Iffat Nasrin Chowdhury, MD**
Clarifying Questions to FDA	

LUNCH

OPEN PUBLIC HEARING

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Please discuss your interpretation of the efficacy results from the REDUCE-IT Trial, including the following:

    a. Overall strengths and limitations of the data, including the use of a single trial to support a first-in-class cardiovascular outcomes indication and the robustness of the results
    b. Confidence in the trial outcomes when considering the mineral oil placebo
    c. Magnitude/clinical relevance of the observed treatment effect
    d. Components of the primary composite endpoint or secondary endpoints, including the robustness of the data to support an indication for CV death

    Committee Discussion: *The committee discussed that the use of a single trial offered limited data to support icosapent ethyl for an indication for primary prevention of cardiovascular outcomes, but was generally sufficient to support an indication for secondary prevention of cardiovascular outcomes. Regarding mineral oil, the committee had differing opinions regarding its use as a placebo. Some committee members suggested that FDA presented an acceptable analysis of the effects of mineral oil on statin absorption, while others were more conservative in their assessment of mineral oil as a non-inert placebo in the REDUCE-IT trial. Although one committee member suggested that additional studies assess for accumulation of mineral oil in adipose tissue in REDUCE-IT placebo patients might be informative, no committee member concluded that mineral oil invalidated the trial result. There was a general consensus that the clinical trial results identified a clinical benefit of icosapent ethyl in patients with established cardiovascular disease, which was less robust in magnitude in lower risk patients. Please see the transcript for details of the committee's discussion.*

2. **DISCUSSION:** Please discuss your level of concern about the new safety findings (increased risk of atrial fibrillation/atrial flutter and bleedings events) from the REDUCE-IT trial and whether labeling can reasonably manage these risks.

    Committee Discussion: *The committee discussed that there was an observed risk of atrial fibrillation and atrial flutter in patients from the REDUCE-IT trial; however, it was recognized that these risks can be monitored and treated. Furthermore, the committee noted that rate of atrial fibrillation and atrial flutter was higher in patients who had experienced these events in the past. The committee also discussed concerns regarding increased bleeding events seen in icosapent ethyl compared to the placebo. One member stated that it would be interesting to see if those who experienced major bleeding had also experienced minor bleeding events. It was also noted that drugs that increase the risk of bleeding are generally discontinued prior to surgery, and information regarding the time before surgery and duration of discontinuation after surgery should be identified. The committee generally agreed that labeling can be a component to managing these risks, but that additional options such as post-marketing surveillance and the use of real-world data should also be considered. Please see the transcript for details of the committee's discussion.*

3. **DISCUSSION:** The applicant has proposed an indication for cardiovascular risk reduction in adult patients with triglyceride levels greater than or equal to 135 mg/dL and additional risk factors for cardiovascular disease (CVD), without regard for age, diabetes status, or adequacy of low-density lipoprotein (LDL-C) control. Please discuss the population – beyond the subset of patients with established CVD – for whom you believe the data from REDUCE-IT provide evidence of cardiovascular risk benefit, addressing the following factors:
    - Age
    - Diagnosis of diabetes
    - Additional risk factors for CVD
    - Plasma LDL-C concentration
    - Plasma triglyceride concentration
    - Intensity of statin therapy
    - Any other factor you believe is important

    Committee Discussion: *The committee held various views regarding the patient population that the REDUCE-IT trial provided evidence of cardiovascular risk benefit for. The majority of members stated that the indication should include a patient population defined by either the inclusion criteria or the characteristics of enrolled patients in the REDUCE-IT study, while others stated that there is not enough information presently available to include the primary prevention group. Regarding the factors listed above, the committee did not have a consensus on age requirements; however, the committee generally recommended that patients have a diagnosis of diabetes, have a LDL-C of less than 100 mg/dL, have a triglyceride concentration greater than 150-200 mg/dL, and be on maximally tolerated statin therapy. Please see the transcript for details of the committee's discussion.*

4. **VOTE:** Has the applicant provided sufficient evidence of efficacy and safety to support the approval of Vascepa for an indication to reduce the risk of cardiovascular events?

    a. If yes, provide your recommendations regarding the indicated population and components of the primary endpoint to include in labeling.

    b. If no, provide your rationale and comment on what additional data would be needed to support approval.

    Vote Result: **Yes: 16** **No: 0** **Abstain: 0**

    Committee Discussion: *The committee unanimously voted "Yes", that the applicant provided sufficient evidence of efficacy and safety to support the approval of Vascepa for an indication to reduce the risk of cardiovascular events. The committee stated that the REDUCE-IT trial showed a benefit of cardiovascular risk reduction for patients with established cardiovascular disease. The majority of members stated that the clinical trial supports icosapent ethyl approval for a wider population for secondary prevention; however, they noted that the product should be limited to the criteria outlined in the REDUCE-IT study for primary prevention. The committee restated their concerns for increased risk of bleeding, and some members stated that post-marketing studies should be conducted to identify patient*

populations at an increased risk for bleeding. Please see the transcript for details of the committee's discussion.

The meeting was adjourned at approximately 4:30 p.m.