Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
December 14, 2015

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

Topic: The committee discussed the results of the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). IMPROVE-IT was a clinical trial that studied the effect of ezetimibe/simvastatin compared with simvastatin on the occurrence of cardiovascular events in patients with recent acute coronary syndrome. The results from this trial have been submitted to support supplemental new drug applications 21445/S-038 and 21687/S-054, ZETIA (ezetimibe) and VYTORIN (ezetimibe/simvastatin) tablets, respectively, by MSD International GmbH. The proposed indication for ZETIA (in combination with a statin) and VYTORIN is to reduce the risk of cardiovascular events in patients with coronary heart disease.

These summary minutes for the December 14, 2015, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on January 20, 2016.

I certify that I attended the December 14, 2015, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	***/s/***
Stephanie L. Begansky, PharmD	Robert J. Smith, MD
Acting Designated Federal Officer, EMDAC	*Chairperson, EMDAC*

Summary Minutes of the
Endocrinologic and Metabolic Drugs Advisory Committee Meeting
December 14, 2015

The following is a final report of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on December 14, 2015. A verbatim transcript will be available in approximately six weeks, sent to the Division of Metabolism and Endocrinology Products and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm426278.htm.

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 14, 2015, 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 MSD International GmbH (Merck). The meeting was called to order by Robert J. Smith, MD (Chairperson). The conflict of interest statement was read into the record by Stephanie L. Begansky, PharmD (Acting Designated Federal Officer). There were approximately 100 people in attendance. There were 2 Open Public Hearing (OPH) speaker presentations.

Issue: The committee discussed the results of the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). IMPROVE-IT was a clinical trial that studied the effect of ezetimibe/simvastatin compared with simvastatin on the occurrence of cardiovascular events in patients with recent acute coronary syndrome. The results from this trial have been submitted to support supplemental new drug applications 21445/S-038 and 21687/S-054, ZETIA (ezetimibe) and VYTORIN (ezetimibe/simvastatin) tablets, respectively, by MSD International GmbH. The proposed indication for ZETIA (in combination with a statin) and VYTORIN is to reduce the risk of cardiovascular events in patients with coronary heart disease.

Attendance:

EMDAC Members Present (Voting): Daniel Budnitz, MD, MPH; Brendan M. Everett, MD, MPH; Diana Hallare, MPH (Consumer Representative); Susan R. Heckbert, MD, PhD; William R. Hiatt, MD, FACP, FAHA (via telephone); Robert J. Smith, MD (Chairperson); Peter W.F. Wilson, MD

EMDAC Members Not Present (Voting): David W. Cooke, MD; James D. Neaton, PhD; Charles A. Stanley, MD

Temporary Members (Voting): Michael J. Blaha, MD, MPH; Thomas R. Fleming, PhD; Sanjay Kaul, MD; Debra McCall, MBA (Patient Representative); Milton Packer, MD; Michael Proschan, PhD; Robert D. Shamburek, MD; John R. Teerlink, MD

Acting Industry Representative to the Committee (Non-Voting): Reshma Kewalramani, MD

FDA Participants (Non-Voting): Curtis J. Rosebraugh, MD, MPH; Jean-Marc Guettier, MD; James P. Smith, MD, MS; Iffat Nasrin Chowdhury, MD; Jennifer Clark, PhD

Open Public Hearing Speakers: Tracey Rupp, PharmD (National Center for Health Research); Sidney Wolfe, MD (Health Research Group at Public Citizen)

The agenda was as follows:

Call to Order and Introduction of Committee	**Robert J. Smith, MD** Chairperson, EMDAC
Conflict of Interest Statement	**Stephanie L. Begansky, PharmD** Acting Designated Federal Officer, EMDAC
FDA Introductory Remarks	**James P. Smith, MD, MS** Deputy Director Division of Metabolism and Endocrinology Products (DMEP) Office of Drug Evaluation II (ODE II) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**MSD International GmbH**
Introduction	**Dr. Andrew M. Tershakovec** Executive Director, Clinical Research Merck Research Laboratories
IMPROVE-IT Results	**Dr. Christopher Cannon** TIMI Study Group Brigham & Women's Hospital Harvard Medical School
IMPROVE-IT Data Completeness	**Dr. Paul DeLucca** Director of Biostatistics Merck Research Laboratories
Clinical Implications of IMPROVE-IT	**Dr. Eugene Braunwald** TIMI Study Group Brigham & Women's Hospital Harvard Medical School
Clarifying Questions	
BREAK	
FDA PRESENTATIONS	

IMPROVE-IT: Introduction	**Iffat Nasrin Chowdhury, MD** Medical Officer DMEP, ODE II, OND, CDER, FDA
Statistical Assessment of Efficacy	**Jennifer Clark, PhD** Mathematical Statistician Division of Biometrics (DB) II Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER, FDA
IMPROVE-IT: Efficacy and Safety	**Iffat Nasrin Chowdhury, MD**

Clarifying Questions

LUNCH

Open Public Hearing

Charge to the Committee

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURN

Questions to the Committee:

1. **DISCUSSION:** In the IMPROVE-IT trial, 2572 (28.4%) of 9067 patients in the ezetimibe/simvastatin arm and 2742 (30.2%) of 9077 patients in the simvastatin arm had at least one primary composite endpoint event, defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, documented unstable angina requiring hospitalizations, or coronary revascularization (at least 30 days after randomization). According to the primary analysis (intent-to-treat), this yielded a 6.4% relative risk reduction for ezetimibe/simvastatin compared with simvastatin (HR 0.94; 95% CI, 0.89-0.99; p=0.016).

   Provide your interpretation of the efficacy results from the IMPROVE-IT trial. Specifically discuss the magnitude of the observed treatment effect; the robustness of the result of the primary composite endpoint (considering, for example, the extent and pattern of missing follow-up time); and any comments you may have regarding observed effects on components of the primary composite endpoint or secondary endpoints.

   Committee Discussion: *The committee agreed that the IMPROVE-IT trial was remarkable in terms of scope, duration, and quality. Generally, the committee expressed uncertainty about*

the clinical significance of the magnitude of effect demonstrated in the study. Universally, the committee expressed the view that the effect on the primary endpoint was relatively small. However, the committee had a difference of opinion on the robustness of the result of the primary composite endpoint and on how to interpret the apparent statistical significance given issues related to missing data and uncertainties surrounding the assumptions and calculations that were used to handle missing information. A number of panel members questioned whether the trial convincingly demonstrated a clinically meaningful effect on its endpoints. Some committee members questioned whether the trial's results were consistent with expectations, including the effects observed in subgroups, based on the experience with statins. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Multiple subgroup analyses of the primary composite endpoint were specified in the statistical analysis plan. The most notable differences in treatment effect were observed in subgroups defined by diabetes status or age (using a threshold at 75 years), as summarized in the table below.

Subgroup	n	HR (95% CI)	P	P (interaction)
Non-Diabetics	13202	0.98 (0.91, 1.04)	0.48	0.021
Diabetics	4933	0.85 (0.78, 0.94)	0.001	
Age <75	15338	0.97 (0.92, 1.03)	0.35	0.005
Age ≥75	2797	0.80 (0.70, 0.90)	0.0003	
Age <75, Non-diabetic	11225	1.03 (0.95, 1.10)	0.51	
Age <75, Diabetic	4113	0.87 (0.78, 0.96)	0.007	
Age ≥75, Non-diabetic	1977	0.79 (0.68, 0.92)	0.003	
Age ≥75, Diabetic	820	0.81 (0.65, 0.99)	0.040	

Provide your interpretation of these subgroup findings.

Committee Discussion: *The committee stated that while there are limitations and hazards in overinterpreting subgroup findings in general, there is substantial interest in the findings within the subgroups. The committee noted that perhaps this information generates a hypothesis and insight into a greater effect of drug in those with more severe disease. While the committee found the subgroup findings interesting, they did not find the information to be useful in addressing the question of overall benefit or in informing recommendations for the use of the product. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** The applicant has proposed that the results from IMPROVE-IT, which tested the addition of ezetimibe to simvastatin among patients with very recent acute coronary syndrome, can be extrapolated to other clinical situations, such as adding ezetimibe onto any statin among patients with stable coronary heart disease. Discuss the extent to which such extrapolation is reasonable.

Committee Discussion: *The committee noted that there was a lack of evidence to support extrapolating the findings from the clinical situation evaluated in this trial to other clinical situations, but views varied with respect to the extent to which extrapolation might be reasonable. Some committee members opined that the trial's findings may not extend to patients with stable coronary heart disease, whereas others noted that they may, with the*

caveat that the absolute benefit would likely be less than that observed in the trial's population. With regard to extrapolation to adding ezetimibe to other members of the statin class, there was a general consensus that there is no basis for concern and that this is reasonable if one accepts that reduction of LDL-C mediates the effect on cardiovascular risk. Please see the transcript for details of the committee discussion.

4. **DISCUSSION:** Discuss the safety findings of the IMPROVE-IT trial.

Committee Discussion: *The committee agreed that the safety findings were generally favorable and consistent with what has been previously reported for ezetimibe. The committee noted that IMPROVE-IT provides the most reassuring evidence to date with respect to the previously identified possibility that ezetimibe might increase the risk of cancer. The committee also stated that it is important to note the higher number of hemorrhagic strokes in the ezetimibe arm, but it was noted that this is not a new observation for lipid-lowering drugs and it remains uncertain whether this might be related to achieved LDL-C as opposed to the drug itself. The committee stated that the FDA should keep hemorrhagic stroke in mind as a potential hazard of very low cholesterol levels in response to various treatments. A committee member also noted that the trial arms were very balanced with regard to muscle-related events, continuing to support the clinical trial experience that these effects are not as common as sometimes suggested. Please see the transcript for details of the committee discussion.*

5. **VOTE:** Do the efficacy and safety data from the IMPROVE-IT trial provide substantial evidence to support approval of a claim that adding ezetimibe to statin therapy reduces the risk of cardiovascular events?

Vote Result: **Yes = 5** **No = 10** **Abstain = 0**

a. If yes, please comment on your rationale and whether such claim should carry any limits (e.g., whether the data support use in only certain clinical situations or subgroups).
b. If no, provide your rationale and comment on what additional data would be needed to support approval.

Committee Discussion: *The majority of the committee agreed that the efficacy and safety data from the IMPROVE-IT trial did not provide substantial evidence to support approval of a claim that adding ezetimibe to statin therapy reduces the risk of cardiovascular events. Those who voted "YES" stated that there is a modest need for add-on LDL-C-lowering therapy and although the effect of ezetimibe in IMPROVE-IT was modest, the results were consistent with expectations based on the degree of LDL-C lowering and not outweighed by major safety concerns. Those who voted "NO" stated that the the results did not provide statistically persuasive evidence of benefit, especially from the standpoint of using a single trial to support approval, and were not convinced that the magnitude of the benefit seen was clinically meaningful. Some committee members stated that they would like to see additional data for patients with higher baseline LDL-C and also in targeted populations such as minorities and women. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:55 p.m.