FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting
October 31, 2024

DRAFT QUESTIONS

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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.

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.

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 m^2, 60 to <90 mL/min/1.73 m^2, and ≥90 mL/min/1.73 m^2.

4. **DISCUSSION**: Discuss your view of the scientific rationale justifying extrapolation of the <u>demonstrated</u> 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.

5. **DISCUSSION**: Discuss other <u>potential</u> 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.

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 <u>OR</u> 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.

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DRAFT QUESTIONS (cont.)

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.

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