U.S. FOOD & DRUG ADMINISTRATION

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

NDA 210934: Sotagliflozin to Improve Glycemic Control in Adults With Type 1 Diabetes Mellitus and Chronic Kidney Disease

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Type 1 Diabetes Mellitus (T1D)

- T1D is characterized by progressive, autoimmune destruction of pancreatic β-cells
  - In the United States, the prevalence of T1D is estimated at 1.7 million adults and 244,000 children or adolescents
  - Patients with T1D are at increased risk of microvascular and macrovascular complications
  - Intensive glycemic control, reflected by reductions in hemoglobin A1c (A1C), reduces the risk of microvascular complications

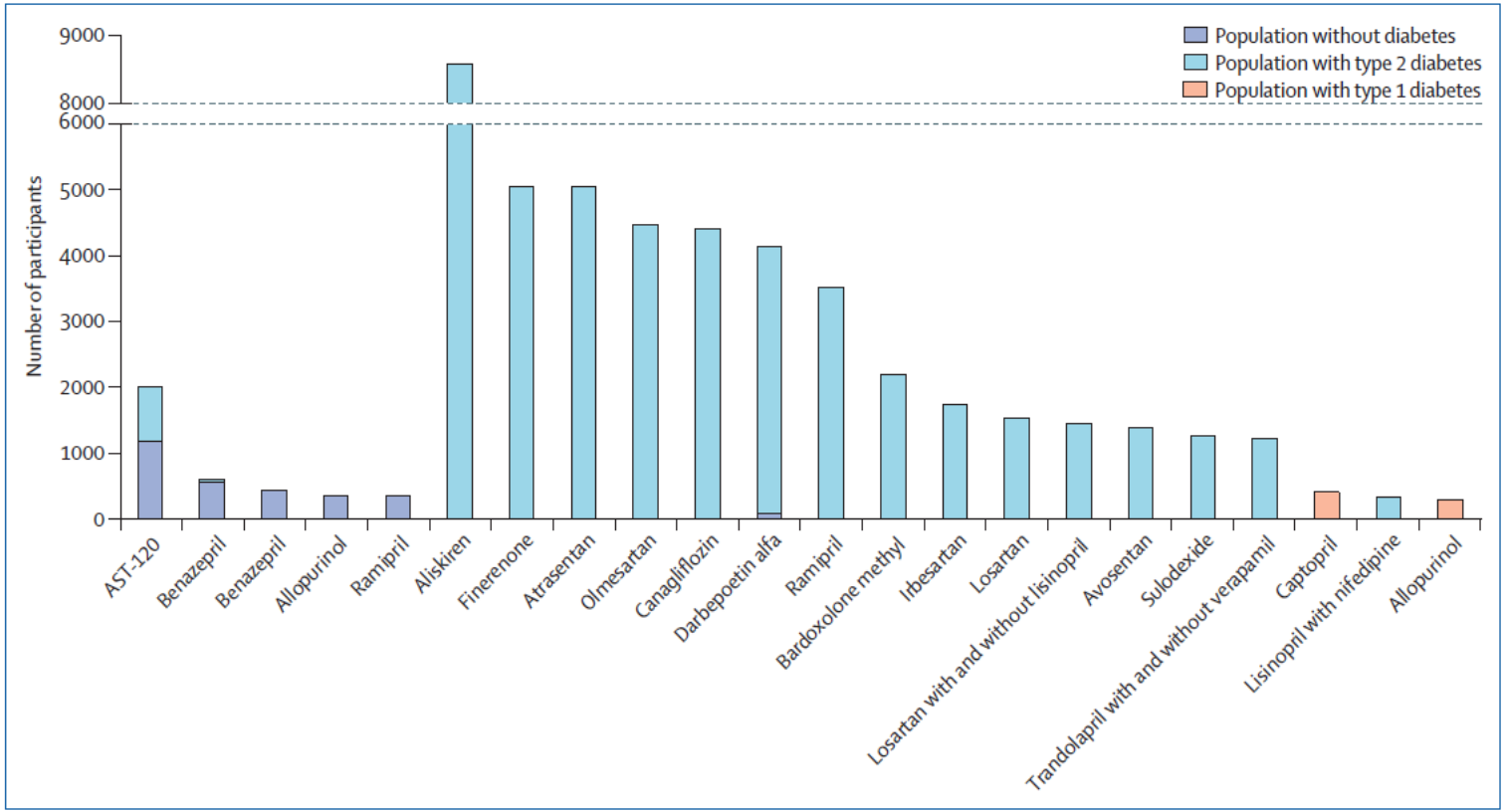
Chronic Kidney Disease (CKD) in Patients With T1D

- CKD is a progressive condition characterized by structural and functional changes to the kidney.
- CKD secondary to diabetes is present in 20 to 40% of patients with diabetes
  - In patients with T1D, CKD typically presents only after a disease duration of 5 to 15 years

Currently Available Treatments

- Treatments to improve glycemic control in patients with T1D:
  - Pharmacotherapy: Insulin and insulin analogs; pramlintide
  - Devices: continuous glucose monitors (CGMs), insulin pumps (including hybrid closed loop pumps)
- Pharmacotherapy for treatment of CKD in patients with T1D
  - FDA approved:
    - Captopril (ACE inhibitor)
    - Dapagliflozin and empagliflozin (SGLT2 inhibitors)
  - American Diabetes Association and KDIGO guidelines
    - Renin-angiotensin system (RAS) inhibitors only

Clinical Trials Investigating CKD in Persons Without Diabetes, With T1D, and With T2D



Reference: Heerspink, HJ, DZ Cherney, PH Groop, C Matthieu, P Rossing, KR Tuttle, JB McGill, 2023, People with type 1 diabetes and chronic kidney disease urgently need new therapies: a call for action, Lancet Diabetes Endocrinol, 11(8): 536-540.

Objective of the Advisory Committee Meeting

- To discuss the benefits and risks of sotagliflozin, an SGLT inhibitor, as an adjunct to insulin therapy to improve glycemic control in adults with T1D and CKD
- For purposes of New Drug Application (NDA) 210934, the Applicant defines CKD as an estimated glomerular filtration rate (eGFR) of 45 to < 60 ml/min/1.73 m^2 or eGFR ≥ 60 ml/min/1.73 m^2 and urine albumin-creatinine ratio (UACR) ≥ 30 mg/g

Pertinent Regulatory History

- NDA 210934 was initially submitted on March 22, 2018, seeking the following indication: (Sotagliflozin) is indicated as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus.
- The original submission was not approved because FDA determined the risk of diabetic ketoacidosis (DKA) outweighed the benefits in patients with T1D

Pertinent Regulatory History

- In 2022, FDA approved sotagliflozin as Inpefa to reduce the risk of cardiovascular (CV) death, hospitalization for heart failure (HHF), and urgent heart failure visit (UHFV) in adults with heart failure or adults with T2D, CKD, and other CV risk factors
- The Applicant did not propose an indication that would encompass all patients with diabetes mellitus, CKD, and other CV risk factors in their submission for Inpefa

Resubmission of NDA 210934

- In the current resubmission, the Applicant asserts that:
  - The effect of sotagliflozin on A1C can be expected to be similar in patients with T1D and CKD, compared to patients with T1D without CKD
  - Patients with T1D and CKD accrue greater benefit from the same reduction in A1C, compared to patients with T1D without CKD
  - The increased risk of DKA associated with sotagliflozin can be expected to be similar in patients with T1D and CKD, compared to patients with T1D without CKD
  - Data from patients with type 2 diabetes (T2D) suggest that patients with T1D and CKD may experience additional non-glycemic benefits

Discussion Point #1 for the Committee

- Discuss the evidence and uncertainties based on the existing clinical trial data as to whether sotagliflozin improves hemoglobin A1c (A1C) across a range of 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.

Discussion Point #2 for the Committee

- Discuss the evidence and uncertainties that 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, and ≥90 mL/min/1.73 m^2) and 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 CKD severity, considering both eGFR and UACR.

Discussion Point #3 for the Committee

- Discuss whether the magnitude of the 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.

Discussion Point #4 for the Committee

- 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 T2D, moderate-to-severe CKD, and other cardiovascular risk factors to patients with T1D and mild-to-moderate CKD.

Discussion Point #5 for the Committee

- 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.

Discussion Point #6 for the Committee

- 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.

Voting Question for the Committee

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.

Overview of Sotagliflozin Development Program

October 31, 2024

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

Mari Suzuki, MD

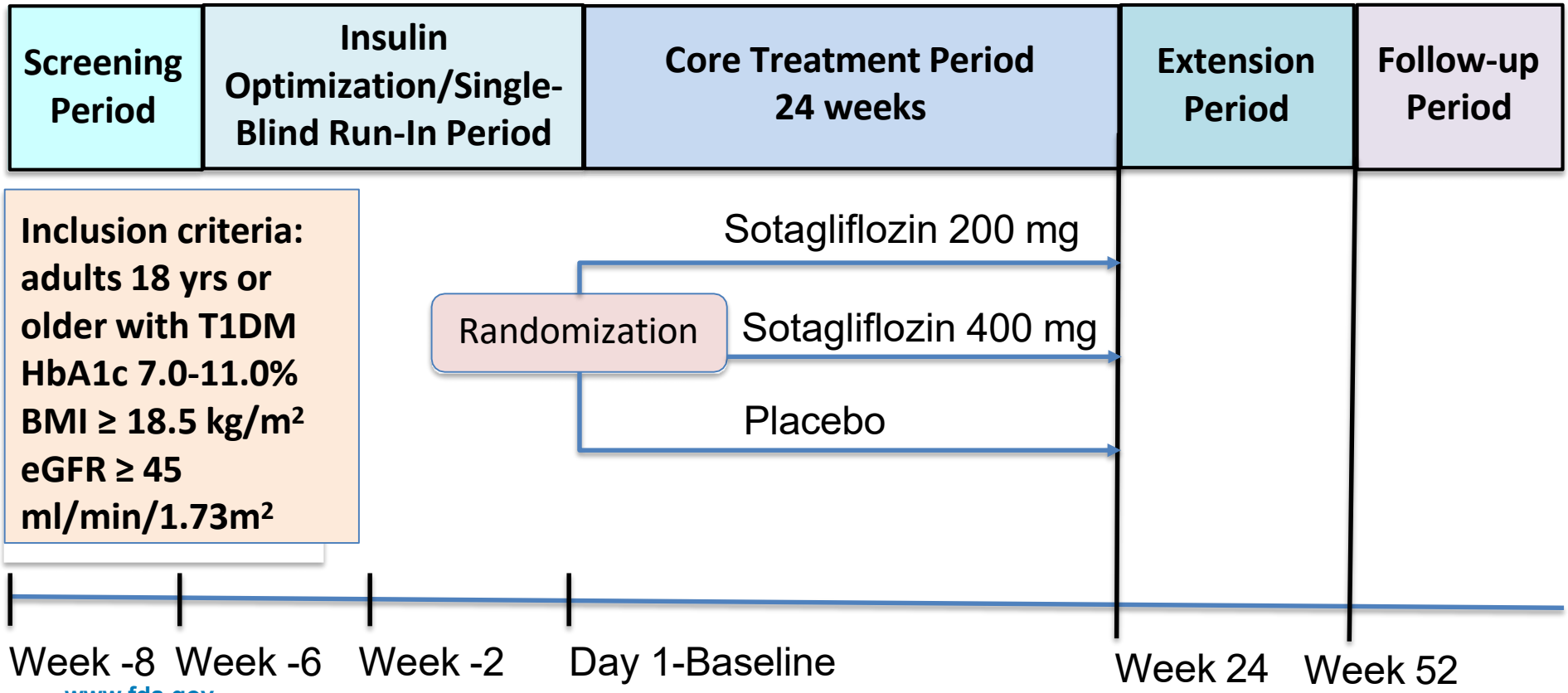
Clinical Reviewer

Division of Diabetes, Lipid Disorders, and Obesity

FDA Presentations

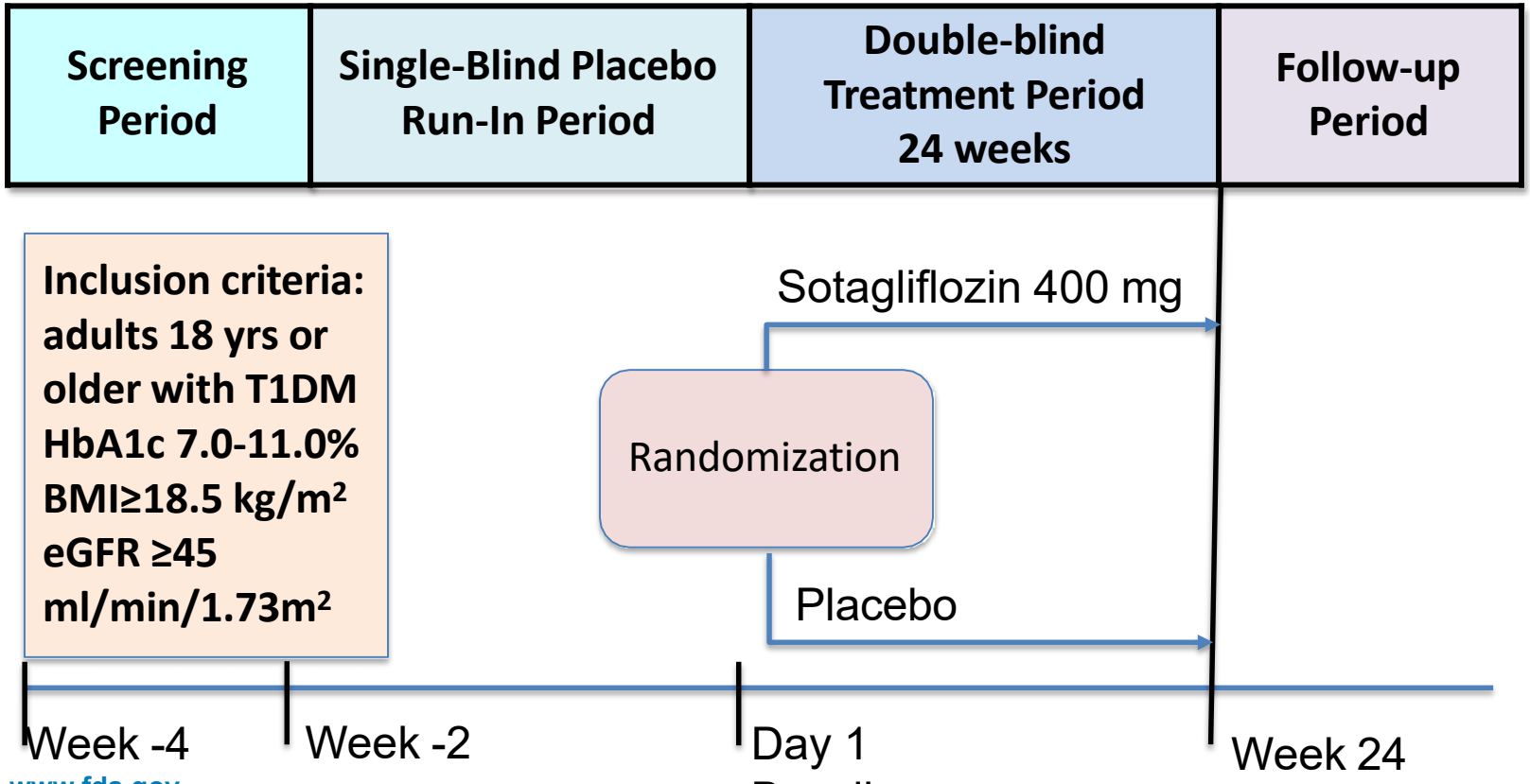
- Overview of Clinical Data
- Assessment of Efficacy in Tandem Program
- Assessment of Safety in Tandem Program
  - Hypoglycemia
  - Diabetic ketoacidosis
- FDA Assessment of Efficacy and Safety in Proposed Target Population
  - Renal benefit of A1C reduction in patients with T1D and CKD
  - Consideration of non-glycemic benefits observed in SCORED (cardiorenal outcomes trial in patients with T2D)
  - Integrated Benefit-Risk Assessment

Study 309/310 - Trial Design



Adapted from 2019 sotagliflozin EMDAC presentation

Study 312 - Trial Design



Adapted from 2019 sotagliflozin EMDAC presentation

Study Composition by eGFR and UACR Subgroups – Studies 309, 310, and 312, by % of Overall Population

		UACR category (mg/g)				
		< 30	30 – 300	300 +		
eGFR category (mL/min/1.73 m^2)	90 +	43.3%	4.2%	1.1%	Totals by eGFR	48.5%
	60-89	40.7%	4.9%	1%		46.6%
	45-59	2.7%	1.2%	0.8%		4.7%
	< 45	0	0.1%	0.1%		0.2%
		Totals by UACR				
		86.8%	10.3%	2.9%		100% (N=2885)

Source: FDA staff

Applicant Approach to Re-Analysis of Efficacy and Safety Data From Tandem Studies

- Groups together all participants with eGFR ≥ 45 to <60 ml/min/1.73 m^2 OR eGFR ≥ 60 ml/min/1.73 m^2 and UACR ≥ 30 mg/g
- Implicitly assumes that efficacy and safety is similar across Tandem subjects meeting Applicant's proposed CKD criteria
- Does not consider well-known relationship between eGFR and glucosuria
- Discards 84% of the data collected in the Tandem program as non-informative

eGFR category (mL/min/1.73 m^2)	UACR < 30 mg/g	UACR 30 – 300 mg/g	UACR 300 + mg/g
Greater than 90			
60-89			
45-59			
Less than 45			

FDA's Approach to Re-Analysis of Efficacy and Safety Data From Tandem Studies

- FDA defined different subgroups in the Tandem studies than the Applicant.
  - The FDA approach provides a complementary perspective to the Applicant's approach. The FDA approach was selected because:
    - It provides estimates of A1C reductions across the range of kidney function included in the Applicant's revised target population
    - It makes use of all of the data collected in Tandem
  - It is intended to provide estimates of A1C reduction to help inform overall benefit-risk assessments for any proposed population, including the Applicant's "T1D-CKD" population (eGFR 45-59 OR eGFR ≥ 60 and UACR ≥ 30)
  - FDA also used the same approach to assess other endpoints, as the pharmacodynamic effect of sotagliflozin may also be relevant for safety

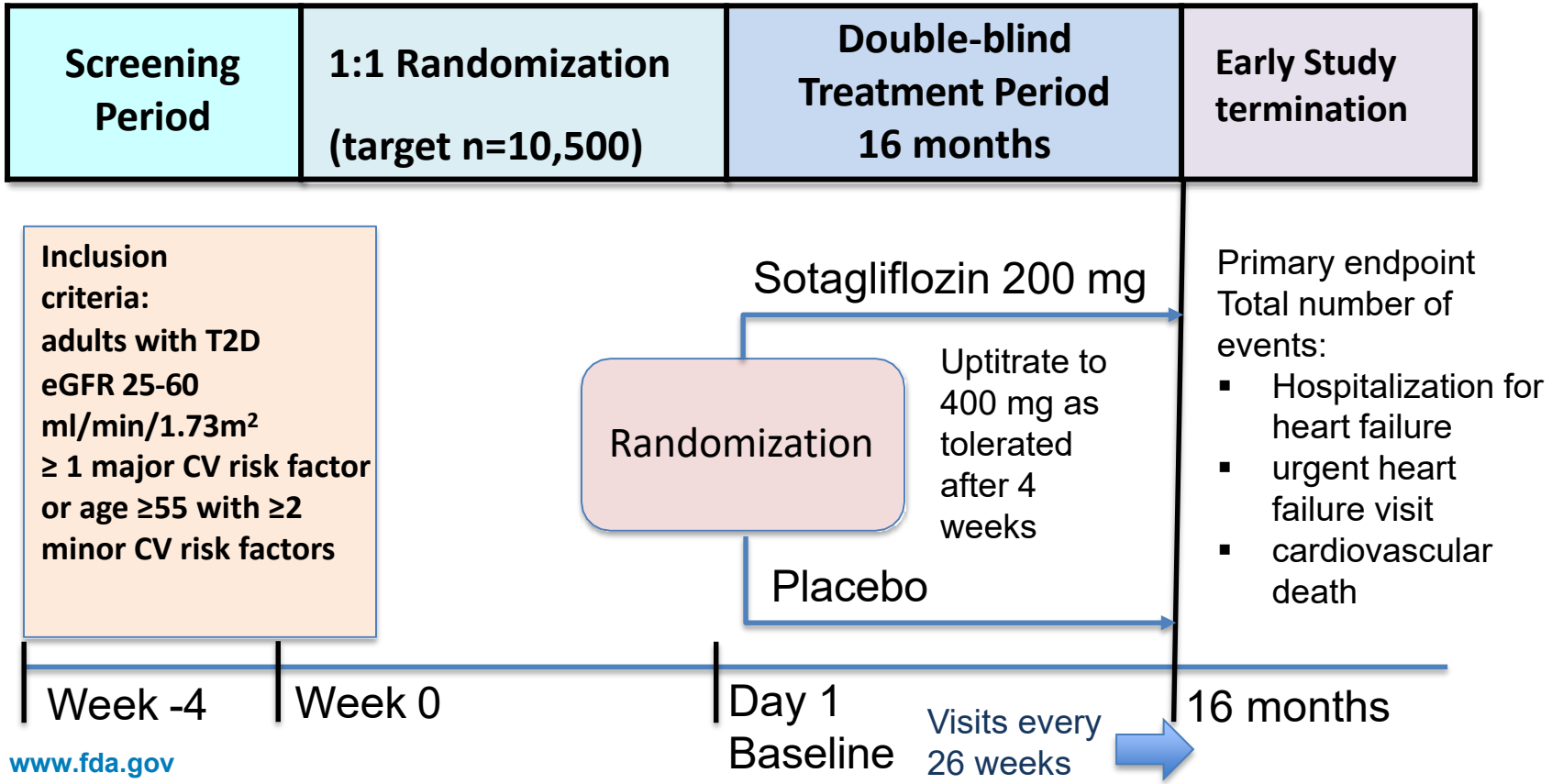
FDA's Approach to Re-Analysis of Efficacy and Safety Data From Tandem Studies

- Separate treatment effects calculated for three distinct subgroups
- Addresses known relationship between eGFR and sotagliflozin effects on glucosuria
- Assumes independent relationship between UACR and glucosuria
- Treats all data collected in Tandem program as informative

	eGFR category (mL/min/1.73 m^2)	UACR < 30 mg/g	UACR 30 – 300 mg/g	UACR 300 + mg/g
Group 1	≥90			
Group 2	60-89			
Group 3	45-59*			
	Less than 45			

* FDA analyses included 7 subjects who had a baseline eGFR between 40 and 45 mL/min/1.73m^2

SCORED - Trial Design



Efficacy Review of Tandem Studies by eGFR Subgroup

Wenda Tu, PhD
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Office of Biostatistics (OB)
Office of Translational Sciences (OTS)

Outline

- Summary of Tandem Studies
- Overview of Subgroup Analyses
- Statistical Method for Subgroup Analyses
- Subgroup Analysis Results & Summary

Summary of Tandem Studies

Study Pool 309/310	Study 312
• Phase 3, multicenter, randomized (1:1:1), double-blind, placebo-controlled, parallel-group • 2-week Screening + **4-week Insulin Optimization + 24-week Core Treatment + 28-week Double-Blind Extension Treatment** + Follow-up	• Phase 3, multicenter, randomized (1:1), double-blind, placebo-controlled, parallel-group • 2-week Screening + **24-week Core Treatment** + Follow-up
• Sotagliflozin 200 mg (N = 524) • Sotagliflozin 400 mg (N = 525) • Placebo (N = 526)	• Sotagliflozin 400 mg (N = 699) • Placebo (N = 703)

N = randomized and treated subjects

Overview of Subgroup Analyses

- Subgroup analyses based on eGFR thresholds
  - eGFR ≥ 90 mL/min/1.73 m^2
  - 60 ≤ eGFR < 90 mL/min/ 1.73 m^2
  - eGFR < 60 mL/min/ 1.73 m^2
- Efficacy endpoints of clinical interest
  - (Primary) A1C (%) change from baseline
  - Body weight (kg) change from baseline
  - Systolic blood pressure (mmHg) change from baseline
- Each endpoint was analyzed at Week 24 (end of Core Treatment); A1C (%) was also analyzed at Week 52 for Study Pool 309/310 (end of Extension Treatment)

Baseline Characteristics by eGFR Subgroup

	Study 309/310				Study 312			
	eGFR < 60	60 ≤ to < 90	eGFR ≥ 90	Total	eGFR < 60	60 ≤ to < 90	eGFR ≥ 90	Total
Sample size, N (%)	71 (4.5)	774 (49.1)	730 (46.3)	1575 (100)	74 (5.3)	612 (43.7)	716 (51.1)	1402 (100)
Age (years), Mean (SD)	57.3 (11.0)	48.0 (12.0)	37.8 (12.4)	43.7 (13.5)	57.3 (12.0)	47.9 (12.5)	37.0 (12.8)	42.8 (14.1)
Sex: Female, N (%)	45 (63)	427 (55)	314 (43)	786 (50)	44 (59)	349 (57)	312 (44)	705 (50)
Race: White, N (%)	68 (96)	734 (95)	681 (93)	1483 (94)	63 (85)	567 (93)	610 (85)	1240 (88)
Region: North America, N (%)	45 (63)	430 (56)	318 (44)	793 (50)	40 (54)	280 (46)	259 (36)	579 (41)
Duration of T1DM (years), Mean (SD)	31.4 (12.7)	23.8 (12.4)	17.9 (10.9)	21.4 (12.3)	25.7 (14.2)	22.7 (13.1)	17.2 (10.4)	20.0 (12.2)
eGFR (mL/min/1.73 m^2), Mean (SD)	53.4 (4.4)	77.7 (8.0)	105.6 (12.7)	89.5 (18.8)	53.9 (4.6)	78.4 (7.7)	107.5 (15.8)	92.0 (20.9)

Abbreviations: SD = standard deviation.

Source: Statistical Reviewer Analysis ; adsl.xpt, adlb.xpt

Statistical Method for Subgroup Analyses

- Analysis set
  - All randomized subjects who took at least 1 dose of study drug
- Handling of missing data
  - Multiple imputation based on placebo washout
- Analysis method
  - Analysis of Covariance (ANCOVA) adjusted for baseline values, treatment, stratification factors[1], and study ID (for study pool 309/310 only)

1. For Study Pool 309/310, stratification factors include baseline A1C (≤ 8.5% vs > 8.5%) and insulin delivery method (MDI vs CSII). For Study 312, stratification factors include body mass index (BMI) (< 25 kg/m^2 vs. ≥ 25 kg/m^2), baseline A1C (≤ 9.0% vs. > 9.0%), and insulin delivery method (MDI vs CSII).

Subgroup Analysis Results

- A1C (%) change from baseline
  - Study 312, Week 24
  - Study Pool 309/310, Week 24
  - Study Pool 309/310, Week 52
- Body weight (BW, kg) change from baseline
  - Study 312, Week 24
  - Study Pool 309/310, Week 24
- Systolic Blood Pressure (SBP, mmHg) change from baseline
  - Study 312, Week 24
  - Study Pool 309/310, Week 24

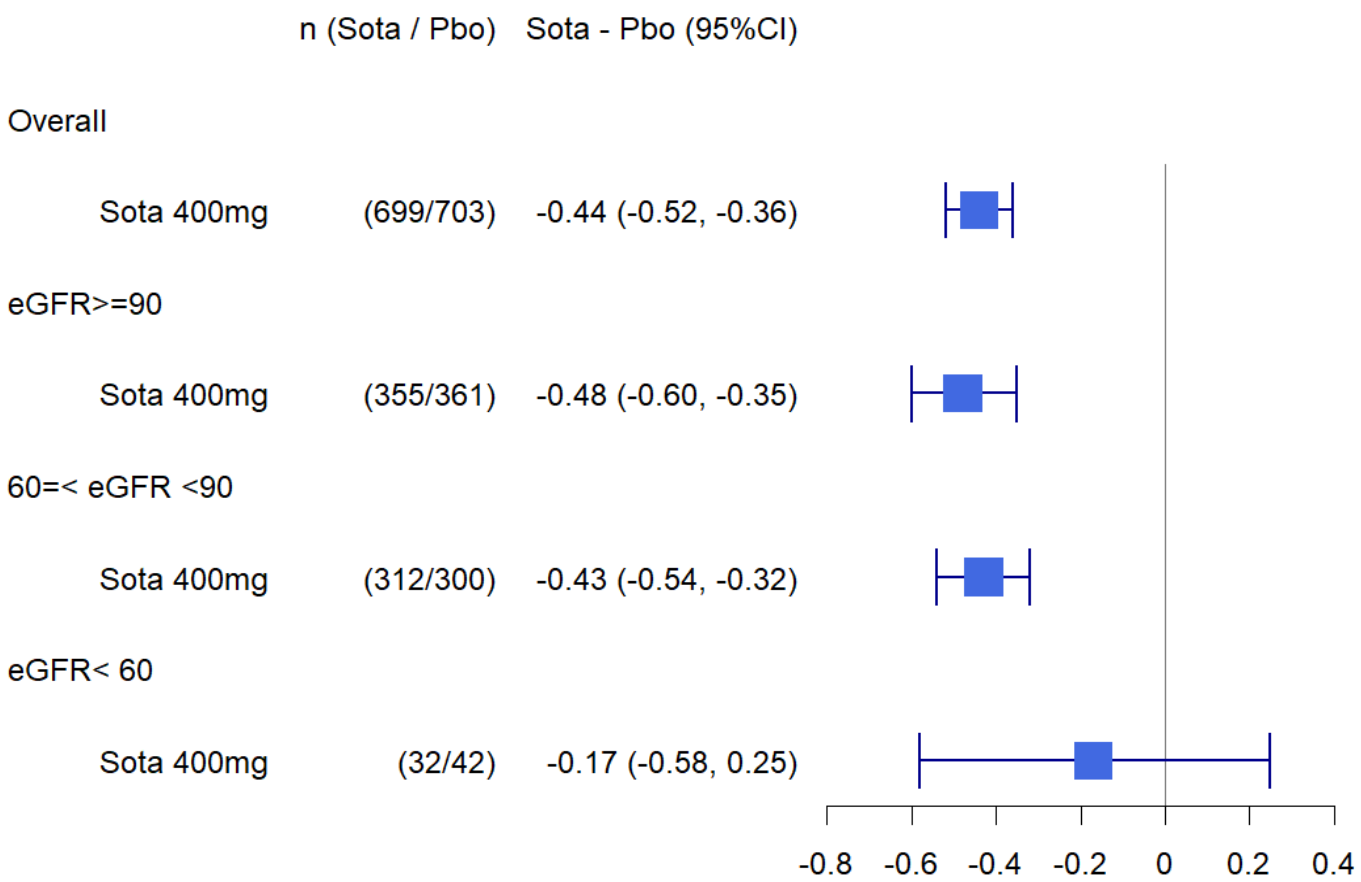
A1C (%) Change From Baseline at Week 24, Study 312

Group	Treatment Arm	Sample Size	Baseline (SD)	Change From Baseline (SE)	Change From Baseline, Placebo-Adjusted (95% CI)
Overall Population	Sota 400 mg	699	8.26 (0.96)	-0.76 (0.03)	-0.44 (-0.52, -0.36)
	Placebo	703	8.21 (0.92)	-0.32 (0.03)	
eGFR ≥ 90	Sota 400 mg	355	8.35 (1.02)	-0.79 (0.04)	-0.48 (-0.60. -0.35)
	Placebo	361	8.29 (0.92)	-0.31 (0.04)	
60 ≤ eGFR < 90	Sota 400 mg	312	8.13 (0.88)	-0.75 (0.04)	-0.43 (-0.54, -0.32)
	Placebo	300	8.11 (0.91)	-0.31 (0.04)	
eGFR < 60	Sota 400 mg	32	8.49 (1.05)	-0.64 (0.16)	-0.17 (-0.58, 0.25)
	Placebo	42	8.25 (0.94)	-0.47 (0.14)	

Abbreviations: SD = standard deviation, SE = standard error. For the overall population, missing rates were 10.3% for SOTA 400 and 10.7% for PBO. Missing data were generally balanced across treatment arms and subgroup levels.

Source: Statistical Reviewer Analysis ; adsl.xpt, adlb.xpt, adeff.xpt

Forest Plot for Placebo-Adjusted A1C Change From Baseline, Week 24, Study 312



 Source: Statistical Reviewer Analysis ; adsl.xpt, adlb.xpt, adeff.xpt

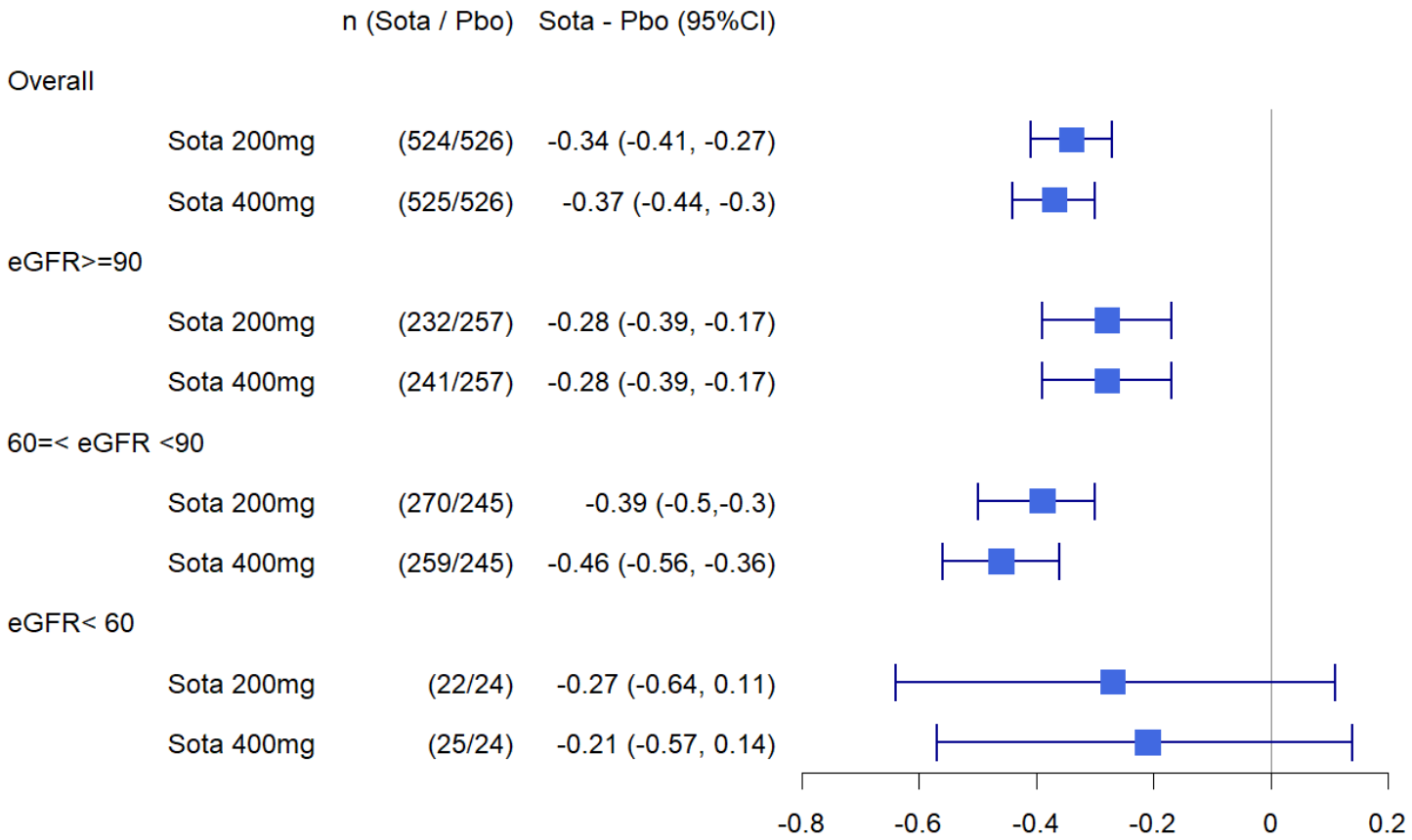
A1C (%) Change From Baseline at Week 24, Study Pool 309/310

Group	Treatment Arm	N	Baseline (SD)	Change From Baseline (SE)	Change From Baseline, Placebo-Adjusted (95% CI)
Overall Population	Sota 200 mg	524	7.68 (0.77)	-0.38 (0.03)	-0.34 (-0.41, -0.27)
	Sota 400 mg	525	7.64 (0.78)	-0.41 (0.03)	-0.37 (-0.44, -0.30)
	Placebo	526	7.66 (0.81)	-0.04 (0.03)	
eGFR ≥ 90	Sota 200 mg	232	7.72 (0.78)	-0.33 (0.04)	-0.28 (-0.39, -0.17)
	Sota 400 mg	241	7.66 (0.82)	-0.33 (0.04)	-0.28 (-0.39, -0.17)
	Placebo	257	7.77 (0.88)	-0.05 (0.04)	
60 ≤ eGFR < 90	Sota 200 mg	270	7.63 (0.78)	-0.40 (0.04)	-0.39 (-0.50, -0.30)
	Sota 400 mg	259	7.60 (0.72)	-0.47 (0.04)	-0.46 (-0.56, -0.36)
	Placebo	245	7.54 (0.70)	-0.00 (0.04)	
eGFR < 60	Sota 200 mg	22	7.82 (0.64)	-0.58 (0.13)	-0.27 (-0.64, 0.11)
	Sota 400 mg	25	7.85 (0.88)	-0.53 (0.12)	-0.21 (-0.57, 0.14)
	Placebo	24	7.74 (0.89)	-0.31 (0.13)	

Abbreviations: SD = standard deviation, SE = standard error. For the overall population, missing rates were 7.6% for SOTA 200, 8.0% for SOTA 400, and 7.8% for PBO. Missing data were generally balanced across treatment arms and subgroup levels.

Source: Statistical Reviewer Analysis ; adsl.xpt, adlb.xpt, adeff.xpt

Forest Plot for Placebo-Adjusted A1C Change From Baseline, Week 24, Study Pool 309/310



Source: Statistical Reviewer Analysis ; adsl.xpt, adlb.xpt, adeff.xpt

A1C (%) Change From Baseline at Week 52, Study Pool 309/310

	Treatment Arm	N	Baseline (SD)	Change From Baseline (SE)	Change From Baseline, Placebo-Adjusted (95% CI)
Overall Population	Sota 200 mg	524	7.68 (0.77)	-0.21 (0.03)	-0.22 (-0.31, -0.13)
	Sota 400 mg	525	7.64 (0.78)	-0.29 (0.03)	-0.31 (-0.39, -0.22)
	Placebo	526	7.66 (0.81)	-0.02 (0.03)	
eGFR ≥ 90	Sota 200 mg	232	7.72 (0.78)	-0.12 (0.05)	-0.17 (-0.31, -0.02)
	Sota 400 mg	241	7.66 (0.82)	-0.25 (0.05)	-0.30 (-0.44, -0.16)
	Placebo	257	7.77 (0.88)	0.05 (0.05)	
60 ≤ eGFR < 90	Sota 200 mg	270	7.63 (0.78)	-0.26 (0.04)	-0.27 (-0.39, -0.16)
	Sota 400 mg	259	7.60 (0.72)	-0.33 (0.04)	-0.34 (-0.46, -0.22)
	Placebo	245	7.54 (0.70)	0.01(0.04)	
eGFR < 60	Sota 200 mg	22	7.82 (0.64)	-0.47 (0.13)	-0.17 (-0.55, 0.21)
	Sota 400 mg	25	7.85 (0.88)	-0.20 (0.14)	0.09 (-0.28, 0.46)
	Placebo	24	7.74 (0.89)	-0.29 (0.14)	

Abbreviations: SD = standard deviation, SE = standard error. For the overall population, missing rates were 12.2% for SOTA 200,13.5% for SOTA 400, and 14.8% for PBO. Missing data were generally balanced across treatment arms and subgroup levels. *Source: Statistical Reviewer Analysis ; adsl.xpt, adlb.xpt, adeff.xpt*

Body Weight (kg) Change From Baseline at Week 24, Study 312

	Treatment Arm	Sample Size	Baseline (SD)	Change From Baseline (SE)	Change From Baseline, Placebo-Adjusted (95% CI)
Overall Population	Sota 400 mg	699	82.4 (17.1)	-2.02 (0.12)	-2.75 (-3.08, -2.41)
	Placebo	703	81.5 (17.0)	0.72 (0.12)	
eGFR ≥ 90	Sota 400 mg	355	81.7 (17.7)	-1.97 (0.17)	-2.90 (-3.38, -2.41)
	Placebo	361	80.5 (16.8)	0.93 (0.17)	
60 ≤ eGFR < 90	Sota 400 mg	312	82.9 (16.2)	-2.05 (0.17)	-2.53 (-3.01, -2.05)
	Placebo	300	83.1 (17.5)	0.48 (0.17)	
eGFR < 60	Sota 400 mg	32	85.3 (19.1)	-2.37 (0.57)	-3.05 (-4.54, -1.56)
	Placebo	42	79.3 (15.3)	0.68 (0.49)	

Abbreviations: SD = standard deviation, SE = standard error.

Source: Statistical Reviewer Analysis ; adsl.xpt, adlb.xpt, adeff.xpt

Body Weight (kg) Change From Baseline at Week 24, Study Pool 309/310

	Treatment Arm	N	Baseline (SD)	Change From Baseline (SE)	Change From Baseline, Placebo-Adjusted (95% CI)
Overall Population	Sota 200 mg	524	84.5 (18.1)	-1.61 (0.14)	-2.03 (-2.41, -1.66)
	Sota 400 mg	525	84.2 (18.1)	-2.32 (0.14)	-2.74 (-3.12, -2.37)
	Placebo	526	84.2 (17.6)	0.42 (0.13)	
eGFR ≥ 90	Sota 200 mg	232	84.1 (18.4)	-1.3 (0.22)	-1.91(-2.48, -1.33)
	Sota 400 mg	241	83.8 (18.9)	-2.23 (0.21)	-2.84 (-3.41, -2.28)
	Placebo	257	82.7 (17.7)	0.61 (0.2)	
60 ≤ eGFR < 90	Sota 200 mg	270	85.1 (17.8)	-1.84 (0.18)	-2.09 (-2.62, -1.57)
	Sota 400 mg	259	84.2 (17.4)	-2.3 (0.19)	-2.56 (-3.09, -2.02)
	Placebo	245	86.0 (17.6)	0.25 (0.19)	
eGFR < 60	Sota 200 mg	22	80.3 (19.3)	-1.97 (0.51)	-1.86 (-3.28, -0.44)
	Sota 400 mg	25	88.7 (17.3)	-3.22 (0.49)	-3.12 (-4.51, -1.72)
	Placebo	24	82.5 (13.4)	-0.11 (0.51)	

Abbreviations: SD = standard deviation, SE = standard error.

Source: Statistical Reviewer Analysis ; adsl.xpt, adlb.xpt, adeff.xpt

Systolic Blood Pressure (mmHg) Change From Baseline at Week 24, Study 312

	Treatment Arm	Sample Size	Baseline (SD)	Change From Baseline (SE)	Change From Baseline, Placebo-Adjusted (95% CI)
Overall Population	Sota 400 mg	699	122.0 (15.3)	-1.97 (0.43)	-2.96 (-4.15, -1.76)
	Placebo	703	121.8 (14.8)	0.98 (0.43)	
eGFR ≥ 90	Sota 400 mg	355	120.2 (14.8)	-1.56 (0.57)	-2.86 (-4.45, -1.28)
	Placebo	361	120.6 (14.2)	1.30 (0.57)	
60 ≤ eGFR < 90	Sota 400 mg	312	123.0 (15.5)	-2.55(0.65)	-2.59 (-4.40, -0.79)
	Placebo	300	122.3 (15.5)	0.05 (0.65)	
eGFR < 60	Sota 400 mg	32	130.6 (14.8)	-0.40 (2.79)	-5.00 (-12.27, 2.27)
	Placebo	42	128.2 (14.2)	4.60 (2.41)	

Abbreviations: SD = standard deviation, SE = standard error.

Source: Statistical Reviewer Analysis ; adsl.xpt, adlb.xpt, adeff.xpt

Systolic Blood Pressure (mmHg) Change From Baseline at Week 24, Study Pool 309/310

	Treatment Arm	N	Baseline (SD)	Change From Baseline (SE)	Change From Baseline, Placebo-Adjusted (95% CI)
Overall Population	Sota 200 mg	524	121.5 (15.0)	-2.66 (0.47)	-1.90 (-3.18, -0.62)
	Sota 400 mg	525	121.3 (14.3)	-3.41 (0.46)	-2.66 (-3.93, -1.38)
	Placebo	526	122.0 (14.5)	-0.76 (0.46)	
eGFR ≥ 90	Sota 200 mg	232	120.3 (14.8)	-3.71 (0.66)	-2.53 (-4.31, -0.75)
	Sota 400 mg	241	120.3 (13.4)	-3.32 (0.64)	-2.14 (-3.86, -0.42)
	Placebo	257	120.9 (14.1)	-1.18 (0.61)	
60 ≤ eGFR < 90	Sota 200 mg	270	122.0 (15.2)	-1.83 (0.66)	-1.47(-3.35, 0.40)
	Sota 400 mg	259	121.8 (14.2)	-3.84 (0.67)	-3.48 (-5.39, -1.58)
	Placebo	245	122.5 (14.2)	-0.36 (0.70)	
eGFR < 60	Sota 200 mg	22	128.4 (12.7)	-1.84 (2.79)	-1.81 (-9.54, 5.93)
	Sota 400 mg	25	126.0 (21.9)	-0.02 (2.63)	0.01 (-7.49, 7.51)
	Placebo	24	128.5 (20.5)	-0.03 (2.74)	

Abbreviations: SD = standard deviation, SE = standard error.

Source: Statistical Reviewer Analysis ; adsl.xpt, adlb.xpt, adeff.xpt

Efficacy Summary in the Revised Target Population

- Substantial evidence for effectiveness was established in the overall T1D population in the original NDA submission
- The estimated treatment effects on A1C in the eGFR ≥ 90 group and the 60 ≤ eGFR < 90 group appears generally consistent with the overall T1D population
- Smaller treatment effect sizes on A1C reduction were observed in the eGFR < 60 group. Given the correlation between glucosuria and eGFR, the finding is biologically plausible. However, the available clinical data are not sufficient to support definitive conclusions.

Efficacy Summary in the Revised Target Population

- For the overall population (from Study Pool 309/310)
  - The effect size in A1C reduction at Week 24 appears to attenuate by week 52
  - The effect size in A1C reduction at Week 24 is similar among the 400 mg dose and the 200 mg dose
- Similar trends were observed among the eGFR subgroups. However, the post-hoc subgrouping strategy resulted in limited sample sizes, particularly for the group with eGFR < 60; and this precludes more definitive conclusions

Major Safety Considerations for Sotagliflozin in Patients with Type 1 Diabetes and Chronic Kidney Disease

October 31, 2024
Endocrinologic and Metabolic Drugs Advisory Committee Meeting
Mari Suzuki, MD
Clinical Reviewer
Division of Diabetes, Lipid Disorders, and Obesity

Safety Discussion Overview

- Safety profile in patients with T1D was generally similar to the safety profile of sotagliflozin in patients with T2D, with two notable exceptions:
  - Hypoglycemia: sotagliflozin was associated with fewer hypoglycemia events in patients with T1D
  - DKA: sotagliflozin was associated with a significantly increased risk of DKA in patients with T1D

ADA Hypoglycemia Definitions

Level 1	Blood Glucose < 70 mg/dL and ≥ 54 mg/dL
Level 2	Blood Glucose < 54 mg/dL
Level 3	A severe event characterized by altered mental status and/or physical status requiring assistance for treatment of hypoglycemia, irrespective of glucose level

Reference: American Diabetes Association Professional Practice Committee; 6. Glycemic Goals and Hypoglycemia: *Standards of Care in Diabetes—2024*. *Diabetes Care* 1 January 2024; 47 (Supplement_1): S111–S125. https://doi.org/10.2337/dc24-S006

Hypoglycemia Ascertainment in Tandem

- All subjects were provided glucometers and instructed to record every hypoglycemia event in a study diary, throughout the entire study period
- Dedicated eCRF included elements to record supporting information about the event, including corroborating self-monitored blood glucose (SMBG) and hypoglycemia event severity
- Severe hypoglycemia events were adjudicated by a blinded Clinical Event Committee
- Prespecified Criteria for Documented Clinically Significant Hypoglycemia required a SMBG value ≤ 55 mg/dL

Comparison of Level 3 Hypoglycemia Risk for Sotagliflozin Versus Placebo – Overall Tandem Population

		Placebo	Sota 200 mg	Sota 400 mg
Studies 309/310 (52 Weeks)	n/N (%)	39/526 (7.4%)	30/524 (5.7%)	23/525 (4.4%)
	Total Events	50	68	33
Study 312 (24 Weeks)	n/N (%)	17/703 (2.4%)	- -	21/699 (3.0%)
	Total Events	22	-	25

n: number of subject with at least 1 event
N: treatment arm number of subjects
Sota: sotagliflozin

Reference: 2024 AC briefing document, Table 7

Comparison of Level 2 Hypoglycemia Risk for Sotagliflozin Versus Placebo – Overall Tandem Population

		Placebo	Sota 200 mg	Sota 400 mg
Studies 309/310 (52 Weeks)	Total Events (event rate per PY)	8995 (18.12)	7129 (14.94)	7133 (15.65)
	Event Rate Ratio (95% CI)	-	0.82 (0.79, 0.86)	0.86 (0.83, 0.90)
Study 312 (24 Weeks)	Total Events (event rate per PY)	4682 (15.41)	- -	3512 (11.78)
	Event Rate Ratio (95% CI)	-	-	0.76 (0.73, 0.80)

n: number of subject with at least 1 event
N: Treatment arm number of subjects
Sota: sotagliflozin

Reference: 2024 AC briefing document, Table 8

Comparison of Level 2 Hypoglycemia Risk for Sotagliflozin Versus Placebo – Overall Tandem Population by eGFR Subgroup

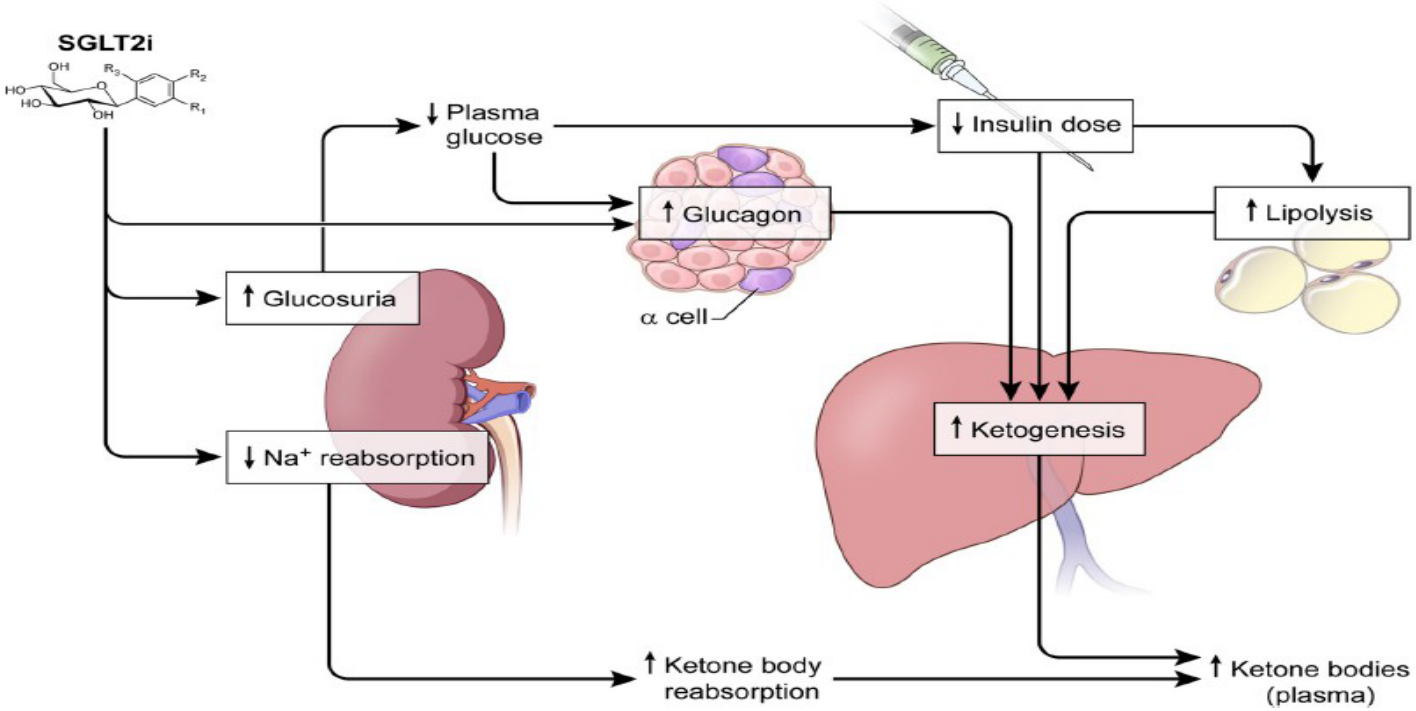
		Studies 309 and 310 (52 Weeks)			Study 312 (24 Weeks)	
eGFR Subgroup (mL/min/1.73m²)	**Statistic**	**Placebo**	**Sota 200 mg**	**Sota 400 mg**	**Placebo**	**Sota 400 mg**
<60	Event rate (PY)	25.7	15.6	21.3	13.9	11.1
	Event rate ratio (95% CI)	-	**0.66 (0.53, 0.78)**	**0.91 (0.75, 1.05)**	-	**0.80 (0.65, 0.98)**
60 – 89	Event rate (PY)	19.7	15.9	16.1	15.4	12.5
	Event rate ratio (95% CI)	-	**0.78 (0.75, 0.84)**	**0.80 (0.76, 0.86)**	-	**0.81 (0.76, 0.87)**
≥90	Event rate (PY)	15.1	13.4	14.0	15.7	11.2
	Event rate ratio (95% CI)	-	**0.87 (0.82, 0.94)**	**0.92 (0.86, 0.99)**	-	**0.72 (0.68, 0.76)**

Reference: 2024 AC briefing document, Table 8

Diabetic Ketoacidosis (DKA)

- DKA is a serious, life-threatening metabolic complication that requires immediate medical intervention
- All FDA-approved SGLT2 inhibitors (including sotagliflozin, marketed as Inpefa) include a Warning and Precaution regarding the risk of DKA
- An increased DKA risk has been demonstrated in randomized clinical trials of multiple SGLT2 inhibitors in patients with T1D

Pathophysiology of SGLT2-Associated DKA



DKA: Diabetic ketoacidosis

SGLT2: sodium glucose co-transporter 2

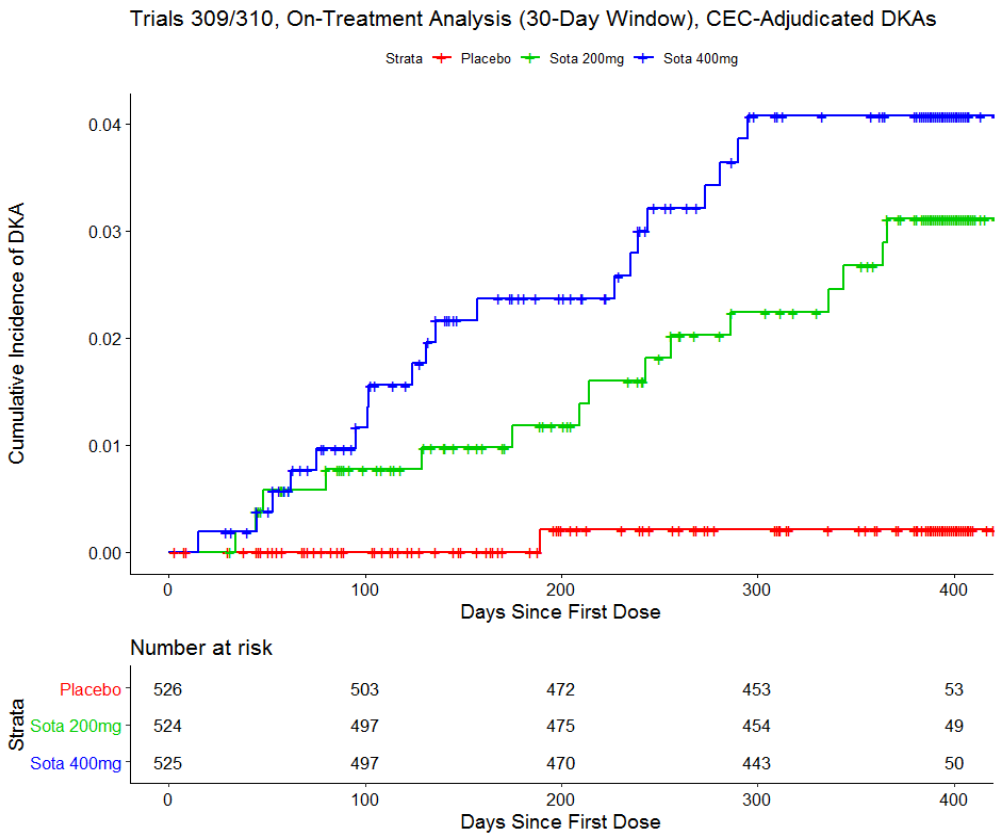
Taylor, et al. SGLT2 Inhibitors May Predispose to Ketoacidosis. *Journal of Clinical Endocrinology and Metabolism.* 2015, 100(8):2949-2853

Comparison of DKA Risk for Sotagliflozin Versus Placebo – Overall Tandem Population

Studies	Sotagliflozin n/N/PY (IR per 100 PY)	Placebo n/N/PY (IR per 100 PY)	IRD [95% CI]	NNH (Per PY) [95% CI]
309/310	35/1049/1028 (3.40)	1/526/515.8 (0.19)	3.21 (2.02, 4.40)	31 [23, 49]
312	21/699/349.9 (6.00)	4/703/358.8 (1.11)	4.89 (2.10, 7.68)	20 [13, 48]

n: number of subject with at least 1 event
N: Number of subjects
IR: Incidence Rate
IRD: Incidence Rate Difference
NNH: Number Needed to Harm
PY: Person-years

Cumulative Incidence for DKA – Overall 309/310 Population



n/N

20/525

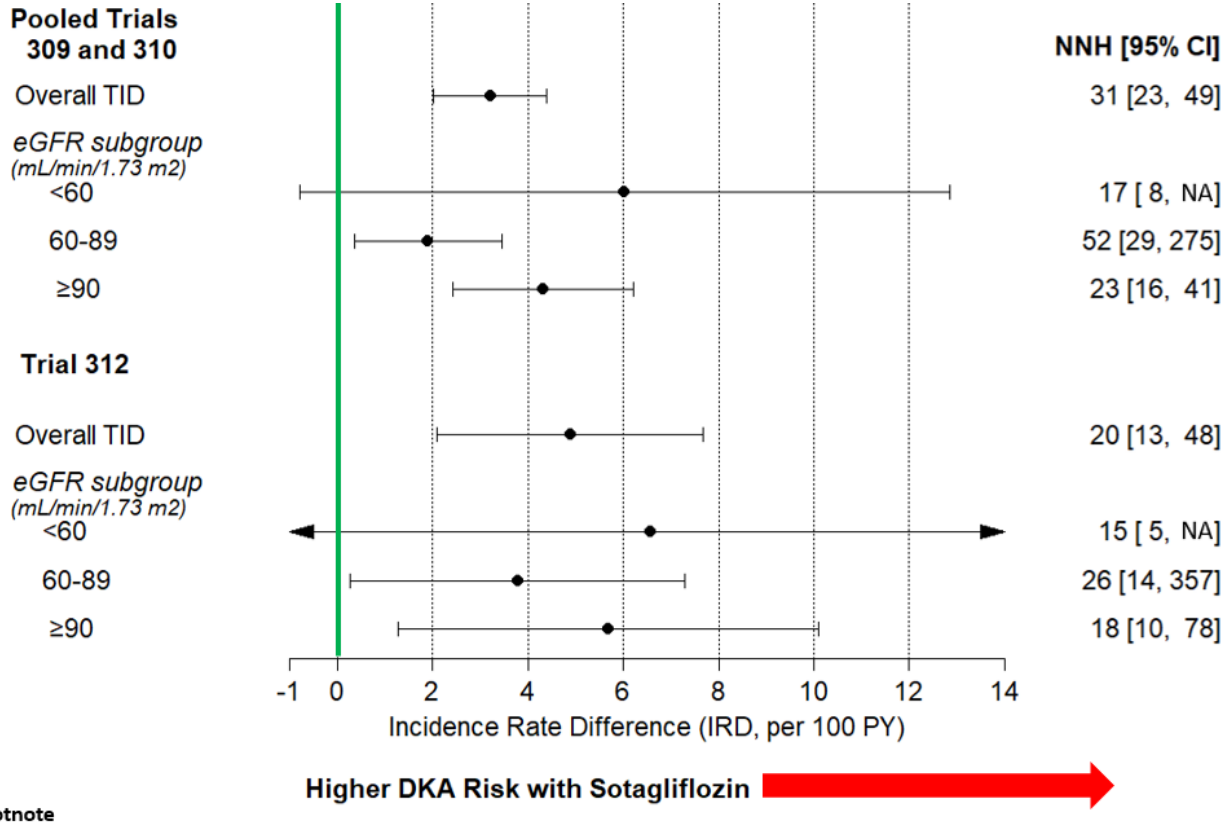
15/524

1/526

400 mg
NNH: 27
[18, 51]

200 mg
NNH: 37
[24, 84]

The Risk of DKA in T1D Population and Subgroup by eGFR



Footnote

Abbreviations: eGFR: estimated glomerular filtration rate; **NNH**: numbers needed to harm; **CEC**: clinical event committee; **DKA**: diabetic ketoacidosis; **CI**: confidence interval; **TID**: type 1 diabetes

Methods: on-treatment approach was used for analysis, **Mantel-Haenszel method** was used for pooling data from multiple studies, **IRD** of sotagliflozin vs. placebo was estimated for first adjudicated DKA event, and **NNH** was estimated as the reciprocal of IRD

Epidemiology Studies of DKA in Patients With CKD

- Finnish Diabetic Nephropathy Study (FinnDiane)
- FDA Sentinel Query
- Applicant's Analysis of T1D-Exchange

The Long-Term Incidence of Hospitalization for Ketoacidosis in Adults with Established T1D—A Prospective Cohort Study

Merlin Thomas,[1,*] Valma Harjutsalo,[2,3,4,5,*] Maija Feodoroff,[2,3,4] Carol Forsblom,[2,3,4,5] Daniel Gordin,[2,3,4] and Per-Henrik Groop[1,2,3,4]; on behalf of the FinnDiane Study Group

[1]Department of Diabetes, Central Clinical School, Monash University, Melbourne, Australia; [2]Folkhälsan Institute of Genetics, Folkhälsan Research Center, Biomedicum Helsinki, Helsinki, Finland; [3]Department of Nephrology, Department of Medicine Helsinki University Central Hospital, Biomedicum Helsinki, Finland; [4]Research Programs Unit, Diabetes and Obesity, University of Helsinki, Helsinki, Finland; and [5]National Institute for Health and Welfare, The Chronic Disease Prevention Unit, Helsinki, Finland

albumin excretion rate, respectively. Patients with an estimated glomerular filtration rate <60 mL/min/1.73 m^2 were also more likely to be hospitalized for DKA (HR 1.71 [95% CI, 1.26–2.67]).

Conclusions: DKA remains a common cause of hospitalization in individuals with longstanding T1D. These data suggest that the goal to use SGLT2 inhibitors for their vasculo- and renoprotective actions may be problematic, as those most likely to benefit may also have the highest risk for DKA. (***J Clin Endocrinol Metab*** **105: 231–241, 2020)**

Incidence Rate of DKA in Patients With T1D by CKD Stages in FDA Sentinel Query

- 690,849 patients with T1D (mean age 41.4 y) from six data partners, from 2013 to 2024
- Crude incidence rates of DKA in patients with T1D increased with advanced CKD stages

CKD Stage	Patients, n	DKA Cases, n	Person-Years	Crude Incidence Rate (95% CI) per 100 PY
Stage 1 or 2	612,800	17,689	169,587	10.4 (10.3, 10.6)
Stage 3	40,091	1,496	10,610	14.1 (13.4, 14.8)
Stage 4 or 5	37,958	2,446	9,094	26.9 (25.9, 28.0)

DKA events identified in inpatient or emergency department settings
Claims-based algorithms for DKA, T1D and CKD were validated
CKD stage 1 or 2 is eGFR ≥60 mL/min/1.73 m^2 , CKD stage 3 is eGFR 30-59 mL/min/1.73 m^2, and CKD stage 4 or 5 is eGFR <30 mL/min/1.73 m^2.

Applicant's Analysis of T1D Exchange

- 49,178 adult patients* with T1D treated at 55 clinics in the US, 2015 to 2023
- Applicant did not submit a detailed protocol or statistical analysis plan, which limited FDA's assessment.

	DKA rate (Per 100 PY)	
Analysis	T1D with CKD	T1D without CKD
Unadjusted	2.9	3.2
PS-matched**	2.6	2.1

*20% of 1,558 patients with T1D with CKD and 78% of 47,620 patients with T1D without CKD were aged 18-39 years
**PS model included age, sex, race/ethnicity, insurance, duration of follow-up, continuous glucose monitor use, and insulin pump use

Summary of Epidemiologic Studies

- Two of three epidemiologic sources suggest patients with CKD have an increased baseline risk of DKA.
  - Whether CKD might be an independent risk factor or might act as a proxy for correlated risk factors for DKA is unknown
  - The data do not directly inform sotagliflozin-related risk
  - The data raise uncertainties about the generalizability of estimates of DKA risk from the overall Tandem population to patients with T1D and CKD

Summary of Safety

- Sotagliflozin reduced the event rate of Level 2 hypoglycemia. A similar effect was observed in the overall population and each eGFR subgroup. A similar trend was not seen in Level 3 hypoglycemic events
- Sotagliflozin increased the risk of DKA. The effect was observed in each eGFR subgroup, but the data are too limited to make conclusions about an interaction between eGFR and sotagliflozin on DKA risk
  - The data are particularly limited for subjects with an eGFR below 60 mL/min/1.73m^2
  - Epidemiologic data raise uncertainties about the generalizability of estimates of DKA risk in Tandem to patients with T1D and CKD

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
Division of Diabetes, Lipid Disorders, and Obesity

October 31, 2024

Integrated Benefit and Risk Assessment

- A1C reduction observed in Tandem and Tandem subgroups
  - Magnitude and durability of A1C reduction
  - Clinical benefit of A1C reduction in patients with T1D and mild-to-moderate CKD
- Additional advantages observed in Tandem and Tandem subgroups
  - Hypoglycemia, body weight, systolic blood pressure
- Potential non-glycemic benefits suggested by SCORED; a cardiorenal outcomes study in patients with T2D
- Increased risk of DKA observed in Tandem and Tandem subgroups
  - Uncertainties regarding magnitude of risk in revised target population

Evidence and Uncertainties in Post Hoc A1C Efficacy Analyses

	Pooled Studies 309/310				Study 312
	24 Weeks		52 Weeks		24 Weeks
	Sota 200 mg	Sota 400 mg	Sota 200 mg	Sota 400 mg	Sota 400 mg
Overall	-0.34 (-0.41, -0.27)	-0.37 (-0.44, -0.30)	-0.22 (-0.31, -0.13)	-0.31 (-0.39, -0.22)	-0.44 (-0.52, -0.36)
T1D-CKD*	-0.32 (-0.53, -0.12)	-0.32 (-0.53, -0.11)	-0.07 (-0.29, 0.16)	-0.08 (-0.32, 0.15)	-0.41 (-0.65, -0.19)
eGFR > 90	-0.28 (-0.39, -0.17)	-0.28 (-0.39, -0.17)	-0.17 (-0.31, -0.02)	-0.30 (-0.44, -0.16)	-0.48 (-0.60, -0.35)
60≤eGFR <90	-0.39 (-0.50, -0.30)	-0.46 (-0.56, -0.36)	-0.27 (-0.39, -0.16)	-0.34 (-0.46, -0.22)	-0.43 (-0.54, -0.32)
eGFR <60	-0.27 (-0.64, 0.11)	-0.21 (-0.57, 0.14)	-0.17 (-0.55, 0.21)	0.09 (-0.28, 0.46)	-0.17 (-0.58, 0.25)

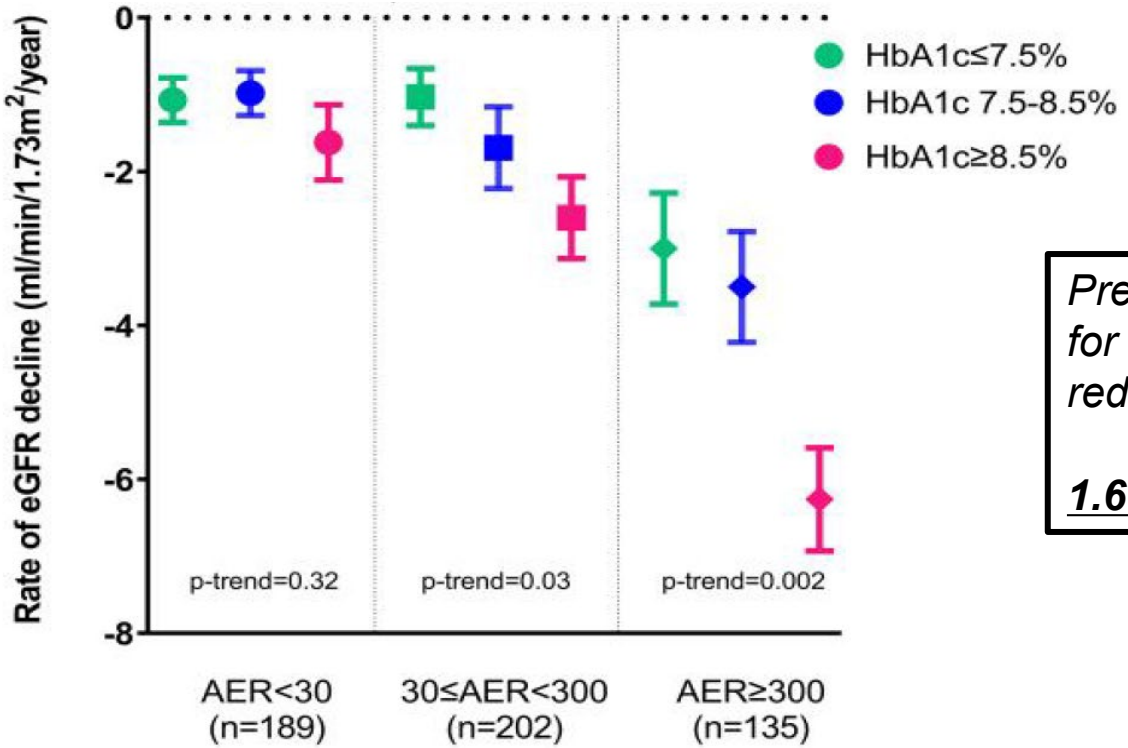
*T1D-CKD is defined as eGFR ≥ 45 to <60 ml/min/1.73 m2 OR eGFR ≥ 60 ml/min/1.73 m^2 and UACR ≥ 30 mg/g
Least-square estimate and 95% confidence limits for placebo-adjusted change from baseline in A1C

Clinical benefit of A1C reduction in patients with T1D and mild-to-moderate CKD

	Eligibility Criteria	Resultant Population
Diabetes Control and Complications Trial (DCCT)	UAER < 40 mg/day (secondary prevention cohort allowed UAER < 200 mg/day)	Mean UAER: 12 - 20 mg/day Mean CrCl: 120 – 130 mL/min
Preventing Early Renal Loss in Diabetes Study (PERL)	UAER > 20 mg/day History of eGFR decline*	Median UAER: 60 mg/day Mean eGFR: 75 mL/min
Tandem-CKD	UACR > 30 mg/g	Median UACR: 53 - 61 mg/g Median eGFR: 77 - 79 mL/min
Joslin Proteinuria Cohort	UACR > 350 mg/g for females, 250 mg/g for males	Median UACR: 687 mg/g Median eGFR: 85 mL/min

UAER – Urinary Albumin Excretion Rate

PERL: Rate of eGFR Decline by Glycemic control and Proteinuria



Predicted preservation of eGFR for a sustained 10-year reduction of A1C of 0.3 to 0.4%:

1.6 – 2.4 mL/min/1.73m²

Source: Shah, HS, JB McGill, IB Hirsch, C Wu, A Galecki, IH de Boer, M Mauer, and A Doria, 2024, Poor Glycemic Control Is Associated With More Rapid Kidney Function Decline After the Onset of Diabetic Kidney Disease, J Clin Endocrinol Metab, 109(8):2124-2135.

Additional Advantages from Post Hoc Tandem Analyses – Level 2 Hypoglycemia

		Studies 309 and 310 (52 Weeks)			Study 312 (24 Weeks)	
		Placebo	Sota 200 mg	Sota 400 mg	Placebo	Sota 400 mg
Overall	Event rate (PY)	18.12	14.94	15.65	15.41	11.78
	Event rate ratio (95% CI)	-	0.82 (0.79, 0.86)	0.86 (0.83, 0.90)	-	0.76 (0.73, 0.80)
T1D-CKD*	Event rate (PY)	21.42	12.65	12.00	15.00	14.23
	Event rate ratio (95% CI)	-	0.59 (0.53, 0.66)	0.58 (0.52, 0.66)	-	0.95 (0.85, 1.05)
eGFR ≥ 90	Event rate (PY)	15.1	13.4	14.0	15.7	11.2
	Event rate ratio (95% CI)	-	0.87 (0.82, 0.94)	0.92 (0.86, 0.99)	-	0.72 (0.68, 0.76)
eGFR 60 – 89	Event rate (PY)	19.7	15.9	16.1	15.4	12.5
	Event rate ratio (95% CI)	-	0.78 (0.75, 0.84)	0.80 (0.76, 0.86)	-	0.81 (0.76, 0.87)
eGFR < 60	Event rate (PY)	25.7	15.6	21.3	13.9	11.1
	Event rate ratio	-	0.66 (0.53, 0.78)	0.91 (0.75, 1.05)	-	0.80 (0.65, 0.98)

*T1D-CKD is defined as eGFR ≥ 45 to <60 ml/min/1.73 m2 OR eGFR ≥ 60 ml/min/1.73 m2 and UACR ≥ 30 mg/g

Additional Advantages from Post Hoc Tandem Analyses – Body Weight, Systolic Blood Pressure

	Study Pool 309/310 (24 Weeks)		Study 312 (24 Weeks)
	200 mg	400 mg	400 mg
CFB Systolic Blood Pressure, mmHg Placebo-Adjusted (Baseline: 121-123 mmHg)	-1.90 (-3.18, -0.62)	-2.66 (-3.93, -1.38)	-2.96 (-4.15, -1.76)
CFB Body Weight, kg Placebo-Adjusted (Baseline: 81-85 kg)	-2.03 (-2.41, -1.66)	-2.74 (-3.12, -2.37)	-2.75 (-3.08, -2.41)

CFB = Change from baseline

Cardiorenal Benefits in Patients With T2D, CKD, and Other CV Risk Factors

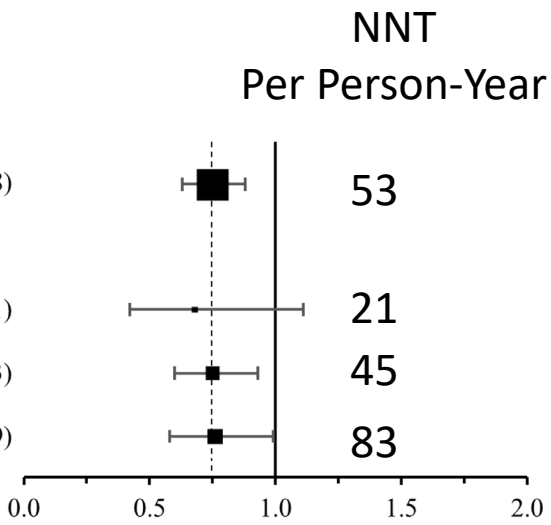
- The Applicant asserts that the results of SCORED are relevant to the proposed target population:
  - SCORED: patients with T2D, moderate-to-severe CKD, and other CV risk factors
  - T1D-CKD: patients with T1D, mild-to-moderate CKD
- SCORED demonstrated a reduced risk for the composite endpoint of CV death, HHF, and UHFV
- SCORED suggested other potential benefits – progression of renal disease, major adverse cardiovascular event (MACE)

Benefits From SCORED - Uncertainties

- There are significant uncertainties when extrapolating benefits in patients with T2D, moderate-to-severe CKD, and other CV risk factors to patients with T1D and mild-to-moderate CKD
  - Beyond etiology of diabetes, the populations potentially differ in important ways (age, comorbid heart disease, hypertension, obesity)
  - Estimates of absolute benefits in SCORED are inversely correlated with eGFR, for both the demonstrated and potential benefits
  - SCORED did not demonstrate a statistically significant benefit on MACE or the renal composite endpoint

Extrapolating Among Different Disease Severities Primary Endpoint of SCORED

Subgroup	No. of patients	Events per 100 PY		HR (95% CI)
		Sotagliflozin	Placebo	
Overall	10,584	5.6	7.5	0.75 (0.63, 0.88)
Baseline eGFR (mL/min/1.73 m^2)				
<30	811	9.4	14.1	0.68 (0.42, 1.11)
≥30 to <45	4655	6.9	9.1	0.75 (0.60, 0.93)
≥45	5116	3.9	5.1	0.76 (0.58, 0.99)



> 60+ ..... ?

Source: Figure 6 of Inpefa USPI;
NNT: Number Needed to Treat
Primary endpoint is total occurrences of CV death, HHF or UVHF

Benefits From SCORED vs DKA Risk in Tandem

Effect	NNH or NNT	Population	Other considerations
HF Composite* (SCORED)	83 person-years	T2D + other CV risk factors eGFR 45 to ≤60 subgroup	Demonstrated benefit Subgroup analysis
Renal Composite (SCORED)**	250 person-years	T2D + other CV risk factors eGFR 45 to ≤60 subgroup	Potential benefit Subgroup analysis
MACE* (SCORED)**	90 person-years	T2D + other CV risk factors eGFR **20 to ≤60**	Potential benefit Overall population
DKA (TANDEM)	20 to 31 person-years	T1D 84% without CKD 16% mild-to-moderate CKD	Significant uncertainty in CKD-targeted population

*Total occurrences of CV death, HHF, and UHFV

**Incidence of 50% decline in eGFR or kidney failure (defined as eGFR <15 mL/min/1.73 m^2), maintenance dialysis, or kidney transplant.

***Incidence of event of myocardial infarction, stroke, or CV death

Summary of DKA Risk in Tandem Program

- **The NNH is approximately 20 (Study 312) and 31 (Study 309 and 310) person-years** for sotagliflozin to cause one additional DKA event
- The majority of DKA events resulted in prolonged hospitalization
- The risk appears to be dose-related, and the DKA risk appears to accumulate steadily over time.
- Limited data precludes meaningful conclusions on the relationship between drug and DKA risk across CKD stage (particularly for eGFR < 60 mL/min/1.73m^2)

DKA and Mortality

TABLE 2. Diabetic ketoacidosis in-hospital case-fatality rates, overall and by age group and sex — National Health Interview Survey, United States, 2000–2014

Characteristic	Year 2000 (N = 101,621) % (95% CI)	First joinpoint year	First joinpoint (N = 141,704*) % (95% CI)	Year 2014 (N = 188,950) % (95% CI)	APC (95% CI) Period 1†	APC (95% CI) Period 2†
No. of deaths§	800	2009	611	620	NA	NA
Total¶	1.1 (0.9 to 1.2)	—**	—**	0.4 (0.4 to 0.5)	-6.8 (-7.1 to -6.4)	—**
Age group (yrs)						
<45	0.3 (0.2 to 0.4)	2007	0.1 (0.1 to 0.2)	0.1 (0.1 to 0.1)	-13.1 (-14.6 to -11.5)	-3.3 (-5.2 to -1.2)
45–64	1.0 (0.7 to 1.2)	—**	—**	0.5 (0.3 to 0.6)	-5.4 (-6.1 to -4.7)	—**
65–74	3.4 (2.2 to 4.6)	2007	1.5 (0.6 to 2.3)	1.4 (0.8 to 1.9)	-10.0 (-13.6 to -6.4)	-2.4 (-6.8 to 2.3)
≥75	7.2 (5.2 to 9.2)	—**	—**	2.6 (1.6 to 3.6)	-7.0 (-7.7 to -6.3)	—**
Sex¶						
Male	1.2 (0.9 to 1.5)	—**	—**	0.5 (0.4 to 0.6)	-6.9 (-7.3 to -6.4)	—**
Female	1.0 (0.8 to 1.2)	—**	—**	0.4 (0.3 to 0.5)	-6.6 (-7.1 to -6.1)	—**

Abbreviations: APC = annual percent change; CI = confidence interval; DKA = diabetic ketoacidosis; NA = not applicable.

* Number of DKA hospitalizations in 2009.

† Period 1 is from 2000 to first joinpoint year (or 2014 if no joinpoint); period 2 is from first joinpoint year to 2014.

§ Estimated number of in-hospital deaths.

¶ Age adjusted to the 2000 U.S. Census using the four age groups listed in the table.

** No joinpoints were found.

Benoit SR, Zhang Y, Geiss LS, Gregg EW, Albright A. Trends in Diabetic Ketoacidosis Hospitalizations and In-Hospital Mortality — United States, 2000–2014. MMWR Morb Mortal Wkly Rep 2018;67:362–365. DOI: http://dx.doi.org/10.15585/mmwr.mm6712a3

Uncertainties of DKA Risk

- Available epidemiology data do not provide reassurance that the magnitude of the DKA risk observed in Tandem applies to patients with T1D and CKD, for either **incidence or severity**
- Similar findings with sotagliflozin could be realized in the post-market setting where patients would not be followed as closely as they are in a clinical trial setting.
- Mitigation strategies to reduce the risk of DKA post-marketing have not been tested in premarket studies.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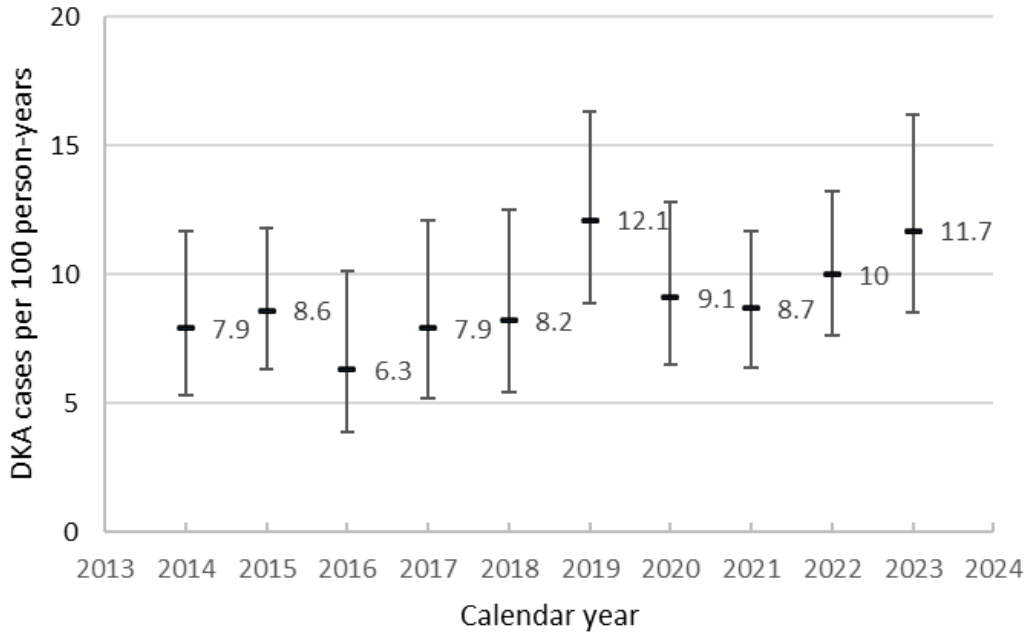
Back Up Slides Shown

DKA Incidence Rate by Calendar Year Among SGLT2 Inhibitor Initiators With T1D in FDA Sentinel Query



Incidence rate of DKA did not appear to decline from 2014 to 2023