Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
October 24-25, 2018

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

Topic: On both days, the committee discussed the "Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" (https://www.fda.gov/downloads/Drugs/Guidances/ucm071627.pdf), and the cardiovascular risk assessment of drugs and biologics for the treatment of type 2 diabetes mellitus.

These summary minutes for the October 24-25, 2018 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on January 30, 2019.

I certify that I attended the October 24-25, 2018 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/
Peter Wilson, MD
Chairperson, EMDAC

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting

October 24-25, 2018

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on October 24 – 25, 2018, 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. The meeting was called to order by Peter Wilson, MD (Chairperson). The conflict of interest statement was read into the record by LaToya Bonner, PharmD (Designated Federal Officer). There were approximately 200 people in attendance. There were 9 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: On both days, the committee discussed the "Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" (https://www.fda.gov/downloads/Drugs/Guidances/ucm071627.pdf), and the cardiovascular risk assessment of drugs and biologics for the treatment of type 2 diabetes mellitus.

Attendance:
EMDAC Members Present (Voting): Michael Blaha, MD, MPH; Daniel Budnitz, MD, MPH; Kenneth D. Burman, MD; James de Lemos, MD; Susan S. Ellenberg, MD; Cecilia C. Low Wang, MD; Anna McCollister-Slipp (*Consumer Representative*); Peter W.F. Wilson, MD (*Chairperson*); Susan Z. Yanovski, MD

EMDAC Members Not Present (Voting): Marvin A. Konstam, MD; Thomas J. Weber, MD

EMDAC Member Not Present (Non-Voting): Reshma Kewalramani, MD, FASN (*Industry Representative*)

Temporary Members (Voting): Brendan M. Everett, MD, MPH; George Grunberger, MD, FACP, FACE; Judith Fradkin, MD; Connie B. Newman, MD, FACP, FAHA, FAMWA; David C. Robbins, MD; Yves Rosenberg, MD, MPH; Fred Kushner, MD, FACC; Thomas J. Wang, MD; Martha Nason, PhD; Richard Dan Lumley (*Patient Representative*)

Acting Industry Representative to the EMDAC (Non-Voting): Scott Wasserman, MD, FACC

FDA Participants (Non-Voting): Patrick Archdeacon, MD; William Chong, MD; Mahtab Niyyati, MD; Mary Thanh Hai, MD; Lisa Yanoff, MD

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

Open Public Hearing Speakers: Anna Carracher and Martin Kurian (Close Concerns); Stephen Gough, MD, FRCP (Novo Nordisk); Varuna Srinivasan, MBBS, MPH (on behalf of Rafael Gonzalez-Barros, MD, MPH, MBA) (National Center for Health Research); Emily Fitts (diaTribe Foundation); Elisabeth Bjork (AstraZeneca Pharmaceuticals); Jay Edelberg, MD, PhD, FAHA, FACC (Sanofi); Jeffrey S. Riesmeyer, MD and Angelyn Bethel, MD (Eli Lilly); Peter Rentzepis; Kelly Close (dQ&A)

The agenda was as follows:

Call to Order and Introduction of Committee	**Peter Wilson, MD** Chairperson, EMDAC
Conflict of Interest Statement	**LaToya Bonner, PharmD, NCPS** Designated Federal Officer, EMDAC
FDA Introductory Remarks	**William Chong, MD** Director (Acting) Division of Metabolism and Endocrinology Products (DMEP) Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA

FDA PRESENTATIONS

History of the 2008 Cardiovascular Guidance and Overview of the Guidance Recommendations	**Lisa Yanoff, MD** Deputy Director (Acting) DMEP, ODE-II, OND, CDER, FDA
Review of Cardiovascular Assessments Prior to the 2008 Guidance	**Patrick Archdeacon, MD** Clinical Team Lead (Acting) DMEP, ODE-II, OND, CDER, FDA
Review of Design and Results of Cardiovascular Outcome Trials	**Tania Condarco, MD** Clinical Team Lead (Acting) **Mahtab Niyyati, MD** Clinical Reviewer DMEP, ODE-II, OND, CDER, FDA

Clarifying Questions to FDA

BREAK

GUEST SPEAKER PRESENTATION

After 10 Years and 26 CVOTs, Where Do We Stand on CV Safety in Diabetes	**Robert E. Ratner, MD** Professor of Medicine Division of Endocrinology Georgetown University School of Medicine

Clarifying Questions for Dr. Ratner

Additional Clarifying Questions

LUNCH

TIMI STUDY GROUP PRESENTATION

Cardiovascular Outcome Trials in Patients with Diabetes: Issues and Opportunities	**Marc S. Sabatine, MD, MPH** Chairman, TIMI Study Group Lewis Dexter, MD Distinguished Chair in Cardiovascular Medicine Brigham and Women's Hospital Professor of Medicine, Harvard Medical School

Clarifying Questions for Dr. Sabatine

SPEAKER PRESENTATION

Impact and Importance of the 2008 Guidance in Diabetes Care	**Jennifer B. Green, MD** Associate Professor of Medicine Division of Endocrinology, Metabolism and Nutrition, Duke University Medical Center Duke Clinical Research Institute Durham VA Medical Center

Clarifying Questions for Dr. Green

Additional Clarifying Questions

ADJOURNMENT

Day 2: Thursday, October 25, 2018

Call to Order and Introduction of Committee	**Peter Wilson, MD** Chairperson, EMDAC
Conflict of Interest Statement	**LaToya Bonner, PharmD** Designated Federal Officer, EMDAC
FDA Introductory Remarks	**William Chong, MD** Director (Acting) Division of Metabolism and Endocrinology Products (DMEP), Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA

OPEN PUBLIC HEARING

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the impact of the recommendations in the 2008 Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes on the assessment of cardiovascular risk for drugs indicated to improve glycemic control in patients with type 2 diabetes mellitus.

   Committee Discussion: *Overall, the committee agreed that the 2008 Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes has been favorable for both patients and physicians alike. Committee members noted that while the Guidance was intended to evaluate a safety concern, that there was cardiovascular benefit demonstrated for some drugs through the trials. Committee members noted that the assessment of cardiovascular risk detailed in the 2008 Guidance has been "incredibly impactful" in terms of providing cardiovascular safety data for new antidiabetic drugs and changing the climate for diabetes care with regard to cardiovascular benefit.*

   Noting that the cardiovascular outcomes trials are enriched with patients at high risk for atherosclerotic cardiovascular events, some committee members expressed concerns with the generalizability of the outcomes due to exclusion of diabetic patients at lower cardiovascular risk, as well as concerns about continuing to focus on atherosclerotic cardiovascular events without considering other outcomes relevant to the diabetic population such as heart failure or nephropathy. The committee suggested that the design and conduct of the trials could be changed by broadening the population, expediting data collection and review, and expanding to other outcomes of interest (e.g., heart failure, chronic kidney disease, peripheral arterial disease). Please see the transcript for details of the Committee discussion.

2. **DISCUSSION:** For each recommendation described in the 2008 guidance, discuss its value in the evaluation of the safety of new antidiabetic drugs. The recommendations we would like you to consider are:

   a. Establishment of an independent cardiovascular endpoints committee for prospective adjudication.

      Committee Discussion: *The Committee members' opinions were split regarding the need to establish an independent cardiovascular endpoints committee for adjudication. Some members agreed that an independent committee may be necessary to improve specificity when looking for safety signals. However, other members made cautionary remarks about the approach, noting the potential for ascertainment bias and effects on the behavior of trial investigators. One committee member emphasized that it is imperative to have an ascertainment committee and adjudication committee with an overall generalized committee as an overseer, dedicated to the events of interest to avoid misguided data (bias). One committee member opined that in the setting of a prespecified outcome that an adjudication committee may not be necessary. Additionally, the Committee stressed the need for quicker, efficient data collection for a broader population, and that modern technology should be considered for its capacity in data retrieval and review, such as meaningful use of*

electronic health records, mobile devices, tablets, etc. Please see the transcript for details of the Committee discussion.

b. Inclusion of patients at higher risk for cardiovascular events in phase 2 and phase 3 trials to obtain sufficient endpoints to allow for a meaningful estimate of risk.

***Committee Discussion**: Unanimously, the panel agreed that patients at higher risk for cardiovascular events should be included in phase 2 and phase 3 trials to obtain sufficient endpoints to allow for a meaningful estimate of risk. However, the Committee also expressed that not all diabetes patients are at high cardiovascular risk and that narrowing the population to patients with high cardiovascular risk may limit generalizability and affect the ability to identify other risk signals and adverse events. Please see the transcript for details of the Committee discussion.*

c. Exclusion of 1.8 from the upper bound of the two-sided 95% confidence interval for the estimated risk ratio prior to approval.

d. Exclusion of 1.3 from the upper bound of the two-sided 95% confidence interval for the estimated risk ratio to conclude that there is no unacceptable increase in cardiovascular risk.

***Committee Discussion**: The Committee lacked consensus on question #2c and #2d; however, the Committee recommended a simpler paradigm in marketing new antidiabetic drugs in general. A majority of the Committee advocated the need to replace the two-step approach of ruling out the pre-market setting (upper bound of the confidence interval for the hazard ratio [HR] <1.8) and lower level of risk post-market setting (upper bound of the confidence interval for the HR <1.3). One alternative approach supported by many members of the Committee was to set a single pre-market expectation (e.g., excluding 1.5 from the upper bound of the confidence interval for the HR). Please see the transcript for details of the Committee discussion.*

3. **DISCUSSION:** Discuss how cardiovascular safety findings from members of a drug class should or should not be applied to all members of the drug class.

***Committee Discussion**: There was no consensus on this discussion point, although the majority of the committee acknowledged that the mechanisms for the cardiovascular safety or cardiovascular benefit of the drugs evaluated in CVOTs are not known. Therefore, those committee members stated that each drug should be considered individually, rather than applying results across all members of a drug class as a "class effect." A few committee members stated that cardiovascular safety findings for a drug during a trial may support the cardiovascular safety for other members of the drug class, as long as there are no cardiovascular safety signals noted in the phase 2 and phase 3 trials of the other drugs in the class. Please see the transcript for details of the Committee discussion.*

4. **VOTE:** The 2008 Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes provided recommendations on excluding an unacceptable increase in cardiovascular risk for all new therapies to improve

glycemic control in patients with type 2 diabetes regardless of the presence or absence of a signal for cardiovascular risk in the development program.

Should an unacceptable increase in cardiovascular risk be excluded for all new drugs to improve glycemic control in patients with type 2 diabetes, regardless of the presence or absence of a signal for cardiovascular risk in the development program?

Vote Result: Yes: 10 No: 9 Abstain: 0

a. If 'Yes', provide your rationale. Include in your discussion what changes, if any, you would recommend to the 2008 guidance and why, and what kind of assessment would be appropriate and when it should be conducted.

b. If 'No', provide your rationale. Include in your discussion what might constitute a signal of cardiovascular risk that would warrant conduct of a cardiovascular outcome trial or other form of cardiovascular risk assessment.

***Committee Discussion**: Although, there was a split vote, all Committee members were in agreement on a need for modifications to the 2008 Guidance to simplify it and to broaden the applicability of data derived from such trials, such as inclusion of non-traditional MACE endpoints (such as heart failure and peripheral artery disease), evaluation of other important complications of diabetes (e.g., nephropathy), and evaluation of other potential safety issues that may not be identified in shorter term trials. The Committee also supported broadening the population in the Phase 2 and 3 trials to include higher CV risk patients. The Committee members urged consideration of ways to modify the design of CVOTs to streamline the conduct while still ascertaining reliable data on important clinical events for patients diagnosed with type 2 diabetes. Some Committee members who voted "No" noted that they voted the way they did due to the wording of the question ("regardless of a CV safety signal"). Please see the transcript for details of the Committee discussion.*

The meeting was adjourned at approximately 3:47 p.m. on October 24, 2018 and at approximately 1:23 p.m. on October 25, 2018.