Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
June 20, 2017

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 a supplemental new drug application for VICTOZA (liraglutide) injection (NDA 022341), sponsored by Novo Nordisk, for the proposed additional indication of: as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk.

These summary minutes for the June 20, 2017 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on August 30, 2017.

I certify that I attended the June 20, 2017, 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
June 20, 2017

The following is the final report of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on June 20, 2017. 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: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm560480.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 20, 2017, 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 Novo Nordisk, Inc. 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 175 people in attendance. There were 13 Open Public Hearing (OPH) speaker presentations.

Issue: The committee discussed a supplemental new drug application for VICTOZA (liraglutide) injection (NDA 022341), sponsored by Novo Nordisk, for the proposed additional indication of: as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk.

Attendance:

EMDAC Members Present (Voting): Michael Blaha, MD, MPH; Daniel Budnitz, MD, MPH; Kenneth D. Burman, MD; Brendan M. Everett, MD, MPH (*via telephone*); Diana Hallare, MPH (Consumer Representative); Cecilia C. Low Wang, MD; James D. Neaton, PhD; Peter W.F. Wilson, MD (Chairperson); Susan Z. Yanovski, MD

EMDAC Members Not Present (Voting): Susan R. Heckbert, MD, PhD; Thomas J. Weber, MD

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

Temporary Members (Voting): Carmen J. Allergra, MD (*via telephone*); Leslie Cho, MD, FACC, FSCAI; James A. de Lemos, MD; Judith Fradkin, MD; Marvin A. Konstam, MD; Debra McCall, MBA (Patient Representative); David Oakes, PhD (*via telephone*); Yves Rosenberg, MD; David C. Robbins, MD; Hanna Sanoff, MD, MPH

FDA Participants (Non-Voting): Jean-Marc Guettier, MD; Lisa Yanoff, MD; Tania Condarco, MD; Kiya Hamilton, PhD; Julie Golden, MD; Shannon Sullivan, MD, PhD

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

Open Public Hearing Speakers: Kelly L. Close (diatribe Foundation); Richard Pratley, MD (Translational Research Institute for Metabolism and Diabetes); Stephanie Fox-Rawlings (National Center for Health Research); Sammy Almashat (Public Citizen's Health Research Group); Mark Warren; Robert Chilton; Mansur Shamali, MD; Vincent Coles (Novo Nordisk); Jonathan Leffert (American Association of Clinical Endocrinologists); Tamar Darsow (American Diabetes Association); Abigail Dove (dQ&A); Helen Gao; Pyal Marathe (Close Concerns)

The agenda was as follows:

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	**Jean-Marc Guettier, MD** Director, Division of Metabolism and Endocrinology Products (DMEP) Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Novo Nordisk Inc.**
Introduction	**Robert Clark** Vice President, Regulatory Affairs Novo Nordisk
LEADER Clinical Design	**Steve Marso, MD** Medical Director, Cardiovascular Services HCA Midwest Health Heart and Vascular Institute
CVOT Results	**Alan Moses, MD** Global Chief Medical Officer Novo Nordisk
Safety	**Todd Hobbs, MD** US Chief Medical Officer Novo Nordisk

APPLICANT PRESENTATIONS (CONT.)

Clinical Implications	**John Buse, MD, PhD** Verne S. Caviness Distinguished Professor Chief, Division of Endocrinology University of North Carolina School of Medicine
Benefit-Risk	**Alan Moses, MD**

Clarifying Questions to Applicant

BREAK

FDA PRESENTATIONS

Clinical and Statistical Overview	**Tania Condarco, MD** Clinical Reviewer DMEP, ODE-II, OND, CDER, FDA
	Kiya Hamilton, PhD Mathematical Statistician Division of Biostatistics II (DB-II) Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER, FDA
Safety Overview	**Julie Golden, MD** Clinical Reviewer DMEP, ODE-II, OND, CDER, FDA
	Shannon Sullivan, MD, PhD Clinical Reviewer DMEP, ODE-II, OND, CDER, FDA

Clarifying Questions to FDA

LUNCH

OPEN PUBLIC HEARING

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial assessed several non-CV safety outcomes including medullary thyroid carcinoma, pancreatic neoplasm, and pancreatitis. Please discuss whether the data presented today inform the potential for a causal relationship between liraglutide use and these non-CV safety outcomes. Please also discuss whether additional studies should be conducted to further evaluate these.

   Committee Discussion: *Altogether, the committee was generally reassured by the non-CV safety outcomes of interest, such as medullary thyroid carcinoma, pancreatic neoplasm, and pancreatitis assessed in the LEADER trial, although it was noted that the number of cases were small in comparison to the CV outcomes. Many committee members expressed that the exposure to liraglutide in LEADER was too short to consider the glucagon-like peptide-1 receptor agonist (GLP-1 RA) as the causative factor for the cancer outcomes of concern, given that agents that are known to cause cancer do so at least a decade after exposure. The committee recommended the sponsor to continue the medullary thyroid carcinoma registry to allow for further investigation of this safety issue. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Please comment on the design, conduct, and results of LEADER and whether LEADER

   a. Adequately addresses the post-approval CV risk assessment as recommended in the 2008 FDA Guidance titled *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*.

   b. Provides substantial evidence establishing that liraglutide reduces the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk.

   In your discussion, consider the patient population enrolled (e.g., baseline cardiovascular disease history), reliability of the results (e.g., impact of missing data), the clinical meaningfulness of the results, and the consistency of the results across the components of the MACE endpoint and subgroups.

   Committee Discussion*: The committee unanimously agreed that the LEADER study fulfilled the recommendations in the 2008 FDA Guidance and addressed the post-approval CV risk assessment in patients with type 2 diabetes mellitus (T2DM). As a whole, the committee members described LEADER as a well-designed clinical trial. Members identified the following as strenghts of the trial: the consistency of the the individual components of MACE, the successful enrollment of a large high risk CV population, and the low amount of missing data.*

   In addition to meeting the recommendations for CV risk assessment as described in the 2008 FDA Guidance, the committee also found that the results of the trial were robust and overall demonstrated cardiovascular (CV) benefit in high risk T2DM patients. However, the

committee voiced concerns with the results for two subgoups: the US (vs. Non-US) and the "3b (vs. 3a) subgroup" both of which had a point estimate greater than 1 for the Hazard Ratio for MACE. The committee struggled with the interpretation of these findings in the context of the primary endpoint results. The Sponsor put forward the hypothesis that the US subgroup results may have resulted from lower exposure to liraglutide (possibly due to lower adherence) among US patients and presented on-treatment analyses to support this position. While some committee members thought this hypothesis had merit, others were unsure whether it could fully account for US subgroup findings. In light of these findings, some members stated their uncertainty as to whether the data were sufficiently robust to support a CV indication that would pertain to these subgroups. Please see the transcript for details of the committee discussion.

3. **VOTE:** Do the results of LEADER establish that use of liraglutide in patients with Type 2 Diabetes Mellitus (T2DM) is not associated with unacceptably high cardiovascular risk? **Provide the rationale for your vote.**

   Vote Result: Yes: 19 No: 0 Abstain: 0

   Committee Discussion: *The committee unanimously voted "Yes", agreeing that the results of LEADER establish that the use of liraglutide in patients with T2DM is not associated with unacceptably high cardiovascular risk. As noted above, committee members commented on the strengths of the LEADER trial. Please see the transcript for details of the committee discussion.*

4. **VOTE:** Does the LEADER trial provide the substantial evidence needed to establish that liraglutide 1.8 mg daily reduces cardiovascular risk in patients with T2DM? **Provide the rationale for your vote.**

   Vote Result: Yes: 17 No: 2 Abstain: 0

   a. If yes, discuss the population for whom you believe this benefit applies.

      Committee Discussion*: The majority of the committee voted "Yes," the LEADER trial provided substantial evidence needed to establish that liraglutide 1.8 mg daily reduces cardiovascular risk in patients with T2DM. The committee members voiced their confidence in their decision based on the primary MACE results, as well as the consistent trends in the individual components of MACE. Members noted that although the subgroup findings described above were notable, they did not refute the overall LEADER results. Members generally agreed that the results of this single trial were compelling enough for them to support including a cardiovascular indication in the liraglutide label. The committee members recommended that patients diagnosed with atherosclerosis would be the population that would benefit the most from daily use of liraglutide 1.8 mg. The committee also noted that there may not be the same benefit in lower risk patients. Please see the transcript for details of the committee discussion.*

   b. If no, comment on what additional data would be needed.

Committee Discussion: *The two committee members who voted "No" noted that the Agency's general standard for approval of an indication is two adequate and well controlled trials. They also voiced concern regarding the subgroup findings, namely, the lack of a clear cardiovascualr benefit for the US subgroup as compared with the Non-US subgroup (vs. Non-US). Even though both members who voted "No" agreed that the LEADER trial was a well-designed study, the evidence did not compel them to vote in favor of the new indication. Please see the transcript for details of the committee discussion.*

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