Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
November 13, 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 (sNDA) 204629/S-020 for empagliflozin oral tablet, sponsored by Boehringer Ingelheim Pharmaceuticals, Inc., for the following proposed indication: as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus.

These summary minutes for the November 13, 2019 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting of the Food and Drug Administration were approved on December 19, 2019.

I certify that I attended the November 13, 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/	**/s/**
LaToya Bonner, PharmD	Kenneth D. Burman, MD
Designated Federal Officer, EMDAC	*Chairperson, EMDAC*

Final Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
November 13, 2019

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on November 13, 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 Boehringer Ingelheim Pharmaceuticals, Inc. The meeting was called to order by Kenneth D. Burman, 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 eight Open Public Hearing speaker presentations.

A verbatim transcription will be available, in most cases, approximately ten to twelve weeks, following the meeting date.

Agenda: The committee discussed supplemental new drug application (sNDA) 204629/S-020 for empagliflozin oral tablet, sponsored by Boehringer Ingelheim Pharmaceuticals, Inc., for the following proposed indication: as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus.

Attendance:
EMDAC Members Present (Voting): Michael Blaha, MD, MPH; Kenneth D. Burman, MD (Chairperson); Elizabeth Chrischilles, PhD, MS; James de Lemos, MD; Cecilia C. Low Wang, MD; Anna McCollister-Slipp (Consumer Representative); Connie Newman, MD; Thomas J. Weber, MD; Jack A, Yanovski, MD, PhD

EMDAC Members Not Present (Voting): Susan S. Ellenberg, PhD and Marvin A. Konstam, MD

EMDAC Member Present (Non-Voting): Gary Meininger, MD (Industry Representative)

Temporary Members (Voting): Erica Brittain, PhD; Brendan M. Everett, MD, MPH, FACC, FAHA; Rita R. Kalyani, MD, MHS; Carling Lellock (Patient Representative); Kashif Munir, MD; Martha Nason, PhD; Manjunath P. Pai, PharmD

FDA Participants (Non-Voting): Shanti Gomatam, PhD; Mahtab Nayyatti, MD; Justin Penzenstadler, PharmD, MSc; Mitra Rauschecker, MD; Lisa Yanoff, MD

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

Open Public Hearing Speakers: Charles Alexander, MD (*statement read by Martin Kurian*); Kelly Close (dQ&A; DiaTribe); Sanjoy Dutta, PhD (JDRF); Helena Rodbard, MD, FACP, MACE; Rhea Teng and Martin Kurian (Close Concerns); Simeon Taylor, MD, PhD; Sidney M. Wolfe, MD (Public Citizen's Health Research Group); Nina Zeldes, MS (National Center for Health Research)

The agenda was as follows:

Call to Order and Introduction of Committee	**Kenneth D. Burman, MD** Chairperson, EMDAC
Conflict of Interest Statement	**LaToya Bonner, PharmD** Designated Federal Officer, EMDAC
FDA Introductory Comments	**Lisa B. Yanoff, MD** 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 Introduction	**Boehringer Ingelheim Pharmaceuticals, Inc.** **Jyothis George, MBBS. PhD, FRCP** Head of Medicine – Empagliflozin Boehringer Ingelheim Pharmaceuticals, Inc.
Unmet Need	**Jennifer Green, MD** Professor of Medicine Duke University Medical Center Division of Endocrinology, Metabolism and Nutrition Faculty, Duke Clinical Research Institute Durham, North Carolina
Efficacy	**Jan Marquard, MD** Clinical Development Lead – Empagliflozin Boehringer Ingelheim Pharmaceuticals, Inc.
Safety	**Ona Kinduryte Schorling, MD, MSc** Head of Drug Safety – Metabolism Boehringer Ingelheim Pharmaceuticals, Inc.
Clinical Implications	**Bruce Perkins, MD** Professor of Medicine and Clinician-Scientist University of Toronto, The Sam and Judy Pencer Family Chair in Diabetes and Director of the Diabetes Clinical Research Unit Leadership Sinai Centre for Diabetes, Sinai Health System Toronto, Canada

Clarifying Questions to the Applicant

FDA PRESENTATIONS

Overview of Development Program for Empagliflozin in Type 1 Diabetes Mellitus	**Mahtab Niyyati, MD** Clinical Reviewer DMEP, ODE-II, OND, CDER, FDA
Clinical Pharmacology Highlights	**Justin Penzenstadler, PharmD, MSc** Clinical Pharmacology Reviewer Division of Clinical Pharmacology II (DCP-II) Office of Clinical Pharmacology (OCP) Office of Translational Sciences (OTS), CDER, FDA
Statistical Assessment of Empagliflozin Efficacy	**Roberto Crackel, PhD** Statistical Reviewer Division of Biometrics II (DB-II) Office of Biostatistics (OB), OTS, CDER, FDA
Diabetic Ketoacidosis in the Empagliflozin Type 1 Diabetes Development Program	**Mahtab Niyyati, MD**
Statistical Assessment of DKA Risk	**Shanti Gomatam, PhD** Mathematical Statistician Division of Biometrics VII (DB-VII) OB, OTS, CDER, FDA
Summary of Safety and Efficacy	**Mahtab Niyyati, MD**

Clarifying Questions

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 whether empagliflozin 2.5 mg as an adjunct to insulin provides benefit for adult patients with type 1 diabetes. Discuss your views of the clinical meaningfulness of the small HbA1c reduction as well as other endpoints studied to evaluate benefits of empagliflozin 2.5 mg including body weight and blood pressure.

Committee Discussion: *There were differing views among the committee members with regard to the clinical meaningfulness of the reduction in HbA1c. Some of the members agreed that the Applicant was successful in demonstrating clinical meaningfulness of the decrease in hemoglobin A1C (HbA1C) by approximately 0.3%. It was noted that there is a significant unmet need for the T1DM population so even a 0.3% reduction in HbA1c likely provides some incremental benefit on microvascular risk reduction, and is in line with another adjunctive therapy (pramlintide). Some members expressed uncertainties toward the meaningfulness of HbA1c reduction as it was not associated with a reduction in hypoglycemia, and noted the lack of longer term data that would confirm the durability of HbA1c lowering beyond 26 weeks. The single available efficacy trial with the 2.5 mg dose was a concern for the majority of the committee. With regard to other endpoints, many of the committee members noted that empagliflozin's effects on the other secondary endpoints were marginal and clinically insignificant, such as the small reduction in blood pressure and weight loss. Please see the transcript for details of the committee's discussion.*

2. **DISCUSSION:** Discuss your level of concern about the risk of diabetic ketoacidosis (DKA) with the use of empagliflozin 2.5 mg in type 1 diabetes patients. Discuss your level of confidence in the ability of the available safety database to accurately characterize the DKA risk given the small number of events observed in a single trial that is only 26 weeks in duration. Discuss your level of confidence in the reliability of the adjudication process to assess DKA risk, including the clinical meaningfulness of the adjudication categories, and the applicability of extrapolating risk management in a clinical trial setting to real world use.

   Committee Discussion: *The majority of the committee expressed low confidence in the safety database due to the limitations of the trial design (i.e., small sample size and short duration of exposure). The committee discussed the need for a larger trial consisting of broader endpoints and longer duration of exposure to better characterize the risk of diabetic ketoacidosis (DKA) in a type 1 diabetic population. The committee emphasized that the efforts used to educate patients and to isolate DKA complications early during the trial would be extremely difficult to implement in real-world settings. The committee acknowledged the risk of DKA in the type 1 diabetic population (even with the use of insulin pumps); however, the committee noted that the addition of empagliflozin to a type 1 diabetic regimen can exacerbate the onset of DKA. Some committee members commented that the adjudication process failed to capture all signals of ketosis or DKA that may have presented itself in the trial. Please see the transcript for details of the committee's discussion.*

3. **DISCUSSION:** Discuss the overall benefit/risk profile of empagliflozin 2.5 mg as an adjunct to insulin therapy for the treatment of adult patients with type 1 diabetes. Discuss the sufficiency of the demonstrated benefit(s) in light of the uncertainties around the DKA risk and other risks of the drug.

   Committee Discussion: *Most of the committee members expressed uncertainties with the overall benefit to risk profile of empagliflozin 2.5 mg as an adjunct to insulin therapy for the treatment of adult patients with type 1 diabetes. The committee expressed the need for an additional trial of a longer duration and a more sensitive DKA adjudication process to sufficiently capture the efficacy and safety of the product discussed. Although the product demonstrated clinical benefits in the reduction of HbA1C over 6 months, the committee*

argued that the potential risk of DKA overshadows that benefit. The committee agreed that the patient monitoring practices during the trials were the best case scenario, thus the DKA rates shown in the studies will be more pronounced in real-world settings. Please see the transcript for details of the committee's discussion.

4. **VOTE:** Do the available data suggest that the benefits outweigh the risks and support approval of empagliflozin 2.5 mg, administered orally once daily, as an adjunct to insulin to improve glycemic control in adults with type 1 diabetes mellitus?

   a. If yes, please explain your rationale and comment on whether any additional studies should be required after approval.

   b. If no, please describe what further data you believe the applicant should provide to establish a favorable benefit risk profile to support approval.

   Vote Result: **Yes: 2** **No: 14** **Abstain: 0**

   Committee Discussion: *The majority of the committee voted "No", indicating that the available data does not suggest that the benefits outweigh the risks and does not support approval of empagliflozin 2.5 mg, administered orally once daily, as an adjunct to insulin to improve glycemic control in adults with type 1 diabetes mellitus. The committee members who voted "No"indicated that the data shown did not suggest that the benefits of empagliflozin 2.5 mg outweighed its risks. The members acknowledged the clinical significance of empagliflozin use in lowering HbA1C by approximately 0.3% and the possible corresponding benefits of that effect if it were maintained and confirmed in a second trial. The committee questioned the durability of this reduction as the Applicant did not provide data supporting glycemic control after 26 weeks. The committee members repeatedly noted concerns with the study design, such as the selectivity of the sample population, the insufficient numbers of participants, missed DKA capturing events and ketosis due to insensitive adjudication, and the short duration of exposure. The committee members recommended an additional longer trial with a larger population, and an adjudication charter with increased sensitivity for capturing clinically significant ketosis and DKA events in order to better characterize the DKA risk and the durability of the HbA1c benefit. The two committee members who voted "Yes" articulated that the data shown was expected and the clinical outcomes were anticipated. These committee members noted that the product can be beneficial to the patient and instrumental to the practitioner with appropriate therapeutic monitoring. Please see the transcript for details of the committee's discussion.*

The meeting was adjourned at approximately 4:45 p.m.