Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
January 17, 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 will discuss new drug application 210934 for sotagliflozin oral tablet, sponsored by Sanofi-Aventis U.S., LLC, for the proposed indication: Adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus.

These summary minutes for the January 17, 2019 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on February 21, 2019.

I certify that I attended the January 17, 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/
LaToya Bonner, PharmD
Designated Federal Officer, EMDAC

/s/
Peter Wilson, MD
Chairperson, EMDAC

Final Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
January 17, 2019

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on January 17, 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 sanofi-aventis, U.S., LLC. 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 300 people in attendance. There were 19 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: The Committee discussed new drug application 210934 for sotagliflozin oral tablet, sponsored by sanofi-aventis U.S., LLC, for the proposed indication: adjunct to insulin therapy to improve glycemic control in adults with type 1 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, PhD; Cecilia C. Low Wang, MD; Anna McCollister-Slipp (*Consumer Representative*); Peter W.F. Wilson, MD (*Chairperson*); Marvin A. Konstam, MD

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

EMDAC Members Not Present (Voting): Thomas J. Weber, MD; Susan Z. Yanovski, MD

Temporary Members (Voting): Rebecca Brown, MD; Susan Lellock (*Patient Representative*); Kashif M. Munir, MD; Martha Nason, PhD; Connie Newman, MD, FACP, FAHA, FAMWA; Abigail B. Shoben, PhD; Jack A. Yanovski, MD, PhD

FDA Participants (Non-Voting): Kiya Hamilton, PhD; Mitra Rauschecker, MD; Mary Thanh Hai, MD; Lisa Yanoff, MD

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

Open Public Hearing Speakers: Sidney M. Wolfe, MD (Public Citizen)); Anne Peters, MD; Stephanie Fox-Rawlings, PhD (National Center for Health Research); Sanjoy Dutta, PhD (JDRF International); William Keller; Claire Pegg; Kristine Whitney; Satish Garg, MD; William T. Cefalu, MD (American Diabetes Association); Margot Carr; Christina Roth (College Diabetes Network); Helena Rodbard, MD; Charles Alexander, MD; Anna Carracher and Brian Levine

(Close Concerns); Kelly Close (diaTribe); Erik Shoger (on behalf of Keaton Stoner) (dQ&A); Todd Hunt; Emily Fitts; Anna Norton

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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	**Lisa 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	**sanofi-aventis, U.S., LLC**
Introduction	**Rene Belder, MD** Vice President Diabetes and Cardiovascular Clinical Development Sanofi
Unmet Medical Needs in Adults with Type 1 Diabetes	**Steven Edelman, MD** Clinical Professor of Medicine University of California San Diego School of Medicine
Clinical Efficacy Results	**Pablo Lapuerta, MD** Executive Vice President and Chief Medical Officer Lexicon Pharmaceuticals
Clinical Safety Results	**Klaus Jensen, MD** Head of Diabetes, Cardiovascular and Metabolism Development Sanofi
Clinical Perspective	**Juan Pablo Frias, MD** Medical Director and Principal Investigator National Research Institute
Benefit / Risk	**Rene Belder, MD**

Clarifying Questions to Applicant

FDA PRESENTATIONS

Overview of the Clinical Pharmacology and Development Program for Sotagliflozin	**Mitra Rauschecker, MD** Acting Team Leader DMEP, ODE-II, OND, CDER, FDA
Statistical Assessment of Sotagliflozin Efficacy	**Kiya Hamilton, PhD** Statistical Reviewer Division of Biometrics II, Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER, FDA
Diabetic Ketoacidosis in the Sotagliflozin Clinical Development Program	**Mitra Rauschecker, MD**
Diabetic Ketoacidosis in Type 1 Diabetes Mellitus Patients Using a Sodium-glucose Co-transporter 2 Inhibitor: Postmarketing Experience	**Christine Chamberlain, PharmD, CDE** Safety Evaluator Division of Pharmacovigilance I Office of Pharmacovigilance and Epidemiology (OPE) Office of Surveillance and Epidemiology (OSE) CDER, FDA
Sentinel Analysis of SGLT2 Inhibitor Use in Patients with Type 1 Diabetes Mellitus and Rates of Diabetic Ketoacidosis	**Christian Hampp, PhD, FISPE** Master Reviewer Epidemiologist Division of Epidemiology I OPE, OSE, CDER, FDA
Summary of FDA Findings for Sotagliflozin	**Mitra Rauschecker, 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 the benefits claimed by the applicant, e.g. glycemic control, effects on body weight and risk for hypoglycemia, for patients with type 1 diabetes. Comment on the strength of the statistical evidence and clinical meaningfulness of each of these claimed benefits.

Committee Discussion: *The committee members questioned the clinical relevance of the modest reduction of hemoglobin A1c (HbA1c) shown with the use of sotagliflozin, but acknowledged that the insulin dose optimization period may have limited that reduction. One committee member noted that since it is unknown what the absolute risk reduction associated with HbA1c reductions is, we don't know how to interpret the benefit with regard to prevention of diabetic related comorbidities, specifically microvascular diseases, e.g. retinopathy, nephropathy. It was also noted that the moderate effects on HbA1c may not fully capture the benefits of sotagliflozin but the "time in range" might be a better assessment to support benefit, even though there are no current validated outcomes on "time in range" and glycemic variability. The committee noted that diabetes drug development programs could be enhanced by additional validated clinical outcome measures or biomarkers. The committee also discussed that the sotagliflozin development program lacked adequate quality of life (QOL) measurements that would have provided data on how the patients felt during the trial. One committee member also noted that the degree of weight loss (5%) was small and would not be considered clinically relevant for an obesity drug. Please see the transcript for details of the Committee discussion.*

2. **DISCUSSION:** Discuss your level of concern about the observed risk of diabetic ketoacidosis (DKA) in adult patients in the sotagliflozin clinical studies and DKA risk associated with sotagliflozin use in a real-world setting.

   Committee Discussion: *Overall, the committee members expressed great concern about the observed risk of diabetic ketoacidosis (DKA) in the phase 3 studies. Some members stated that DKA could be manageable with proper education and strategic monitoring. However, other members were concerned, citing the number of observed DKA events relative to placebo in the phase 3 studies and the probability that the risk could be even higher in the real-world setting outside the confines of a clinical trial. The committee members noted that there was no evidence the risk mitigation strategy proposed by the applicant works. One committee member stressed that it was imperative for the applicant to propose a successful risk mitigation strategy that involves education to patients and their providers prior to the approval of sotagliflozin. Please see the transcript for details of the Committee discussion.*

3. **DISCUSSION:** Comment on any relevant differences in efficacy and/or safety observed between the two proposed doses of sotagliflozin (200 mg and 400 mg). In your discussion please consider the clinical pharmacology data as well as clinical trial data, i.e. improvement in glycemic control and risk for DKA.

   Committee Discussion*: Several committee members commented that there was no meaningful difference in glycemic control in the data shown for the two proposed doses, and that the 400 mg dose did not show clinical superiority to the 200 mg dose. In addition, those members in favor of the 200 mg dose expressed reluctance to recommend approval of the 400 mg dose due to its association with increased incidences of DKA, genital mycotic infections, and osmotic diarrhea. In contrast, other members acknowledged the increased rate of DKA amongst the patients administered 400 mg, but also noted clinical improvements in these patients, such as increase number of subjects who achieve "time in range", weight loss, and blood pressure reduction when administered sotagliflozin 400 mg as an adjunct to insulin therapy when compared to insulin alone. Overall, the committee agreed that further*

studies are needed, like an evaluation of a titration approach to the dosing regimen. Please see the transcript for details of the Committee discussion.

4. **DISCUSSION:** Discuss the overall benefit risk profile of sotagliflozin for patients with type 1 diabetes. What specific benefits and risks did you consider; what was your approach and rationale for how they were weighed against each other? Specifically comment on the composite endpoint used by the applicant (HbA1c<7% with no episodes of severe hypoglycemia or diabetic ketoacidosis) to represent net benefit. If you would recommend an alternative strategy, please explain your rationale.

   Committee Discussion: *The committee acknowledged the anecdotal evidence of improved outcomes with use of sotagliflozin as an adjunct to insulin therapy from the patient testimonies during the Open Public Hearing portion of the meeting. Although convincing, the committee members voiced their disappointment on the lack of quantitative measures supporting the testimonials given. The committee expressed concerns regarding the approval of sotagliflozin due to the DKA risk, and lack of clarity with regard to favorable benefits to balance against this substantial risk. In addition, the committee agreed that the primary composite endpoint data used by the applicant was not informative to weigh the increased risk of a life-threatening event against the benefit. One member commented that there was only a net harm without a convincing risk mitigation strategy proposed by the applicant, and the applicant should propose an acceptable risk mitigation strategy tested within the context of a clinical trial. Another member suggested that this may be a regimen suited for a select group of patients in which the patient and prescriber would discuss the trade-offs for the use of this drug, e.g. quality of life (QOL) versus the risk of DKA. Please see the transcript for details of the Committee discussion.*

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

   Vote Result: Yes: 8 No: 8 Abstain: 0

   a. If yes, comment on whether you recommend any labeling restrictions, whether any additional studies should be required after approval, and comment on whether your vote indicates support for both proposed doses of sotagliflozin (200 mg and 400 mg).

   b. If no, please describe your rationale and what further studies you believe the applicant should conduct to establish a favorable benefit risk profile to support approval.

   Committee Discussion*: The committee vote was split on whether the available data suggest that the benefits outweigh the risks and support approval of sotagliflozin, 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 "yes" suggested that this drug product may be patient-to-provider specific. They agreed that prior to prescribing the medication, the patient should be well informed of the risk and strict monitoring methods should be implemented to support drug safety and efficacy. Those who voted "yes" also agreed that a post-marketing*

trial to assess the benefits versus risk on a larger and diverse population should be implemented. Also, these committee members encouraged the FDA to utilize the applicant's risk management plan as a starting point for discussions with the applicant on risk mitigation strategies. One committee member indicated that sotagliflozin could be viewed similarly to insulin pumps, which were approved with a known risk of DKA. Some of the committee members who voted "yes" noted that only the 200 mg dose should be approved due to data showing the 400 mg dose associated with an increase of DKA in patients with type 1 diabetes mellitus, while others abstained or commented that both doses should be approved since they were both studied in the clinical trials.

Those who voted "no" noted that although innovative therapies for patients with type 1 diabetes are needed, there is a concerning risk of DKA, and the applicant did not demonstrate sufficient data to support benefit beyond modest reductions in HbA1c, and has not shown data supporting ketone monitoring or other risk mitigation strategies to be effective in mitigating DKA risk. These committee members were also concerned that the risk of DKA would be higher in the real world. Please see the transcript for details of the Committee discussion.

The meeting was adjourned at approximately 4:54 p.m.