Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
October 18, 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 the safety and efficacy of new drug application (NDA) 209637 for semaglutide injection, submitted by Novo Nordisk, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

These summary minutes for the October 18, 2017 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on November 27, 2017_.

I certify that I attended the October 18, 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 Endocrinologic and Metabolic Drugs
Advisory Committee Meeting
October 18, 2017

The following is the final report of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on October 18, 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/default.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 October 18, 2017, at the Tommy Douglas Conference Center, The Ballroom, 10000 New Hampshire Avenue, Silver Spring, Maryland 20903. 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 200 people in attendance. There were 13 Open Public Hearing (OPH) speaker presentations.

Issue: The committee discussed the safety and efficacy of new drug application (NDA) 209637 for semaglutide injection, submitted by Novo Nordisk, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Attendance:
EMDAC Members Present (Voting): Michael Blaha, MD, MPH; Daniel Budnitz, MD, MPH; Brendan M. Everett, MD, MPH; Cecilia C. Low Wang, MD; James D. Neaton, PhD; Thomas J. Weber, MD; Peter W. F. Wilson, MD (Chairperson); Susan Z. Yanovski, MD

EMDAC Members Not Present (Voting): Kenneth D. Burman, MD; Susan R. Heckbert, MD, PhD

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

Temporary Members (Voting): Erica Brittain, PhD; Luciano V. Del Priore, MD, PhD; Frederick L. Ferris III, MD; William R. Hiatt, MD, FAHA; Melissa Li-Ng, MD, FACP; Richard Lumley, EdD (Patient Representative); Paul M. Palevsky, MD; Yves D. Rosenberg, MD, MPH; Suzanne Robotti (Acting Consumer Representative)

Acting Industry Representative to the Committee (Non-Voting): Darryl Sleep, MD (Acting Industry Representative)

FDA Participants (Non-Voting): Mary T. Thanh Hai, MD; James P. Smith, MD, MS; William H. Chong, MD; Ya-Hui Hsueh, PhD; Andreea Lungu, MD

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

Open Public Hearing Speakers: Lawrence Blonde, MD (American Association of Clinical Endocrinologists); Virginia Valentine, APRN; Vanita Aroda, MD; Chris Brown; James Connor; Helena Rodbard, MD; Robert Ratner, MD; Dennis Murphy; Megan Polanin, MD (National Center for Health Research); Ann Carracher (DiaTribe); Abigail Dove (dQ&A); Pyal Marathe (Close Concerns); Tamar Darsow, MD (American Diabetes Association)

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** Clinical Team Lead Division of Metabolism and Endocrinology Products (DMEP), Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA
NIH PRESENTATION	
Review of Medical Risk Factors Associated with Diabetic Retinopathy	**Emily Y. Chew, MD** Deputy Director Division of Epidemiology and Clinical Applications National Eye Institute, National Institutes of Health
Clarifying Questions to Guest Speaker	
APPLICANT PRESENTATIONS	**Novo Nordisk Inc.**
Introduction	**Stephanie DeChiaro** Director, Regulatory Affairs Novo Nordisk
Design, Efficacy and Primary Outcomes	**Anders Hvelplund, MD, PhD** Senior Director, Medical and Science Novo Nordisk

APPLICANT PRESENTATIONS (CONT.)

Safety	**Stephen Gough, MD, FRCP (UK)** Senior Principal Clinical Scientist Novo Nordisk
Diabetic Retinopathy	**Lloyd Paul Aiello, MD, PhD** Professor and Vice Chair Department of Ophthalmology Harvard Medical School Director, Beetham Eye Institute and Vice President Joslin Diabetes Center
Retinal Safety	**Stephen Gough, MD, FRCP (UK)**
Clinical Perspective	**Richard Pratley, MD** Samuel E. Crockett, MD Chair in Diabetes Research Director, Florida Hospital Diabetes Institute Senior Scientist, Translational Research Institute for Metabolism and Diabetes
Benefit:Risk	**Stephen Gough, MD, FRCP (UK)**
Clarifying Questions to Applicant	

BREAK

FDA PRESENTATIONS

FDA Overview of Efficacy and Safety of Semaglutide	**Andreea Lungu, MD** Clinical Reviewer DMEP, ODE-II, OND, CDER, FDA
Statistical Assessment of Cardiovascular Safety and Retinopathy Safety of Semaglutide in the SUSTAIN 6 Trial	**Ya-Hui Hsueh, PhD** Mathematical Statistician Division of Biometrics VII Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER, FDA
Further Discussion of Findings for Diabetic Retinopathy	**Andreea Lungu, MD**
Summary of FDA Findings for Semaglutide	**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:** The applicant has proposed that semaglutide be indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Discuss the efficacy of semaglutide with respect to glycemic control.

   Committee Discussion: *Overall, the committee agreed that semaglutide was shown to reduce hyperglycemia in adults with type 2 diabetes mellitus. Many members expressed that they were impressed by semaglutide's ability to sustain a favorable hemoglobin A1c (HbA1c) over the 2-year trial period. One member highlighted the weight lowering effects of the drug and commented that this may contribute to the HbA1c reduction shown in the trial. Please see the transcript for details of the committee discussion.*

   2. **DISCUSSION:** Semaglutide once weekly injection has been studied in seven phase 3 studies and a two-year cardiovascular outcomes trial (SUSTAIN 6). Excluding issues related to diabetic retinopathy and CV risk, which will be considered subsequently, discuss any safety concerns you have related to semaglutide, if any.

   Committee Discussion*: The committee agreed that the data shown did not present any concerning safety findings with semaglutide. It was noted that the safety findings (excluding discussion of diabetic retinopathy and CV risk) are consistent with what is expected for the drug class. One member commented that the safety database is relatively small and limited for assessing rare events such as malignancies. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** In SUSTAIN 6 (CVOT), a pre-specified secondary safety endpoint was time from randomization to the first occurrence of either a need for retinal photocoagulation, vitreous hemorrhage, treatment with intravitreal agents, or diabetes-related blindness. The results for this composite endpoint showed an increased risk with semaglutide (HR: 1.76 [95% CI: 1.11, 2.78]).

   a. Discuss the strengths and limitations of this assessment (e.g., endpoint definitions, methods of ascertainment, adjudication, trial design, and any other considerations relevant to the interpretation of the results).

      Committee Discussion*: The committee members noted concerns over the duration of the trial and the procedures in place to evaluate retinopathy at baseline and during the trial. The ophthalmologists also commented that the selected endpoints were not adequate for assessing retinopathy. These issues limit the interpretation of the results. Some members commented that longer duration of follow-up would have*

been useful to better evaluate this finding. Please see the transcript for details of the committee discussion.

b. One hypothesis regarding this finding is that rapid and large reductions in HbA1c can be expected to increase the short-term risk of diabetic retinopathy complications. Discuss the extent to which you are convinced that a reduction in blood glucose/HbA1c is the mediator of the observed increase in diabetic retinopathy complications in SUSTAIN 6.

***Committee Discussion**: Committee members expressed reservations with concluding that reduction in blood glucose was the sole mediator of the observed increase in risk for diabetic retinopathy complications. One member identified a small group with a lower reduction in HbA1c and a higher amount of retinopathy complications, alluding to the notion that there were more mediators associated with the retinopathy complications. A few members expressed that there may be a plausible correlation between the two, but more data are needed to conclude a causal association. Please see the transcript for details of the committee discussion.*

c. Improving glycemic control should be expected to reduce the risk of retinopathy over the long term. Discuss whether the increase in diabetic retinopathy complications in this two-year controlled trial affects your assessment of the clinical benefits expected from long-term use of semaglutide for glycemic control.

***Committee Discussion**: Collectively, the committee members expressed that their expectation for a reduced risk of diabetic retinopathy progression with better long-term glycemic control was not changed by the data shown. The committee noted some challenges in drawing conclusions due to limitations of the study (e.g., short duration, procedures for assessing retinopathy, selected endpoints). Committee members reiterated that a trial longer than two years would have been more informative. Please see the transcript for details of the committee discussion.*

d. In SUSTAIN 6, the increase in absolute risk of diabetic retinopathy complications was greater among those with diabetic retinopathy at baseline (8.2% semaglutide, 5.2% placebo) compared to those without diabetic retinopathy at baseline (0.7% semaglutide, 0.4% placebo), although the relative risk increases were similar. Patients with diabetic retinopathy are often among those most in need of improved glycemic control. Discuss whether you would have any concerns about the use of semaglutide among patients with diabetic retinopathy, if approved.

***Committee Discussion**: The endocrinologists on the committee stated that they would not withhold semaglutide, but that it would be important to ensure appropriate ophthalmologic exams. Please see the transcript for details of the committee discussion.*

e. Comment on your level of concern related to the observed increased risk in diabetic retinopathy complications observed in SUSTAIN 6.

Committee Discussion*: The committee members noted that there is a signal of increased risk, but they did not express that this signal was reason for significant concern. The data did not deviate from earlier studies which showed transient increase in retinopathy with intensive glycemic control. The committee noted that diabetic retinopathy is a manageable co-morbid disease. However, the committee recognized that there were limitations to the data and some members commented that a longer-term trial may be helpful to further allay concerns. Please see the transcript for details of the committee discussion.*

4. **DISCUSSION:** In SUSTAIN 6, a total of 254 first major adverse cardiovascular events (MACE) occurred during a median 2-year follow-up. The estimated hazard ratio of MACE and the components of MACE for semaglutide vs. placebo (ITT) are shown below:

	Semaglutide N=1648 PY=3408.2	**Placebo** N=1649 PY=3401.1	**Hazard Ratio (95% CI)**
MACE	**108 [3.2]**	**146 [4.3]**	**0.74 (0.58, 0.95)**
Cardiovascular death	44	46	0.98 (0.65, 1.48)
Non-fatal MI	47	64	0.74 (0.51, 1.08)
Non-fatal Stroke	27	44	0.61 (0.38, 0.99)
MI (fatal+nonfatal)	54	67	0.81 (0.57, 1.16)
Stroke (fatal+nonfatal)	30	46	0.65 (0.41, 1.03)

PY: person-years; [] indicates incidence rate per 100 PY
Numbers for components of MACE

Discuss these results and comment whether these data are adequate to characterize the CV safety of semaglutide.

Committee Discussion*: The majority of the committee expressed confidence that the available data do not suggest increased cardiovascular risk with semaglutide. However, one committee member noted that the study and the development program included small proportions of patients from minority groups with a high prevalence of type 2 diabetes mellitus. A broader representation of the population would have been informative. Please see the transcript for details of the committee discussion.*

5. **VOTE:** Do the available efficacy and safety data support approval of semaglutide 0.5 mg and 1 mg, administered subcutaneously once weekly, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 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 studies you believe the applicant must conduct to establish favorable benefit/risk to support approval.

Vote Result: Yes: 16 No: 0 Abstain: 1

Committee Discussion: *The committee members overwhelmingly voted "Yes", agreeing that the available efficacy and safety data support approval of semaglutide 0.5 mg and 1 mg, administered subcutaneously once weekly, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The committee agreed that the primary endpoint was met. Benefits of semaglutide included better glycemic control and favorable findings for weight. The identified risks did not outweigh these benefits. The one member who abstained noted that an extended and larger trial would have been helpful due to the retinopathy data presented and the limited data on subgroups. The majority of committee members suggested that additional study of diabetic retinopathy would be useful but did not feel that this should be required of the sponsor. Committee members agreed that there was no signal of unacceptable cardiovascular risk with semaglutide and did not believe that additional study to further characterize cardiovascular safety was needed.. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:53 p.m.