Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
October 31, 2024

Location: FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public also had the option to participate via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform.

Topic: The Committee discussed new drug application 210934, for sotagliflozin oral tablet, submitted by Lexicon Pharmaceuticals, Inc., for the proposed indication, as an adjunct to insulin therapy, to improve glycemic control in adults with type 1 diabetes mellitus and chronic kidney disease.

These summary minutes for the October 31, 2024 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on December 18, 2024.

I certify that I attended the October 31, 2024 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/**
Joyce Frimpong, PharmD	Cecilia C. Low Wang, MD
Acting Designated Federal Officer, EMDAC	Chairperson, EMDAC

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
October 31, 2024

The Endocrinologic and Metabolic Drugs Advisory Committee Meeting (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on October 31, 2024, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public also had the option to participate via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Lexicon Pharmaceuticals, Inc. The meeting was called to order by Cecilia C. Low Wang, MD (Chairperson). The conflict of interest statement was read into the record by Joyce Frimpong, PharmD (Acting Designated Federal Officer). There were approximately 100 people in attendance. There were 22 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, submitted by Lexicon Pharmaceuticals, Inc., for the proposed indication, as an adjunct to insulin therapy, to improve glycemic control in adults with type 1 diabetes mellitus and chronic kidney disease.

Attendance:
Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting):
Matthew T. Drake, MD, PhD; Cecilia C. Low Wang, MD; Thomas Wang, MD

Endocrinologic and Metabolic Drugs Advisory Committee Members Not Present (Voting):
Robert Alan Greevy, Jr., PhD

Endocrinologic and Metabolic Drugs Advisory Committee Member Present (Non-Voting):
Ilan Irony, MD (*Industry Representative)*

Temporary Members (Voting): Elizabeth A. Chrischilles, PhD; Brendan M. Everett, MD, MPH; Marvin A. Konstam, MD; Martha Nason, PhD; Connie Newman, MD, MACP; Barbara Onumah, MD; Afshin Parsa, MD, MPH; Prabir Roy-Chaudhury, MD, PhD, FRCP; Steve Seliger, MD, MS; Abigail B. Shoben, PhD; Paul Tibbits, Jr. (*Patient Representative*)

FDA Participants (Non-Voting): Lisa Yanoff, MD; Patrick Archdeacon, MD; Justin Penzenstadler, PharmD; Mari Suzuki, MD; Wenda Tu, PhD

Acting Designated Federal Officer (Non-Voting): Joyce Frimpong, PharmD

Open Public Hearing Speakers: Nina Zeldes (Public Citizen); Anna Norton; Donald Hannaford; Robert Busch, MD; Sanjoy Dutta (BreakthroughT1D (formerly JDRF)); Helena W. Rodbard, MD; Pablo Lapuerta, MD (Lapuerta Consulting, LLC); Christel Marchand Aprigliano; Sylvia E. Rosas, MD (National Kidney Foundation); Donna Rice (DiabetesSisters); Chris Bryant; Julie Keller Heverly (The diaTribe Foundation); Christian W. Mende, MD; Brittany Carney (Taking Control of Your Diabetes (TCOYD)); Ginine Cilenti (Diabetes Foundation, Inc.); Kelly Close, Elaine Young, Esther Min, Kat Moon, Nayeli Yanez (Close Concerns); Richard M. Bergenstal, MD; Janet McGill, MD, Nirali Shah, MD (American Association of Clinical Endocrinology); Carolina Solis-Herrera, MD; Kristen Hohmann; Alexander Fleming, MD; John Sjolund

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The agenda was as follows:

Call to Order and Introduction of Committee	**Cecilia C. Low Wang, MD** Chairperson, EMDAC
Conflict of Interest Statement	**Joyce Frimpong, PharmD** Acting Designated Federal Officer, EMDAC
FDA Introductory Remarks NDA 210934: Sotagliflozin to Improve Glycemic Control in Adults with Type 1 Diabetes Mellitus and Chronic Kidney Disease (T1D-CKD)	**Patrick Archdeacon, MD** Deputy Director Division of Diabetes, Lipid Disorders, and Obesity (DDLO) Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Lexicon Pharmaceuticals, Inc.**
Introduction: T1D-CKD Indication	**Brian Corrigan** Senior VP Regulatory & Quality Assurance Lexicon Pharmaceuticals, Inc.
Overview of T1D-CKD Disease, Burden, and Unmet Need	**Steven Edelman, MD** Professor of Medicine Division of Endocrinology, Diabetes & Metabolism University of California, San Diego Founder and Director Taking Control of Your Diabetes 501(c)(3)
Sotagliflozin Efficacy	**Michael Davies, PhD** Executive Director, Clinical Development Lexicon Pharmaceuticals, Inc.

Sotagliflozin Safety	**Craig Granowitz, MD, PhD** Senior Vice President and Chief Medical Officer Lexicon Pharmaceuticals, Inc.
T1D-CKD Management, Risk Management, and Education	**Richard Pratley, MD** Medical Director AdventHealth Diabetes Institute Senior Investigator, Diabetes Program Lead AdventHealth Translational Research Institute
Conclusion	**Craig Granowitz, MD, PhD**

Clarifying Questions to Applicant

BREAK

FDA PRESENTATIONS

Overview of Sotagliflozin Development Program	**Mari Suzuki, MD** Clinical Reviewer DDLO, OCHEN, OND, CDER, FDA
Efficacy Review of Tandem Studies by estimated glomerular filtration rate (eGFR) Subgroup	**Wenda Tu, PhD** Statistical Reviewer Division of Biometrics II (DBII) Office of Biostatistics (OB) Office of Translational Sciences, CDER, FDA
Major Safety Considerations for Sotagliflozin in Patients with Type 1 Diabetes and Chronic Kidney Disease	**Mari Suzuki, MD**
The Evidence and Uncertainties Regarding Benefits and Risks for Sotagliflozin to Improve Glycemic Control in Adults with Type 1 Diabetes and Chronic Kidney Disease	**Justin Penzenstadler, PharmD** Clinical Team Leader DDLO, OCHEN, OND, CDER, FDA

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 evidence and uncertainties based on the existing clinical trial data as to whether sotagliflozin improves hemoglobin A1c (A1C) across a range of estimated glomerular filtration rates (eGFRs), including the following categories: 45 to <60 mL/min/1.73 m^2, 60 to <90 mL/min/1.73 m^2, and ≥90 mL/min/1.73 m^2. Consider the durability of the treatment effect demonstrated**.**

   Committee Discussion: *Committee members discussed that the data presented was not conclusive, but the trend was concerning. One Committee member mentioned that the data was not a predefined subgroup; that it was ad hoc, the sample sizes were small, and there was no accounting for multiple comparisons. Committee members stated that there did appear to be A1C lowering across the eGFR categories, especially in the 60 mL//min to less than 90 mL/min group, but that there was more uncertainty in the A1C lowering for the eGFR less than 60 mL/min group, since the sample size was extremely small. Regarding durability, Committee members stated that since the data beyond 24 weeks was unblinded, it was difficult to draw conclusions, and the durability was questionable. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Discuss the evidence and uncertainties as to whether patients with type 1 diabetes (T1D) and chronic kidney disease (CKD) accrue a greater benefit with respect to microvascular disease than patients with T1D without CKD for any given reduction in A1C. In your discussion, consider different KDIGO categories of CKD, classified by both eGFR (45 to <60 mL/min/1.73 m^2; 60 to <90 mL/min/1.73 m^2; ≥90 mL/min/1.73 m^2) and urine albumin-creatinine ratio (UACR) (<30 mg/g; 30 to <300 mg/g; ≥300 mg/g). Discuss the magnitude of clinical benefit conferred by the A1C reductions expected with use of sotagliflozin across the range of CKD severity, considering both eGFR and UACR.

   Committee Discussion: *Committee members discussed the distinction between relative and absolute risk reduction, and while a higher risk population does have greater potential for benefit, they were unable to draw conclusions about whether there was indeed greater benefit with a certain level of A1C reduction based on the data presented. Committee members stated that there are other potential benefits, but these were not quantified, so overall it was difficult to conclude from the available data. Committee members felt there was great uncertainty, but felt the magnitude of benefit from the small improvement in A1c was expected to be small. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** Discuss whether the magnitude of the diabetic ketoacidosis (DKA) risk in patients with T1D and CKD using sotagliflozin has been sufficiently characterized. Discuss the evidence and uncertainties regarding DKA risk for patients with T1D and eGFRs in the

following ranges: 45 to <60 mL/min/1.73 m2, 60 to <90 mL/min/1.73 m2, and ≥90 mL/min/1.73 m2.

Committee Discussion: *Committee members mentioned that there was substantial uncertainty in the magnitude of DKA risk in T1D with CKD, partly due to the short duration of the trials. Some members noted that the Sentinel data showed a much higher background rate of DKA than the clinical trials which may better reflect real world, and that the DKA risk with sotagliflozin in patients with T1D and CKD was insufficiently characterized across the eGFR categories, because the clinical trials enrolled relatively few subjects with CKD. Committee members also discussed that data from Sentinal and FinnDiane suggested that patients with lower eGFRs may be at higher baseline risk of DKA. Committee members also discussed that risk of DKA may be increased with higher doses of sotagliflozin. Please see the transcript for details of the committee discussion.*

4. **DISCUSSION**: Discuss your view of the scientific rationale justifying extrapolation of the demonstrated benefit of sotagliflozin to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in patients with type 2 diabetes (T2D), moderate-to-severe CKD, and other cardiovascular risk factors to patients with T1D and mild-to-moderate CKD.

   Committee Discussion: *Committee members noted that it was challenging to extrapolate the SCORED data generated in subjects with T2D and moderate-to-severe CKD to the population (patients with T1D and mild-to-moderate CKD) in support of the indication proposed by the Applicant in the current submission. Committee members also discussed the differences in the mechanisms of cardiovascular disease between T2D and TID, and that it was difficult to conclude that sotagliflozin had similar benefits in reducing cardiovascular death, hospitalization for heart failure, and urgent heart failure in patients with T1D and mild-to-moderate CKD. Overall, Committee members agreed that they did not know the magnitude of benefit, so they did not know what the absolute risk reduction would be so could not balance the potential benefit with risk of DKA - there was just not enough data. Please see the transcript for details of the committee discussion.*

5. **DISCUSSION**: Discuss other potential benefits of sotagliflozin suggested by SCORED. Discuss your view of the scientific rationale justifying extrapolation of such potential benefits to patients with T1D and mild-to-moderate CKD.

   Committee Discussion: *Overall, Committee members agreed that they were unable to extrapolate the potential benefits of sotagliflozin from the SCORED secondary endpoints, but there may be a benefit for renal outcomes, which could translate into a benefit for patients with T1D who have moderate to severe CKD and additional cardiovascular risk factors. Please see the transcript for details of the committee discussion.*

6. **DISCUSSION**: Discuss the overall benefit-risk assessment for sotagliflozin as an adjunct to insulin to improve glycemic control in patients with T1D and eGFR ≥ 45 to < 60

mL/min/1.73 m^2 OR eGFR ≥ 60 mL/min/1.73 m^2 and UACR ≥ 30 mg/g. Address how to consider the increased risk of DKA relative to the benefit of an A1C improvement in the population proposed by the Applicant. Discuss how you weigh other advantages of sotagliflozin in the benefit-risk assessment for the proposed indication.

Committee Discussion: *Committee members agreed that there was evidence for small but significant A1C lowering across the eGFR categories; noting that it was more modest in the eGFR less than 60 category. Committee members also discussed that the estimated 20% reduction in hypoglycemia as well as the reduction in body weight, was beneficial. Lastly, some Committee members brought up the point of whether a lower dose might change the benefit risk balance. Please see the transcript for details of the committee discussion.*

7. **VOTE:** Do the available data demonstrate that the benefits of sotagliflozin outweigh the risks for the indication of improved glycemic control in a population of patients with T1D and eGFR ≥ 45 to < 60 mL/min/1.73 m^2 or eGFR ≥ 60 mL/min/1.73 m^2 and UACR ≥ 30 mg/g?

    - If yes, provide your rationale and suggest specific risk mitigation approaches.
    - If no, do the data demonstrate that the benefits outweigh the risks for the indication of improved glycemic control for another population of patients with T1D and CKD, defined by different eGFR and/or UACR categories? Explain and clarify the population in which the benefits of improved glycemic control outweigh the risks, if any.

    Vote Result: **Yes: 3** **No: 11** **Abstain: 0**

    Committee Discussion: *The majority of the panel agreed that the available data did not demonstrate that the benefits of sotagliflozin outweigh the risks for the indication of improved glycemic control in a population of patients with T1D and eGFR ≥ 45 to < 60 mL/min/1.73 m2 or eGFR ≥ 60 mL/min/1.73 m2 and UACR ≥ 30 mg/g. Many members stated that there was a lot of uncertainty in the data and did not feel that the data supported a subgroup of patients with T1D and CKD that would benefit. Other Committee members mentioned that the subgroup with eGFR of 60 to less than 90 ml/min and a UACR greater than 30 mg/g could possibly benefit from sotagliflozin. Committee members also discussed the need for adequate risk mitigation strategies such as ketone monitoring and continuous glucose monitoring. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 5:05 p.m.