Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
June 28, 2016

Location: Hilton Washington DC/Rockville Hotel & Executive Meeting Center, Plaza Ballroom, 1750 Rockville Pike, Rockville, MD 20852.

Topic: The committee discussed supplemental new drug application (sNDA) 204629 for empagliflozin (JARDIANCE) tablets and sNDA 206111 for empagliflozin and metformin hydrochloride (SYNJARDY) tablets. Both sNDAs are sponsored by Boehringer Ingelheim Pharmaceuticals, Inc., for the proposed additional indication in adult patients with type 2 diabetes mellitus and high cardiovascular risk to reduce the risk of all-cause mortality by reducing the incidence of cardiovascular death and to reduce the risk of cardiovascular death or hospitalization for heart failure.

These summary minutes for the June 28, 2016, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on August 4, 2016.

I certify that I attended the June 28, 2016, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
LaToya Bonner, PharmD
Designated Federal Officer, EMDAC

/s/
Robert J. Smith, MD
Chairperson, EMDAC

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
June 28, 2016

The following is the final report of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on June 28, 2016. 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/ucm491062.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 June 28, 2016, at the Hilton Washington DC/Rockville Hotel and Executive Meeting Center, Plaza Ballroom, 1750 Rockville Pike, Rockville, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Boehringer Ingelheim Pharmaceuticals, Inc. The meeting was called to order by Robert J. Smith, MD (Chairperson). The conflict of interest statement was read into the record by LaToya Bonner, PharmD (Designated Federal Officer). There were approximately 150 people in attendance. There were 3 Open Public Hearing (OPH) speaker presentations.

Issue: The committee discussed supplemental new drug application (sNDA) 204629, empagliflozin (JARDIANCE) tablets, and sNDA 206111, empagliflozin and metformin hydrochloride (SYNJARDY) tablets. Both sNDAs are sponsored by Boehringer Ingelheim Pharmaceuticals, Inc., for the proposed additional indication in adult patients with type 2 diabetes mellitus and high cardiovascular risk to reduce the risk of all-cause mortality by reducing the incidence of cardiovascular death and to reduce the risk of cardiovascular death or hospitalization for heart failure.

Attendance:

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

EMDAC Member Not Present (Voting): Charles A. Stanley, MD

EMDAC Member Present (Non-Voting): Reshma Kewalramani, MD, FASN (Industry Representative)

Temporary Members (Voting): Leslie Cho, MD; James de Lemos, MD; David Good, MD; Judith Fradkin, MD; Marvin A. Konstam, MD; Melissa Li-Ng, MD; Richard Lumley, EdD; Kevin D. McBryde, MD; Paul Palevsky, MD; Michael Proschan, PhD; Yves Rosenberg, MD, MPH; Morris Schambelan, MD; Abraham Thomas, MD, MPH

Designated Federal Officer (Non-Voting): LaToya Bonner, PharmD, NCPS

FDA Participants (Non-Voting): Jean-Marc Guettier, MDCM; William H. Chong, MD; ; Norman L. Stockbridge, MD, PhD; Jennifer Clark, PhD; Andreea Lungu, MD

Open Public Hearing Speakers: George Grunberger, MD (American Association of Clinical Endocrinologists); Emily Regier (Close Concerns); Helen Gao (diaTribe Foundation)

The agenda was as follows:

Call to Order and Introduction of Committee	**Robert J. Smith, MD** Chairperson, EMDAC
Conflict of Interest Statement	**LaToya Bonner, PharmD** Designated Federal Officer, EMDAC
FDA Introductory Remarks	**Jean-Marc Guettier, MDCM** Director Division of Metabolism and Endocrinology Products (DMEP) Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Boehringer Ingelheim Pharmaceuticals, Inc.**
Introduction	**Hans-Juergen Woerle, MD** Vice President Therapeutic Area Metabolism Boehringer Ingelheim
Context and Background	**Prof. Bernard Zinman** Chairman, EMPA-REG OUTCOME Steering Committee Director, Leadership Sinai Centre for Diabetes Professor of Medicine, University of Toronto
	Hans-Juergen Woerle, MD
Cardiovascular Outcomes	**Uli Broedl, MD** Head of Clinical Development Therapeutic Area Metabolism Boehringer Ingelheim

Safety, Data Quality and Integrity	**Hans-Juergen Woerle, MD**
Clinical Perspective	**Prof. Bernard Zinman**
Summary	**Hans-Juergen Woerle, MD**

BREAK

FDA PRESENTATIONS

The EMPA-REG OUTCOME Study	**Andreea Lungu, MD** Clinical Reviewer DMEP, ODE-II, OND, CDER, FDA
Statistical Assessment	**Jennifer Clark, PhD** Mathematical Statistician Division of Biometrics II (DB-II) Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER FDA
Clinical Assessments	**Andreea Lungu, 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:** Discuss your interpretation of the EMPA-REG OUTCOME study conduct. definitions, and analyses plan (e.g., specific exclusion of silent MI from the primary endpoint) during the course of the EMPA-REG OUTCOME study alter or do not alter your level of confidence in a conclusion that excess CV-risk was excluded and CV-benefit was established.

   Committee Discussion: *The committee acknowledged that multiple changes occurred during the conduct of the EMPA-REG OUTCOME study but struggled to provide a clear interpretation on how these changes influenced their level of confidence in the study results. Some committee members were of the opinion that the changes only had a minor influence on their interpretation of the primary results. The committee noted that important changes (exclusion of silent MI) appeared to have occurred prior to interim data-unblinding and were*

re-assured by this fact. Some committee members stated that the changes could have had their greatest influence on the non-fatal components of the primary endpoints and the secondary endpoints in the trial. For some, these changes affected their level of confidence in the interpretation of the overall results. In their view, the mortality findings could only be interpreted if they were absolutely confident in the results of the primary analysis (superiority on 3-point MACE). Some committee members were reassured by the fact that the primary analysis results were driven by the most objective of the three components in the primary endpoint (i.e., CV-death), the component least likely to be affected by the changes noted above. The committee members noted that the mortality findings appeared to be robust when considering overall deaths or excluding deaths that could not be determined. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Please discuss the persuasiveness of the statistical results for the primary analysis. Please also comment on how results for the individual components in the primary composite endpoint impact your level of confidence in the study findings. Finally, comment on concerns you may have related to potentially incomplete ascertainment of some myocardial infarction events (i.e., silent MI) in this trial and whether these concerns, if any, alter your level of confidence in the results for the primary analysis.

   ***Committee Discussion**: The committee expressed uncertainty around the statistical persuasiveness of the results for the primary endpoint (3-point MACE) analysis. Some of the points stated in discussion 1 were again raised. The committee's uncertainty was in part related to the potential for missing data for some non-fatal events (i.e., silent MI), a large number of CV-deaths that could not be determined, residual questions surrounding the impact of the interim unblinding on trial conduct, and changes made to the various charters as the trial was progressing. The committee was of the opinion that the findings for 3-point MACE were not particularly statistically persuasive and that, based on the results, the benefit of the drug was unlikely to be attributable to atherosclerotic cardiovascular disease risk reduction. Some committee members stated that the trial results do not clearly point to a readily identifiable mechanism to explain the CV mortality results. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** Discuss the persuasiveness of the mortality findings in the EMPA-REG OUTCOME study. In your discussion, please address any potential limitations of these data including but not limited to:

   a. Issues raised in Discussion Point #2

   b. The proportion of deaths that were determined "non-assessable" by adjudicators

   c. The lack of granular data on potentially important information such as baseline heart failure history and dose of relevant baseline and concomitant medications

   d. The lack of pre-specified alpha-adjustment for this endpoint

   Committee Discussion: *The committee members generally found the mortality findings persuasive based on the very low p-value, the number of death events that occurred, the apparent consistency in the directionality of the findings across two dose strengths evaluated*

(10mg and 25mg tablets). However, committee members struggled with how to interpret the definitiveness of the mortality findings in light of the low level of confidence on the robustness of the primary results, with the fact that no clear mechanism of action (MOA) could be readily identified to explain on the mortality results, and in light of some of the study conduct issues (missing data). Questions related to the potential influence of differential treatment (i.e., unmeasured co-interventions; differential use of background medications) on the study results were raised. Some committee members postulated that the findings could perhaps be explained by a combination of benefit from empagliflozin and by greater use of potentially harmful therapies in the control arm. A few members argued that knowledge of the MOA is not required to be confident in the mortality data. Collectively, the members agreed that the cardiovascular mortality findings were statistically persuasive but that additional data from another trial would further strengthen the confidence in the findings. Please see the transcript for details of the committee discussion.

4. **DISCUSSION:** Discuss the heart failure findings in the EMPA-REG OUTCOME study. Please comment on the potential limitations of these data, if any, and on whether the results of the study establish a benefit of empagliflozin on heart failure and heart-failure related outcomes.

   Committee Discussion: *The committee generally found the findings with respect to heart failure to be less than persuasive. Limitations noted included concerns with the changing definitions, uncertainty around background management, and absent data on NYHA classification and other disease characteristics. One committee member acknowledged the diuretic properties of empagliflozin and its probable effects on volume management. Overall, the committee noted that the results were intriguing, certainly worth exploring, but not convincing. As a result, the committee recommended that the heart failure findings be substantiated before conclusions could be accepted. Please see the transcript for details of the committee discussion.*

5. **DISCUSSION:** Discuss the renal findings in the EMPA-REG OUTCOME study. Please comment on the potential limitations of these data, if any, and on whether the results of the study establish a benefit of empagliflozin on kidney disease related to diabetes.

   Committee Discussion: *The committee members commented that the findings on renal endpoints were interesting but not convincing. The committee noted that the observed effects were transient and that the laboratory findings reverted back to baseline once therapy was stopped. Additionally, the committee noted major deficiencies in the assessment of the renal endpoints such as: endpoints were not adjudicated, it was unclear if the findings reflected acute kidney injury or chronic renal effects, limited information on co-management, and potential contribution of other variables (such as HbA1c). Overall, the committee members agreed that the data shown was not convincing due to major deficiencies and the failure to show sustained or long-term effects. Thus, the committee recommended that an additional study would be needed before drawing conclusions on renal endpoints. Please see the transcript for details of the committee discussion.*

6. **VOTE:** Based on data in the briefing materials and presentations at today's meeting, do you believe the EMPA-REG OUTCOME study results have fulfilled the recommendations laid

out in the 2008 Guidance for Industry by demonstrating that use of empagliflozin to improve glycemic control would not result in an unacceptable increase in cardiovascular risk?

Vote Result: Yes: 23 No: 0 Abstain: 0

a. If yes, please provide the rationale for your vote.
b. If no, please provide the rationale for your vote and comment on what additional data would be needed.

Committee Discussion: *The committee unanimously voted "Yes", agreeing that the EMPA-REG OUTCOME study fulfilled the recommendations laid out in the 2008 Guidance for Industry by meeting the criteria proposed and demonstrating cardiovascular safety. Please see the transcript for details of the committee discussion.*

7. **VOTE:** Based on data in the briefing materials and presentations at today's meeting, do you believe the EMPA-REG OUTCOME study results provide substantial evidence to establish that empagliflozin reduces cardiovascular mortality in the population studied?

Vote Result: Yes: 12 No: 11 Abstain: 0

a. If yes, please provide the rationale for your vote.

Committee Discussion: *A slight majority of the committee voted "Yes", agreeing that the EMPA-REG OUTCOME study results provided substantial evidence to establish that empagliflozin reduces cardiovascular mortality in the population studied. The majority of the committee was convinced of the CV mortality endpoint findings due to its ability to withstand all sensitivity analysis, even missing data. One member noted that a 38% reduction may be an overstatement; however, a 20% endpoint may be more likely and is still considered a good benefit. Please see the transcript for details of the committee discussion.*

b. If no, please provide the rationale for your vote and comment on what additional data would be needed.

Committee Discussion: *The committee members who voted "No" agreed that the CV mortality reduction endpoint was intriguing but argued that a second trial with a similar design would be needed. Overall, the committee was in consensus in recognizing that therapies that provide a benefit on cardiovascular outcomes are needed. However, some found it difficult to vote "Yes" for an additional indication without a better understanding of the mechanism or a second trial producing similar results. One committee member expressed low confidence in adding empagliflozin to patients' regimen since it will be difficult to express to patients the need for the drug without understanding its MOA. Other committee members expressed their concurrence with the Agency's standard for approval, in which two well controlled trials are encouraged prior to the approval of any new indication. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:43 p.m.