SOTAGLIFLOZIN AS AN ADJUNCT TO INSULIN THERAPY TO IMPROVE GLYCEMIC CONTROL IN ADULTS WITH TYPE 1 DIABETES MELLITUS AND CHRONIC KIDNEY DISEASE

SPONSOR BRIEFING DOCUMENT

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Abbreviation	Definition
A1C	hemoglobin A1C
ADA	American Diabetes Association
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{0\text{-inf}}$	area under the concentration-time curve from time 0 to infinity
BHB	blood beta hydroxybutyrate
BMI	body mass index
CAC	Coronary artery calcium
CDC	Centers for Disease Control and Prevention
CGM	continuous glucose monitoring
CKD	chronic kidney disease
CI	Confidence interval
CL	confidence limit
C_{max}	maximum plasma concentration
CRL	Complete Response Letter
CSII	continuous subcutaneous insulin infusion
CV	Cardiovascular
DCCT	Diabetes Control and Complications Trial
DDS2	2-item Diabetes Distress Score
DKA	diabetic ketoacidosis
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EAIR	exposure-adjusted incidence rate
EASD	European Association for the Study of Diabetes
EDIC	Epidemiology of Diabetes Interventions and Complications
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EMDAC	Endocrinologic and Metabolic Drugs Advisory Committee
E-R	exposure-response
ER	emergency room
ESKD	end-stage kidney disease
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide
GLP-1 RA	glucagon-like peptide receptor agonist
HF	heart failure

Abbreviation	Definition
HR	hazard ratio
ICU	intensive care unit
IDMC	independent insulin dose monitoring committee
ITT	intent-to-treat
KDIGO	Kidney Disease: Improving Global Outcomes
Lexicon	Lexicon Pharmaceuticals, Inc.
LS	least squares
MACE	Major adverse cardiovascular events
MAR	Missing at random
MDI	multiple daily injections
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
NDA	New Drug Application
PD	Pharmacodynamic
PERL	Preventing Early Renal Loss
PK	Pharmacokinetic
PPG	postprandial glucose
PT	preferred term
QTcl	QT interval corrected for heart rate using the individual method
RR	relative risk
SAE	serious adverse event
SBP	systolic blood pressure
SGLT1	sodium-glucose cotransporter 1
SGLT2	sodium-glucose cotransporter 2
SMBG	self-monitoring blood glucose
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
UACR	urine albumin-to-creatinine ratio
UGCR	urinary glucose-to-creatinine ratio
UGT	UDP-glycosyltransferase
UGE	urinary glucose excretion
US	United States

1 EXECUTIVE SUMMARY

1.1 Introduction

Lexicon Pharmaceuticals, Inc. (Lexicon) developed sotagliflozin, an oral antihyperglycemic drug that exerts its action by inhibiting both sodium-glucose cotransporter 1 (SGLT1) and sodium-glucose cotransporter 2 (SGLT2), as an adjunct to insulin therapy in patients with type 1 diabetes mellitus (T1D). The efficacy of sotagliflozin was established through 3 Phase 3 studies (309, 310, and 312) with statistically significant primary and key secondary glycemic endpoints ($p<0.001$ for all studies) in an adult T1D population. Despite the acknowledged effectiveness for controlling blood glucose in patients with T1D, the Food and Drug Administration (FDA) issued a complete response letter (CRL) in March of 2019 for the sotagliflozin New Drug Application (NDA). This decision was primarily driven by the FDA's conclusion that the risk-benefit assessment was not favorable, which was based on concerns related to the increased risk of diabetic ketoacidosis (DKA) in sotagliflozin-treated study participants. In subsequent meetings with the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) to identify a path forward, alignment was reached that an improvement in the benefit-risk profile for sotagliflozin could be accomplished through the identification of a population within T1D for whom additional benefits and/or diminished risk could be demonstrated.

In the sotagliflozin Phase 3 program, the improvements in glycemic control and the key safety risks of hypoglycemia and DKA were relatively consistent across many demographic and disease characteristic subgroups. Lexicon therefore determined that the most appropriate target population was one where:

- The unmet medical need for new interventions to improve glycemic control is significantly greater than in the overall T1D population based on the heightened risk of T1D disease progression and resulting increased morbidity and mortality.
- There is demonstrated efficacy of sotagliflozin in improvement of glycemic control, and the resulting near-term and long-term benefits in a high-risk population.
- The additional near-term and long-term benefits do not come with an increased risk in hypoglycemia (including severe events) or DKA compared to the overall T1D population.

The T1D-chronic kidney disease (CKD) subgroup is a high-risk patient population where treatment with insulin alone is not enough and is a population with a clear unmet medical need for new innovative therapies. The established efficacy of sotagliflozin to improve glycemic control in this patient subgroup, with a safety profile consistent with that of the overall T1D population studied, leads to a favorable benefit-risk profile that should support approval.

Lexicon's assessment of an appropriate target T1D subpopulation was further refined by the results of a Phase 3 randomized, controlled, registration study of sotagliflozin in patients with type 2 diabetes mellitus (T2D), moderate to severe renal impairment, and other cardiovascular (CV) risk factors (SCORED). This study demonstrated that the use of sotagliflozin resulted in clinically meaningful and statistically significant reductions in risk for CV death, hospitalization for heart failure (HF), and urgent visit for HF. On 26 May 2023, FDA approved sotagliflozin, under the brand name INPEFA® to reduce the risk of CV death, hospitalization for HF, and urgent HF visit in adults with a.) HF or b.) T2D, chronic kidney disease, and other CV risk factors. While not in a T1D population, SCORED provides evidence of sustained glycemic control and cardiorenal benefits in patients with CKD.

The 3 pivotal T1D Phase 3 studies demonstrated consistent improvements in glycemic control and body weight and had a similar safety profile for risks of hypoglycemia and DKA across the evaluated demographic and disease characteristic subgroups. These observations along with the observed benefits in cardiorenal outcomes from SCORED, led to the selection of the T1D and CKD subpopulation in which patients have significant risk for increased morbidity and mortality, lack access to available antihyperglycemic therapies beyond insulin, and would realize both near-term and long-term benefits from improved glycemic control.

Without effective glycemic control and other CV risk factor modifications, patients with T1D are at a significantly higher risk of CV and kidney complications compared to those without diabetes, leading to a 2 to 5 times greater risk of all-cause mortality (Ruiz 2022). CKD itself is a recognized independent predictor of increased morbidity and mortality, adding to the risks from T1D and magnifying the significant unmet medical need in this patient population (Sud 2016). This underscores the critical importance for targeted interventions to treat this high-risk subset of patients.

Table 1: Overview of Disease Burden in Patients with T1D

Disease Characteristic	Statistic
Risk compared to population without diabetes	▪ 10X greater risk cardiovascular disease[4] ▪ 4X greater risk of HF hospitalization[5] ▪ 2-5X greater risk of all-cause mortality[6] ▪ 6X greater risk of ESKD[7]
CKD is an independent predictor of increased morbidity and mortality	▪ Higher A1C associated with accelerated eGFR decline[1] ▪ Higher A1C associated with more rapid progression to ESKD[2] ▪ Lower eGFR associated with increased risk of hospitalization for HF[5] ▪ Decreased TIR associated with elevation in risk of eye and kidney complications[3] ▪ Relative to patients without CKD, those with T1D and CKD have an increased risk of death.[8]

A1C: hemoglobin A1C; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; HF: heart failure; T1D: type 1 diabetes; TIR: time-in-range
1. Shah 2024; 2. Skupien 2014; 3. Beck 2019; 4. de Ferranti 2014; 5. Rosengren 2015; 6. Ruiz 2022; 7. United States Renal Data System 2023 and Rosolowsky 2011; 8. Liao 2023

The proposed indication for sotagliflozin is as an adjunct to insulin therapy to improve glycemic control in adults with T1D and CKD. Lexicon defines the CKD patient population in alignment with Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, which establish thresholds for increased disease progression risk (KDIGO 2024). This definition of CKD includes patients with a.) estimated glomerular filtration rate (eGFR) of 45 to <60 mL/min/1.73m^2 or b.) eGFR ≥60 mL/min/1.73m^2 and urine albumin-to-creatinine ratio (UACR) ≥30 mg/g (Figure 1).

The recommended dose is 200 mg once daily before the first meal of the day. In patients tolerating sotagliflozin 200 mg and requiring additional glycemic control, the dose may be increased to 400 mg once daily.

Figure 1: Target Population for Sotagliflozin Based on eGFR and Albuminuria Categories

Prognosis of CKD by GFR and UACR Categories[1,2]			Urine Albumin to Creatinine Ratio (UACR) Categories		
			Normal to Mild UACR < 30 mg/g	Moderate UACR 30-299 mg/g	Severe UACR ≥ 300 mg/g
eGFR (ml/min/1.73m²)	Normal	≥ 90	Low Risk (82%)	Moderate Risk (7%)	High Risk (1%)
	Mild	60-89			
	Moderate	45-59	Moderate Risk (7%)	High Risk (2%)	Very High Risk (0.2%)
		30-44	High Risk (< 1%)		
	Severe	15-29	Very High Risk (< 1%)		
	Kidney failure	< 15			

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; KDIGO: Kidney Disease: Improving Global Outcomes; T1D: type 1 diabetes mellitus; UACR: urine to creatinine ratio
Target population outlined in blue: T1D-CKD: eGFR of 45 to < 60 mL/min/1.73 m^2 OR eGFR ≥ 60 mL/min/1.73 m^2 and UACR ≥ 30 mg/g
Adapted from KDIGO
1. American Diabetes Association Professional Practice Committee. Diabetes Care 2024b;
2. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. Kidney Int 2022
Source: KDIGO 2024; Lexicon data on file.

Patients in the Phase 3 program with T1D and CKD receiving sotagliflozin achieved nominally significant and clinically meaningful improvement in hemoglobin A1C (A1C) as well as reductions in body weight and improved time in range. These benefits will all contribute to effectively addressing risk factors in this population with a greater propensity for disease progression (Table 2).

The safety profile of sotagliflozin in the T1D-CKD population is consistent with that seen in the overall population with T1D and with that demonstrated in the population studied for the approved HF indication. In the T1D-CKD population, the risk of hypoglycemia is not increased with sotagliflozin use, including severe events. While the risk of DKA is increased with sotagliflozin use, this risk can be managed with appropriate patient selection and education.

Table 2: Comparison of Key Efficacy and Safety Endpoints in the Overall T1D Population vs the T1D-CKD Subgroup in Pooled Studies 309/310 and Study 312

	T1D-CKD Population					Overall T1D Population				
	Pooled Studies 309/310			Study 312		Pooled Studies 309/310			Study 312	
	SOTA 200 mg N = 85	SOTA 400 mg N = 75	Placebo N = 74	SOTA 400 mg N = 114	Placebo N = 110	SOTA 200 mg N = 524	SOTA 400 mg N = 525	Placebo N = 526	SOTA 400 mg N = 699	Placebo N = 703
LS Mean Δ A1C (%) at 24 Weeks	-0.47	-0.44	-0.13	-0.85	-0.40	-0.41	-0.43	-0.05	-0.79	-0.33
LS Mean Δ Body Weight (kg) at 24 Weeks	-1.55	-2.61	-0.16	-2.02	0.82	-1.70	-2.55	0.47	-2.21	0.77
% TIR (70–180 mg/dL)	66%	70%	51%	NA	NA	58%	64%	52%	NA	NA
Severe Hypoglycemia (EAIR per 100 PYE)**	7.6	4.4	20.1	17.1	10.7	6.3	4.8	8.2	7.0	5.6
DKA (EAIR per 100 PYE)**	5.1	2.9	1.5	6.4	2.1	3.1	4.2	0.2	7.0	1.3

**Safety data are presented for 52 weeks for the pooled 309 and 310 studies.
A1C: hemoglobin A1C; CKD: chronic kidney disease; DKA: diabetic ketoacidosis; EAIR: exposure-adjusted incidence rate; LS: least squares; NA: not assessed; PYE: patient-years of exposure; SH: severe hypoglycemia; SOTA: sotagliflozin; T1D: type 1 diabetes mellitus; TIR: time in range

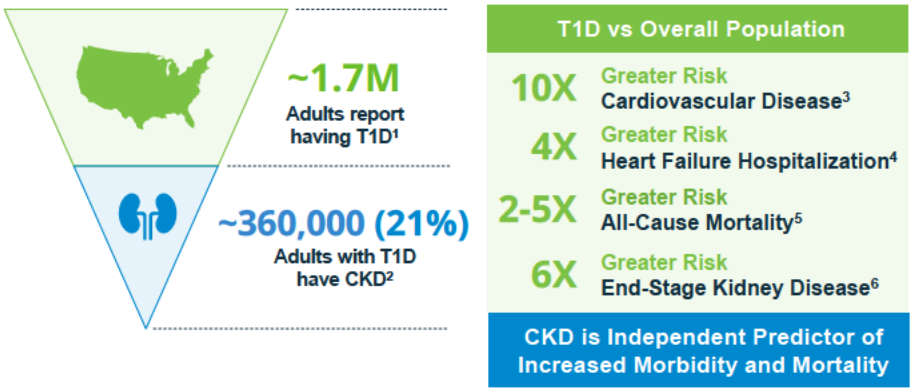
In a high risk T1D-CKD population with a clear unmet need for new innovative therapies and where insulin is not enough, sotagliflozin presents a favorable benefit-risk profile to support approval for this population.

1.2 Background and Unmet Need

1.2.1 Type 1 Diabetes and Chronic Kidney Disease

Despite advances in insulin therapies, delivery methods, and management, only 20% of patients with T1D achieve optimal glycemic control (Akturk 2023). Without effective glycemic control, patients with T1D remain at risk of complications, including progression to end-stage kidney disease (ESKD), CV disease, and death (Figure 2). For the 21% of patients with T1D who are also affected by CKD, these risks are even greater since CKD is a recognized independent predictor of increased morbidity and mortality (Rossing 2024). Patients with T1D and CKD have a greater need to control their blood glucose to avoid hyper- and hypoglycemic events that are concerning on their own and are associated with other comorbid sequelae, including deterioration in kidney function.

Figure 2: Increased Risks for Patients for T1D-CKD



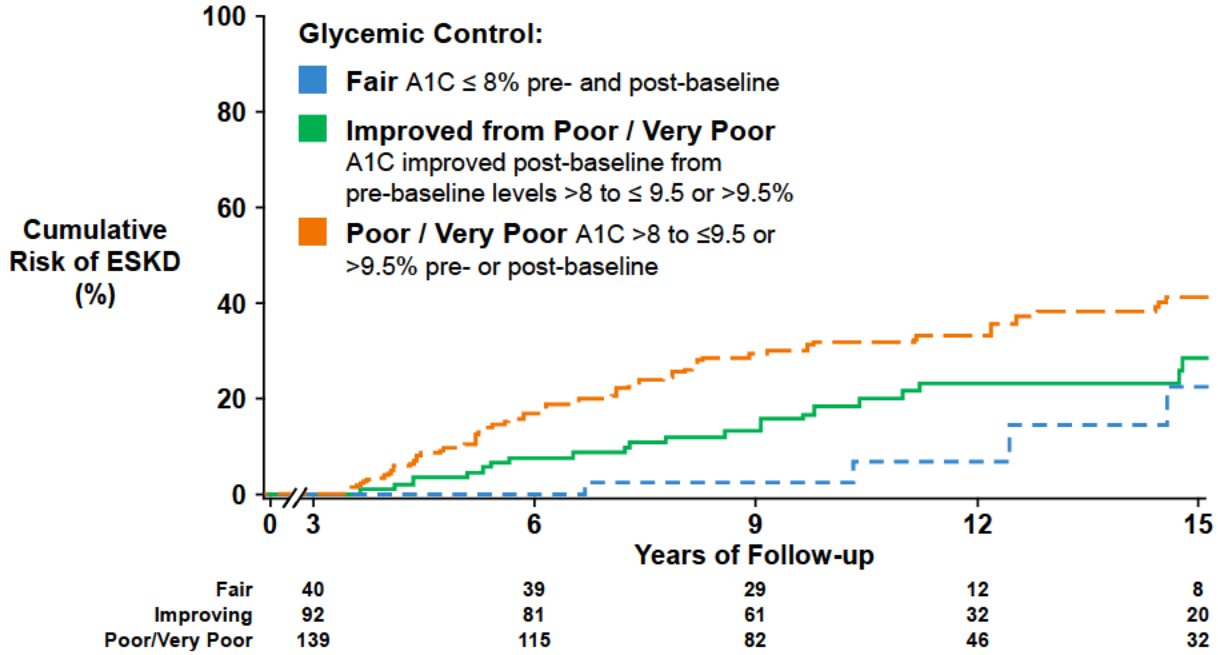
CDC: Centers for Disease Control and Prevention; CKD: chronic kidney disease; T1D: type 1 diabetes mellitus
1. CDC National Diabetes Statistics Report 2024; 2. Rossing 2024; 3. de Ferranti 2014; 4. Rosengren 2015; 5. Ruiz 2022; 6. United States Renal Data System 2023 and Rosolowsky 2011

Given the increased risks associated with CKD, the KDIGO group recommends initiating interventions to slow kidney function decline and reduce the risk of ESKD in patients at moderate to high risk of progression (KDIGO 2024). Notably, KDIGO recognizes that both kidney function (as measured by eGFR) and kidney damage (as measured by UACR) contribute importantly and independently to the risk for CKD and its progression (see Figure 9).

Importantly, literature also supports that improvement in glycemic control in patients with T1D and CKD is associated with delayed progression to ESKD. In a prospective natural history study of 349 patients with T1D and CKD from the Joslin Proteinuria Cohort, with follow-up ranging between 7 to 15 years, patients who improved their glycemic control had delayed progression to ESKD compared to those with persistently

poor control (Figure 3; Skupien 2014). Additionally, evaluation of patients with T1D from the Diabetes Control and Complications Trial (DCCT) showed that patients with tight glucose control (≥50% time in range [70–180 mg/dL]) had lower risk for microvascular complications compared to patients with <50% time in range (Beck 2019). Conversely, for each 10% decrease in time in range, there was a 40% increase in relative risk [RR] of progression to microalbuminuria. Thus, patients who spend more time outside their target glucose range are at increased risk for kidney damage.

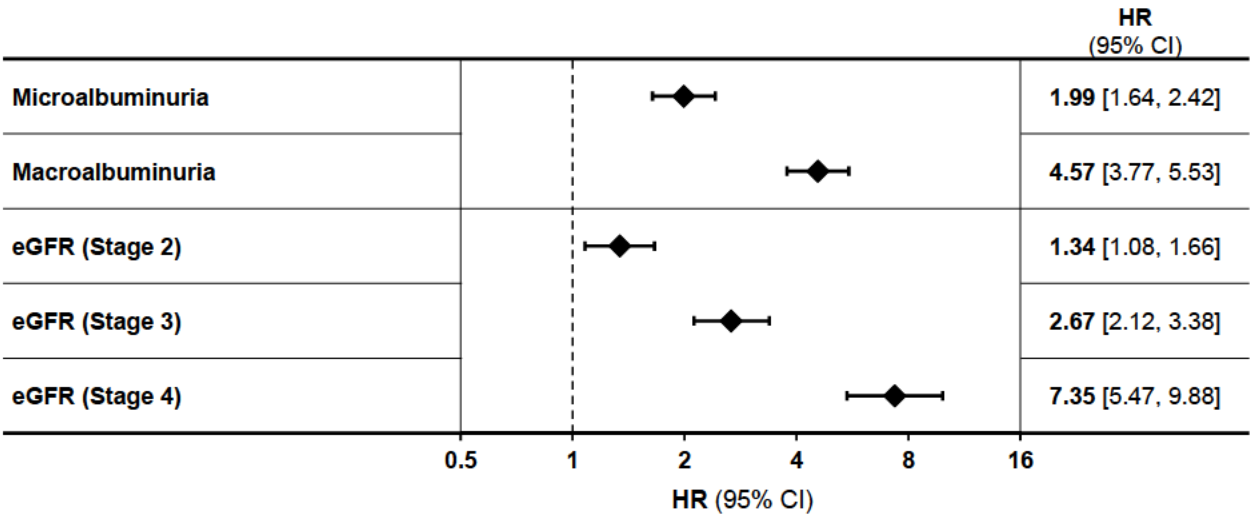
Figure 3: Cumulative Risk of ESKD over Time by Glycemic Control Category in Patients with T1D and CKD (Skupien 2014)



A1C: hemoglobin A1C; CKD: chronic kidney disease; ESKD: end-stage kidney disease: T1D: type 1 diabetes mellitus
Source: Skupien 2014

There is also an association of kidney function and albuminuria with risk of hospitalization for HF in patients with T1D (Rosengren 2015). Results from more than 33,000 patients with T1D who were followed for approximately 8 years showed that increases in albuminuria and decreases in eGFR were associated with a higher risk of hospitalization for HF (Figure 4). These findings support that both albuminuria and declines in eGFR are independent risk factors for HF in patients with T1D.

Figure 4: Hazard Ratios for Admission to Hospital for Heart Failure by Kidney Function and Kidney Damage (Rosengren 2015)



CI: confidence interval; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; HR: hazard ratio; LDL: low-density lipoprotein; T1D: type 1 diabetes mellitus
Adjusted for age, sex, diabetes duration, education, birth in Sweden, comorbidities, mean HDL and LDL, and treatment with lipid-lowering drugs.
Source: Rosengren 2015

1.2.2 Diabetes Management

Diabetes management aims to reduce the risks of micro- and macrovascular complications by improving glycemic control while minimizing the risk of severe hypoglycemia. Treatment guidelines recommend A1C below 7% for most adults (American Diabetes Association Professional Practice Committee [ADA] 2024a). Unfortunately, treatment options are limited, with only insulin and pramlintide as adjunct to insulin being approved for patients with T1D. There are also limitations of subcutaneous insulin replacement, and many patients experience excessive weight gain and peripheral insulin resistance, both of which are risk factors for hypertension and CV disease due to increased risk for incidence of hyperglycemia. The resulting need to lower blood glucose with greater insulin levels or concomitant therapies in turn increases the risk for incidence of severe hypoglycemia. The burden of current treatment options has been shown to adversely affect quality of life, particularly in patients that have experienced disease progression following decades living with T1D.

Effective management of T1D with insulin requires proactive monitoring and timely interventions to prevent severe hypoglycemia and DKA events, both of which can be acute, serious, and potentially life-threatening. For both, regular glucose monitoring is critical. Patients should be aware of risks factors that could trigger an episode and look for and recognize early warning signs so they can take immediate action. Insulin dose

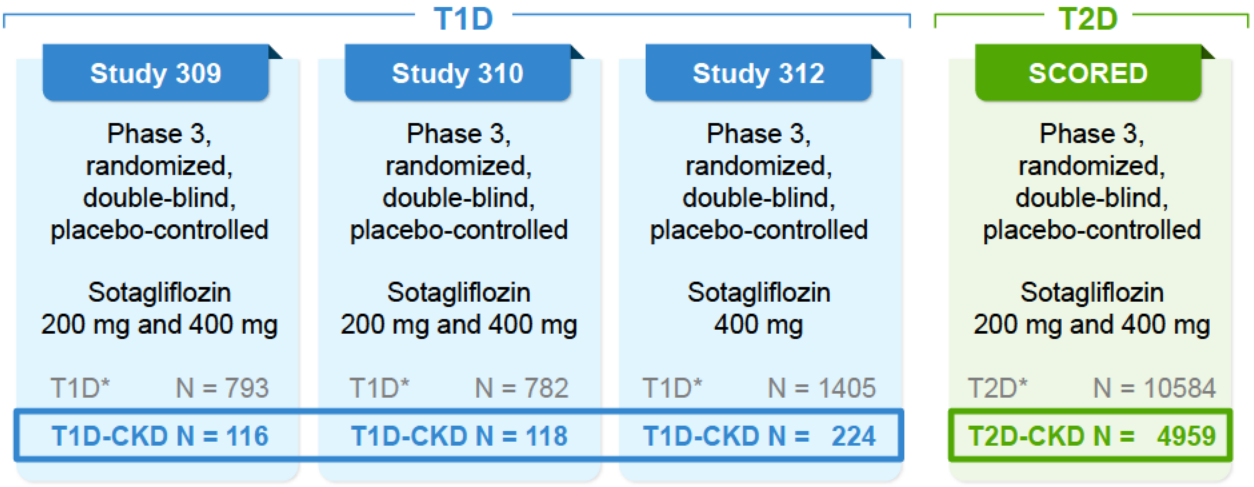
adjustments, particularly during periods of increased activity or illness, are essential for preventing hypoglycemia. For DKA, patients must be aware of the common evaluation methods, including elevated blood glucose levels, the presence of ketones, and metabolic acidosis. Ketone testing, either through urine or blood, should be performed when DKA is suspected to confirm the presence of ketones. Early detection and prompt action, including insulin administration, carbohydrate ingestion, and increased fluid intake, are effective at preventing the progression of ketosis and DKA.

In summary, without effective glycemic control, patients with T1D and CKD remain at an increased risk of complications including progression to ESKD, CV disease, and mortality. There is a need for therapeutic options that improve glycemic control and reduce the risk of CV and kidney disease progression in patients with T1D and CKD.

1.3 Clinical Program

The primary evidence supporting the proposed indication includes the same 3 Phase 3 randomized, double-blind, placebo-controlled studies (Studies 309, 310, and 312) that demonstrated statistically significant benefits with both the 200 and 400 mg doses of sotagliflozin compared with placebo for patients with T1D. The subgroup of patients with T1D and CKD includes 458 patients, of whom 274 received sotagliflozin (Figure 5).

Figure 5: Phase 3 Clinical Development Program Supporting Use of Sotagliflozin in Patients with T1D-CKD



CKD: chronic kidney disease; T1D: type 1 diabetes mellitus; T2D: type 2 diabetes mellitus
* Statistically significant primary and key secondary endpoints ($p<0.001$)

Additional support is provided from the SCORED trial, a Phase 3 multicenter, randomized, double-blind, placebo-controlled study in more than 10,500 patients with T2D, CKD (screening eGFR ≥25 to <60 mL/min/1.73m^2 regardless of albuminuria), and other CV risk factors. Almost 5000 participants, including nearly 2500 who received sotagliflozin, met the CKD definition being proposed by the Sponsor for the T1D-CKD

cohort. Thus, SCORED provides relevant information on the potential glycemic and long-term clinical benefit of sotagliflozin in patients with T1D and CKD.

1.4 Efficacy

Studies 309 and 310 were identically designed Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies to evaluate sotagliflozin as an adjunct to optimized insulin therapy in adults with T1D who had inadequate glycemic control with insulin therapy at the time of screening (A1C between 7% and 11%) and an eGFR ≥45 mL/min/1.73m^2. Eligible patients were randomized to receive sotagliflozin 200 mg, sotagliflozin 400 mg, or placebo.

The primary endpoint in Studies 309 and 310 was change from baseline to Week 24 in A1C in sotagliflozin treatment groups (200 mg and 400 mg) compared with placebo. Secondary endpoints included changes from baseline to Week 24 in body weight, insulin dosing (total dose, basal dose, and bolus dose), and fasting plasma glucose (FPG).

The total duration of the study was up to 64 weeks, including a 6-week insulin optimization period prior to randomization, a 24-week double-blind treatment period, and a 28-week double-blind safety extension (see Figure 19). Studies 309 and 310 included an insulin optimization period beginning 6 weeks before randomization, which continued throughout the study, and a 2-week single-blind placebo run-in period to allow for diabetes education; optimization of compliance with diet, exercise, and the insulin regimen; and stabilization of metabolic parameters. Investigators were to adjust insulin dose to meet fasting and postprandial glucose targets using the patient's self-monitoring blood glucose (SMBG) and insulin dose diaries during screening and 52-week study period. The independent insulin dose monitoring committee (IDMC) reviewed SMBG and insulin dose diary results for each patient and made insulin dosing recommendations to the Investigators during screening and up to Week 24 following randomization. It is important to note the Investigators were unmasked to A1C and FPG values at Week 24 to appropriately manage glycemic control, but were still blinded to study treatment during the 28-week safety extension.

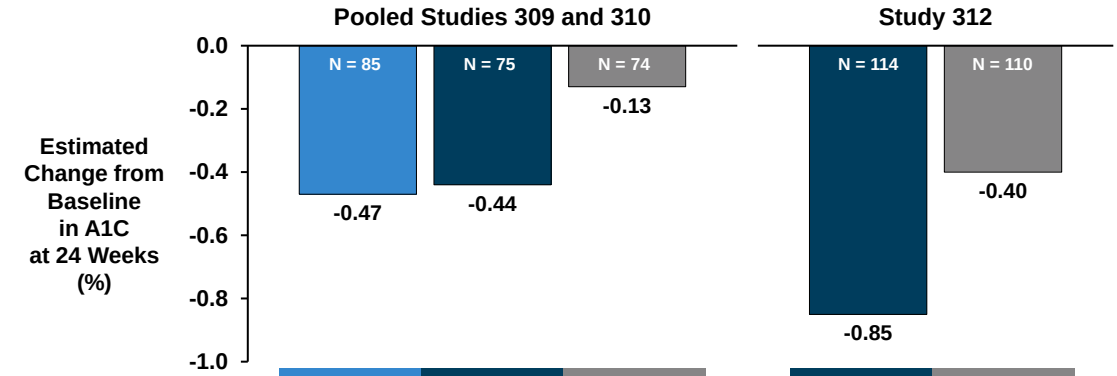
Study 312 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate sotagliflozin as an adjunct to insulin in patients with T1D. Enrollment criteria were similar to that of Studies 309 and 310. No insulin optimization run-in period or IDMC were included in this trial, but as with Studies 309 and 310, Investigators were to adjust insulin over the course of the study to meet pre- and postprandial glucose targets using SMBG and insulin dose diary results (A1C and FPG values were masked to Investigators during the treatment period) over the full treatment period. The total duration of the study was up to 30 weeks, including 24 weeks of double-blind treatment. The primary endpoint was a composite of an A1C <7.0% without severe hypoglycemia or DKA at Week 24. A1C change from baseline at Week 24 was prespecified as a key secondary endpoint.

In Studies 309, 310, and 312, sotagliflozin demonstrated statistically significant benefits compared to placebo across the primary endpoints and most key secondary endpoints (Table 2). The addition of sotagliflozin to insulin therapy resulted in a difference in reduction in A1C compared to placebo between 0.35% and 0.46% compared to placebo at Week 24 (Table 11).

The statistically significant efficacy results demonstrated in the three Phase 3 randomized controlled studies allowed for evaluation of subgroups of patients who could gain substantial benefits, with T1D-CKD identified as the patient group where benefits observed in the overall population would be the most valuable and clinically meaningful. The population of patients with T1D and CKD was identified based on inclusion criteria from the studies and using the definitions outlined by the KDIGO group: baseline 45 to <60 mL/min/1.73m^2 or an eGFR ≥60 mL/min/1.73m^2 with UACR ≥30 mg/g. Change from baseline to Week 24 in A1C was the primary efficacy endpoint for the T1D-CKD population and was analyzed in the pooled Studies 309 and 310 due to the identical study designs; Study 312 was analyzed separately.

In the T1D-CKD population, both doses of sotagliflozin demonstrated nominally significant and clinically meaningful reductions in A1C from baseline compared to placebo at 24 weeks (Figure 6). The larger A1C reductions from baseline observed with sotagliflozin in Study 312 were likely due to the higher baseline A1C.

Figure 6: LS Mean Change from Baseline to Week 24 in A1C (%) in the T1D-CKD Population in Pooled Studies 309 and 310 and in Study 312



	200 mg	400 mg	Placebo	400 mg	Placebo
Baseline A1C (%)	**7.7**	**7.9**	**7.8**	**8.7**	**8.3**
Difference from Placebo [95% CI]	**-0.34** [-0.55, -0.12]	**-0.31** [-0.53, -0.09]		**-0.45** [-0.69, -0.21]	
p-value	**0.002**	**0.006**		**< 0.001**	

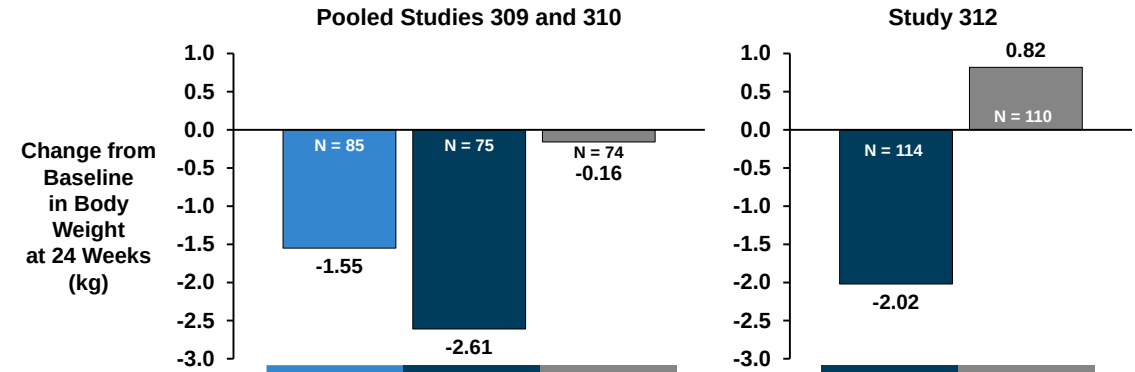
A1C: hemoglobin A1C; CI: confidence interval; CKD: chronic kidney disease; T1D: type 1 diabetes mellitus

Changes in time in range provide valuable information about whether the frequency and duration of hypoglycemia or hyperglycemia improve over time. Furthermore, increased time in range decreases the likelihood of developing additional diabetes complications

such as CV disease, progression to ESKD, and retinopathy (ADA Professional Practice Committee 2024b). In a small subset of patients who participated in a blinded continuous glucose monitor (CGM) substudy (pooled 309/310), sotagliflozin increased time in range (blood glucose 70–180 mg/dL) compared to placebo, with a larger effect observed with sotagliflozin 400 mg (see Figure 23). Importantly, the improvements in time in range were at the expense of time above range (blood glucose >180 mg/dL) and not time below range (blood glucose <70 mg/dL), potentially confirming hypoglycemia is not increased with sotagliflozin in the T1D-CKD population.

Sotagliflozin provided nominally significant, dose-related reductions in body weight from baseline to Week 24 compared to placebo in the T1D-CKD population (Figure 7). These results are important given that a majority of patients in the T1D-CKD population were overweight or obese, and reduction in body weight is considered an important modifiable risk factor.

Figure 7: LS Mean Change from Baseline to Week 24 in Body Weight in the T1D-CKD Population in Pooled Studies 309 and 310 and in Study 312



	200 mg	400 mg	Placebo	400 mg	Placebo
Baseline body weight (kg)	**86.7**	**83.4**	**85.0**	**82.6**	**81.3**
Difference from Placebo [95% CI]	**-1.39** [-2.33, -0.45]	**-2.45** [-3.41, -1.49]		**-2.84** [-3.76, -1.91]	
p-value	**0.004**	**< 0.001**		**< 0.001**	

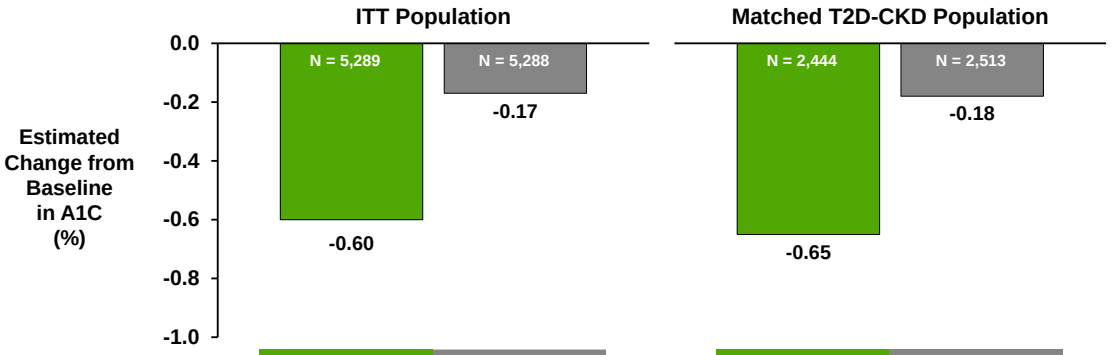
CI: confidence interval; CKD: chronic kidney disease; T1D: type 1 diabetes mellitus

Furthermore, results from the Diabetes Treatment Satisfaction Questionnaire (DTSQ) support that the benefits achieved with sotagliflozin are clinically meaningful for these patients (see Figure 26). Numeric reductions in the 2-item Diabetes Distress Score (DDS2) were observed with sotagliflozin.

The efficacy results from the T1D-CKD population in Studies 309, 310, and 312 are supported by the Phase 3 SCORED study in patients with T2D and CKD, described in Section 6.6. In the matched population of SCORED patients with T2D-CKD, consistent A1C lowering effects were observed, which aligned with the results in the T1D-CKD population. Over a median follow-up period of 16 months in SCORED, the

placebo-adjusted treatment difference in A1C was -0.47% with sotagliflozin (Figure 8). These results also provide evidence of sustained improvements in glycemic control with sotagliflozin in patients with CKD.

Figure 8: Change from Baseline in A1C During Follow-up Period of SCORED



	ITT Population		Matched T2D-CKD Population	
	Sotagliflozin	Placebo	Sotagliflozin	Placebo
Baseline A1C (%)	**8.7**	**8.7**	**8.7**	**8.7**
Difference from Placebo [95% CI]	**-0.42** [-0.47, -0.38]		**-0.47** [-0.53, -0.40]	
p-value	**< 0.0001**		**< 0.0001**	

A1C: hemoglobin A1C; CI: confidence interval; CKD: chronic kidney disease; ITT: intent-to-treat; T2D: type 2 diabetes mellitus.

1.5 Safety

The safety profile of sotagliflozin in the proposed population includes 274 treated patients with T1D-CKD (160 sotagliflozin-treated patients in Studies 309 and 310 and 114 in Study 312). The majority of patients remained on treatment through 6 months with approximately 60% treated for ≥1 year.

The safety profile of sotagliflozin in the T1D-CKD population is similar to the safety profile of sotagliflozin in the overall T1D population (Table 3). Similar proportions of patients in each treatment group experienced at least 1 treatment-emergent adverse event (TEAE), and the events were mostly mild or moderate in severity. Serious adverse events (SAEs) were similar in frequency between groups, and sotagliflozin treatment did not result in an increase in TEAEs leading to study drug discontinuation compared to placebo through 52 weeks. In the T1D-CKD population, 2 patients (3%) in the placebo group experienced fatal TEAEs.

Table 3: Summary of Adverse Events in Pooled Studies 309 and 310 and in Study 312

	T1D-CKD Population					T1D mITT Population				
	Pooled Studies 309 and 310 52-Week			Study 312 24-Week		Pooled Studies 309 and 310 52-Week			Study 312 24-Week	
Proportion of Patients, %	SOTA 200 mg N=85	SOTA 400 mg N=75	Placebo N=74	SOTA 400 mg N=114	Placebo N=110	SOTA 200 mg N=524	SOTA 400 mg N=525	Placebo N=526	SOTA 400 mg N=699	Placebo N=703
Any TEAE	80%	68%	76%	59%	49%	75%	74%	71%	55%	53%
Any severe TEAE	13%	8%	14%	11%	6%	10%	9%	7%	6%	4%
Any SAE	14%	11%	14%	11%	7%	10%	10%	7%	7%	3%
Any TEAE leading to discontinuation	4%	5%	5%	7%	4%	4%	7%	4%	6%	2%
Deaths	0	0	3%	0	0	0	0	0.6%	0.1%	0

CKD: chronic kidney disease; HF: heart failure; SAE: serious adverse event; SOTA: sotagliflozin; TEAE: treatment-emergent adverse event; T1D: type 1 diabetes mellitus

In the pooled T1D-CKD population from Studies 309 and 310, the most frequently reported TEAEs in the sotagliflozin groups were urinary tract infection (13% and 3% in sotagliflozin 200 mg and 400 mg, respectively), diarrhea (9% and 11%, respectively), and viral upper respiratory tract infection (8% and 19%, respectively; see Table 31). The most common events in the placebo group were viral upper respiratory tract infection (12%), upper respiratory tract infection (12%), and urinary tract infection (7%).

Given that the proposed indication is in patients with CKD, the effect of sotagliflozin on kidney function was evaluated. While there was an expected initial decline in eGFR immediately following initiation of treatment, eGFR returned toward baseline levels over the 52 weeks such that there was no difference in change in eGFR at Week 52 (see Figure 36). This stabilization of kidney function with sotagliflozin is expected to continue with ongoing therapy. Sotagliflozin treatment also demonstrated improvement in albuminuria in patients with T1D-CKD, specifically those with elevated baseline UACR (≥30 mg/g); the greatest benefit was observed in patients receiving sotagliflozin 400 mg (see Figure 37).

DKA and hypoglycemia were the only SAEs that were reported in more than 1 patient per sotagliflozin treatment arm in the T1D-CKD pooled Studies 309 and 310 population. Serious DKA occurred in 5% of patients for both the 200 mg and 400 mg doses and 3% of patients in the placebo group. In the sotagliflozin 200 mg and 400 mg groups, serious hypoglycemia occurred in 2% and 1% of patients, respectively. No patients in the placebo group experienced events of serious hypoglycemia.

Positively adjudicated severe hypoglycemia occurred at a lower rate in sotagliflozin-treated patients than in placebo-treated patients in pooled Studies 309 and 310. These results are meaningful given that patients with T1D report that their greatest safety concern is the risk for severe hypoglycemia episodes (Martyn-Nemeth 2017; Runge 2018), and sotagliflozin does not increase that risk.

Positively adjudicated DKA and severe hypoglycemia were further evaluated as key events of special interest (Table 4). Additional events of special interest are presented in Section 7.12.

Table 4: Overview of Key Events of Special Interest in the Pooled Studies 309 and 310 and in Study 312

	T1D-CKD Population					T1D Safety Population				
	Pooled Studies 309 and 310 52-Week			Study 312 24-Week		Pooled Studies 309 and 310 52-Week			Study 312 24-Week	
Proportion of Patients, n (%)	SOTA 200 mg N=85	SOTA 400 mg N=75	Placebo N=74	SOTA 400 mg N=114	Placebo N=110	SOTA 200 mg N=524	SOTA 400 mg N=525	Placebo N=526	SOTA 400 mg N=699	Placebo N=703
Positively Adjudicated Severe hypoglycemia	6 (7.1)	3 (4.0)	13 (17.6)	8 (7.0)	5 (4.5)	30 (5.7)	23 (4.4)	39 (7.4)	21 (3.0)	17 (2.4)
Total number of events	8	3	18	8	7	68	33	50	25	22
EAIR per 100 PYE	7.6	4.4	20.1	17.1	10.7	6.3	4.8	8.2	4	14
Positively Adjudicated Diabetic ketoacidosis	4 (4.7)	2 (2.7)	1 (1.4)	3 (2.6)	1 (0.9)	15 (2.9)	20 (3.8)	1 (0.2)	21 (3.0)	4 (0.6)
Total number of events	4	2	1	3	1	16	20	1	21	4
EAIR per 100 PYE	5.1	2.9	1.5	6.4	2.1	3.1	4.2	0.2	NC	NC

BG: blood glucose; CKD: chronic kidney disease; EAIR: exposure-adjusted incidence rate; PYE: patient-years of exposure; SOTA: sotagliflozin; T1D: type 1 diabetes mellitus

A rigorous system was implemented in the Phase 3 studies to screen for and identify all possible ketosis-related events, including metabolic acidosis and DKA events. In addition to data mining of events reported by Investigators, laboratory values, and study medical monitors, all suspect cases were then reviewed by an adjudication committee.

Positively adjudicated DKA occurred more frequently in the sotagliflozin treatment groups than in the placebo treatment groups. Overall, the rates of DKA in the

sotagliflozin-treated T1D-CKD population were not increased compared to rates of DKA in sotagliflozin-treated patients in the overall study population. Most DKA events had a known precipitant event such as illness or insulin dose interruption.

The risks of severe hypoglycemia and DKA can be managed with patient selection, education, and labeling. All patients will be educated on the signs and symptoms of ketoacidosis and when to seek medical attention. Measurement of ketone levels is a reliable method to confirm imminent DKA and allow earlier intervention prior to progression to a serious event (Kilpatrick 2022). Patients should check ketone levels with any acute illness, glucose >250 mg/dL for >2 hours, or ketosis symptoms regardless of glucose levels (Danne 2019). If ketoacidosis is suspected, sotagliflozin should be discontinued, and the patient should be promptly evaluated and treated with supplemental insulin, carbohydrates, and fluids. If the urine ketones are positive or blood BHB level >0.6 mmol/L, the patient should immediately contact their clinician. For a hyperglycemia episode, the patients will increase hydration, administer insulin, and eat carbohydrates until urine ketones or BHB level normalizes. These strategies, along with patient and healthcare provider materials, are further discussed in Section 7.13. Importantly, Lexicon will continue to work with the FDA, Investigators, professional groups, and patient advocacy organizations to evaluate and improve the mitigation strategies.

Additionally, patients with T1D-CKD have a lifetime of experience in managing diabetes. This also means that they have an established history of strong engagement in actively managing their diabetes. Education will align with best practices for mitigation of DKA, which include attention to total daily insulin and dose changes, understanding the factors that influence insulin levels, awareness of pump/accessory performance, and early recognition of signs and symptoms.

1.6 Benefit-Risk Summary

In the original NDA submission, the benefit-risk profile was assessed by FDA to be unfavorable in the entire cohort of patients with T1D. Our subgroup analyses have shown that the efficacy endpoint and safety profile results are the same in our T1D-CKD population as the overall T1D population. A critical difference when considering the “new” benefit-risk profile (in the studied population of patients with T1D and CKD) is that the benefit, ie, the impact and consequence of the improvement in glycemic control and reduction in risk of HF events, in this population with greater unmet need is more substantial. Therefore, the new benefit-risk profile is positive.

As demonstrated across multiple Phase 3 trials, sotagliflozin, a dual inhibitor of SGLT1 and SGLT2, provides benefits including improved A1C, body weight, time in range, and UACR. The statistically significant primary and key secondary glycemic endpoints shown in Studies 309, 310, and 312 allowed for evaluation of subgroups. Of the possible subgroups identified, patients with T1D and CKD were identified as the patient group where benefits observed in the overall population would be the most valuable and

clinically meaningful if also observed in the T1D-CKD subgroup. Even with a smaller sample size, patients with T1D-CKD receiving sotagliflozin achieved nominally significant and clinically meaningful improvement in A1C along with reductions in body weight that will help manage other risk factors in this population with a greater risk for disease progression.

Compared to the overall T1D population, patients with T1D and CKD are at a greater risk for CV and kidney disease progression and have higher all-cause mortality. Given the significant proportion of patients who do not meet glycemic control targets with insulin alone, there is clear unmet need for an adjunctive therapy to insulin that would enable individuals living with T1D and CKD to achieve recommended levels of glycemic control with the potential to minimize the long-term complications from uncontrolled diabetes. It is in the T1D-CKD population that the efficacy demonstrated in the Phase 3 program will provide the most profound near-term and long-term benefits with a comparable risk profile to that observed in the overall T1D population treated with sotagliflozin.

Results from the matched T2D-CKD population of the SCORED trial, in which a consistent benefit in long-term clinical outcomes was achieved, also may support the benefits demonstrated in the T1D-CKD population. In the matched T2D-CKD population of SCORED, consistent A1C lowering effects were observed along with reduced risk of major adverse CV events (MACE) and post-hoc review of kidney outcomes.

Due to underlying DKA risk in T1D, sotagliflozin is not intended for those who have inadequate control contributed to inadequate or inconsistent care, but for those patients where consistent management does not get them to the goal (ie, ≤7% A1C and 70% time in range). In these appropriately selected patients who are actively engaged with their care team in their diabetes management, the safety profile of sotagliflozin supports its use as an adjunct to insulin in a setting of education and monitoring for DKA. The overall safety profile of sotagliflozin in the T1D-CKD population is largely similar to the established safety profile of sotagliflozin in the approved indication. The greater time-in-target glucose range achieved by adding sotagliflozin was directly due to a meaningful reduction in hyperglycemia, without an increase in time below range. Thus, evidence supports that treatment with sotagliflozin, compared to placebo, achieves improved glycemic control without an increase in risk of severe hypoglycemia.

In the T1D-CKD population studied, there was an increased risk for DKA compared to placebo. There were no deaths associated with DKA in the T1D-CKD population. Appropriate patient selection, monitoring symptoms, and modifying patient behaviors to decrease the risk of DKA are key factors in managing DKA risk. In addition, measurement of ketone levels for suspected DKA events is a reliable method to confirm progression of ketosis that may lead to DKA, allowing for earlier intervention.

Overall, the totality of evidence establishes a favorable benefit-risk profile for sotagliflozin as an adjunct therapy to insulin for adults with T1D and CKD.

2 DISEASE BACKGROUND AND UNMET NEED IN PATIENTS WITH TYPE 1 DIABETES MELLITUS AND CHRONIC KIDNEY DISEASE

Summary

- Conservative estimates suggest 21% of adults with T1D are also affected by CKD, related to cumulative damage over many years of managing diabetes.
- Despite advances in insulin therapies, delivery methods, and management, 79% of patients with T1D do not achieve optimal glycemic control (A1C <7%).
- Without effective glycemic control, patients with T1D remain at an increased risk of complications compared to patients without T1D:
  - 10× greater risk of CV disease
  - 4× greater risk of HF hospitalization
  - 2–5× greater risk of all-cause mortality
  - 6× greater risk of ESKD
- CKD is an independent predictor of increased morbidity and mortality.
- Because of the increased risks of complications with a more progressed disease, patients with T1D-CKD have a greater need to control blood glucose within the target range than patients without CKD.
- Control of blood glucose, blood pressure, and lipids are associated with lower likelihood for disease progression or kidney function decline.
- Conversely, high A1C and increased albumin excretion rates result in more pronounced renal function decline.
- There is an urgent need for a new adjunct therapy to insulin that will improve glycemic control and could help diminish the long-term complications from uncontrolled diabetes without increasing the risk for hypoglycemia.
- Patients with a long history of managing diabetes, like patients with T1D-CKD, have significant experience with following sick day rules that address DKA risk factors and onset of early physical symptoms of ketosis and act accordingly. This knowledge can help lessen the risk for progression to life-threatening events.

2.1 Type 1 Diabetes Mellitus and Chronic Kidney Disease

2.1.1 Introduction

Despite advances in insulin therapies, delivery methods, and management, approximately 20% of patients with T1D achieve optimal glycemic control (Akturk 2023).

Without effective glycemic control, patients with T1D remain at risk of complications, including progression to ESKD, CV disease, and death.

CKD is a common progressive complication of T1D linked to the duration of disease. It has been shown that in patients with T1D, the risk of developing microalbuminuria, a risk factor for CKD progression, is associated with both poor A1C control and decreasing time in range (Beck 2019; Hahr and Molitch 2015; Perkins 2019; Shah 2024).

Per National Health and Nutrition Examination Survey (NHANES) data from 2015 through 2016 and 2017 through 2018, the weighted estimate of CKD in adults in the United States (US) with T1D was conservatively 21% (Rossing 2024). In fact, diabetic kidney disease remains the leading cause of CKD, rising in frequency in parallel to the epidemic of diabetes (United States Renal Data System 2022). Unfortunately, patients with T1D and CKD are at higher risk of kidney failure, HF, and atherosclerotic cardiovascular disease than patients with T1D without CKD, and therefore, have a greater need for risk factor management including glycemic control (Eliasson 2022).

2.1.1.1 Chronic Kidney Disease Nomenclature and KDIGO Definition

CKD can be classified and diagnosed using clinical measurements of eGFR and albuminuria (quantified using UACR). The KDIGO 2024 classification categories and the risk of CKD progression for each category are shown in Figure 9. The relative risks of complications, including progression of CKD to ESKD, CV disease, and mortality, are increased with both reduced eGFR and elevated UACR levels.

Figure 9: Current Chronic Kidney Disease Nomenclature Used by KDIGO and Prognosis of Chronic Kidney Disease

Prognosis of CKD by GFR and Albuminuria Categories[1,2]			Albuminuria Categories		
			Normal to Mild < 30 mg/g	Moderate 30-299 mg/g	Severe ≥ 300 mg/g
eGFR (ml/min/1.73 m^2)	Normal	≥ 90	Low Risk (82%)	Moderate Risk (7%)	High Risk (1%)
	Mild	60-89			
	Moderate	45-59	Moderate Risk (7%)	High Risk (2%)	Very High Risk (< 1%)
		30-44	High Risk (< 1%)		
	Severe	15-29	Very High Risk (< 1%)		
	Kidney failure	< 15			

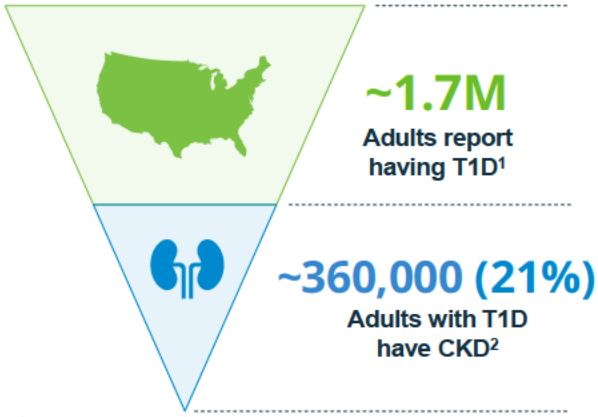
CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; KDIGO: Kidney Disease: Improving Global Outcomes; UACR: urine albumin to creatinine ratio
Adapted from KDIGO
1. American Diabetes Association Professional Practice Committee. Diabetes Care 2024b;
2. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. Kidney Int 2022

When defining and investigating CKD, it is important to consider both eGFR and albuminuria to identify all patients. To put the public health impact of albuminuria into context, in the US population, the percentage of patients with eGFR below 60 mL/min/1.73m^2 with or without albuminuria is 6.7%. However, another 3.8% of patients have albuminuria with eGFR of 60 mL/min/1.73m^2 or greater (Levey 2011). Therefore, considering only CKD patients with reduced eGFR as being at risk for comorbid conditions would exclude over one-third of the total patients at high risk.

2.1.2 Epidemiology

In the US, the estimated prevalence of T1D in adults aged 20 years or older was 1.7 million in 2021 (Centers for Disease Control and Prevention [CDC] National Diabetes Statistics Report 2024), and the prevalence of CKD (eGFR <60 mL/min/1.73m^2 and/or UACR ≥30 mg/g) is conservatively 21% of adults with T1D (Figure 10) (Rossing 2024). Epidemiological studies of diabetic kidney disease have estimated the overall residual (lifetime) risk of patients with T1D developing kidney disease is 30% (Alicic 2017; Hoogeveen 2022).

Figure 10: Prevalence of Adults with T1D and CKD



CDC: Centers for Disease Control and Prevention; CKD: chronic kidney disease; T1D: type 1 diabetes mellitus
1. CDC National Diabetes Statistics Report 2024; 2. Rossing 2024

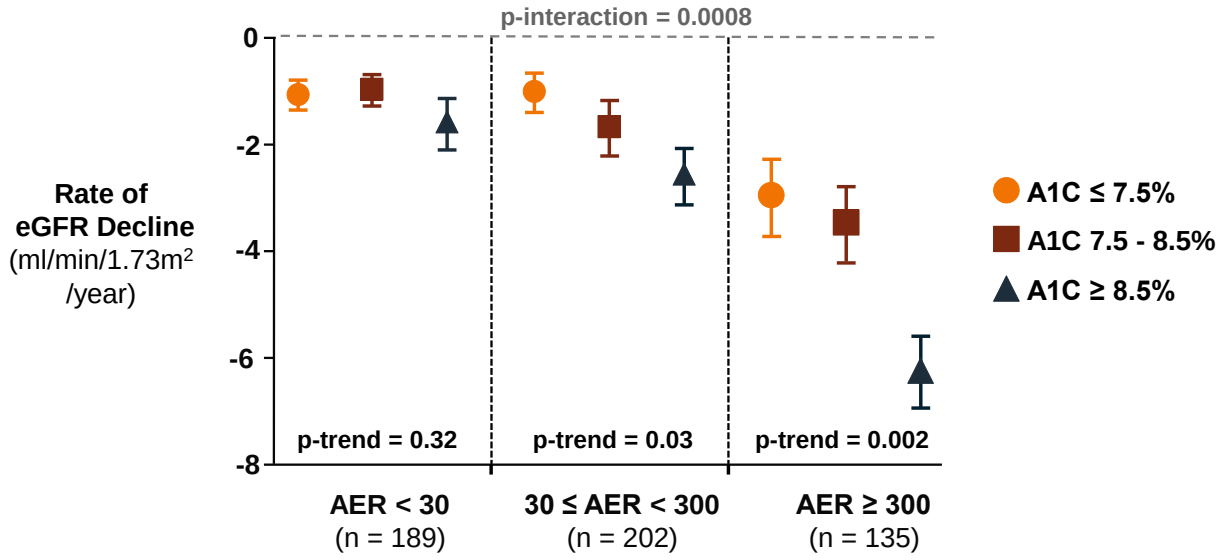
2.1.3 Complications and Patient Prognosis

Without effective glycemic control, patients with T1D remain at risk of complications, including progression to ESKD, CV disease, and mortality. Compared to the overall population, patients with T1D have a 10 times higher risk of CV disease (de Ferranti 2014), a 4 times greater risk of HF hospitalization (Rosengren 2015), a 2 to 5 times greater risk of all-cause mortality (Ruiz 2022), and a 6 times greater risk of progression to ESKD (United States Renal Data System 2023; Rosolowsky 2011). These risks are even greater for patients with T1D and CKD. Published data from the DCCT/Epidemiology of Diabetes Interventions and Complications [EDIC] trial establish that CKD in patients with T1D accelerates kidney disease progression (DCCT/EDIC Research Group 2011). CKD in T1D is associated with a greater mortality risk compared to those without CKD, and patients with both T1D and CKD are at a markedly increased risk of CV complications and premature death (Eliasson 2022; Miller 2019; Orchard 2010, Shah 2020; Sridhar 2024a).

2.1.4 Importance of Glycemic Control

Glycemic control has been shown to have benefits across multiple body systems in patients with diabetes, and poor glycemic control is an important and modifiable risk factor for attenuating kidney disease progression risk in adults with T1D and CKD (ElSayed 2023a; Perkins 2019; Shah 2024). In an analysis of the PERL data, elevated baseline A1C was associated with a greater rate of kidney function decline during the follow-up period in patients with T1D and CKD (Shah 2024). Greater kidney function decline was associated with greater baseline albuminuria (Figure 11).

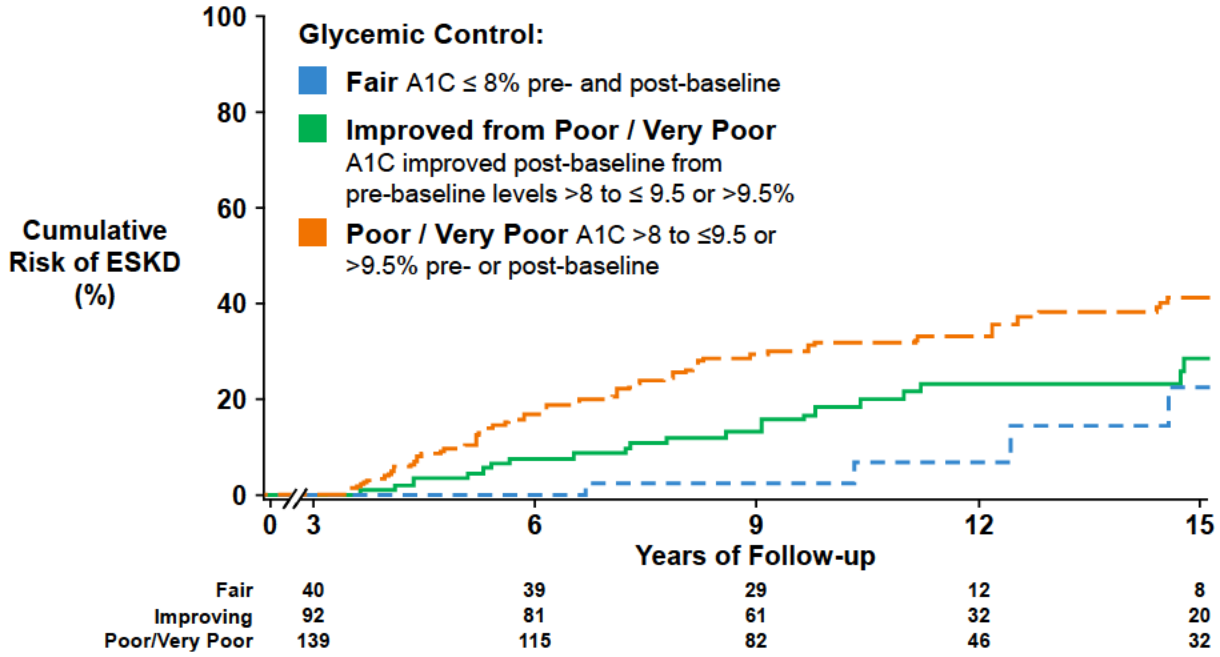
Figure 11: Rate of eGFR Decline by Albumin Excretion Rate and A1C Strata in Patients with T1D and CKD (Shah 2024)



A1C: hemoglobin A1C; AER: albumin excretion rate; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SE: standard error; T1D: type 1 diabetes mellitus
Data points represent beta estimates (±SE) from mixed-effects linear regression models.
Source: Shah 2024

Additionally, during the DCCT/EDIC trial, control of blood glucose, blood pressure, and lipids were all associated with a lower likelihood of progression and higher likelihood of regression of kidney disease and albuminuria in patients with T1D, including those whose disease had advanced to microalbuminuria (DCCT/EDIC Research Group 2011, 2014; de Boer 2011). In a long-term prospective cohort study of 349 patients from the Joslin Proteinuria Cohort, sustained improvements in A1C reduced eGFR loss and delayed the onset of ESKD in patients with T1D and proteinuria (Figure 12) (Skupien 2024). Specifically, a 1% absolute reduction in A1C corresponded to a 24% lower risk of ESKD, highlighting the importance of improving glucose control in patients with T1D and CKD. These results suggest that hyperglycemia contributes to both the onset of CKD and progression to ESKD. Thus, continued focus on glycemic control remains important in patients with established CKD.

Figure 12: Cumulative Risk of ESKD over Time by Glycemic Control Category in Patients with T1D-CKD (Skupien 2014)

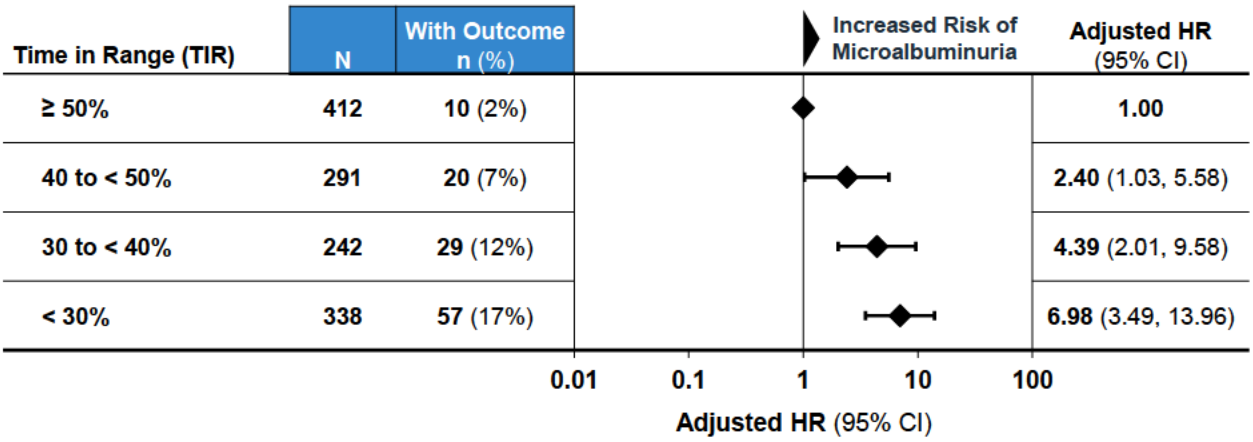


A1C: hemoglobin A1C; CKD: chronic kidney disease; ESKD: end-stage kidney disease; T1D: type 1 diabetes mellitus
Source: Skupien 2014

Reductions in A1C also accounted for nearly all the beneficial effects on retinopathy, nephropathy, and neuropathy endpoints in the DCCT (Lachin 2008). Furthermore, A1C was the major modifiable risk factor to lower the risk of initial and subsequent CV events in patients with T1D (Bebu 2020).

Evaluation of patients from the DCCT also showed that patients with tight glucose control (≥50% time in range [70–180 mg/dL] from SMBG) had lower risk for microvascular complications than patients with <50% time in range (Figure 13) (Beck 2019). Furthermore, for each 10% decrease in time in range, there was a 40% increased risk of progression to microalbuminuria. Thus, patients who spend more time outside their target glucose range are at increased risk for kidney damage.

Figure 13: Hazard Ratios for Development of Microalbuminuria According to Time in Range (Beck 2019)



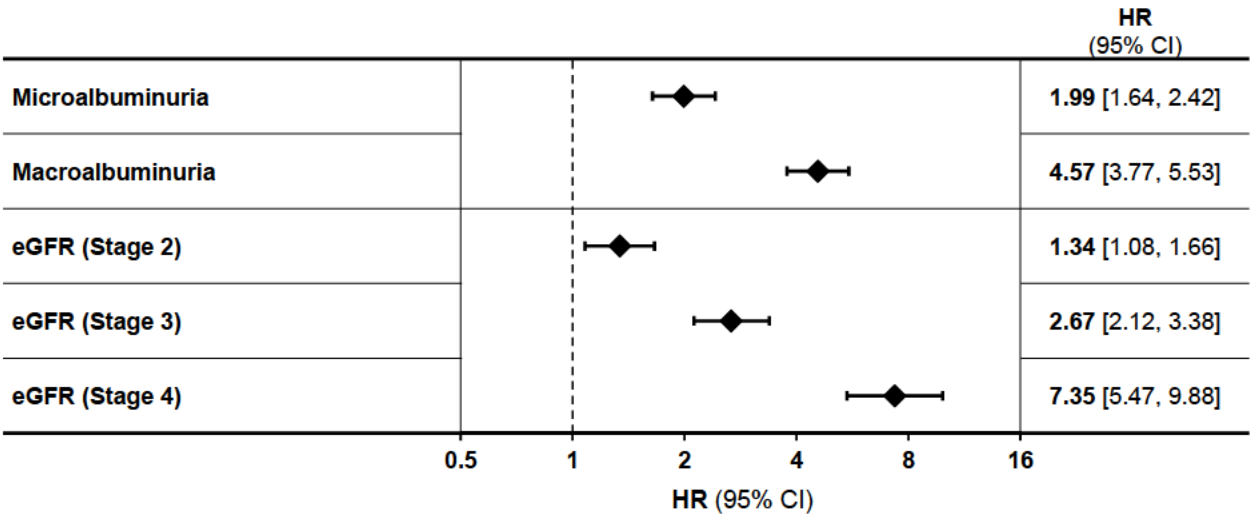
CI: confidence interval; HR: hazard ratio
Adapted from Beck 2019.

2.1.5 Risk Factors for Kidney Function Deterioration in Patients with T1D and CKD

Additional risk factors for CKD progression in T1D include high blood pressure and albuminuria. Treatment of hypertension slows kidney disease progression and coupled with glucose control can induce regression of proteinuria and slow kidney function decline (de Boer 2014).

Increases in albuminuria and development of microalbuminuria or macroalbuminuria are consistently associated with an increased risk of kidney and CV outcomes in people with T1D (Heerspink 2023; Rosengren 2015). Research and clinical experience provide evidence suggesting that albuminuria is a “progression promoter” of CKD (Hong 2021; Hovind 2001; Ioannou 2017). Results from more than 33,000 patients with T1D who were followed for approximately 8 years showed that increases in albuminuria and decreased eGFR were associated with a higher risk of hospitalization for HF (Figure 14) (Rosengren 2015). These findings support that both albuminuria and declines in eGFR are independent risk factors for HF in patients with T1D.

Figure 14: Hazard Ratios for Admission to Hospital for Heart Failure by Kidney Function in T1D Patients (Rosengren 2015)



CI: confidence interval; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; HR: hazard ratio; LDL: low-density lipoprotein; T1D: type 1 diabetes mellitus
Note: Adjusted for age, sex, diabetes duration, education, birth in Sweden, comorbidities, mean HDL and LDL, and treatment with lipid-lowering drugs.
Source: Rosengren 2015

2.2 Diabetes Management

2.2.1 Standard of Care

Exogenous insulin is required for survival and treatment in T1D. Treatment guidelines recommend that most adult patients with T1D maintain their A1C <7.0% to prevent long-term diabetic vascular complications. Intensive insulin therapy is delivered in the form of either multiple daily injections (MDI) of basal and prandial insulin or by continuous subcutaneous insulin infusion (CSII) (ADA Professional Practice Committee 2024a). There are also limitations of subcutaneous insulin replacement, and many patients experience excessive weight gain and peripheral insulin resistance, both of which are risk factors for hypertension and CV disease due to increased risk for incidence of hyperglycemia.

Current treatment approaches for T1D and CKD also emphasize lifestyle interventions; glucose, blood pressure, and lipid control; and use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for individuals with hypertension or proteinuria regardless of blood pressure (de Boer 2022; ElSayed 2023b).

Given the high prevalence and comorbid risks, there is a large unmet need for improved early diagnosis and therapeutic options to treat hyperglycemia and cardiorenal risk in people with T1D and CKD.

2.2.2 Evolution in Management of T1D with CKD

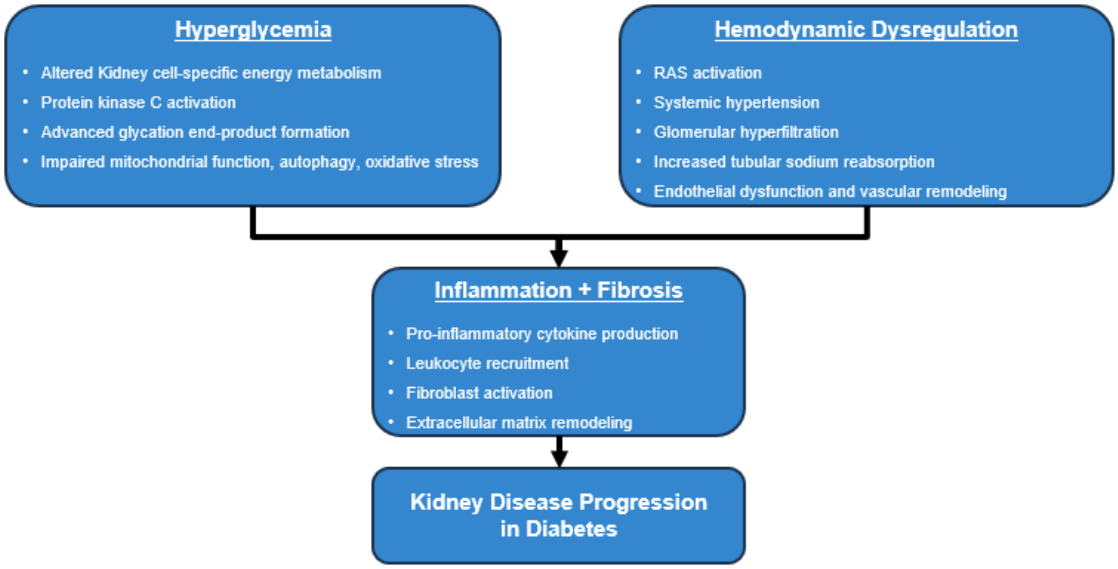
Treatment options are limited for patients with T1D, with only insulin and pramlintide as adjunct to insulin being approved for patients with T1D. Few pharmacologic agents are being developed to improve glycemic control in patients with T1D. Growing bodies of evidence from clinical trials of new therapeutic options, such as SGLT inhibitors, nonsteroidal mineralocorticoid receptor antagonists, and glucagon-like peptide receptor agonists (GLP-1 RAs), to treat hyperglycemia and/or reduce the risk of cardiorenal outcomes in patients with CKD with T2D or no diabetes have largely excluded people with T1D. The omission of people with T1D has resulted in a recent call to action to address the treatment gap in the T1D population (Heerspink 2023).

2.2.2.1 Utility of Type 2 Diabetes Data in Type 1 Diabetes Studies

Due to the unique challenges and relatively small population of people with T1D, data from larger studies of patients with T2D are extrapolated to apply to the T1D population, particularly as related to the complications associated with CKD and diabetes.

The pathophysiologic abnormalities that contribute to progression of CKD in people with diabetes are well established, and not dissimilar between T1D and T2D (DeFronzo 2021). Chronic hyperglycemia and hypertension are both contributing factors that lead to dysfunctional cellular processes causing altered tubuloglomerular feedback, renal hypoxia, lipotoxicity, podocyte injury, inflammation, mitochondrial dysfunction, and cause inflammation and renal fibrosis (Sridhar 2024b). Based in part on this information, the American Diabetes Association Standards of Care for CKD risk management carries a level A recommendation on control of both blood glucose and blood pressure to slow disease progression irrespective of T1D or T2D diabetes status (ADA Professional Practice Committee 2024b).

Figure 15: Mechanisms of Kidney Disease Progression in Diabetes, Regardless of Type



The mechanisms involved in the development of CV disease in T1D are similar to T2D (Manrique Acevedo 2024). CKD, hypercoagulation, dyslipidemia, endothelial dysfunction, and glycation end products from persistent hyperglycemia all contribute to increasing CV risk and disease progression. As the prevalence of obesity increases in the adult T1D population with at least 60% of adult patients being obese or overweight (Fang 2023), insulin resistance (a traditional hallmark feature in T2D) is becoming equally present in people with T1D (Duca 2016). Insulin resistance is itself an independent risk factor for the development of CV disease and MACEs (Fazio 2024; Gast 2012). It is also thought to be both causal HF and a result of HF-related events (Lopaschuk 2021). In a comprehensive review of mechanistic studies of insulin insensitivity in people with T1D, the authors concluded that available insulin therapies cannot fully reduce cardiometabolic risk due to increased insulin resistance tied to increased cardiometabolic risk (Gregory 2020).

As no randomized trials have been specifically conducted to assess CV event risk reduction in people with T1D, current clinical treatment guidelines for risk factor modification are extrapolated from data generated in large scale clinical trials in people with T2D (ElSayed 2023c).

These clinical treatment guidelines can be extrapolated directly to the sotagliflozin development program. The SCORED Phase 3 clinical trial enrolled 10,584 patients, all of whom had a history of type 2 diabetes (A1C ≥7%), CKD defined by eGFR 25 to 60 mL/min/1.73m^2, and additional CV risk factors (Bhatt 2021). In contrast, the T1D Phase 3 program of 3 studies enrolled 2980 total patients with T1D, with 458 of those

patients having both T1D and CKD (including those with microalbuminuria). Coexisting CKD in patients with T2D raises the risk of HF and ischemic events (Udell 2015), making the SCORED treatment group a high-risk patient population for both cardiovascular events and progression of kidney disease, and an important population to expand the available safety and efficacy profile of sotagliflozin in T1D and T2D.

2.2.3 Inadequacy of Insulin for Patients with T1D

Patients with T1D have limited therapeutic options to improve glycemic control and the majority of patients do not reach the recommended target of A1C <7%. Achieving A1C levels for optimal disease control with insulin treatment is challenging, in part because of the imperfect nature of subcutaneous insulin replacement. Despite many advances in insulin replacement therapy, it is estimated that approximately 20 of patients with T1D have an A1C <7% (Akturk 2023; Foster 2019, Pettus 2020).

During the FDA EMDAC Meeting held 24 May 2024, for the product insulin icodec, Advisory Committee members and FDA participants agreed that existing therapies for T1D are inadequate and that more effective and convenient ways to manage glucose are needed (FDA EMDAC 2024). As described in Section 2.1.4, patients not achieving A1C targets remain at a significantly greater risk of complications associated with their condition.

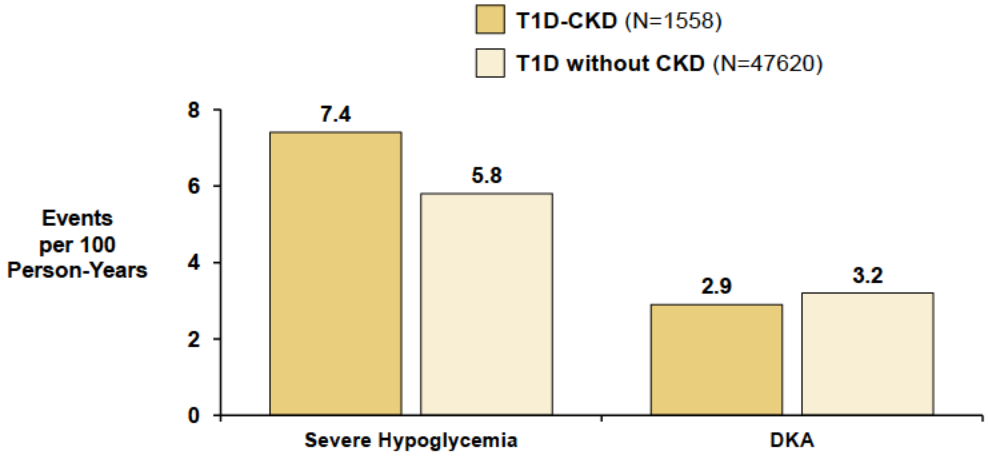
2.2.4 Additional Challenges for Patients with T1D in Reaching Their A1C Goals

Risks such as weight gain and hypoglycemia, the latter of which can be acutely life-threatening, are well-recognized risks associated with intensive insulin therapy. Excess weight gain, a known risk factor for CV disease, is frequently associated with insulin treatment and subsequent insulin resistance, potentially increasing the treatment and disease burden of T1D (Mottalib 2017; Russell-Jones 2007). The prevalence of patients with T1D in the US who are overweight (body mass index [BMI] of 25.0 to 29.9 kg/m^2) or obese (BMI ≥30 kg/m^2) has been increasing (Fang 2023) and may contribute to the high prevalence of hypertension and CV disease observed in this population (de Ferranti 2014; Maahs 2005). Thus, intensive insulin replacement therapy and the concomitant weight gain add to the already high burden of CV disease in the population of adult patients with T1D.

2.2.5 Safety Concerns for Patients with T1D

Both hypoglycemia and DKA are acute, serious, and potentially life-threatening complications of T1D and its treatment. Importantly, the risk of severe hypoglycemia and DKA is similar regardless of CKD status (Figure 16) (T1D Exchange 2024).

Figure 16: Event Rate of Severe Hypoglycemia and DKA by CKD Status



CKD: chronic kidney disease; DKA: diabetic ketoacidosis; T1D: type 1 diabetes mellitus
Source: T1D Exchange 2024

2.2.5.1 Severe Hypoglycemia

2.2.5.1.1 Risk Factors in Patients with T1D and CKD

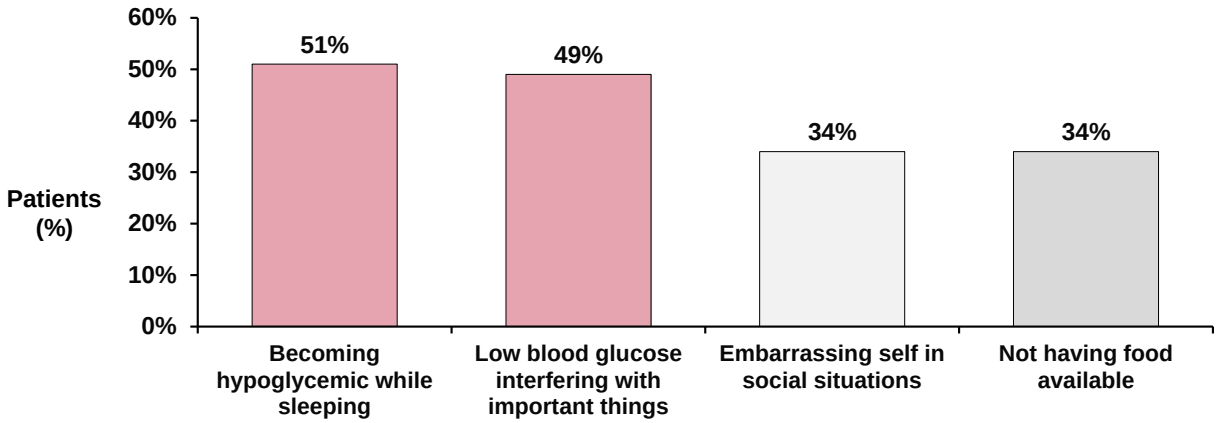
Risk factors for hypoglycemia in T1D include not eating enough, too much insulin, insulin pump errors, other diabetes medications (sulfonylureas, metformin), poor glucose control, prior hypoglycemia, impaired liver or kidney function, alcohol intake, increased strenuous activity, acute illnesses such as infection, and socioeconomic disadvantages (ADA 2019; McCoy 2020; Seaquist 2013). Severe hypoglycemia is any event that is characterized as altered mental and/or physical status requiring assistance to with correct (Seaquist 2013).

Outside of clinical studies, people with T1D experience severe hyperglycemia at an annual incidence of 3.3% to 13.5%, higher than that experienced by people with T2D due to the absolute requirement of exogenous insulin needed by people with T1D (Pettus 2019). Various studies have investigated the risk factors for severe hypoglycemia and have identified the type of diabetes, aging, insulin therapy, A1C values outside of a healthy range, long duration of diabetes, and poor cognitive function as risk factors (Matsuhisa 2019; Weinstock 2016). Having recurrent severe hypoglycemic events of ≥2 per year is the greatest most predictive risk factor for severe hypoglycemic events (Henriksen 2014). Severe hypoglycemia further precipitates hypoglycemia unawareness characterized by the diminished or lack of ability to recognize symptoms of hypoglycemia is estimated to occur in 25% of people with T1D (Weinstock 2016). In older adults with long-standing T1D, greater hypoglycemia unawareness as well as glucose variability are associated with an increased risk of severe hypoglycemia (Weinstock 2016), highlighting the need for therapies that improve glycemic control without further increasing events particularly in high-risk patients.

2.2.5.1.2 Patient Concerns Regarding Severe Hypoglycemia

Approximately 77% of patients reported having daily fears of hypoglycemia at least once during a 6-day study (Martyn-Nemeth 2017). When asked about their biggest concerns associated with hypoglycemia, roughly half of patients noted the fear of becoming hypoglycemic while sleeping or concerns about low blood glucose interfering with important daily activities (Figure 17). This fear has been shown to be a barrier to optimal glycemic control and can have negative impacts on quality of life for patients with T1D (Aschner 2010; Seaquist 2013).

Figure 17: Highest Worry Rankings among People with T1D



T1D: type 1 diabetes mellitus
Source: Martyn-Nemeth 2017

2.2.5.1.3 Management of Hypoglycemia

For hypoglycemia, regular glucose monitoring is critical. Patients should recognize early warning signs and take immediate action. Insulin dose adjustments, particularly during periods of increased activity or illness, are essential for preventing hypoglycemia.

2.2.5.2 Diabetic Ketoacidosis

2.2.5.2.1 Diagnosis

The ADA diagnostic criteria for DKA includes a triad of hyperglycemia with a plasma glucose >250 mg/dL; metabolic acidosis, with a pH of <7.30; a serum bicarbonate of <18 mmol/L; and elevated plasma and/or urinary ketones. This condition is classified as mild, moderate, or severe, depending on the extent of metabolic acidosis. The key diagnostic criterion is an elevation in the serum concentration of ketone bodies. In adults, a BHB concentration of 3.0 and 4.4 mmol/L corresponds to a bicarbonate of 18.0 and 15.0 mmol/L, respectively. Therefore, international guidelines have recommended a BHB concentration >3 mmol/L and a bicarbonate concentration <18 mmol/L as the prime diagnostic features of DKA (Galindo 2021). With the use of SGLT2 inhibitors and wider recognition of euglycemic DKA, a lower glucose threshold (>200 mg/dL) or prior history of diabetes can be considered for the diagnosis of DKA (Umpierrez 2024).

The symptoms of DKA can develop over several hours to several days and include nausea, vomiting, polyuria, and excessive thirst (Ehrmann 2020). These symptoms are considered prompts to follow “sick day rules” because illness caused by infection may be a precursor to DKA. Sick day rules include testing for ketones, stopping any medication that may increase risk of DKA (as advised by the prescribing physician), taking insulin, consuming carbohydrates, hydrating with electrolytes and water, and continuing to monitor ketones and glucose while illness and symptoms persist. If ketones do not return to normal within 4 hours, patients should contact their physician for next steps.

2.2.5.2.2 Risk Factors in Patients with T1D and CKD

Risk factors for DKA in T1D include acute illnesses such as infection, recent diabetes onset, insulin omission or reduction, insulin pump failure, alcohol intake, and increased strenuous activity (Peters 2015). Other nonmodifiable and modifiable risk factors that have been identified include socioeconomic disadvantages, female sex, previous DKA, poor glucose control, nonprescription drug use, quality of diabetes care, poor mental health, and somatic comorbidities (Ehrmann 2020). Drugs that affect carbohydrate metabolism, such as corticosteroids, thiazides, sympathomimetic agents, and pentamidine may precipitate DKA (Lizzo 2023).

SGLT2 inhibitor use has also been identified as a risk factor for DKA in patients with T1D or T2D. This risk is increased in those who require insulin therapy, most commonly patients with T1D (Peters 2015).

Among patients using pumps for insulin delivery, the most frequently reported cause of DKA include missed insulin doses and pump malfunctions, including insulin delivery interruptions caused by problems with the infusion set, subcutaneous catheter, or disconnections. These problems were common in the first 5 to 10 years after insulin pumps were introduced and led many patients to discontinue pump therapy. This trajectory prompted technological advances, such as hyperglycemic alerts and improved catheters as well as patient education and training on DKA, which has significantly reduced DKA risk (Garg 2018).

In retrospective database analyses, the incidence of DKA is increased with poor glycemic control (Foster 2019; Pettus 2019). Glycemic control appears to be better in older versus younger adults. The incidence of DKA appears to decline with advancing age in patients with T1D. Thus, better adherence to insulin therapy may contribute to the improved glycemic control and lower DKA incidence in older adults.

However, older adults have an increased incidence of CKD. CKD has been associated with a greater risk of metabolic acidosis, especially in those with severe kidney disease or ESKD. Some have postulated that DKA may also be increased in those with CKD. In a retrospective analysis, we evaluated the DKA rate in patients with T1D with and without CKD. This assumption of increased risk has not borne out over time. In current analyses of the Type 1 Diabetes Exchange Quality Index (T1DX-QI) database, the

proportions of patients experiencing DKA events are similar in patients with T1D regardless of their CKD status, despite marked differences in the age and demographic makeup of the two groups (T1DX-QI 2024). The event rates for DKA ranged from 2.6 to 2.1 per 100 person-years (T1DX-QI 2024). This overall rate is consistent with literature reports in older adults with annualized rates of DKA 2 to 3 events per 100 person-years (Ebrahimi 2022; Weinstock 2013).

2.2.5.2.3 Monitoring for and Mitigation of DKA Events

Patients need to be aware of the typical diagnostic criteria for DKA including elevated blood glucose levels, the presence of ketones, and metabolic acidosis. Atypical presentations, such as euglycemic DKA are also important for patient awareness, and ketones indicating onset of DKA will be present despite glucose levels that are lower than typically seen in DKA onset. For DKA, blood glucose monitoring is essential, and ketone testing, either through urine or blood, is necessary to confirm the presence of ketones when blood glucose levels are persistently high or when patients have typical DKA symptoms. Early detection through use of “sick day rules” and ketone testing, and prompt action through use of protocols that include insulin administration and hydration, are effective at preventing the progression of DKA.

2.3 Summary of Patient Unmet Medical Need

Adult patients with T1D and CKD have unmet needs of far greater consequence than those of patients with T1D alone. Those with T1D and CKD have needs related to the following:

- Direct consequences of T1D-related poor glycemic control (including hypoglycemia, hyperglycemia, and poor time in range)
- Direct consequences of impaired kidney function and/or micro- or macroalbuminuria
- Comorbidities of CKD, such as retinopathy, neuropathy, CV disease, and HF, which may increase in number, frequency, or severity with years of progression of CKD.

Despite advances in insulin therapy and glucose monitoring, most patients with T1D and CKD do not achieve glycemic control targets with insulin alone. There is an urgent need for a new adjunct therapy that will improve glycemic control and could help diminish the long-term complications from uncontrolled diabetes.

3 PRODUCT DESCRIPTION

Summary

- Sotagliflozin is an oral, once-daily, dual inhibitor of SGLT1 and SGLT2.
- Sotagliflozin is approved to reduce the risk of CV death, hospitalization for HF, and urgent HF visit in adults with HF or T2D, CKD, or other CV risk factors.
- Sotagliflozin is an adjunct to insulin therapy to improve glycemic control in adults with T1D and CKD.

3.1 Product Overview

Sotagliflozin, an oral antihyperglycemic drug that exerts its action by inhibiting both SGLT1 and SGLT2, was developed by Lexicon as an adjunct to insulin therapy to fill the unmet medical need in patients with T1D.

3.2 Regulatory Approvals

Sotagliflozin is currently approved to reduce the risk of CV death, hospitalization for HF, and urgent HF visit in adults with HF or T2D, CKD, or other CV risk factors[1] (see Section 4.1.2).

3.3 Proposed Supplemental Indication and Dosing

For this supplemental NDA, the proposed indication of sotagliflozin is as an adjunct to insulin therapy to improve glycemic control in adults with T1D and CKD.

The recommended dose is 200 mg once daily not more than one hour before the first meal of the day. In patients tolerating sotagliflozin 200 mg, the dose may be increased to 400 mg once daily for patients requiring additional glycemic control.

3.3.1 Intended Patient Population

Informed by KDIGO guidance, Lexicon defines the CKD patient population as patients with T1D with eGFR of 45 to <60 mL/min/1.73m^2 or eGFR ≥60 mL/min/1.73m^2 and UACR ≥30 mg/g.

The proposed CKD definition reflects the categories of patients with CKD with a moderate to much higher risk of kidney disease progression and for whom the KDIGO group recommends intervention be initiated to slow kidney function decline and reduce

[1] To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with: 1.) heart failure or 2.) type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors

the risk of ESKD (Figure 18) (de Boer 2022; KDIGO 2024). The KDIGO categories recognize albuminuria as a risk factor independent from and as important as eGFR on risk of kidney disease progression and other comorbidities.

Figure 18: Target Population

Prognosis of CKD by GFR and UACR Categories[1,2]			Urine Albumin to Creatinine Ratio (UACR) Categories		
			Normal to Mild UACR < 30 mg/g	**Moderate** UACR 30-299 mg/g	**Severe** UACR ≥ 300 mg/g
eGFR (ml/min/1.73m^2)	**Normal**	≥ 90	Low Risk (82%)	**Moderate Risk (7%)**	**High Risk (1%)**
	Mild	60-89			
	Moderate	45-59	**Moderate Risk (7%)**	**High Risk (2%)**	**Very High Risk (0.2%)**
		30-44	High Risk (< 1%)		
	Severe	15-29	Very High Risk (< 1%)		
	Kidney failure	< 15			

eGFR: estimated glomerular filtration rate; KDIGO: Kidney Disease: Improving Global Outcomes
Target population outlined in blue.
Source: KDIGO 2024; Lexicon data on file.

3.4 Mechanism of Action

Sotagliflozin is a dual inhibitor of SGLT1 and SGLT2. In patients with T1D, sotagliflozin improves glycemic control by both reducing glucose absorption in the intestine (SGLT1) and enhancing glucose excretion in the urine (SGLT2). Local intestinal inhibition of SGLT1, the major transporter for glucose absorption, delays and reduces glucose absorption in the proximal intestine, resulting in a blunting and delay of postprandial hyperglycemia.

SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, sotagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion (UGE).

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- INPEFA (sotagliflozin) was approved in 2023 to reduce the risk of CV death, hospitalization for HF, and urgent HF visit in adults with 1) HF or 2) T2D, CKD, and other CV risk factors.
- The original NDA for sotagliflozin in T1D was submitted in March 2018. A CRL was issued by the FDA, citing an unfavorable benefit-risk assessment for the proposed indication based on an increased risk for DKA.
- The NDA was resubmitted for sotagliflozin as adjunct to insulin therapy to improve glycemic control in adults with T1D and CKD.
    - Patients with T1D and CKD are a high-risk population with increased need for glycemic control.
- Primary efficacy and safety data are provided by three Phase 3 studies in patients with T1D (Studies 309, 310, and 312). Supportive data are provided from a Phase 3 CV outcomes study in patients with T2D and CKD (SCORED).

4.1 Regulatory History and Interactions for the Type 1 Diabetes Mellitus Indication

4.1.1 Type 1 Diabetes Mellitus Indication

The NDA for sotagliflozin was originally submitted for an indication as an adjunct to insulin for glycemic control in adults with T1D. During the NDA review period, an EMDAC meeting was held in January 2019 to discuss the application. There was broad acknowledgement that sotagliflozin was effective, demonstrated by the consistent evidence from three randomized controlled Phase 3 studies, which each showed statistically significant reductions in A1C and weight (ie, $p<0.001$ for A1C endpoints). There was no increase in severe hypoglycemia risk in patients treated with sotagliflozin; however, there was an increased occurrence of DKA compared to placebo. Based on this evidence, the committee rendered an 8-8 vote on the benefit-risk profile of sotagliflozin in the overall population of patients with T1D.

The FDA issued a CRL on 22 March 2019 based on the determination that the benefit-risk assessment of sotagliflozin was not favorable for the originally sought indication. Within the CRL and in other subsequent interactions between the FDA and Lexicon, including a Type A Meeting held in September 2021, Lexicon proposed defining a subpopulation in which the benefit-risk profile of sotagliflozin may be more favorable than that of the overall T1D population based on either an enhanced benefit or a reduction in DKA risk, which the FDA found to be a reasonable approach.

In light of this guidance, Lexicon resubmitted the NDA in June 2024 for sotagliflozin as adjunct to insulin therapy to improve glycemic control in adults with T1D and CKD. The NDA resubmission reflects a dedicated effort by Lexicon to understand and apply the feedback and guidance received from the Agency in the CRL and in subsequent interactions to identify a subpopulation of patients with T1D that has a favorable benefit-risk profile because of potential additional benefits and/or a lower risk of DKA. The resulting proposed indication in T1D-CKD patients reflects the subpopulation with the greatest unmet medical need. These patients will benefit the most from improved glycemic control with no greater risk than that seen in the overall T1D population. Further, sotagliflozin's robust risk reduction on long-term cardiovascular outcomes in a T2D-CKD population provides additional compelling supportive data that the T1D-CKD subpopulation may achieve even greater long-term benefits.

The CRL identified the following proposed path forward for the sotagliflozin program.

Table 5: Elements in Complete Response Letter FDA and Lexicon Actions to Address

Item in "Path Forward" Section of CRL	Action or Resolution
FDA: "You will need prospectively collected clinical data that provide substantial evidence of additional clinical benefits of sotagliflozin therapy other than HbA1c reduction and/or identify strategies to reduce the risk of DKA…"	FDA later agreed that Lexicon's proposal for the NDA resubmission to rely on analyses from subgroups of participants from Studies 309, 310, 312, and SCORED was reasonable.
FDA: "Identify and evaluate the effect of sotagliflozin on other efficacy outcomes beyond HbA1c reduction, and demonstrate how these endpoints translate into a clinically meaningful benefit through assessments that directly measure how a patient feels, functions, or survives…"	Lexicon has evaluated body weight, time in range, and the composite risk of CV death, hospitalization for heart failure and urgent visit for heart failure and has included these results in the benefit-risk assessment.
FDA: "Monitoring scheme: Clarify the role of ketone monitoring in mitigating the risk of DKA. For example, demonstrate whether ketone monitoring is meaningfully effective in mitigating DKA risk and provide evidence to support any particular testing regimen (urine/blood, devices, frequencies) that you will employ."	The ADA-EASD Consensus Report on the management of T1D in adults (Holt 2022) recommends CGM and blood ketone measurement during periods of illness or hyperglycemia to facilitate the management of the hyperglycemia and prevent and/or treat DKA. The risk management plan included in the NDA resubmission describes measures for monitoring and management consistent with this Consensus Report.
FDA: "Patient and Prescriber interventions: As the risk of DKA is heightened in the setting of inadequate insulin dosing, establish evidence-based instructions to patients and prescribers on how to adequately adjust insulin when adding sotagliflozin to the treatment regimen without significantly increasing the risk for DKA, i.e., establish criteria for 'adequate insulinization' and provide guidance as to when sotagliflozin should be reduced or stopped due to 'inadequate insulinization'. Also, establish evidence-based	The recent publication of "Hyperglycemic Crises in Adults With Diabetes: A Consensus Report" (Umpierrez 2024) provides for the measurement of ketones (β-Hydroxybutyrate concentration ≥3.0 mmol/L; direct measurement from venous or capillary blood preferred) as one of three important criteria for the diagnosis of DKA. The same report describes treatment pathways for DKA as well as a framework for follow-up treatment after a DKA event. Lexicon has included guidance

Item in "Path Forward" Section of CRL	Action or Resolution
instructions to patients and prescribers on how to adequately adjust insulin and sotagliflozin dosing during discrete clinical situations that may predispose the patient to DKA…"	and instructions in the draft labeling text and draft patients' instructions (MedGuide) which are consistent with the principles of this report and that of the 2022 ADA-EASD Report.
FDA: "Modified Dosing: Evaluate whether lower dosing regimens will result in a lower rate of DKA while still conferring a clinical benefit. You might also consider dose titration to minimize concurrent insulin dose reduction."	Lexicon has reexamined Phase 2 data and analyses where a 75 mg sotagliflozin dose was evaluated, and A1C efficacy was not demonstrated. Lexicon determined that a new study at dose levels below 200 mg would not produce meaningful or useful results, and therefore Lexicon has not conducted such a study.
FDA: "Patient Selection: Identify a group of patients for whom the benefit of sotagliflozin may outweigh the risks and prospectively study these patients employing your proposed monitoring schemes and/or dosing regimens to establish a favorable benefit-risk profile associated with sotagliflozin therapy."	Lexicon has addressed patient selection in the Risk Management Plan of the NDA resubmission, which includes patient selection guidance to healthcare providers and a presentation of currently used (in 2024) structured clinical protocols for DKA risk management and treatment, including those described in the International Consensus on Risk Management of Diabetic Ketoacidosis (Danne 2019)

A1C: hemoglobin A1C; ADA: American Diabetes Association; CGM: continuous glucose monitoring: CRL: Complete Response Letter; CV: cardiovascular; DKA: diabetic ketoacidosis; EASD: European Association for the Study of Diabetes; FDA: Food and Drug Administration; NDA: New Drug Application; T1D: type 1 diabetes mellitus

During follow-up discussions with the FDA (Table 6), Lexicon and the FDA reached alignment that a positive benefit-risk profile could be accomplished by identifying a population with either a) additional benefit and/or b) with diminished DKA risk.

Table 6: Key Regulatory Milestones for NDA 210934 (T1D-CKD)

Date	Regulatory Milestone
Key Early Milestones for NDA 210934 (T1D: glycemic control)	
22 March 2019	Complete Response Letter (CRL)
05 July 2019	End of Review Meeting
14 September 2021	Type A Meeting
13 October 2021	Type A Meeting
21 December 2021	General Advice Letter to Lexicon
Key Later Milestones for NDA 210934 (T1D-CKD: glycemic control)	
04 December 2023	Type A Meeting
01 March 2024	Type A Meeting
19 April 2024	Type A Meeting - Written Responses Only
20 June 2024	NDA 210934 Resubmission
31 October 2024	EMDAC Meeting (scheduled)
20 December 2024	NDA 210934 PDUFA Goal Date

CKD: chronic kidney disease; EMDAC: Endocrinologic and Metabolic Drugs Advisory Committee; NDA: New Drug Application; PDUFA: Prescription Drug User Fee Act; T1D: type 1 diabetes mellitus

Table 7: Key Discussion Points and FDA Direction / Decisions – Type A Meetings (Held December 2023, March 2024, April 2024)

Date	Item
03 January 2024	Lexicon Question: Does the Agency agree that a revised indication for adults with T1D and CKD as an adjunct to insulin therapy to improve glycemic control would be acceptable for review, anchored by the results of Studies 309, 310 and 312 and the additional analyses of subgroup data from these studies, and supported by data from the sotagliflozin Phase 3 T2D and HF programs? FDA Response: "…We would be willing to review a resubmission of NDA 210934 with a revised indication in a subpopulation of patients with T1DM that you believe has a favorable benefit risk assessment because of potential additional benefits and/or a lower risk of diabetic ketoacidosis (DKA)…"
01 March 2024	FDA Comments: "The rationale you have provided for your revised glycemic control indication (i.e., improved glycemic control may confer greater benefit to patients with T1D and CKD than to patients with T1D and normal renal function) is reasonable… We are uncertain that there is evidence that sotagliflozin 200 mg will provide clinically meaningful A1C reduction in CKD patients as defined in your proposal (at the time, Lexicon definition of CKD was {eGFR ≥ 30 and < 60 ml/min/1.72m^2} OR {eGFR ≥ 30 ml/min/1.72m^2 and UACR ≥ 30 mg/g}). If a pooled analysis of subjects from Studies 309 and 310 with eGFR ≥ 60 ml/min/1.72m^2 and UACR ≥ 30 mg/g demonstrates evidence of an effect of sotagliflozin 200 mg vs placebo on A1C, you might consider proposing a revised glycemic control indication in patients with T1DM, UACR ≥ 30 mg/g, and eGFR > 60 ml/min/1.72m^2. Your rationale regarding the extrapolation of safety (e.g., based on PK/PD arguments) from your T2DM studies would remain review issues for an NDA resubmission…"
19 April 2024	FDA Questions and Requests: "What is the basis for selecting the to be marketed dose and dose regimen for the new population? What are the overall exposure-response relationships for efficacy and diabetic ketoacidosis (DKA) (and biomarkers predictive for DKA risk)? How is the exposure-response relationships for efficacy and DKA affected by renal function (i.e., how does the exposure-response relationship for safety and efficacy compare between the original population, and the new proposed population)." Lexicon Actions: A new Population PK study was conducted in order to answer the FDA questions. Modeling, exposure-response analyses and stochastic simulations provided results very similar to those observed in the pivotal Phase 3 studies, with no remarkable differences noted between the results for the original population and those for the new proposed population. Module 2.7.2 Summary of Clinical Pharmacology was updated to include the results of the new Population PK study.

A1C: hemoglobin A1C; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; FDA: Food and Drug Administration; HF: heart failure; PD: pharmacodynamic; PK: pharmacokinetic; T1D: type 1 diabetes mellitus; T2D: type 2 diabetes mellitus; UACR: urine albumin to creatinine ratio

While these collaborative discussions were ongoing with the FDA, Lexicon was also completing work on a large cardiovascular outcomes program, generating a robust data set in T2D-CKD patients that would contribute to the approval of sotagliflozin for a HF indication and further reinforce the proposal to target the T1D-CKD subpopulation.

Table 8: Key Regulatory Milestones for NDA 216203 (Heart Failure)

Date	Key Milestones for NDA 216203 (heart failure)
02 March 2020	Type C Meeting
25 March 2020	Termination of SCORED and SOLOIST Clinical Studies
11 January 2021	Type C Meeting
14 July 2021	Type B Pre-NDA Meeting - Written Responses Only
29 December 2021	NDA 216203 (INPEFA - Heart Failure) Submission
28 February 2022	NDA 216203 (INPEFA - Heart Failure) Voluntary Withdrawal
26 May 2022	NDA 216203 (INPEFA - Heart Failure) Resubmission
26 May 2023	NDA 216203 (INPEFA - Heart Failure) Action Letter – NDA Approved

NDA: New Drug Application

4.1.2 Approved Indications

Sotagliflozin was approved in the US on 26 May 2023 for a HF indication[2] and has been marketed in the US since June 2023 under the proprietary name INPEFA. The approval of sotagliflozin for the HF indication is relevant to patients with T1D and to the NDA resubmission. Patients with T1D and T2D often experience comorbid CKD, which is a major risk factor for macrovascular complications such as HF. Therefore, cardiorenal benefits can be reasonably extrapolated to T1D and CKD from the SCORED study in patients with T2D and CKD per the INPEFA label for the HF indication.

The clinical efficacy results supporting this indication are found in Section 6.6.2.

4.2 Sotagliflozin T1D Clinical Development Program

The Phase 2 and 3 clinical development program in T1D includes a total of 2175 patients with T1D who received sotagliflozin, of whom 93 received the 75 mg dose, 631 received the 200 mg dose, and 1452 received the 400 mg dose. Additionally, in single- and multiple-dose Phase 1 studies, 409 individuals were treated with sotagliflozin across multiple dose levels.

Three Phase 3 studies (Studies 309, 310, and 312) are the primary sources of efficacy data and evaluations supporting this indication (Table 9). A subset of patients with T1D

[2] To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with: 1.) heart failure or 2.) type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors

and CKD (defined as baseline eGFR of 45 to <60 mL/min/1.73m^2 or an eGFR ≥60 mL/min/1.73m^2 with UACR ≥30 mg/g) were identified in these studies as a population who will gain benefit from improved glycemic control compared to the overall T1D population. The additional benefit is derived from the reduction of risk or rate of kidney disease progression and due to the reduction in risk or severity of CV comorbidities.

Efficacy analyses from Studies 309 and 310 were pooled due to their identical 52-week design. Studies 309 and 310 included intensive insulin optimization and evaluated sotagliflozin 200 mg versus 400 mg versus placebo. Study 312 was 24 weeks in duration without insulin optimization (but Investigators were instructed to adjust insulin to achieve glycemic targets), evaluated 400 mg versus placebo, conducted globally, and analyzed and presented individually.

Additional supportive efficacy results are included from the SCORED study, which was conducted in patients with T2D, CKD, and additional CV risk factors. Analyses were conducted in patients who matched the definition of CKD in the T1D-CKD population. The mechanisms of action of sotagliflozin on UGE and blunting and delaying postprandial glucose (PPG) excursion are similarly present in patients with T1D and T2D. Therefore, the efficacy results in a matching T2D-CKD cohort coupled with those from the T1D-CKD cohort provide a robust dataset to establish substantial evidence of effectiveness in the CKD setting.

Table 9: Overview of Phase 3 Studies Supporting T1D-CKD Indication

Study	Design	Dosing Schema and Design	Patient Population	Randomized Patients	Primary Endpoint
LX4211.309[a] (Study 309)	Phase 3, Placebo-controlled Study in T1D with Optimized Insulin Therapy	200 mg or 400 mg sotagliflozin or placebo qd for 52 weeks (24-week Core Treatment; 28-week LTE)	T1D North America	793 total; 116 with T1D-CKD	Change in A1C at 24 weeks
LX4211.310[a] (Study 310)	Phase 3, Placebo-controlled Study in T1D with Optimized Insulin Therapy	200 mg or 400 mg sotagliflozin or placeboqd for 52 weeks (24-week Core Treatment; 28-week LTE)	T1D Europe & Israel	782 total; 118 with T1D-CKD	Change in A1C at 24 weeks
LX4211.312[b] (Study 312)	Phase 3, Placebo-controlled Study to Evaluate the Net Clinical Benefit[c] of Sotagliflozin as Adjunct to Insulin Therapy in T1D	400 mg sotagliflozin or placebo qd for 24 weeks	T1D Worldwide	1405 total; 224 with T1D-CKD	Proportion of patients with A1C <7.0% and no episode of SH and no episode of DKA from randomization to Week 24
SCORED	Phase 3, Randomized, Double-blind, Placebo-controlled	200 mg sotagliflozin titrated to 400 mg	T2D Worldwide	10,584 total; 4959 with T2D-CKD	Total occurrences (first and potentially subsequent) after randomization of CV death, hospitalization for heart failure, and urgent visit for heart failure

A1C: hemoglobin A1C; CKD: chronic kidney disease; CV: cardiovascular; DKA: diabetic ketoacidosis; LTE: long-term extension; qd: once daily; SH: severe hypoglycemia; T1D: type 1 diabetes mellitus; T2D: type 2 diabetes mellitus
a For Studies 309 and 310, insulin therapy was optimized prior to randomization.
b For Study 312, insulin was not optimized prior to randomization.
c Net benefit was defined as the proportion of patients with A1C <7.0% and no episode of SH and no episode of DKA from randomization to Week 24

5 CLINICAL PHARMACOLOGY

Summary

- Exposure parameters of sotagliflozin increased in a dose proportional manner over the suggested therapeutic dose range.
- Sotagliflozin has shown dose-dependent effects consistent with SGLT1 and SGLT2 inhibition at the 200 mg and 400 mg doses.
- The proposed dosing for patients with T1D-CKD matches the approved dosing for the current HF indication.

5.1 Overview

Sotagliflozin pharmacology has been evaluated in 51 studies. Of those, 28 were Phase 1 studies in nondiabetic healthy volunteers, patients with T2D, or in special populations and these included dose-finding, food-effect, bioavailability, bioequivalence, drug-interaction, pharmacokinetic (PK), pharmacodynamic (PD), hepatic impairment, and renal impairment studies. A total of 6 studies were conducted in patients with T1D who had inadequate glycemic control and 13 studies were conducted in patients with T2D, 2 of which were CV outcome studies.

A population PK model was developed and used to characterize the population PK of sotagliflozin, and to determine the effects of covariates including sex, age, body weight, and eGFR on the PK of sotagliflozin. Additionally, the population PK model was used to simulate the impact of varying degrees of renal impairment on the PK profile of sotagliflozin.

5.2 Pharmacokinetics

Sotagliflozin is highly bound to plasma proteins (>93% bound) and is rapidly glucuronidated, mainly by UGT1A9. The predominant metabolite in the plasma was M19, which did not show pharmacological activity compared to the parent compound.

Exposure parameters of sotagliflozin, maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC), increased in a dose proportional manner over the suggested therapeutic dose range between 200 mg and 400 mg. Sotagliflozin median time to maximum concentration values ranged from 2.5 to 4 hours following administration of multiple doses.

When sotagliflozin tablets were administered with a high-caloric breakfast compared to fasting conditions, plasma exposure to sotagliflozin as measured by C_{max} and $AUC_{0\text{-}inf}$ increased by 149% and 50%, respectively. Multiple doses of sotagliflozin 400 mg given immediately before breakfast, 30 minutes prior to breakfast, and 1 hour before breakfast

in healthy individuals showed a consistent effect of sotagliflozin on UGE, insulin, and PPG across all dose schedules. It is recommended that sotagliflozin be taken not more than one hour before the first meal of the day.

Accumulation was observed after administration of multiple doses, with steady-state generally achieved by Day 5.

Following oral administration mean terminal half-life for sotagliflozin ranged from 20.9 to 35.0 hours. The main route of elimination was through the urine.

5.3 Pharmacodynamics

Sotagliflozin has shown dose-dependent effects consistent with SGLT1 and SGLT2 inhibition at the 200 mg and 400 mg doses. SGLT1 inhibition resulted in reduced PPG, increases in GLP-1 and peptide YY, and reduction in FPG. Sotagliflozin increases UGE, consistent with SGLT2 inhibition.

In a thorough corrected QC interval (QTc) study, supratherapeutic doses of sotagliflozin (800 mg and 2000 mg) did not cause prolongation of the QTcI in excess of the threshold of 10 ms stated by the International Council for Harmonisation E14 guidance.

5.4 Drug-Drug Interactions

Several studies were conducted to evaluate potential interaction between sotagliflozin and drugs commonly used in the T1D population. Results from these studies indicated no clinically relevant interaction between sotagliflozin and metformin, rosuvastatin (a sensitive breast cancer resistance protein substrate), Ortho-Cyclen® (an oral contraceptive containing norgestimate and ethinyl estradiol), and mefenamic acid (a UGT1A9 inhibitor). Therapeutic doses of 200 and 400 mg sotagliflozin are not expected to cause clinically relevant interactions with substrates of CYP3A4 and CYP2D6.

Coadministration of a multiple-dosing regimen of rifampicin, an inducer of various UGT and CYP metabolizing enzymes, with a single dose of 400 mg sotagliflozin resulted in a decrease in exposure to sotagliflozin, which may decrease efficacy. It is recommended that if an inducer of UGT (eg, rifampin, phenytoin, phenobarbital, ritonavir) must be coadministered with sotagliflozin, frequent monitoring of glucose levels should be considered.

Sotagliflozin was identified as a weak P-glycoprotein inhibitor and concurrent administration of sotagliflozin and digoxin may result in the elevation of digoxin levels. It is recommended that patients taking sotagliflozin with concomitant digoxin should be monitored appropriately.

Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations. Serum lithium concentration should be monitored more frequently during sotagliflozin initiation and dosage changes.

5.5 Population Pharmacokinetic Model and Exposure Response Analysis

For the overall T1D population, a population PK model was developed and used to characterize the population PK of sotagliflozin, and to determine the effects of covariates (sex, age, body weight, eGFR) on the PK of sotagliflozin. Population exposure-response (E-R) models were used to characterize the relationship between sotagliflozin exposure and A1C and body weight.

In the overall T1D population, the apparent oral clearance was shown to increase in an almost proportional manner with body weight. Apparent clearance of sotagliflozin decreased with decreasing renal function. The E-R models demonstrated that increases in sotagliflozin exposures were associated with improvements in A1C and body weight.

For the new analysis, the previously developed PK and E-R (A1C, weight, and adjudicated severe hypoglycemic) datasets were leveraged for the purposes of comparing the T1D-CKD population to the original T1D population. Additional E-R models were developed to investigate the relationship between sotagliflozin exposure and BHB and urinary glucose-to-creatinine ratio (UGCR).

The previously developed population PK model well characterized the PK of sotagliflozin in the CKD population and the original T1D population. The distributions of sotagliflozin exposure were similar in both populations. For the efficacy endpoints A1C and body weight, as sotagliflozin exposure increased, there was a similar decrease in the mean A1C response and decrease in body weight for both the CKD and the non-CKD cohorts. Similarly, the E-R model for UGCR demonstrated that as sotagliflozin exposure increased, change from baseline in UGCR increased, and this response was similar in the CKD and non-CKD cohorts. For the safety endpoints, there was a flat E-R relationship for adjudicated severe hypoglycemia across the range of steady-state sotagliflozin exposures in both CKD and non-CKD cohorts. In the CKD cohort, there was a higher occurrence of adjudicated severe hypoglycemia in the patients administered placebo when compared to those who received sotagliflozin. E-R response analysis of BHB indicated that there was a slight trend for an increase in BHB with increasing sotagliflozin exposure. BHB responses over the range of sotagliflozin exposures were similar in both CKD and non-CKD cohorts.

Stochastic simulations were performed to understand the range of expected efficacy and safety outcomes associated with the proposed daily dosing regimens (200 mg and 400 mg) in the CKD population as compared to the original T1D population. Stochastic simulations of the proposed 200 and 400 mg daily sotagliflozin dosing regimens in virtual patients with CKD and virtual patients representing the original T1D population revealed similar distributions of A1C and body weight reductions for each dose at Weeks 24 and 52.

5.6 Dose Justification

The recommended dose is 200 mg, administered orally, once daily. This may be increased to 400 mg for patients requiring additional glycemic control.

Results from the population PK modeling in the overall T1D population, patients with eGFR ≥60 mL/min/1.73m^2 and <90 mL/min/1.73m^2 and eGFR ≥45 mL/min/1.73m^2 and <60 mL/min/1.73m^2 are simulated to have similar exposures with 1.52- and 1.54-fold higher sotagliflozin AUCs compared to individuals with normal renal function, indicating that CKD status (eGFR ≥45 and <90 mL/min/1.73m^2) did not result in clinically relevant increases in sotagliflozin exposure. It should be noted that the distributions of sotagliflozin exposure were similar CKD and the original T1D populations.

Population modeling and stochastic simulations have demonstrated that sotagliflozin exposures following administration of 400 mg were higher than those of 200 mg, as expected. Patients administered sotagliflozin (200 mg and 400 mg dose) demonstrated greater reduction in A1C when compared to those on placebo. Similarly, sotagliflozin administration was associated with a greater reduction in body weight when compared to that of placebo. Patients administered the 400 mg dose had greater increases in UGCR and more reduction in body weight compared to 200 mg dose.

It should also be noted that the proposed dosing for patients with T1D-CKD matches the approved dosing for the current indication of HF.

Taken together, the data support and justify the appropriateness of the 200 mg and 400 mg sotagliflozin daily regimens in patients with T1D and CKD.

6 CLINICAL EFFICACY

Summary

- The statistically significant primary and secondary glycemic endpoints in the three Phase 3 studies allow selection of a T1D-CKD population who have a greater unmet medical need and will benefit the most from improved glycemic control with no greater risk compared to overall T1D population.
- In the T1D-CKD population, both doses of sotagliflozin demonstrated nominally significant and clinically meaningful reductions in A1C (%) from baseline compared to placebo at 24 weeks.
    - Pooled Studies 309 and 310: least squares (LS) mean difference from placebo at Week 24 was -0.34% for 200 mg (p=0.002) and -0.31% for 400 mg doses (p=0.006), respectively.
    - Study 312: LS mean difference from placebo at Week 24 was -0.45% for 400 mg (p<0.001).
- Nominally significant reductions in body weight from baseline to Week 24 were achieved with both sotagliflozin doses compared to placebo in the Pooled 309 and 310 T1D-CKD population as well as Study 312 T1D-CKD population.
- In the Phase 3 SCORED study overall population of patients with T2D, sotagliflozin improved long-term CV outcomes, including HF and MACE, and kidney-related outcomes.
- The matched T2D-CKD population of SCORED demonstrated comparable glycemic efficacy with sotagliflozin to that in the present T1D-CKD population and also provided evidence of sustained efficacy over a longer time period.

6.1 Study 309, 310, and 312 Phase 3 Study Design

6.1.1 Overview

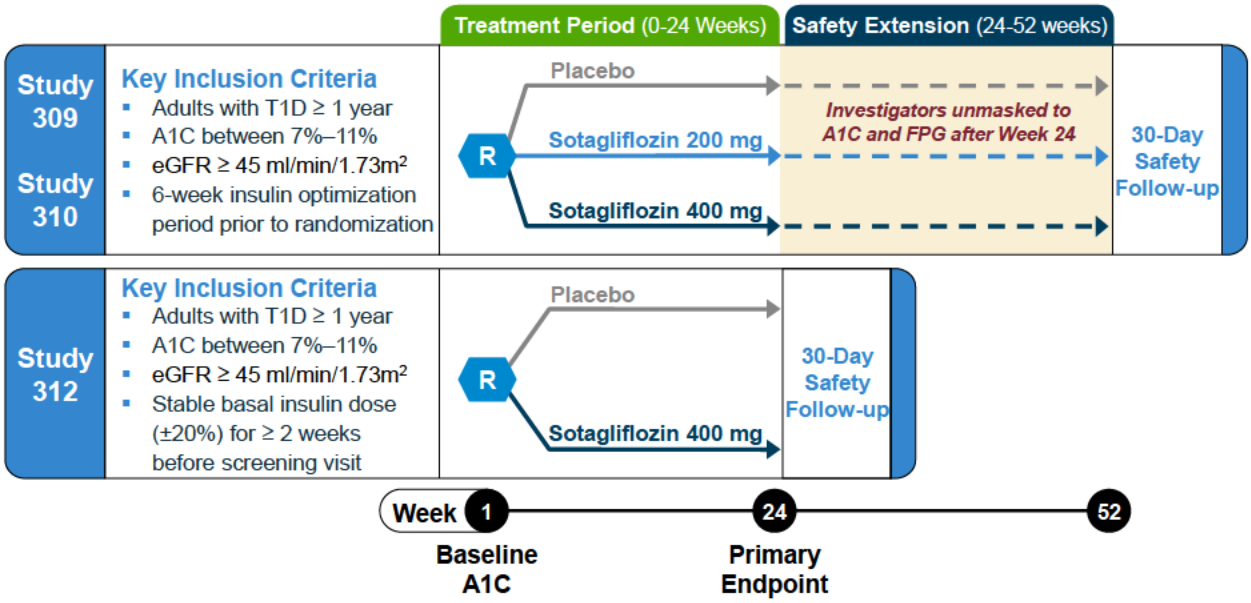
Studies 309 and 310 were identically designed Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies to evaluate sotagliflozin as an adjunct to optimized insulin therapy in adults with T1D who had inadequate glycemic control with insulin therapy at the time of screening (A1C between 7% and 11%) and an eGFR ≥45 mL/min/1.73m^2. Eligible patients were randomized to receive sotagliflozin 200 mg, sotagliflozin 400 mg, or placebo. The total duration of the study was up to 64 weeks, including a 6-week insulin optimization period prior to randomization, a 24-week double-blind treatment period, and a 28-week double-blind safety extension (Figure 19).

Study 312 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of sotagliflozin as an adjunct to insulin in patients with T1D. The total duration of the study was up to 30 weeks, including 24 weeks of double-blind treatment. Enrollment criteria were similar to that of Studies 309 and 310.

Studies 309 and 310 included an insulin optimization period beginning 6 weeks before randomization, which continued throughout the study, and a 2-week single-blind placebo run-in period to allow for diabetes education; optimization of compliance with diet, exercise, and the insulin regimen; and stabilization of metabolic parameters. Investigators were to adjust insulin dose to meet fasting and postprandial glucose targets using the patient's SMBG and insulin dose diaries during screening and 52-week study period. The IDMC reviewed SMBG and insulin dose diary results for each patient and made insulin dosing recommendations to the Investigators during screening and up to Week 24 following randomization. It is important to note the Investigators were unmasked to A1C and FPG values at Week 24 to appropriately manage glycemic control, but were still blinded to study treatment during the 28-week safety extension.

Study 312 did not include insulin optimization but did include the 2-week single-blind placebo run-in period. Investigators were to adjust insulin dose to meet fasting and postprandial glucose targets using the patient's SMBG and insulin dose diaries during the 24-week study period (A1C and FPG values were masked to Investigators during the treatment period). No IDMC was used for Study 312.

Figure 19: Phase 3 T1D Studies Design Schematic



A1C: hemoglobin A1C; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; R: randomization; SC: subcutaneous; T1D: type 1 diabetes mellitus

6.1.2 Enrollment Criteria

Studies 309, 310, and 312 enrolled adult patients (≥18 years) with T1D diagnosed at least 1 year previously, a screening A1C of 7.0% to 11.0% inclusive, and eGFR ≥45 mL/min/1.73m^2. Patients could use MDI or CSII in the trials. Insulin was the only antihyperglycemic medication allowed as background therapy in the trials. Patients with a history of severe hypoglycemia or DKA within 1 month prior to Screening were excluded.

6.1.3 Endpoints

Prespecified efficacy endpoints in the overall T1D population are summarized in Table 10.

Table 10: Efficacy Endpoints in Studies 309, 310, and 312

	Studies 309 and 310	Study 312
Primary Endpoint	A1C change from baseline at Week 24	Net benefit at Week 24[a]
Secondary Endpoints (in hierarchical order)	Net benefit at Week 24[a]	A1C change from baseline at Week 24
	Body weight change from baseline at Week 24	Body weight change from baseline at Week 24
	Bolus insulin change from baseline at Week 24	SBP change from baseline at Week 16 (in patients with SBP ≥130 mm Hg at Baseline)
	FPG change from baseline at Week 24	Bolus insulin change from baseline at Week 24
	DTSQs score change from baseline at Week 24	
	DDS2 score change from baseline at week 24	
Other Endpoints	SBP change from baseline at Week 12 (in patients with SBP ≥130 mm Hg at Baseline)	FPG change from baseline at Week 24
	Composite endpoints evaluating benefit/risk: other clinical benefits (achieving benefit, defined as A1C reduction, while having low risk in other parameters such as SH, DKA, body weight, and insulin dosing)	Composite endpoints evaluating benefit/risk: other clinical benefits (achieving benefit, defined as A1C reduction, while having low risk in other parameters such as SH, DKA, body weight, and insulin dosing)

A1C: hemoglobin A1C; DDS2: Two-item Diabetes Distress Scale; DKA: diabetic ketoacidosis; DTSQ: Diabetes Treatment Satisfaction Questionnaire; FPG: fasting plasma glucose; SBP: systolic blood pressure; SH: severe hypoglycemia
a. Net benefit defined as the proportion of patients with A1C <7.0% at Week 24 and no episode of SH and no episode of DKA after randomization.

6.2 Overview of Phase 3 Efficacy Results in Modified Intent-to-Treat Population

In Studies 309, 310, and 312, sotagliflozin demonstrated statistically significant benefits compared to placebo across the primary endpoints and most key secondary endpoints. The addition of sotagliflozin to insulin therapy resulted in a difference in reduction in A1C compared to placebo between 0.35% and 0.46% compared to placebo at Week 24.

In each of the Phase 3 studies, the primary and key secondary glycemic endpoints were highly statistically significant ($p<0.001$; Table 11).

The statistically significant efficacy results demonstrated in the three Phase 3 randomized controlled studies allowed for evaluation of subgroups of patients who could

gain substantial benefits, with T1D-CKD identified as the patient group where benefits observed in the overall population would be the most valuable and clinically meaningful. The population of patients with T1D and CKD was identified based on inclusion criteria from the studies and using the definitions outlined by the KDIGO group: baseline 45 to <60 mL/min/1.73m^2 or an eGFR ≥60 mL/min/1.73m^2 with UACR ≥30 mg/g. Change from baseline to Week 24 in A1C was the primary efficacy endpoint for the T1D-CKD population and was analyzed in the pooled Studies 309 and 310 due to the identical study designs; Study 312 was analyzed separately.

In the T1D-CKD population, both doses of sotagliflozin demonstrated nominally significant and clinically meaningful reductions in A1C from baseline compared to placebo at 24 weeks (Table 15). The larger A1C reductions from baseline observed with sotagliflozin in Study 312 were likely due to the higher baseline A1C.

Table 11: Efficacy Endpoint Results in the Phase 3 Studies (mITT Population)

	Study 309			Study 310			Study 312	
	SOTA 200 mg (N=263)	SOTA 400 mg (N =262)	Placebo (N=268)	SOTA 200 mg (N=261)	SOTA 400 mg (N=263)	Placebo (N=258)	SOTA 400 mg (N=699)	Placebo (N=703)
Mean A1C (%) at Baseline	7.61	7.56	7.54	7.74	7.71	7.79	8.26	8.21
Mean A1C (%) at Week 24	7.17	7.08	7.50	7.36	7.35	7.79	7.41	7.88
Primary and Key Second Endpoints								
Δ A1C (Week 24)								
LS mean difference from placebo in A1C% at Week 24	-0.36	-0.41	NA	-0.37	-0.35	NA	-0.46	NA
p-value	**<0.001**	**<0.001**	**NA**	**<0.001**	**<0.001**	NA	**<0.001**	NA
A1C <7.0% w/o SH or DKA (Week 24)								
Proportion (%) with A1C <7.0% at Week 24 and no SH and no DKA from randomization to Week 24	33.5	43.5	21.6	31.4	32.3	15.1	28.6	15.2
p-value	**0.002**	**<0.001**	NA	**<0.001**	**<0.001**	NA	**<0.001**	NA
Difference from placebo in proportion (%) with A1C <7.0% at Week 24 and no SH and no DKA from randomization to Week 24	11.8	21.9	NA	16.3	17.2	NA	13.4	NA
p-value	**0.002**	**<0.001**	NA	**<0.001**	**<0.001**	NA	**<0.001**	NA
Proportion (%) with A1C <7.0% at Week 24	36.9	46.9	22.8	33.3	33.8	15.1	29.6	15.8
Body weight (Week 24)								
LS mean difference from placebo in body weight (kg) at Week 24	-2.35	-3.45	NA	-1.98	-2.58	NA	-2.98	NA

	Study 309			Study 310			Study 312	
	SOTA 200 mg (N=263)	SOTA 400 mg (N =262)	Placebo (N=268)	SOTA 200 mg (N=261)	SOTA 400 mg (N=263)	Placebo (N=258)	SOTA 400 mg (N=699)	Placebo (N=703)
p-value	**<0.001**	**<0.001**	NA	**<0.001**	**<0.001**	NA	**<0.001**	NA
Δ Daily bolus insulin dose (Week 24)								
LS mean difference from placebo in bolus insulin (IU/day) at Week 24	-1.50	-3.30	NA	-3.20	-3.59	NA	-2.84	NA
p-value	0.10	**<0.001**	NA	**<0.001**	**<0.001**	NA	**<0.001**	NA
Fasting plasma glucose (Week 24)								
LS mean difference from placebo in FPG (mg/dL) at Week 24 (p-value)	-9.8	-17.8	NA	-21.6	-25.7	NA	-23.2	NA
p-value	**0.036**	**<0.001**	NA	**<0.001**	**<0.001**	NA		NA
Systolic BP (Week 12/16)*								
LS mean difference from placebo in systolic BP (mm Hg) at Week 12	-3.5	-4.2	NA	-0.4	-2.8	NA	-3.8	NA
p-value	**<0.001**	**<0.001**	NA	0.64	**0.001**	NA		NA

A1C: hemoglobin A1C; BP: blood pressure; DKA: diabetic ketoacidosis; FPG: fasting plasma glucose; LS: least squares; mITT: modified intent-to-treat; NA: not applicable; SH: severe hypoglycemia; SOTA: sotagliflozin; w/o: without
*Systolic BP evaluated in subset of patient with systolic BP ≥130 mm Hg; systolic BP endpoint evaluated at Week 12 in Study 309 and 310 and Week 16 in Study 312.

6.3 T1D-CKD Population Analysis

6.3.1 Identification of T1D-CKD Population

The T1D-CKD population was defined as baseline eGFR of 45 to <60 mL/min/1.73m^2 or an eGFR ≥60 mL/min/1.73m^2 with UACR ≥30 mg/g.

6.3.2 Endpoints Evaluated in T1D-CKD Population

Change from baseline in A1C was the primary endpoint of interest for the T1D-CKD population. In Studies 309 and 310, the prespecified primary endpoint was the change from baseline to Week 24 in A1C in either sotagliflozin treatment group (200 mg or 400 mg) compared with placebo. In Study 312 (sotagliflozin 400 mg and placebo), change from baseline to Week 24 in A1C was the prespecified first secondary endpoint in the statistical hierarchy.

Secondary efficacy endpoints evaluated at Week 24 for the T1D-CKD population were change in body weight, percent change in insulin dose (total dose, basal dose, and bolus dose), FPG, and systolic blood pressure (SBP). Time in range was included as an exploratory endpoint.

6.3.3 Statistical Methods

Efficacy endpoints were analyzed using mixed model for repeated measures (MMRM) methods with treatment, randomization stratification factors, study, time (study week), and a treatment-by-time interaction term as fixed effects, and the baseline value of the dependent variable and a baseline-by-time interaction term as covariates. The MMRM analysis was conducted under the missing at random (MAR) framework based on the restricted maximum likelihood. The MAR assumption appeared plausible for the dataset(s) under analysis given the small number of premature treatment discontinuations and that use of all observed data using this model seemed to have explained much of the missingness. An unstructured (co)variance structure was used to estimate the within-patient error term. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom. The adjusted mean (ie, LS mean) change from baseline to Week 24 for each treatment group and the 95% confidence intervals (CIs) were estimated from this model, as well as point estimates of between-group differences in LS means comparing each sotagliflozin group to placebo, and the associated 95% CIs computed on this difference.

Efficacy analyses from Studies 309 and 310 were pooled due to their identical 52-week design. Results were analyzed separately for Study 312, which was 24 weeks in duration.

The same analytical methods were applied to the pooled Studies 309 and 310 dataset and the Study 312 dataset, with a noted exception being that a fixed term of “study” was not included in the MMRM for the Study 312 analysis.

6.4 Study 309, 310, and 312 T1D-CKD Population

6.4.1 Disposition

In Studies 309 and 310, a total of 234 patients had CKD; 160 patients received sotagliflozin (n=85 for 200 mg; n=75 for 400 mg), and 74 received placebo (Table 12). Of the patients with T1D-CKD who received sotagliflozin, 148 (92.5%) completed 24 weeks and 141 (88.1%) completed 52 weeks of the study. Twelve (7.5%) patients (6 in each sotagliflozin dose group) discontinued from the study before Week 24. Of the 74 patients who received placebo, 64 (86.5%) and 60 (81.1%) completed 24 weeks and 52 weeks of the study, respectively; 10 (13.5%) patients discontinued from the study before Week 24. For all patients in the T1D-CKD population regardless of treatment, the most frequently reported reasons for discontinuing the entire study or discontinuing before Week 24 were withdrawal by patient and AE.

In Study 312, a total of 224 patients had CKD: 114 received sotagliflozin and 110 received placebo.

Overall, no differences in patient disposition were noted between the pooled Studies 309/310 and Study 312. In addition, when the disposition of the T1D-CKD population was compared to that of the overall population, no apparent differences were noted.

Table 12: Patient Disposition in the Pooled Studies 309 and 310 and in Study 312

	T1D-CKD Population					T1D mITT Population				
	Pooled Studies 309 and 310			Study 312		Pooled Studies 309 and 310			Study 312	
Disposition, n (%)	SOTA 200 mg	SOTA 400 mg	Placebo	SOTA 400 mg	Placebo	SOTA 200 mg	SOTA 400 mg	Placebo	SOTA 400 mg	Placebo
Total randomized	524	525	526	700	705	524	525	526	700	705
T1D-CKD or mITT population[a]	85 (16.2)	75 (14.3)	74 (14.1)	114 (16.3)	110 (15.6)	524 (100)	525 (100)	526 (100)	699 (99.9)	703 (99.7)
Completed treatment (24 weeks)	79 (92.9)	69 (92.0)	64 (86.5)	95 (83.3)	96 (87.3)	479 (91.4)	476 (90.7)	471 (89.5)	605 (86.4)	624 (88.5)
Completed study (52 weeks)	77 (90.6)	64 (85.3)	60 (81.1)	-	-	454 (86.6)	448 (85.3)	443 (84.2)	-	-
Reason for discontinuation before Week 24										
Withdrawal by patient	4 (4.7)	3 (4.0)	5 (6.8)	8 (7.0)	5 (4.5)	27 (5.2)	22 (4.2)	29 (5.5)	32 (4.6)	44 (6.2)
Adverse event	2 (2.4)	3 (4.0)	2 (2.7)	8 (7.0)	4 (3.6)	12 (2.3)	23 (4.4)	13 (2.5)	45 (6.4)	16 (2.3)
Lost to follow-up	0	0	1 (1.4)	2 (1.8)	1 (0.9)	2 (0.4)	1 (0.2)	2 (0.4)	11 (1.6)	8 (1.1)
Non-compliance with study drug	0	0	1 (1.4)	0	1 (0.9)	0	1 (0.2)	2 (0.4)	3 (0.4)	8 (1.1)
Protocol deviation	0	0	1 (1.4)	0	1 (0.9)	1 (0.2)	0	3 (0.6)	1 (0.1)	1 (0.1)
Physician decision	0	0	0	0	1 (0.9)	2 (0.4)	2 (0.4)	2 (0.4)	0	1 (0.1)
Death	0	0	0	0	0	0	0	1 (0.2)	1 (0.1)	0
Pregnancy	0	0	0	0	0	0	0	1 (0.2)	0	0
Other	0	0	0	1 (0.9)	1 (0.9)	1 (0.2)	0	2 (0.4)	2 (0.3)	3 (0.4)

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; T1D: type 1 diabetes mellitus; UACR: urine albumin-to-creatinine ratio
a. T1D-CKD population defined by eGFR of 45 to <60 mL/min/1.73m^2 or eGFR ≥60 mL/min/1.73m^2 and UACR ≥30 mg/g.

6.4.2 Demographics and Baseline Characteristics

Patient demographics and baseline characteristics of the T1D-CKD population are provided in Table 13 and Table 14, respectively. Demographics and baseline characteristics of patients in the randomized population from the Studies 309 and 310 individually are provided in Appendix Section 10.2.

Table 13: Summary of Demographics Studies 309 and 310 and Study 312

	T1D-CKD Population					T1D mITT Population				
	Pooled Studies 309 and 310			Study 312		Pooled Studies 309 and 310			Study 312	
Demographic	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Mean (SD) age at study entry (years)	46.9 (15.11)	45.5 (13.59)	48.6 (15.68)	47.6 (16.03)	47.3 (14.80)	44.4 (13.69)	44.0 (13.37)	42.5 (13.34)	43.3 (14.17)	42.4 (14.04)
Age at study entry (years), n (%)										
≥18 to <26	8 (9.4)	5 (6.7)	8 (10.8)	11 (9.6)	12 (10.9)	60 (11.5)	58 (11.0)	63 (12.0)	*	*
≥26 to <50	42 (49.4)	43 (57.3)	27 (36.5)	49 (43.0)	46 (41.8)	266 (50.8)	281 (53.5)	291 (55.3)	*	*
≥50 to <65	22 (25.9)	19 (25.3)	25 (33.8)	33 (28.9)	36 (32.7)	166 (31.7)	154 (29.3)	139 (26.4)	*	*
≥65 to <75	12 (14.1)	7 (9.3)	13 (17.6)	19 (16.7)	16 (14.5)	28 (5.3)	29 (5.5)	31 (5.9)	*	*
≥75	1 (1.2)	1 (1.3)	1 (1.4)	2 (1.8)	0	4 (0.8)	3 (0.6)	2 (0.4)	5 (0.7)	1 (0.1)
Mean (SD) age at T1D diagnosis (years)	20.0 (11.91)	21.6 (14.38)	23.0 (15.42)	24.1 (15.75)	24.1 (15.34)	22.8 (13.18)	22.6 (12.83)	21.3 (12.73)	22.8 (13.65)	22.8 (13.51)
Age at T1D diagnosis (years), n (%)										
<18	42 (49.4)	37 (49.3)	32 (43.2)	47 (41.2)	49 (44.5)	208 (39.7)	211 (40.2)	230 (43.7)	294 (42.1)	296 (42.1)
≥18	43 (50.6)	38 (50.7)	42 (56.8)	67 (58.8)	61 (55.5)	316 (60.3)	314 (59.8)	296 (56.3)	405 (57.9)	407 (57.9)
Sex, n (%)										
Male	50 (58.8)	32 (42.7)	34 (45.9)	60 (52.6)	55 (50.0)	265 (50.6)	253 (48.2)	271 (51.5)	358 (51.2)	339 (48.2)
Female	35 (41.2)	43 (57.3)	40 (54.1)	54 (47.4)	55 (50.0)	259 (49.4)	272 (51.8)	255 (48.5)	341 (48.8)	364 (51.8)
Race, n (%)										
White	79 (92.9)	70 (93.3)	69 (93.2)	98 (86.0)	90 (81.8)	493 (94.1)	496 (94.5)	494 (93.9)	619 (88.6)	621 (88.3)
Black	2 (2.4)	1 (1.3)	2 (2.7)	7 (6.1)	10 (9.1)	11 (2.1)	8 (1.5)	10 (1.9)	24 (3.4)	22 (3.1)

Demographic	T1D-CKD Population					T1D mITT Population				
	Pooled Studies 309 and 310			Study 312		Pooled Studies 309 and 310			Study 312	
	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
American Indian or Alaska Native	0	0	0	0	0	0	1 (0.2)	0	1 (0.1)	5 (0.7)
Asian	1 (1.2)	1 (1.3)	0	0	1 (0.9)	7 (1.3)	5 (1.0)	4 (0.8)	7 (1.0)	5 (0.7)
Native Hawaiian or other Pacific Islander	1 (1.2)	0	0	1 (0.9)	0	2 (0.4)	0	2 (0.4)	1 (0.1)	0
Other	2 (2.4)	3 (4.0)	3 (4.1)	6 (5.3)	6 (5.5)	10 (1.9)	16 (3.0)	16 (3.0)	31 (4.4)	37 (5.3)
Unknown/Not applicable	0	0	0	2 (1.8)	3 (2.7)	NA	NA	NA	16 (2.3)	13 (1.8)
Mean (SD) body weight (kg)	86.7 (21.1)	83.4 (20.1)	85.0 (17.8)	82.6 (18.1)	81.3 (17.1)	84.46 (18.132)	84.23 (18.109)	84.25 (17.558)	82.40 (17.131)	81.55 (17.032)
Mean (SD) BMI (kg/m^2)	29.2 (6.5)	28.67 (6.2)	29.3 (5.7)	28.7 (5.3)	28.3 (5.2)	28.89 (5.556)	28.74 (5.184)	28.54 (5.275)	28.29 (5.128)	28.10 (5.183)
BMI (kg/m^2), n (%)										
<18.5	0	2 (2.7)	0	1 (0.9)	0	3 (0.6)	2 (0.4)	0	3 (0.4)	1 (0.1)
≥18.5 to <25	24 (28.2)	19 (25.3)	20 (27.0)	31 (27.2)	31 (28.2)	139 (26.5)	125 (23.8)	141 (26.8)	201 (28.8)	205 (29.2)
≥25 to <30	26 (30.6)	26 (34.7)	18 (24.3)	38 (33.3)	44 (40.0)	177 (33.8)	206 (39.2)	199 (37.8)	259 (37.1)	279 (39.7)
≥30	35 (41.2)	28 (37.3)	36 (48.6)	44 (38.6)	35 (31.8)	205 (39.1)	192 (36.6)	186 (35.4)	236 (33.8)	218 (31.0)
Geographic region, n (%)										
North America (US and Canada)	45 (52.9)	32 (42.7)	39 (52.7)	47 (41.2)	50 (45.5)	263 (50.2)	262 (49.9)	268 (51.0)	277 (39.6)	302 (43.0)
Outside North America	40 (47.1)	43 (57.3)	35 (47.3)	67 (58.8)	60 (54.5)	261 (49.8)	263 (50.1)	258 (49.0)	422 (60.4)	401 (57.0)

BMI: body mass index; CKD: chronic kidney disease; NA: not applicable; SD: standard deviation; SOTA: sotagliflozin; T1D: type 1 diabetes mellitus; US: United States

*Age groupings summarized by ≥ 75 years and < 75 years in Stuyd 312.

Table 14: Summary of Baseline Characteristics in Pooled Studies 309 and 310 and in Study 312

	T1D-CKD Population					T1D mITT Population				
	Pooled Studies 309 and 310			Study 312		Pooled Studies 309 and 310			Study 312	
Baseline Characteristic:	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Duration of T1D (years), n (%)										
<20	23 (27.1)	30 (40.0)	28 (37.8)	55 (48.2)	46 (41.8)	259 (49.4)	264 (50.3)	265 (50.4)	373 (53.4)	385 (54.8)
≥20 to <40	47 (55.3)	35 (46.7)	31 (41.9)	45 (39.5)	50 (45.5)	211 (40.3)	214 (40.8)	210 (39.9)	268 (38.3)	270 (38.4)
≥40	15 (17.6)	10 (13.3)	15 (20.3)	14 (12.3)	14 (12.7)	54 (10.3)	47 (9.0)	51 (9.7)	58 (8.3)	48 (6.8)
Insulin delivery method, n (%)										
CSII	31 (36.5)	29 (38.7)	27 (36.5)	39 (34.2)	45 (40.9)	224 (42.7)	224 (42.7)	226 (43.0)	275 (39.3)	280 (39.8)
Non-CSII	54 (63.5)	46 (61.3)	47 (63.5)	75 (65.8)	65 (59.1)	300 (57.3)	301 (57.3)	300 (57.0)	424 (60.7)	423 (60.2)
A1C (%) at Week -2, n (%)										
≤8.5%	65 (76.5)	56 (74.7)	55 (74.3)	52 (45.6)	62 (56.4)	431 (82.3)	435 (82.9)	430 (81.72)	423 (60.5)	417 (59.3)
>8.5%	20 (23.5)	19 (25.3)	19 (25.7)	62 (54.4)	47 (42.7)	93 (17.7)	90 (17.1)	96 (18.3)	276 (39.5)	284 (40.4)
Missing	0	0	0	0	1 (0.9)	NA	NA	NA	0	2 (0.3)
Mean (SD) A1C (%)	7.70 (0.829)	7.90 (0.798)	7.81 (0.883)	8.71 (1.219)	8.26 (0.966)	7.68 (0.773)	7.64 (0.776)	7.66 (0.808)	8.26 (0.965)	8.21 (0.921)
Baseline eGFR (mL/min/1.73m²), n (%)										
45 to <60	22 (25.9)	24 (32.0)	22 (29.7)	31 (27.2)	39 (35.5)	22 (4.2)	25 (4.8)	24 (4.6)	32 (4.6)	42 (6.0)
≥60 to <90	38 (44.7)	24 (32.0)	29 (39.2)	43 (37.7)	35 (31.8)	270 (51.5)	259 (49.3)	245 (46.6)	312 (44.6)	300 (42.7)
≥90	25 (29.4)	27 (36.0)	23 (31.1)	40 (35.1)	36 (32.7)	232 (44.3)	241 (45.9)	257 (48.9)	355 (50.8)	361 (51.4)
Mean (SD) FPG (mg/dL)	164.6 (77.98)	150.2 (63.21)	170.5 (76.69)	173.8 (81.25)	158.2 (70.71)	159.34 (71.704)	156.87 (67.622)	156.99 (64.966)	165.1 (71.60)	163.4 (69.08)
Mean (SD) total daily	68.6	61.5	70.1	58.3	60.6	62.71	62.77	64.37	56.88	58.35

	T1D-CKD Population					T1D mITT Population				
	Pooled Studies 309 and 310			Study 312		Pooled Studies 309 and 310			Study 312	
Baseline Characteristic:	**SOTA 200 mg (N=85)**	**SOTA 400 mg (N=75)**	**Placebo (N=74)**	**SOTA 400 mg (N=114)**	**Placebo (N=110)**	**SOTA 200 mg (N=524)**	**SOTA 400 mg (N=525)**	**Placebo (N=526)**	**SOTA 400 mg (N=699)**	**Placebo (N=703)**
insulin dose (IU/day)	(44.67)	(28.48)	(50.05)	(27.92)	(28.15)	(36.553)	(33.453)	(36.583)	(27.601)	(29.085)
Mean (SD) ratio of daily bolus vs. total insulin doses (IU/IU)	0.45 (0.124)	0.48 (0.149)	0.47 (0.136)	0.47 (0.165)	0.47 (0.155)	0.48 (0.138)	0.49 (0.129)	0.48 (0.132)	0.47 (0.152)	0.48 (0.151)
Mean (SD) sitting SBP (mm Hg)	128.2 (15.59)	125.4 (16.60)	127.9 (18.87)	127.8 (17.06)	125.4 (16.48)	121.5 (15.03)	121.3 (14.32)	122.0 (14.55)	122.0 (15.25)	121.8 (14.82)
Baseline UACR (mg/g)										
Median	51.1	65.8	48.6	59.7	61.3	6.98	6.25	6.60	7.4165	7.2960
≥30	87.1%	77.3%	82.4%	83.3%	80.0%	14.1%	11.2%	12.0%	13.7%	12.8%

A1C: hemoglobin A1C; CKD: chronic kidney disease; CSII: continuous subcutaneous insulin infusion; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; SBP: systolic blood pressure; SD: standard deviation; SOTA: sotagliflozin; T1D: type 1 diabetes mellitus; UACR: urine albumin-to-creatinine ratio

6.5 Study 309, 310, and 312 Phase 3 Efficacy Results – T1D-CKD Population

6.5.1 Primary Efficacy Endpoint

6.5.1.1 Change from Baseline to Week 24 in A1C

In the T1D-CKD population, both doses of sotagliflozin demonstrated nominally significant and clinically meaningful reductions in A1C (%) from baseline compared to placebo at 24 weeks (Table 15). In Studies 309 and 310, from a baseline A1C of approximately 7.8%, the estimated treatment difference for change in A1C at 24 weeks was -0.34% and -0.31% for the 200 and 400 milligram doses, respectively, demonstrating glycemic control favoring sotagliflozin. From a baseline A1C of approximately 8.5% in Study 312, sotagliflozin 400 mg significantly decreased by -0.45% compared to placebo at Week 24.

Table 15: Analysis of Change from Baseline to Week 24 in A1C (%) in the Pooled Studies 309 and 310 and in Study 312

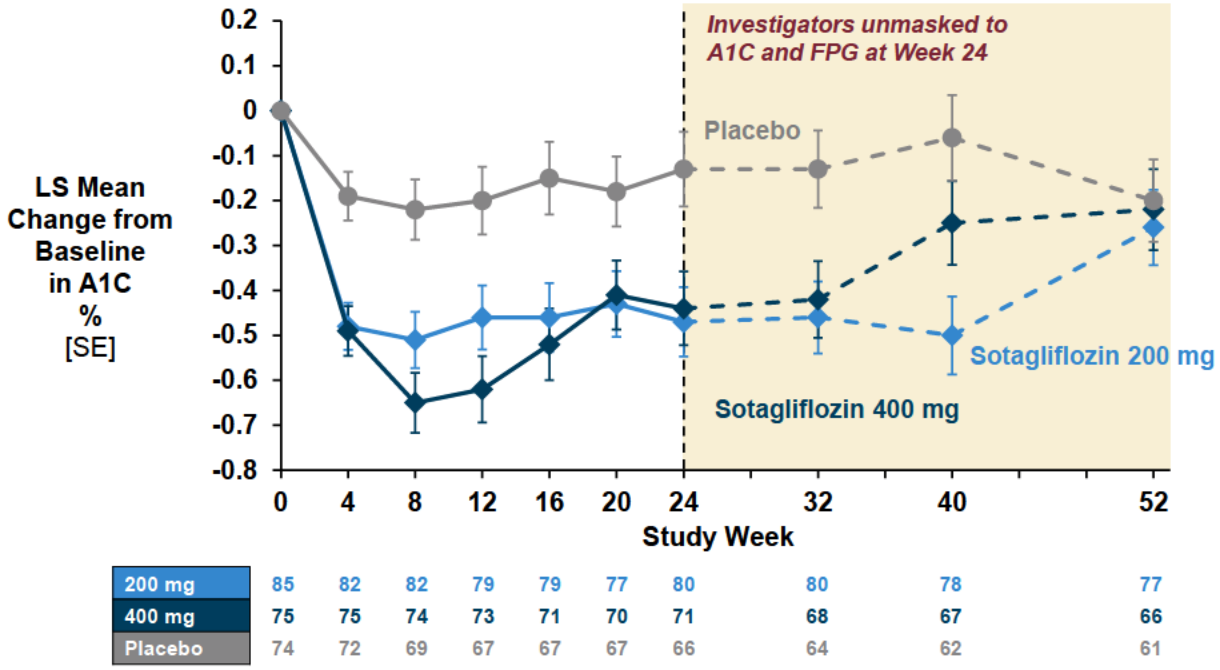
	T1D-CKD Population					T1D mITT Population				
	Pooled Studies 309 and 310			Study 312		Pooled Studies 309 and 310			Study 312	
A1C, %	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Baseline, mean (SD)	7.70 (0.829)	7.90 (0.798)	7.81 (0.883)	8.71 (1.219)	8.26 (0.966)	7.68 (0.773)	7.64 (0.776)	7.66 (0.808)	8.26 (0.965)	8.21 (0.921)
Week 24, mean (SD)	7.32 (0.856)	7.50 (0.950)	7.74 (0.872)	7.71 (1.019)	8.01 (1.074)	7.26 (0.810)	7.21 (0.830)	7.64 (0.855)	7.41 (0.952)	7.88 (1.031)
Change from baseline at Week 24, mean (SD)	-0.40 (0.670)	-0.44 (0.780)	-0.07 (0.627)	-0.88 (0.942)	-0.26 (0.819)	-0.41 (0.638)	-0.44 (0.613)	-0.03 (0.589)	-0.81 (0.783)	-0.31 (0.775)
LS mean change from baseline (95% CLs)	-0.47 (-0.62, -0.32)	-0.44 (-0.60, -0.28)	-0.13 (-0.30, 0.03)	-0.85 (-1.03, -0.67)	-0.40 (-0.57, -0.22)	-0.41 (-0.47, -0.36)	-0.43 (-0.49, -0.38)	-0.05 (-0.10, 0.01)	-0.79 (-0.85. -0.73)	-0.33 (-0.39, -0.27)
Difference from placebo (95% CLs)	-0.34 (-0.55, -0.12)	-0.31 (-0.53, -0.09)	—	-0.45 (-0.69, -0.21)	—	-0.36 (-0.44, -0.29)	-0.38 (-0.45, -0.31)	—	-0.46 (-0.54, -0.38)	—
p-value	0.002	0.006	—	<0.001	—	<0.001	<0.001	—	<0.001	—

A1C: hemoglobin A1C; CKD: chronic kidney disease; CL: confidence limit; LS: least squares; SD: standard deviation; SOTA: sotagliflozin; T1D: type 1 diabetes mellitus

Looking at the long-term effects of sotagliflozin on A1C, the LS mean difference in A1C between sotagliflozin and placebo was not significant in the T1D-CKD population at Week 52 (Figure 20). Sotagliflozin treatment effect may also have been impacted by the unmasking of A1C and FPG at Week 24 for the remainder of the trial to allow for appropriate diabetes management. The attenuation was also observed in the ITT population but the between-group difference in A1C was still significant with both doses of sotagliflozin.

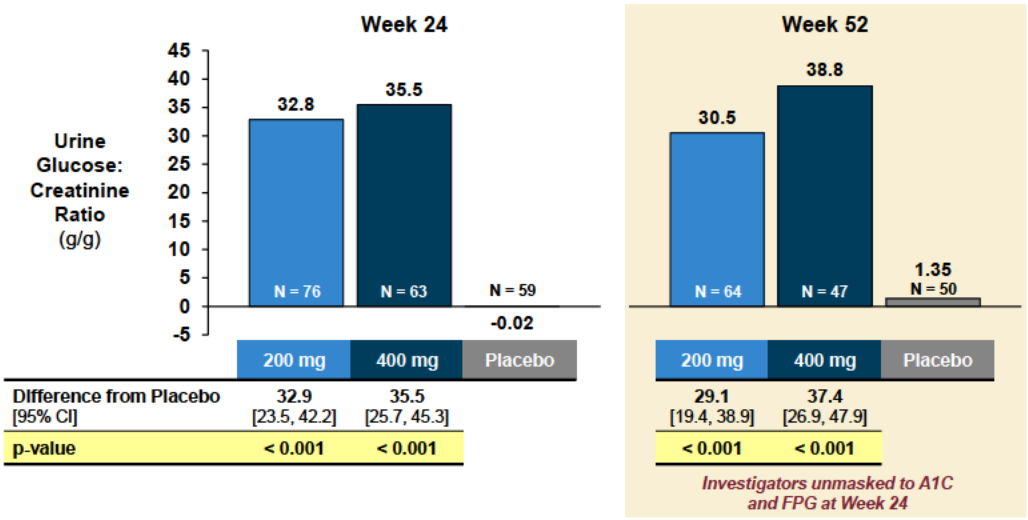
Despite not achieving significance in A1C at Week 52, dose-related increases in UGCR over 52 weeks supports that the PD effect of sotagliflozin is still present (Figure 21). These results suggest that the attenuation of glucose control from 24 to 52 weeks is likely due to extrinsic factors such as unmasking A1C and glucose values rather than the effect of sotagliflozin on the mechanistic target.

Figure 20: Change from Baseline in A1C (%) by Study Visit in the T1D-CKD Population in Pooled Studies 309 and 310



A1C: hemoglobin A1C: CKD: chronic kidney disease; FPG: fasting plasma glucose; SE: standard error; T1D: type 1 diabetes mellitus

Figure 21: UGCR Change from Baseline at Week 24 and Week 52 in the T1D-CKD Population in Pooled Studies 309 and 310



A1C: hemoglobin A1C; CI: confidence interval; CKD: chronic kidney disease; FPG: fasting plasma glucose; T1D: type 1 diabetes mellitus; UGCR: urinary glucose-to-creatinine ratio

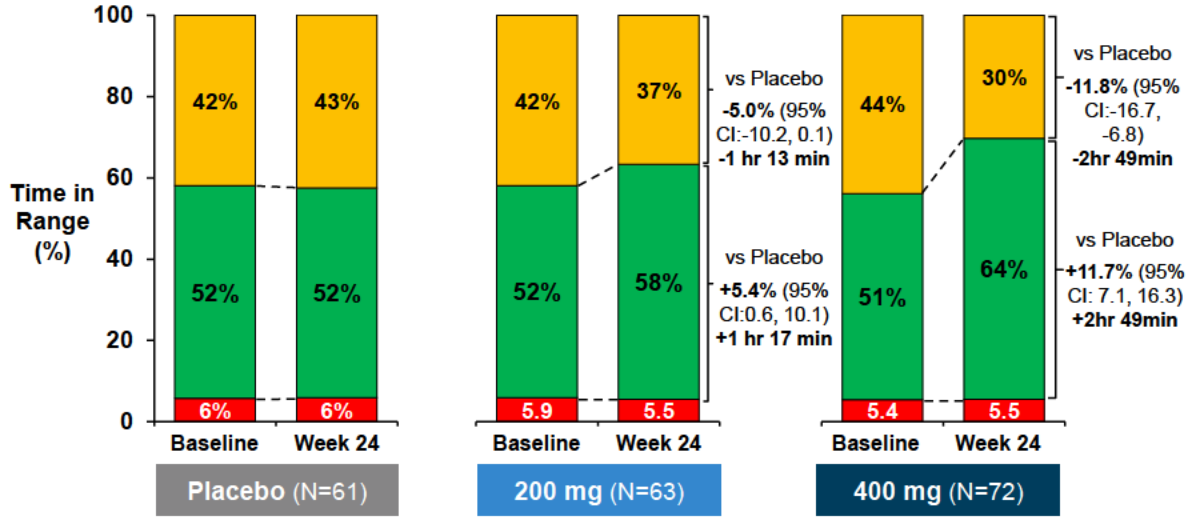
6.5.1.2 Time in Range

To capture how patients experience their diabetes control on a day-to-day basis, time in range, defined as the percentage of time an individual spends between blood glucose of 70 and 180 mg/dL, was evaluated to better understand the benefits of sotagliflozin. Patients were randomized to a CGM substudy with the goal to randomize 70 patients per arm. Patients underwent masked CGM with a Dexcom G4 monitor during specified 1-week intervals throughout the first 24 weeks. Data from Studies 309 and 310 were pooled prior to unblinding to meet randomization goals, with enough data available for 63, 72, and 61 patients in the 200, 400, and placebo groups, respectively.

In the overall T1D population, at Week 24, patients receiving sotagliflozin spent a statistically significant ($p < 0.001$) greater time in range versus placebo in both the 200 mg and the 400 mg sotagliflozin groups (Figure 22).

Compared to placebo patients, patients treated with sotagliflozin 200 mg and 400 mg spent an average of 1.3 and 2.8 more hours in range, respectively. Mean total time in range for these patients at 24 weeks is therefore 13 hours and 52 minutes in the 200 mg sotagliflozin group and 15 hours 25 minutes in the 400 mg sotagliflozin group. Patients in the placebo group remained nearly the same at Week 24, spending a mean 12 hours and 22 minutes in range (Danne 2019). ADA time in range guidelines target at least 70% of the day with glucose between 70 and 180 mg/dL (ie, 17 hours per day).

Figure 22: Time within A1C Target Range in the T1D Population in Pooled Studies 309 and 310

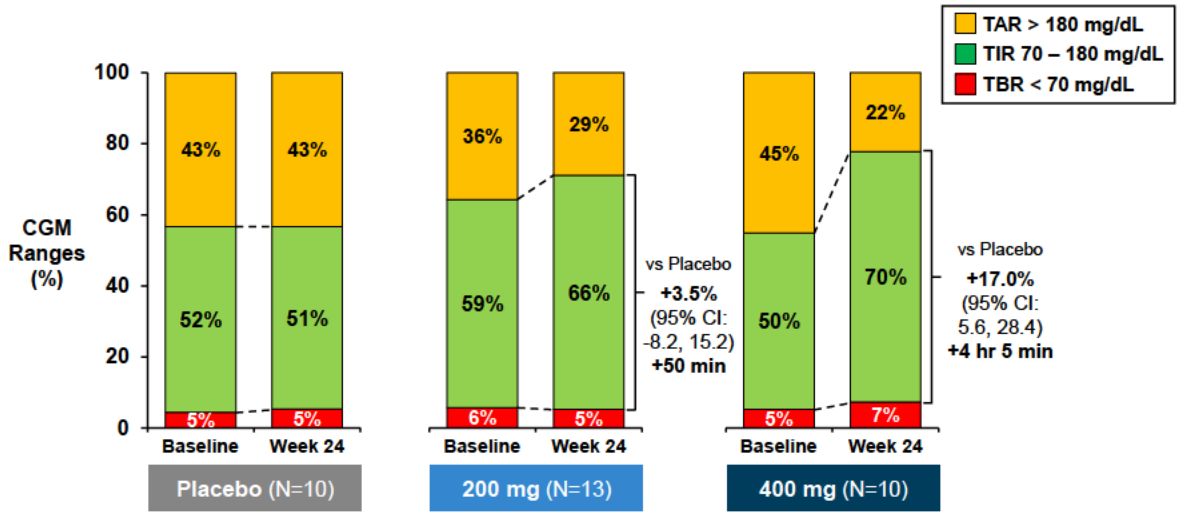


:A1C: hemoglobin A1C; CI: confidence interval;

Results in the T1D-CKD population were similar, although the small number of patients did not permit analysis for statistical significance. At 24 weeks, patients treated with sotagliflozin spent 0.83 and 4.08 more hours in range compared to placebo in the 200 mg and 400 mg sotagliflozin groups, respectively. This brings the mean total time in range at Week 24 to 66% in the 200 mg group and the target 70% time in range in the 400 mg sotagliflozin group. The placebo group remained nearly the same at 24 weeks compared to baseline, with patients spending 12.5 hours in range (51%).

The improvement ranging from about 1 hour to just over 4 hours represents a clinically meaningful outcome especially given the correlation between time in range and microvascular complications (Beck 2019). Importantly, the improvement in time in range was at the expense of time above range (or a blood glucose >180 mg/dL) without increasing the time below range (or a blood glucose <70 mg/dL).

Figure 23: Time within A1C Target Range in the T1D-CKD Population in Pooled Studies 309 and 310

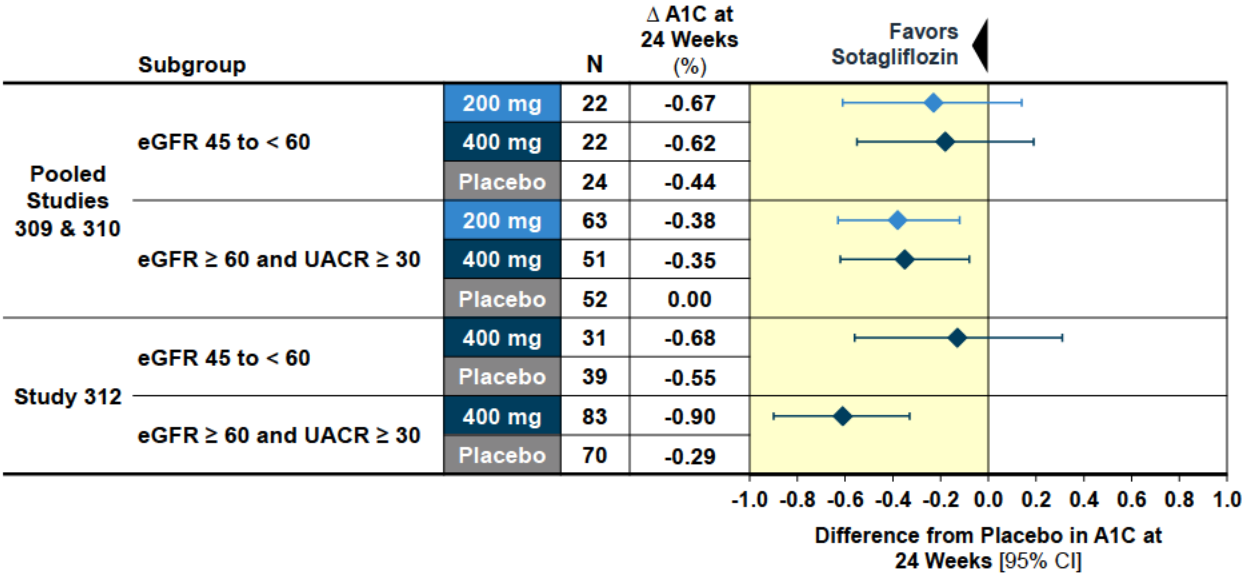


A1C: hemoglobin A1C; CGM: continuous glucose monitoring; CKD: chronic kidney disease; TAR: time above range; TBR: time below range; TIR: time in rage; T1D: type 1 diabetes mellitus
Patients with available data

6.5.1.3 Subgroup Analyses

Reductions in A1C with sotagliflozin compared to placebo were also seen when evaluating glycemic efficacy by baseline eGFR (Figure 24). In Studies 309 and 310, reductions in A1C with sotagliflozin 200 and 400 mg were observed in both subgroups. Treatment differences compared to placebo were larger among patients with a baseline eGFR ≥60 mL/min/1.73m^2. This is consistent with the known attenuated effects of SGLT inhibitors on glycemic control with declining kidney function. A similar effect was observed in Study 312.

Figure 24: Effect of Sotagliflozin vs Placebo on A1C at Week 24 by eGFR Range in the T1D-CKD Population in Pooled Studies 309 and 310 and Study 312



A1C: hemoglobin A1C; CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; T1D: type 1 diabetes mellitus; UACR: urine albumin-to-creatinine ratio

6.5.2 Secondary and Other Efficacy Endpoints

6.5.2.1 Body Weight

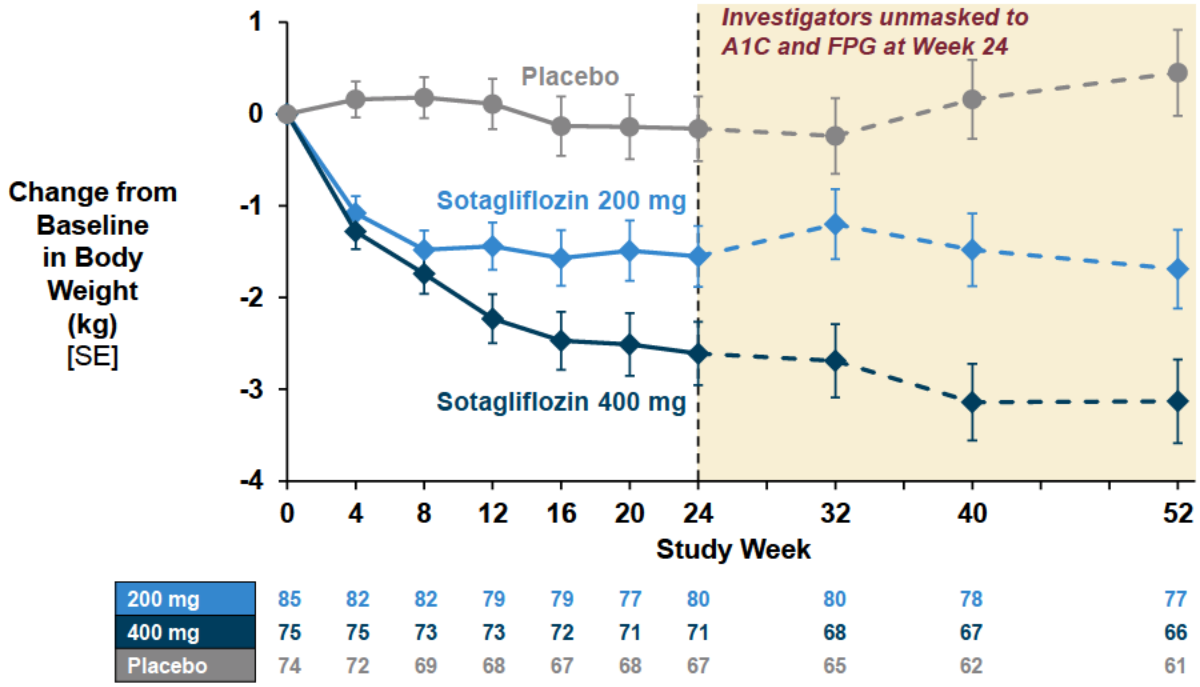
A majority of patients with T1D and CKD included in the Phase 3 studies were overweight or obese. The decrease in body weight was nominally significant across the T1D-CKD population in the pooled Studies 309/310 and in Study 312 for sotagliflozin compared to placebo (Table 16). Dose-related reductions in body weight with sotagliflozin ranged from 1.6 to 2.6 kg with the 200 and 400 mg doses, respectively. Importantly, reductions in body weight were sustained through 52 weeks in the pooled Studies 309 and 310 T1D-CKD population (Figure 25). At 52 weeks, the treatment difference compared to placebo was 2.1 and 3.6 kg for sotagliflozin 200 and 400 mg, respectively. This is consistent with the persistent, dose-related effects of sotagliflozin on UGE.

Table 16: Analysis of Change from Baseline to Week 24 in Absolute Body Weight in Pooled Studies 309 and 310 and in Study 312

	T1D-CKD Population					T1D mITT Population				
	Pooled Studies 309 and 310			Study 312		Pooled Studies 309 and 310			Study 312	
Body weight, kg	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Baseline, mean (SD)	86.66 (21.075)	83.41 (20.099)	85.04 (17.827)	82.61 (18.145)	81.28 (17.073)	84.46 (18.132)	84.23 (18.109)	84.25 (17.558)	82.40 (17.131)	81.55 (17.032)
LS mean change from baseline (95% CL)	-1.55 (-2.20, -0.90)	-2.61 (-3.29, -1.93)	-0.16 (-0.86, 0.54)	-2.02 (-2.69, -1.35)	0.82 (0.13, 1.50)	-1.70 (-1.97, -1.44)	-2.55 (-2.82, -2.28)	0.47 (0.20, 0.74)	-2.21 (-2.45, -1.97)	0.77 (0.53, 1.01)
Difference from placebo (95% CL)	-1.39 (-2.33, -0.45)	-2.45 (-3.41, -1.49)	—	-2.84 (-3.76, -1.91)	—	-2.17 (-2.54, -1.80)	-3.02 (-3.39, -2.65)	—	-2.98 (-3.31, -2.66)	—
p-value	0.004	<0.001	—	<0.001	—	<0.001	<0.001	—	<0.001	—

CKD: chronic kidney disease; CL: confidence limit; LS: least squares; SD: standard deviation; SOTA: sotagliflozin; T1D: type 1 diabetes mellitus

Figure 25: Mean Change from Baseline in Absolute Body Weight by Visit in the T1D-CKD Population in Pooled Studies 309 and 310



A1C: hemoglobin A1C; CKD: chronic kidney disease; FPG: fasting plasma glucose; SE: standard error; T1D: type 1 diabetes mellitus

6.5.2.2 Fasting Plasma Glucose

FPG was nominally significantly reduced from baseline with sotagliflozin 400 mg versus placebo in the T1D-CKD population in Study 312 (Table 17). In the pooled 309 and 310 T1D-CKD population, FPG was numerically reduced with sotagliflozin, but not significantly.

Table 17: Analysis of Change from Baseline to Week 24 in Fasting Plasma Glucose in Pooled Studies 309 and 310 and Study 312

	T1D-CKD Population					T1D mITT Population				
	Pooled Studies 309 and 310			Study 312		Pooled Studies 309 and 310			Study 312	
Fasting Plasma Glucose, mg/dL	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Baseline, mean (SD)	164.6 (77.98)	150.2 (63.21)	170.5 (76.69)	173.7 (81.25)	158.2 (70.71)	159.3 (71.70)	156.9 (67.62)	157.0 (64.97)	165.1 (71.60)	163.4 (69.08)
LS mean change from baseline (95% CL)	-15.0 (-28.6, -1.3)	-20.0 (-34.3, -5.6)	-5.6 (-20.4, 9.2)	-7.8 (-21.7, 6.2)	13.1 (-1.0, 27.3)	-10.0 (-15.1, -4.9)	-15.7 (-20.9, -10.6)	5.7 (0.6, 10.8)	-14.2 (-19.6, -8.9)	8.9 (3.6, 14.3)
Difference from placebo (95% CL)	-9.3 (-29.0, 10.3)	-14.3 (-34.6, 5.9)	—	-20.9 (-39.8, -2.0)	—	-15.7 (-22.7, -8.7)	-21.4 (-28.4, -14.4)	—	-23.2 (-30.4, -16.0)	—
p-value	0.35	0.17	—	0.031	—	<0.001	<0.001	—	<0.001	—

CKD: chronic kidney disease; CL: confidence limit; LS: least squares; SD: standard deviation; SOTA: sotagliflozin; T1D: type 1 diabetes mellitus

6.5.2.3 Systolic Blood Pressure

SBP was nominally significantly reduced from baseline with sotagliflozin 400 mg versus placebo in the T1D-CKD population of Study 312 and similar with sotagliflozin and placebo in the pooled studies (Table 18).

Table 18: Change from Baseline in Systolic Blood Pressure at Week 24 in Pooled Studies 309 and 310 and in Study 312

	T1D-CKD Population					T1D mITT Population				
	Pooled Studies 309 and 310			Study 312		Pooled Studies 309 and 310			Study 312	
Systolic Blood Pressure, mm Hg	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Baseline, mean (SD)	128.2 (15.59)	125.4 (16.60)	127.9 (18.87)	127.8 (17.06)	125.4 (16.48)	121.5 (15.03)	121.3 (14.32)	122.0 (14.55)	122.0 (15.25)	121.8 (14.82)
LS mean change from baseline (95% CL)	-2.7 (-5.6, 0.1)	-2.7 (-5.7, 0.2)	-2.6 (-5.7, 0.4)	-1.4 (-4.3, 1.5)	3.7 (0.7, 6.7)	-2.9 (-3.9, -2.0)	-3.7 (-4.7, -2.8)	-0.9 (-1.8, 0.1)	-2.5 (-3.4, -1.7)	0.7 (-0.2, 1.6)
Difference from placebo (95% CL)	-0.1 (-4.1, 3.9)	-0.1 (-4.2, 4.0)	—	-5.1 (-9.1, -1.1)	—	-2.0 (-3.3, -0.7)	-2.8 (-4.1, -1.6)	—	-3.3 (-4.4, -2.1)	—
p-value	0.96	0.97	—	0.013	—	0.002	<0.001	—	<0.001	—

CKD: chronic kidney disease; CL: confidence limit; LS: least squares; SD: standard deviation; SOTA: sotagliflozin; T1D: type 1 diabetes mellitus

6.5.2.4 Mean Total Daily Insulin Dose

At Week 24, in both the pooled Studies 309/310 and Study 312, there were no statistical differences in the percent change from baseline in insulin dose (total, basal, and bolus) between sotagliflozin and placebo in the T1D-CKD population (Table 19). Conversely, significant percent reductions in total daily insulin dose were noted with sotagliflozin compared to placebo at Week 52 (Table 20).

Table 19: Analysis of Percent Change from Baseline to Week 24 in Mean Daily Insulin Dose in Pooled Studies 309 and 310 and in Study 312

	T1D-CKD Population					T1D mITT Population				
	Pooled Studies 309 and 310			Study 312		Pooled Studies 309 and 310			Study 312	
	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Total insulin dose, IU/day										
Baseline, mean (SD)	68.63 (44.666)	61.46 (28.480)	70.12 (50.046)	58.26 (27.920)	60.61 (28.151)	62.71 (36.553)	62.77 (33.453)	64.37 (36.583)	56.88 (27.601)	58.35 (29.085)
LS mean % change from baseline (95% CL)	-4.53 (-8.13, -0.92)	-4.78 (-8.49, -1.07)	-0.89 (-4.70, 2.92)	-1.93 (-6.91, 3.05)	2.50 (-2.56, 7.57)	-6.05 (-7.71, -4.38)	-8.42 (-10.08, -6.76)	1.13 (-0.52, 2.79)	-6.77 (-8.75, -4.80)	2.93 (0.97, 4.89)
Difference from placebo (95% CL)	-3.64 (-8.68, 1.41)	-3.89 (-9.06, 1.27)	—	-4.43 (-11.18, 2.31)	—	-7.18 (-9.41, -4.95)	-9.56 (-11.78, -7.33)	—	-9.71 (-12.30, -7.12)	—
p-value	0.16	0.14	—	0.20	—	p <0.001	p <0.001	—	<0.001	—
Basal insulin dose, IU/day										
Baseline, mean (SD)	37.20 (27.294)	31.51 (17.070)	34.74 (19.466)	30.73 (17.085)	31.09 (14.540)	32.02 (20.457)	31.44 (16.893)	32.46 (17.519)	29.54 (16.294)	29.63 (15.539)
LS mean % change from baseline (95% CL)	-2.69 (-8.97, 3.60)	1.14 (-5.38, 7.66)	0.85 (-5.88, 7.59)	-0.86 (-6.82, 5.09)	6.82 (0.81, 12.83)	-2.76 (-4.72, -0.80)	-3.99 (-5.94, -2.04)	2.91 (0.96, 4.86)	-3.11 (-6.16, -0.07)	6.76 (3.74, 9.78)
Difference from placebo (95% CL)	-3.54 (-12.65, 5.56)	0.28 (-9.01, 9.58)	—	-7.68 (-15.75, 0.40)	—	-5.67 (-8.32, -3.02)	-6.90 (-9.54, -4.26)	—	-9.88 (-13.75, -6.00)	—
p-value	0.44	0.95	—	0.06	—	p <0.001	p <0.001	—	<0.001	—
Bolus insulin dose, IU/day										
Baseline, mean	31.42	29.95	35.38	27.54	29.52	30.69	31.32	31.90	27.34	28.72

	T1D-CKD Population					T1D mITT Population				
	Pooled Studies 309 and 310			Study 312		Pooled Studies 309 and 310			Study 312	
	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
(SD)	(21.717)	(17.526)	(34.071)	(18.070)	(18.653)	(20.821)	(21.068)	(23.352)	(16.969)	(19.035)
LS mean % change from baseline (95% CL)	-1.73 (-12.83, 9.38)	3.07 (-8.43, 14.56)	1.61 (-10.16, 13.39)	3.68 (-6.17, 13.53)	4.57 (-5.44, 14.57)	-4.88 (-8.78, -0.98)	-9.98 (-13.87, -6.09)	4.41 (0.52, 8.30)	-5.71 (-10.19, -1.22)	6.62 (2.16, 11.08)
Difference from placebo (95% CL)	-3.34 (-19.11, 12.44)	1.45 (-14.69, 17.60)	—	-0.88 (-14.25, 12.48)	—	-9.29 (-14.50, -4.07)	-14.39 (-19.60, -9.18)	—	-12.32 (-18.17, -6.48)	
p-value	0.68	0.86	—	0.90	—	<0.001	<0.001	—	<0.001	

CKD: chronic kidney disease; CL: confidence limit; LS: least squares; SD: standard deviation; SOTA: sotagliflozin; T1D: type 1 diabetes mellitus

Table 20: Analysis of Percent Change from Baseline to Week 52 in Mean Daily Insulin Dose in Pooled Studies 309 and 310

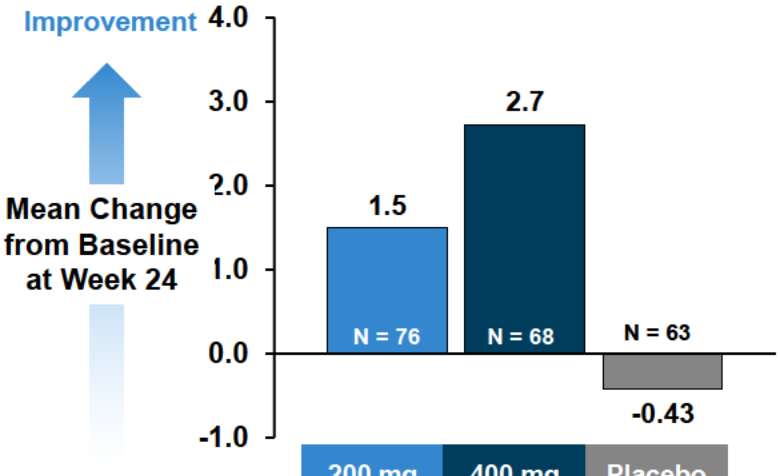
	Pooled Studies 309 and 310 T1D-CKD Population			Pooled Studies 309 and 310 T1D mITT Population		
	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)
Total insulin dose, IU/day						
Baseline, mean (SD)	68.63 (44.666)	61.46 (28.480)	70.12 (50.046)	62.71 (36.553)	62.77 (33.453)	64.37 (36.583)
LS mean % change from baseline (95% CL)	-5.03 (-9.04, -1.02)	-6.37 (-10.60, -2.13)	1.91 (-2.46, 6.28)	-4.98 (-6.86, -3.11)	-8.21 (-10.09, -6.33)	2.12 (0.23, 4.00)
Difference from placebo (95% CL)	-6.94 (-12.69, -1.18)	-8.28 (-14.23, -2.33)	—	-7.10 (-9.65, -4.55)	-10.33 (-12.88, -7.77)	—
p-value	0.018	0.007	—	<0.001	<0.001	—
Basal insulin dose, IU/day						
Baseline, mean (SD)	37.20 (27.294)	31.51 (17.070)	34.74 (19.466)	32.02 (20.457)	31.44 (16.893)	32.46 (17.519)
LS mean % change from baseline (95% CL)	-3.27 (-9.83, 3.28)	-0.04 (-6.87, 6.79)	3.93 (-3.12, 10.99)	-2.36 (-4.59, -0.13)	-4.50 (-6.73, -2.27)	4.75 (2.52, 6.98)
Difference from placebo (95% CL)	-7.21 (-16.73, 2.32)	-3.97 (-13.71, 5.77)	—	-7.11 (-10.16, -4.06)	-9.25 (-12.30, -6.20)	
p-value	0.14	0.42	—	<0.001	<0.001	
Bolus insulin dose, IU/day						
Baseline, mean (SD)	31.42 (21.717)	29.95 (17.526)	35.38 (34.071)	30.69 (20.821)	31.32 (21.068)	31.90 (23.352)
LS mean % change from baseline (95% CL)	-1.32 (-11.79, 9.14)	-4.84 (-15.89, 6.22)	3.58 (-7.82, 14.98)	-1.48 (-6.06, 3.09)	-8.58 (-13.17, -4.00)	5.14 (0.56, 9.73)
Difference from placebo (95% CL)	-4.90 (-19.94, 10.14)	-8.41 (-23.96, 7.13)	—	-6.63 (-12.87, -0.38)	-13.73 (-19.98, -7.47)	—
p-value	0.52	0.29	—	0.037	<0.001	—

CKD: chronic kidney disease; CL: confidence limit; LS: least squares; SD: standard deviation; SOTA: sotagliflozin; T1D: type 1 diabetes mellitus

6.5.2.5 *Patient-Reported Outcomes*

Results from the DTSQ, which evaluates patients' satisfaction with their diabetes treatment with sotagliflozin showed significantly higher dose-related improvements in satisfaction compared to placebo (Figure 26). Numeric reductions in DDS2 were observed with sotagliflozin.

Figure 26: Patient-Reported Outcomes in the T1D-CKD Population in Pooled Studies 309 and 310



	200 mg	400 mg	Placebo
LS Mean Change from Baseline (95% CI)	**1.9** (0.87, 2.99)	**2.6** (1.52, 3.70)	**-0.25** (-1.39, 0.88)
LS Mean Difference from Placebo (95% CI)	**2.2** (0.71, 3.65)	**2.9** (1.35, 4.38)	
p-value	**0.004**	**< 0.001**	

CI: confidence interval; CKD: chronic kidney disease; LS: least squares; T1D: type 1 diabetes mellitus; DTSQ: Diabetes Treatment Satisfaction Questionnaire

6.6 SCORED: Supportive Phase 3 Study

6.6.1 SCORED Study Design

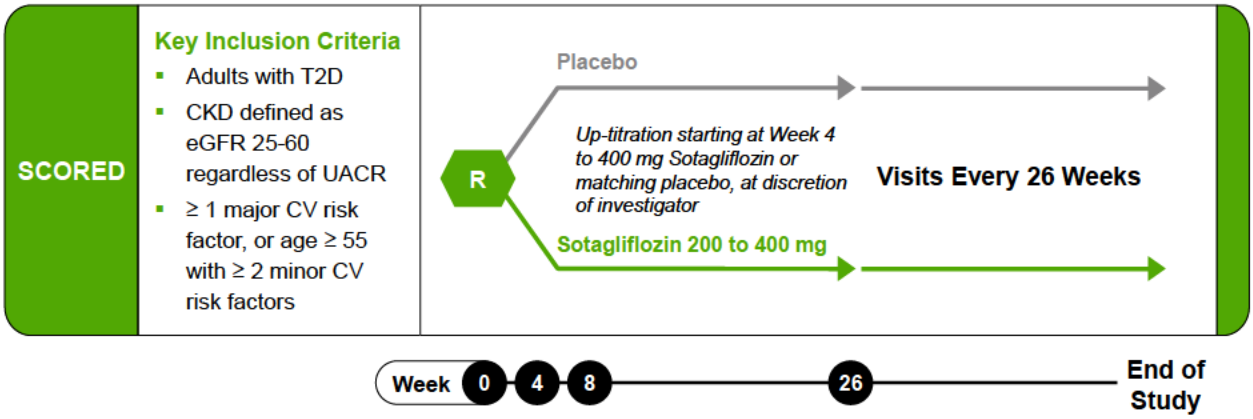
6.6.1.1 *Overview*

The SCORED study was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to compare the effect of sotagliflozin to placebo on total occurrences of CV death, hospitalization for HF, and urgent visit for HF in patients with T2D, moderate to severe renal impairment, and other CV risk factors.

The study consisted of 3 periods: Screening (1 to 4 weeks), treatment period including up-titration, and a post-treatment of 14 (± 4) days (Figure 27). Randomization was

stratified by region and by HF-related criteria. Patients received 200 mg sotagliflozin or matching placebo from Day 1 onward. The dose of sotagliflozin was increased to 400 mg sotagliflozin or matching placebo at Week 4 unless up-titration was not appropriate for safety reasons. If up-titration did not occur at Week 4 for safety reasons, all attempts were made to up-titrate at Week 8 or Week 26. The 400 mg dose (or 200 mg dose for those who could not tolerate up-titration by Visit 5) or corresponding matching placebo were maintained for the duration of the remaining treatment period. Approximately 75% of patients titrated their blinded study drug (sotagliflozin 400 mg or placebo).

Figure 27: SCORED Study Design



CV: cardiovascular; eGFR: estimated glomerular filtration rate (mL/min/1.73 m^2); T2D: type 2 diabetes mellitus; UACR: urine albumin-to-creatinine ratio

6.6.1.2 Enrollment Criteria

SCORED enrolled patients with T2D, A1C ≥7%, and either 1 major or 2 minor CV risk factors. Major risk factors included: hospitalization for HF during previous 2 years, left ventricle ejection fraction ≤40%, diagnosis of left ventricular hypertrophy, coronary artery calcium (CAC) score ≥300 Agatston Units, NT-proBNP ≥400 pg/mL, high-sensitivity troponin T >15.0 pg/mL for men and >10.0 pg/mL for women, high-sensitivity C-reactive protein (>3 mg/L), UACR ≥300 mg/g. Minor risk factored included: BMI ≥35 kg/m^2, dyslipidemia despite maximally tolerated statin therapy, currently smoking tobacco, CAC score >100 and <300 Agatston Units, UACR ≥30 mg/g and <300 mg/g, and resistant hypertension: SBP >140 mm Hg and diastolic BP >90 mm Hg despite antihypertensive therapy.

The CKD criteria for enrollment in SCORED was a screening eGFR ≥25 and ≤60 mL/min/1.73m^2 by the Modification of Diet in Renal Disease equation, regardless of UACR.

6.6.1.3 Efficacy Endpoints and Analysis Methods

The primary endpoint of SCORED was the total occurrences (first and potentially subsequent) after randomization of CV death, hospitalization for HF, and urgent visit for HF, evaluated in the intent-to-treat (ITT) population. The hierarchical testing in SCORED was terminated after the CV death endpoint was not met (Bhatt 2021). The prespecified kidney-related composite and MACE endpoints were after CV death in the hierarchy and thus discussion of these results below should be considered with this caveat.

In addition to clinical outcomes, other endpoints collected during the trial were A1C, body weight, and systolic blood pressure.

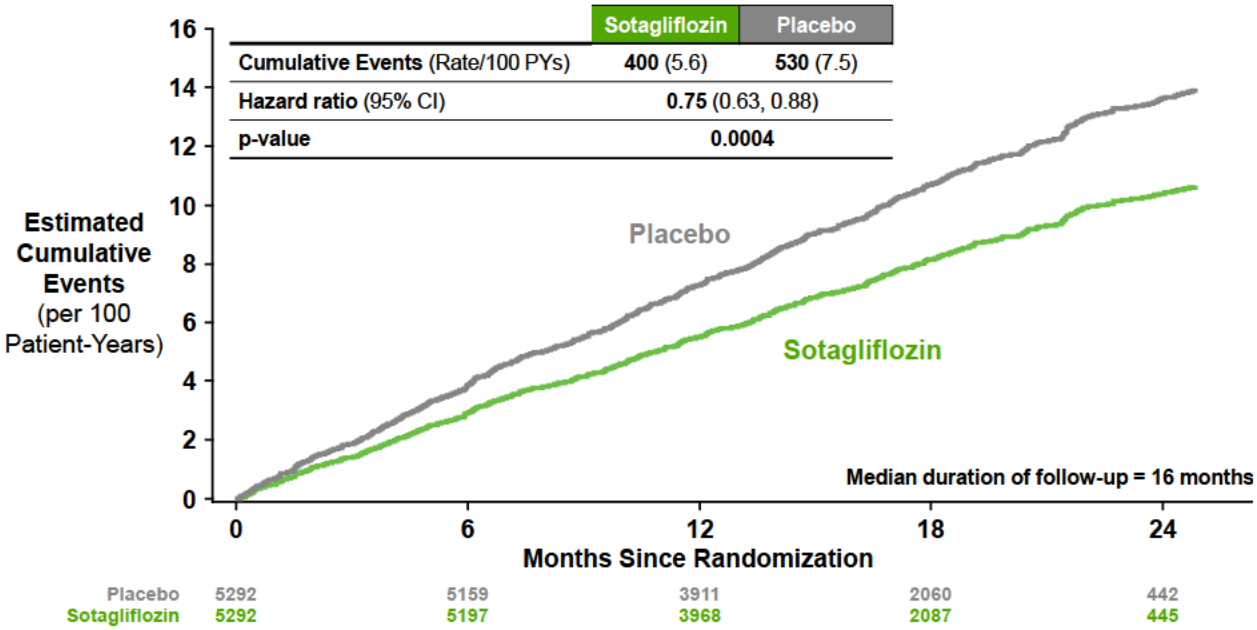
6.6.2 SCORED Efficacy Results ITT Population

6.6.2.1 Primary Endpoint (ITT Population)

In the overall population of patients with T2D, sotagliflozin met the primary objective. Sotagliflozin was superior to placebo in reducing the risk of the primary composite endpoint (hazard ratio [HR] [95% CI]: 0.75 [0.63, 0.88]; p=0.0004), demonstrating a 25% reduction in risk of CV death, hospitalization for HF, and urgent visit for HF. The median duration of follow up was 16 months.

In a cumulative events plot of the primary endpoint, the sotagliflozin and placebo event curves separated early and continued to diverge over the study period (Figure 28). These results demonstrated the benefits of sotagliflozin on long-term CV outcomes and supported approval for the HF indication.

Figure 28: Total Number of Occurrences of CV Death, Hospitalization for Heart Failure, and Urgent Visit for Heart Failure in SCORED ITT Population

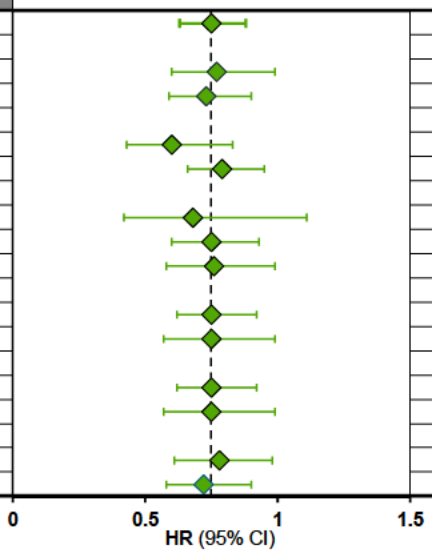


CI: confidence interval; CV: cardiovascular; ITT: intent-to-treat; PY: patient-year

Analyses showed consistent benefits on the primary endpoint across multiple prespecified subgroups (Figure 29). Considering that the Sponsor is proposing to limit the T1D-CKD population to those with an eGFR at least 45 mL/min/1.73m^2, we focus the discussion on this subgroup. Although the absolute risk of events was lowest in the subgroup with eGFR ≥45 mL/min/1.73m^2, the RR reduction of the primary composite endpoint was consistent across baseline eGFR subgroups (INPEFA PI).

Figure 29: Treatment Effect for Primary Composite Endpoint (Total Occurrences of Cardiovascular Death, Hospitalization for Heart Failure, and Urgent Heart Failure Visit) Subgroup Analysis (SCORED Study)

Subgroups, events per 100 PY	N	Sotagliflozin	Placebo	HR (95% CI)
Overall	10,584	5.6	7.5	**0.75** (063, 0.88)
Sex				
Female	4,754	5.1	6.5	**0.77** (0.60, 0.99)
Male	5,830	6.1	8.3	**0.73** (0.59, 0.90)
Age, years				
<65	3,224	3.8	6.4	**0.60** (0.43, 0.83)
≥65	7,360	6.4	8.0	**0.79** (0.66, 0.95)
Baseline eGFR (mL/min/1.73m²)				
<30	811	9.4	14.1	**0.68** (0.42, 1.11)
≥30 to <45	4,655	6.9	9.1	**0.75** (0.60, 0.93)
≥45	5,116	3.9	5.1	**0.76** (0.58, 0.99)
History of CVD				
Yes	5,144	7.8	10.6	**0.75** (0.62, 0.92)
No	5,440	3.6	4.6	**0.75** (0.57, 0.99)
History of HF at baseline				
Yes	3,283	12.6	16.8	**0.75** (0.62, 0.92)
No	7,301	2.6	3.4	**0.75** (0.57, 0.99)
LVEF at screening (%)				
<50	2,160	14.0	18.2	**0.78** (0.61, 0.98)
≥50	8,405	3.6	4.9	**0.72** (0.58, 0.90)



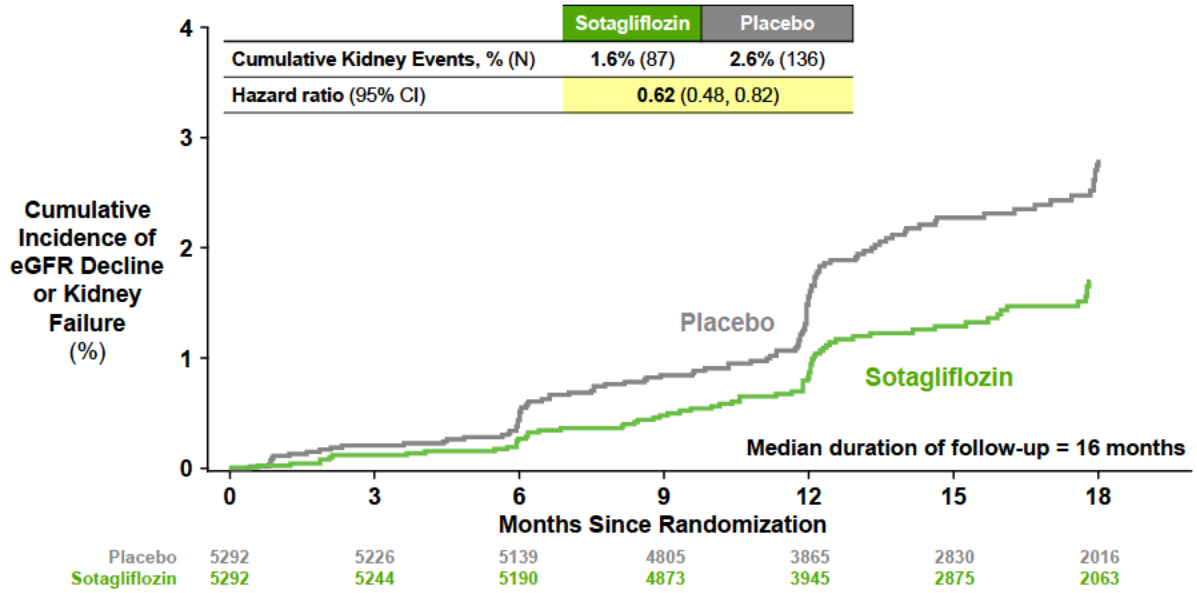
CI: confidence interval; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio; LVEF: left ventricular ejection fraction; PY: patient-years

6.6.2.2 Kidney Outcomes

In the initial analysis of the SCORED trial, because of early trial termination and suspension of adjudication, reconciliation of eGFR laboratory data and case report forms had not been completed. This resulted in a small number of kidney composite events (n=89) and a non-significant effect of sotagliflozin versus placebo on the predefined kidney composite outcome (HR [95% CI]: 0.71 [0.46, 1.08], p = 0.10) (Sridhar 2024b). Although not significant, the magnitude of the effect on kidney-related outcomes was consistent with those observed with SGLT2 inhibitors.

In an exploratory analysis conducted by the SCORED Steering Committee that used laboratory eGFR data, regardless of case report form completion, the effect of sotagliflozin was reassessed on the predefined kidney composite endpoint (first event of sustained ≥50% decline in eGFR, sustained eGFR <15 mL/min/1.73m^2, dialysis, or kidney transplant). The number of kidney composite events increased to 223. A nominal effect of sotagliflozin versus placebo was observed on the predefined kidney composite outcome (HR [95% CI]: 0.62 [0.48, 0.82]; Figure 30) (Sridhar 2024b).

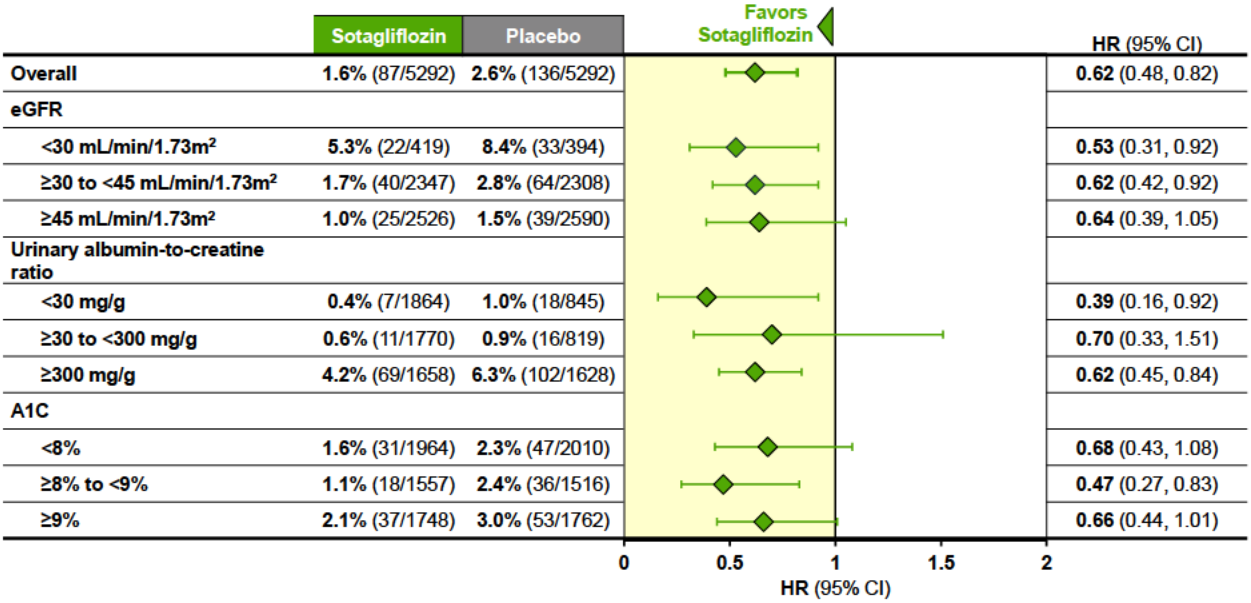
Figure 30: Cumulative Incidence of the Composite First Event of 50% Decline in eGFR or Kidney Failure Using Laboratory Data for eGFR Results



CI: confidence interval; eGFR: estimated glomerular filtration rate
Source: Sridhar 2024b

The effect of sotagliflozin was consistent across subgroups. Although the absolute risk of events was lowest in the subgroup with eGFR ≥45 mL/min/1.73m^2, the RR reduction for the kidney composite endpoint was consistent across baseline eGFR subgroups (Figure 31) (Sridhar 2024b).

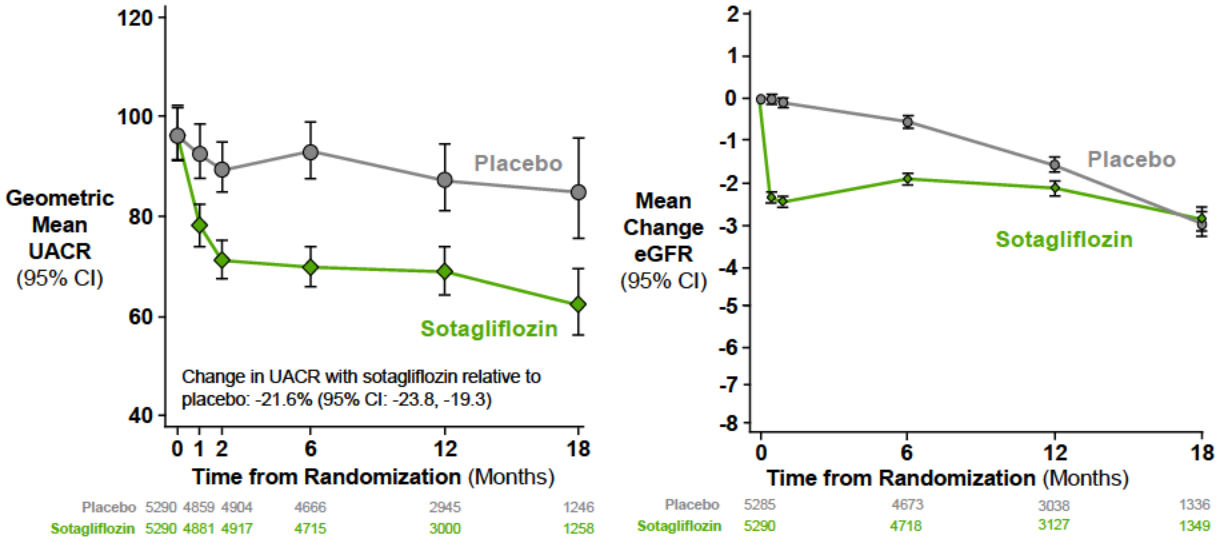
Figure 31: Subgroup Analysis of Composite First Event of 50% Decline in eGFR or Kidney Failure



A1C: hemoglobin A1C; CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio

In other kidney-related endpoints from SCORED, treatment with sotagliflozin led to a 22% difference in UACR from placebo (Figure 32) (Cherney 2023). Treatment with sotagliflozin led to an expected acute reduction in eGFR and then stabilized compared to progressive reduction in eGFR with placebo over time.

Figure 32: Change from Baseline in Kidney-related Endpoints (UACR and eGFR) in the SCORED Trial

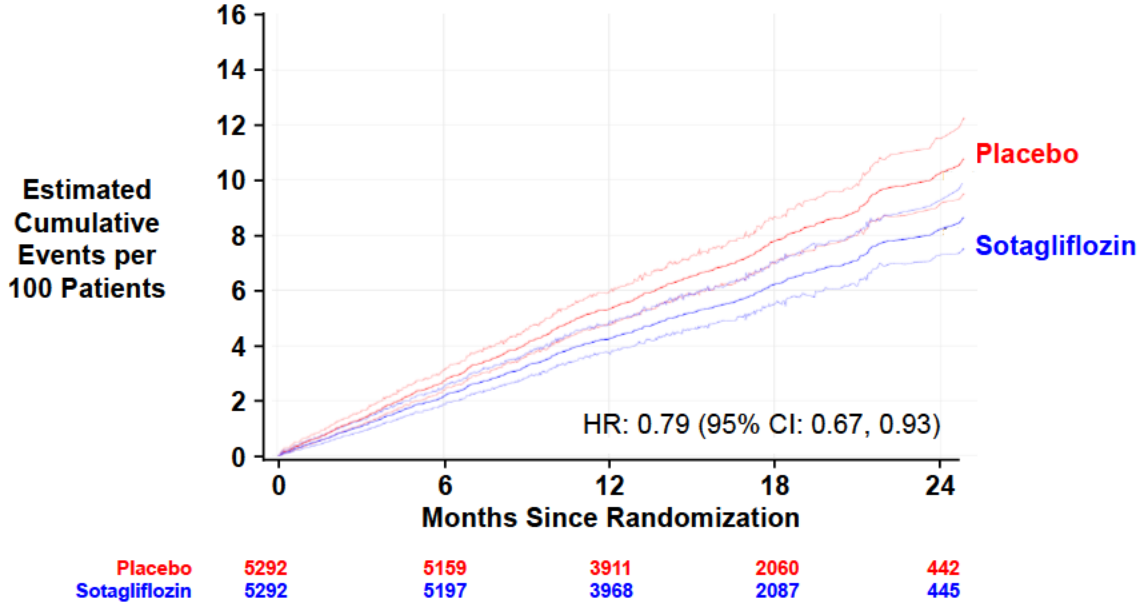


CI: confidence interval; eGFR: estimated glomerular filtration rate; UACR: urine albumin-to-creatinine ratio
Cherney 2023

6.6.2.3 Major Adverse Cardiovascular Events (MACE)

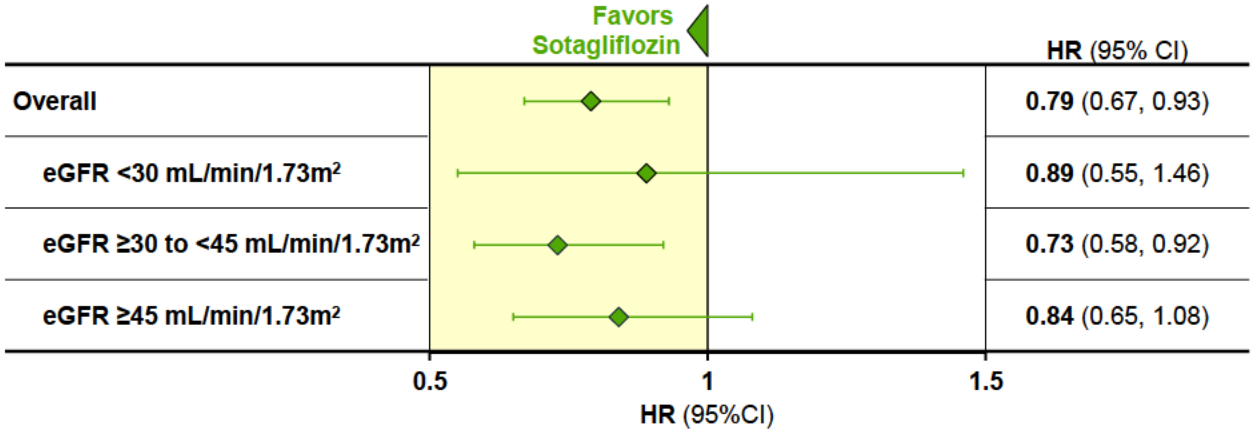
Sotagliflozin reduced the risk of total occurrence of MACE including CV death, non-fatal myocardial infarction, and non-fatal stoke by 21% (HR [95% CI]: 0.79 [0.67, 0.93]) Figure 33). Although the absolute risk of MACE was lowest the subgroup with eGFR ≥45 mL/min/1.73 m^2, the RR reduction for MACE was consistent across baseline eGFR subgroups (Figure 34).

Figure 33: Total Occurrences of MACE (CV Death, Non-fatal MI or Non-fatal MI) (Investigator-Reported) – ITT Population



CI: confidence interval; CV: cardiovascular; HR: hazard ratio; ITT: intent-to-treat; MACE: major adverse cardiovascular events; MI: myocardial infarction

Figure 34: Subgroup Analysis of MACE Event



CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; MACE: major adverse cardiovascular events

Overall, these results demonstrate that although CKD patients with a baseline eGFR ≥45 mL/min/1.73m^2 have a lower absolute risk of cardiorenal events compared to those with lower kidney function, treatment with sotagliflozin improved cardiorenal outcomes regardless of baseline eGFR.

6.6.3 SCORED Matching T2D-CKD Patient Population

6.6.3.1 Subgroup

For the efficacy analyses supporting the proposed indication, and to remain consistent with the T1D-CKD population, a matching T2D-CKD population was defined as patients with T2D and a baseline eGFR 45 to <60 mL/min/1.73m^2 or an eGFR ≥60 mL/min/1.73m^2 and UACR ≥30 mg/g.

Analysis of the change from Baseline over time in A1C, body weight, and SBP for the T2D-CKD population in the SCORED dataset was performed by a repeated-measures mixed-effects model with absolute change in the dependent variable as the outcome of interest, a random effect for intercept, and fixed effects for treatment, Baseline value, and time. The variance-covariance matrix was specified to be unstructured.

In SCORED, 10,584 patients with T2D, moderate to severe renal impairment, and other CV risk factors were randomized. Of the 10,584 randomized patients in the SCORED study, 4959 (46.9%) were included in the T2D-CKD population who matched the T1D-CKD criteria (Table 21). In the matched cohort, a total of 105 patients who received placebo and 98 patients who received sotagliflozin had a Baseline eGFR ≥60 mL/min/1.73m^2 and UACR ≥30 mg/g.

Table 21: SCORED Matching T2D-CKD Population

	SCORED	
	Sotagliflozin	**Placebo**
Total T2D cohort, N	5,292	5,292
Matched T2D-CKD population, n (%) (eGFR 45 to <60 mL/min/1.73m^2 or eGFR ≥60 mL/min/1.73m^2 and UACR ≥30 mg/g)	2,444 (46.2%)	2,515 (47.5%)
Baseline eGFR ≥45 to <60, n %	2,346 (96.0%)	2,408 (95.7%)
Baseline eGFR ≥60 and UACR ≥30, n %	98 (4.0%)	105 (4.2%)

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; UACR: urine albumin-to-creatinine ratio; T2D: type 2 diabetes mellitus

6.6.3.2 Demographics and Baseline Characteristics

Mean age of the matching T2D-CKD population was 68.0 years, and approximately 40% of the patients were female (Table 22). Baseline mean BMI was 32.3 kg/m^2. At Baseline, the mean A1C value was 8.71%, and mean SBP was 137.8 mm Hg (Table 23).

Table 22: Summary of Demographics in the SCORED Matching T2D-CKD Population

	Matching T2D-CKD Population	
	SOTA (N=2444)	Placebo (N=2515)
Age at study entry (years), mean (SD)	68.0 (8.4)	68.0 (8.4)
Sex, n (%)		
Male	1445 (59.1)	1458 (58.0)
Female	999 (40.9)	1057 (42.0)
Race, n (%)		
White	2041 (83.5)	2079 (82.7)
Black or African American	79 (3.2)	101 (4.0)
Asian	142 (5.8)	151 (6.0)
American Indian or Alaska Native	100 (4.1)	94 (3.7)
Native Hawaiian or other Pacific Islander	12 (0.5)	6 (0.2)
Multiple	49 (2.0)	64 (2.5)
Not reported	10 (0.4)	8 (0.3)
Unknown	9 (0.4)	10 (0.4)
BMI (kg/m^2)		
Mean (SD)	32.3 (6.1)	32.2 (6.1)

BMI: body mass index; CKD: chronic kidney disease; SD: standard deviation; SOTA: sotagliflozin; T2D: type 2 diabetes mellitus

Table 23: Summary of Baseline Characteristics in the SCORED Matching T2D-CKD Population

	Matching T2D-CKD Population	
	SOTA (N=2444)	Placebo (N=2515)
Baseline A1C (%) categories, n (%)		
<8.0	915 (37.4)	942 (37.5)
≥8.0 to <9.0	685 (28.0)	723 (28.7)
≥9.0 to <10.0	427 (17.5)	417 (16.6)
≥10.0	417 (17.1)	431 (17.1)
A1C (%)		
Mean (SD)	8.7 (1.5)	8.7 (1.5)
Baseline eGFR (mL/min/1.73m²)		
Mean (SD)	51.9 (4.8)	52.0 (4.8)
Baseline UACR (mg/g)		
Median (min, max)	61 (0, 14430)	56 (0, 10796)
Baseline UACR (mg/g) categories, n (%)[a]		
<30 (normal)	850 (34.8)	948 (37.7)
≥30 to 300 (microalbuminuria)	960 (39.3)	963 (38.3)
≥300 (macroalbuminuria)	633 (25.9)	603 (24.0)
Baseline SBP (mm Hg)		
Mean (SD)	137.9 (16.1)	137.8 (16.3)

A1C: hemoglobin A1C; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; UACR: urine albumin-to-creatinine ratio; SBP: systolic blood pressure; SD: standard deviation; SOTA: sotagliflozin; T2D: type 2 diabetes mellitus

a. Baseline UACR was defined as the average of all spot urine values assessed by the central laboratory from Screening up to and including randomization. However, if the 24-urine value during Screening indicated the patient was ≥300, the patient was included in the macroalbuminuria category.

6.6.3.3 Change in A1C

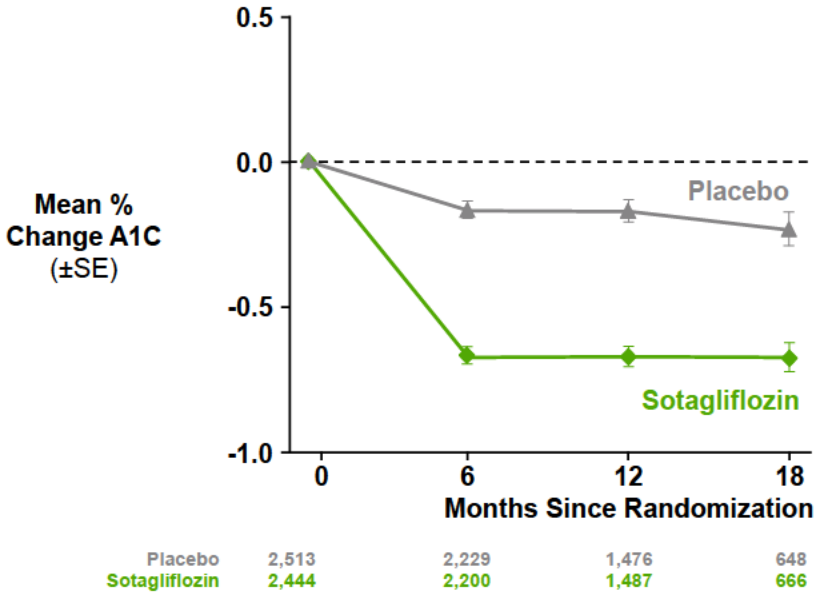
The decrease in A1C was significant in the T2D-CKD population compared with placebo. The LS mean change from baseline in A1C was -0.65% for sotagliflozin, and the placebo-subtracted LS mean A1C reduction was -0.47% over the follow-up period (nominal p <0.0001; Table 24). Importantly, the benefits on A1C control were sustained through long-term follow-up (Figure 35).

Table 24: Effect of Sotagliflozin Versus Placebo on Change in A1C in the SCORED Matching T2D-CKD Population

	SOTA (N=2444)	Placebo (N=2515)
N	2444	2513
Baseline A1C (%), mean (SD)	8.7 (1.5)	8.7 (1.5)
LS mean change from baseline (95% CI), %	-0.65 (-0.70, -0.60)	-0.18 (-0.23, -0.14)
Difference from placebo (95% CI), %	-0.47 (-0.53, -0.40)	—
Nominal p-value	<0.0001	—

A1C: hemoglobin A1C; CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; LS: least squares; SBP: systolic blood pressure; SD: standard deviation; SOTA: sotagliflozin; T2D: type 2 diabetes mellitus; UACR: urine albumin-to-creatinine ratio
Notes: CKD was defined as a baseline eGFR of 45 to <60 mL/min/1.73m^2 or a baseline eGFR ≥60 mL/min/1.73m^2 and baseline UACR ≥30 mg/g. The p-value is obtained from the repeated-measures mixed effects model with change in parameter from baseline as the outcome, a random effect for intercept, and fixed effects for treatment, baseline A1C, body weight, or SBP value and time. The variance-covariance matrix was specified to be unstructured.

Figure 35: Mean Change from Baseline in A1C in the SCORED Matching T2D-CKD Population



A1C: hemoglobin A1C; CKD: chronic kidney disease; SE: standard error; T2D: type 2 diabetes mellitus

6.6.3.4 *Change in Body Weight*

In the T2D-CKD population, the decrease in body weight for sotagliflozin was nominally significant compared to placebo. The LS mean difference from placebo was -1.19 kg (nominal p<0.0001; Table 25).

Table 25: Effect of Sotagliflozin Versus Placebo on Change in Body Weight in the SCORED Matched T2D-CKD Population

	SOTA (N=2444)	Placebo (N=2515)
N	2444	2514
Baseline body weight (kg), mean (SD)	89.0 (19.9)	88.5 (19.4)
LS mean change from baseline (95% CI), kg	-1.48 (-1.59, -1.37)	-0.29 (-0.39, -0.18)
Difference from placebo (95% CI), kg	-1.19 (-1.34, -1.05)	—
Nominal p-value	<0.0001	

A1C: hemoglobin A1C; CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; LS: least squares; SBP: systolic blood pressure; SD: standard deviation; SOTA: sotagliflozin; T2D: type 2 diabetes mellitus; UACR: urine albumin-to-creatinine ratio
Notes: CKD was defined as a baseline eGFR of 45 to <60 mL/min/1.73m^2 or a baseline eGFR ≥60 mL/min/1.73m^2 and baseline UACR ≥30 mg/g. The p-value is obtained from the repeated-measures mixed effects model with change in parameter from baseline as the outcome, a random effect for intercept, and fixed effects for treatment, baseline A1C, body weight, or SBP value and time. The variance-covariance matrix was specified to be unstructured.

6.6.3.5 *Change in Systolic Blood Pressure*

In the matching T2D-CKD population, the decrease in SBP for sotagliflozin was nominally significant compared to placebo. The LS mean difference from placebo was -2.4 mm Hg (nominal p<0.0001; Table 26).

Table 26: Effect of Sotagliflozin Versus Placebo on Change in SBP in the SCORED Matching T2D-CKD Population

	SOTA (N=2444)	Placebo (N=2515)
N	2444	2514
Baseline (mm Hg), mean (SD)	137.9 (16.1)	137.8 (16.3)
LS mean change from baseline (95% CI), mm Hg	-4.0 (-4.4, -3.6)	-1.6 (-2.0, -1.2)
Difference from placebo (95% CI), mm Hg	-2.4 (-2.9, -1.8)	—
Nominal p-value	<0.0001	

CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; LS: least squares; SBP: systolic blood pressure; SD: standard deviation; SOTA: sotagliflozin; T2D: type 2 diabetes mellitus; UACR: urine albumin-to-creatinine ratio
Notes: CKD was defined as a baseline eGFR of 45 to <60 mL/min/1.73m^2 or a baseline eGFR ≥60 mL/min/1.73m^2 and baseline UACR ≥30 mg/g. The p-value is obtained from the repeated-measures mixed effects model with change in parameter from baseline as the outcome, a random effect for intercept, and fixed effects for treatment, baseline SBP value and time. The variance-covariance matrix was specified to be unstructured.

6.6.3.6 *Primary CV Endpoint in Matching T2D with CKD Population*

In the matching T2D-CKD population, sotagliflozin was superior to placebo in reducing the risk of the primary composite endpoint (HR [95% CI]: 0.75 [0.57, 0.98]), demonstrating a 25% reduction in risk of CV death, hospitalization for HF, and urgent visit for HF (Table 27). This is consistent with the overall SCORED population and the subgroup analysis by baseline eGFR (see Figure 28 and Figure 31).

Table 27: Total Occurrences of CV Death, Hospitalization for HF, and Urgent HF Visit Clinical Events (Investigator Reported) in the SCORED Matching T2D-CKD Population

Variable:	Sotagliflozin (N=2444)	Placebo (N=2515)
Cumulative duration at risk (years)[a]	3316.4	3375.5
Cumulative number of events (event rate per 100 patient-years)[b]	133 (4.0)	177 (5.2)
HR (95% CI)[d]	0.75 (0.57, 0.98)	

CI: confidence interval; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio; T2D: type 2 diabetes mellitus; UACR: urine albumin-to-creatinine ratio
a Duration at risk for each patient=date of study completion or discontinuation – date of first dose + 1.
b Event rate is calculated as the cumulative number of events/[cumulative duration at risk (years)/100].
c Difference in absolute risk is calculated as sotagliflozin event rate – placebo event rate.
HR is the ratio of sotagliflozin compared to placebo, therefore a HR less than 1 indicates a lower rate with sotagliflozin than with placebo.
CKD is defined as (eGFR of 45 to <60 mL/min/1.73m^2) or (eGFR ≥60 mL/min/1.73m^2 and UACR ≥30 mg/g).

6.7 Efficacy Conclusions

In two distinct datasets evaluating subgroups of patients with T1D and CKD, treatment with sotagliflozin 200 and 400 mg had similar significant and beneficial effects on A1C and body weight compared to placebo over 24 weeks. The effect on A1C was attenuated, but body weight changes were sustained over the 52-week period. SBP was improved with sotagliflozin 400 mg in Study 312, but not in the pooled 309/310 T1D-CKD population.

Results in the matching T2D-CKD population in the SCORED study were generally aligned with the results in the T1D-CKD population, providing evidence of sustained glycemic control in patients with CKD. Furthermore, in SCORED, treatment with sotagliflozin led to long-term cardiorenal benefits in patients with T2D and CKD.

These efficacy results collectively support the indication of sotagliflozin as an adjunct to insulin therapy to improve glycemic control in adults with T1D and CKD.

7 CLINICAL SAFETY

Summary

- The safety profile of sotagliflozin in the T1D-CKD population is consistent with that of the approved indication.
- The most frequently reported TEAEs in the sotagliflozin groups were urinary tract infection, diarrhea, and viral upper respiratory tract infection.
- TEAEs were mostly mild or moderate in severity. Compared with placebo, fewer patients receiving sotagliflozin experienced a severe event.
- SAEs were similar in frequency between treatment groups. DKA and hypoglycemia were the only SAEs that were reported in more than 1 patient per sotagliflozin treatment arm.
- Sotagliflozin treatment did not result in an increase in AEs leading to study drug discontinuation through 52 weeks.
- In the T1D-CKD population sotagliflozin does not increase the risk of hypoglycemia including severe events. Thus, evidence supports that treatment with sotagliflozin, compared to placebo, achieves improved glycemic control without an increase in risk of severe hypoglycemia.
- While sotagliflozin increases the risk for DKA, this can be managed with patient selection and education.
- Overall, the safety profile of sotagliflozin supports its use as an adjunct to insulin in the setting of education and monitoring for DKA.

7.1 Overall Safety Profile in Approved Indication

In the Phase 3 trials supporting the approved indication of sotagliflozin, the incidence of AEs was similar between treatment groups (Table 28).

Table 28: Safety Overview in Patients with T2D in SCORED

Patients with Event, n (%)	SCORED	
	SOTA N=5291	Placebo N=5286
Any TEAE	3718 (70.3)	3738 (70.7)
Mild	2833 (53.5)	2879 (54.5)
Moderate	2089 (39.5)	2161 (40.9)
Severe	780 (14.7)	845 (16.0)
TEAE leading to interruption of study drug	885 (16.7)	806 (15.2)
TEAE leading to permanent discontinuation	228 (4.3)	199 (3.8)
SAE	1234 (23.3)	1334 (25.2)
Death	170 (3.2)	188 (3.6)

SAE: serious adverse event; SOTA: sotagliflozin; TEAE: treatment-emergent adverse event; T2D: type 2 diabetes mellitus
Sotagliflozin dose: 200 mg titrated to 400 mg

7.2 Safety Populations Supporting T1D-CKD

Safety data supporting the proposed indication are derived from pooled data from Studies 309 and 310 through 52 weeks, as well as data from Study 312 through 24 weeks.

7.3 Exposure in Patients with T1D-CKD

In the pooled Studies 309 and 310 T1D-CKD population, a total of 160 patients were treated with sotagliflozin (200 mg or 400 mg once daily) for a mean of 336 days (median: 364 days). The total duration of treatment exposure was 147 patient-years. Overall, 149 patients (93.1%) in Studies 309 and 310 were treated with sotagliflozin for at least 6 months (Table 29).

In the Study 312 T1D-CKD population, a total of 114 patients were treated with 400 mg sotagliflozin for a mean duration of 150 days (median: 168 days). The total duration of treatment was 46.8 patient-years.

Table 29: Summary of Treatment Exposure in Pooled Studies 309 and 310 and in Study 312

	T1D-CKD Population					T1D Safety Population				
	Pooled Studies 309 and 310 52-Week			Study 312 24-Week		Pooled Studies 309 and 310 52-Week			Study 312 24-Week	
Characteristic	SOTA 200 mg	SOTA 400 mg	Placebo	SOTA 400 mg	Placebo	SOTA 200 mg	SOTA 400 mg	Placebo	SOTA 400 mg	Placebo
Overall duration of exposure (days)										
N	85	75	74	114	110	524	525	526	699	703
Mean (SD)	339.1 (82.3)	332.4 (83.1)	319.8 (103.0)	150.0 (46.9)	154.9 (39.5)	334.6 (84.92)	331.9 (86.72)	329.3 (89.87)	155.8 (40.58)	157.9 (36.79)
Median	364.0	364.0	364.0	168.0	168.0	364.0	364.0	364.0	168.0	168.0
Minimum, Maximum	16, 380	10, 375	2, 387	1, 188	8, 189	1, 392	2, 395	2, 390	1, 205	1, 236
Total exposure (patient-years)	78.9	68.3	64.8	46.8	46.6	480.02	477.13	474.20	298.18	303.92
Duration categories, n (%)										
<28 days	2 (2.4)	1 (1.3)	4 (5.4)	5 (4.4)	2 (1.8)	6 (1.1)	6 (1.1)	10 (1.9)	25 (3.6)	17 (2.4)
≥6 months*	79 (92.9)	70 (93.3)	65 (87.8)	77 (67.5)	73 (66.4)	480 (91.6)	478 (91.0)	477 (90.7)	486 (69.5)	481 (68.4)
≥1 year	50 (58.8)	47 (62.7)	41 (55.4)	-	-	333 (63.5)	335 (63.8)	319 (60.6)	-	-

CKD: chronic kidney disease; SD: standard deviation; SOTA: sotagliflozin; T1D: type 1 diabetes mellitus
*Duration was ≥168 days in Study 312. Note: The denominator for percentages is the number of patients with non-missing data in the T1D-CKD population for each treatment group. Duration of exposure is calculated as (date of last dose - date of first dose) + 1. If a patient was lost to follow-up without a date of last dose of double-blind study drug, duration was assumed to be 1 day. Total exposure in patient-years is calculated as: sum of duration of exposure for all patients/365.25.

7.4 Overall Summary of Adverse Events in Patients with T1D-CKD

In the pooled Studies 309 and 310 T1D-CKD population, TEAEs were relatively common and the incidences were similar across treatment groups (Table 30). A general increase in TEAEs at the higher sotagliflozin dose was not apparent. TEAEs were mostly mild or moderate in severity and severe TEAEs were similar across treatment arms. SAEs were similar in frequency in sotagliflozin-treated patients through 52 weeks, and sotagliflozin treatment did not result in an increase in AEs leading to study drug discontinuation. Two patients (2.7%) experienced AEs leading to death through 52 weeks, both in the placebo group.

The AE pattern across study treatment in the Study 312 T1D-CKD population was similar to the pooled Studies 309 and 310 T1D-CKD population.

Table 30: Overall Summary of Treatment-Emergent Adverse Events in Pooled Studies 309 and 310 and in Study 312

	T1D-CKD Population					T1D Safety Population				
	Pooled Studies 309 and 310 52-Week T1D-CKD Population			Study 312 24-Week T1D-CKD Population		Pooled Studies 309 and 310 52-Week Population			Study 312 24-Week Population	
TEAE, n (%)	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Patients with any TEAE	68 (80.0)	51 (68.0)	56 (75.7)	67 (58.8)	54 (49.1)	393 (75.0)	390 (74.3)	374 (71.1)	385 (55.1)	369 (52.5)
Patients with Severe TEAE	11 (12.9)	6 (8.0)	10 (13.5)	12 (10.5)	7 (6.4)	50 (9.5)	48 (9.1)	37 (7.0)	42 (6.0)	25 (3.6)
Patients with SAE	12 (14.1)	8 (10.7)	10 (13.5)	12 (10.5)	8 (7.3)	53 (10.1)	50 (9.5)	37 (7.0)	48 (6.9)	23 (3.3)
Patients with TEAE leading to study drug discontinuation	3 (3.5)	4 (5.3)	4 (5.4)	8 (7.0)	4 (3.6)	23 (4.4)	35 (6.7)	20 (3.8)	44 (6.3)	16 (2.3)
Patients with TEAE leading to death	0	0	2 (2.7)	0	0	0	0	3 (0.6)	1 (0.1)	0

CKD: chronic kidney disease; SAE: serious adverse event; SOTA: sotagliflozin; T1D: type 1 diabetes mellitus; TEAE: treatment-emergent adverse event
Note: The denominator for percentages is the number of patients in the T1D-CKD population for each treatment group within the subgroup.
Note: TEAEs are events with onset date on or after the date of first dose of study drug and up to 30 days after the date of last dose of study drug. Some events of special interest (cardiovascular events [including death], bone fractures, venous thrombotic events, drug-induced liver injury, and malignancies) may be attributed to long-term effects of study drug and are included in the analysis of TEAEs even if the onset was more than 30 days after the last dose of study drug. For hypoglycemic events that were reported as adverse events, the date of the last dose of study drug was the cut-off date for inclusion in the analysis of TEAEs.

7.5 Common Adverse Events in Patients with T1D-CKD

In the pooled Studies 309 and 310 T1D-CKD population, the most frequently reported TEAEs by system organ class included Infections and Infestations and Gastrointestinal Disorders. The most frequently reported preferred terms (PTs) were viral upper respiratory tract infection, diarrhea, and urinary tract infection (Table 31).

Among the most common TEAEs, some of the individual PTs of interest having a difference in incidence between sotagliflozin-treated patients and placebo-treated patients included the following:

- Investigator-reported DKA (4 patients [4.7%], 5 patients [6.7%], and 2 patients [2.7%] in the sotagliflozin 200 mg, sotagliflozin 400 mg, and placebo groups, respectively);
- Blood ketone body increased (7 patients [8.2%], 4 patients [5.3%], and 1 patient [1.4%], respectively);
- Diarrhea (8 patients [9.4%], 8 patients [10.7%], and 3 patients [4.1%], respectively);
- Genital infection fungal (1 patient [1.2%], 3 patients [4.0%], and 0 patients, respectively).

DKA (positively adjudicated) is described in Section 7.12.

TEAEs in the Study 312 T1D-CKD population were similar to the sotagliflozin 400 mg arm of the pooled T1D-CKD population.

Table 31: Summary of Most Common TEAEs (PTs Reported by ≥3% of Patients in T1D-CKD Population) in Pooled Studies 309 and 310 and in Study 312

	T1D-CKD Population					T1D Safety Population				
	Pooled Studies 309 and 310 52-Week			Study 312 24-Week		Pooled Studies 309 and 310 52-Week			Study 312 24-Week n	
Preferred Term, n (%)	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Patients with TEAE	68 (80.0)	51 (68.0)	56 (75.7)	67 (58.8)	54 (49.1)	393 (75.0)	390 (74.3)	374 (71.1)	385 (55.1)	369 (52.5)
Urinary tract infection	11 (12.9)	2 (2.7)	5 (6.8)	5 (4.4)	5 (4.5)	32 (6.1)	20 (3.8)	26 (4.9)	22 (3.1)	24 (3.4)
Diarrhea	8 (9.4)	8 (10.7)	3 (4.1)	8 (7.0)	3 (2.7)	34 (6.5)	49 (9.3)	29 (5.5)	35 (5.0)	17 (2.4)
Blood ketone body increased	7 (8.2)	4 (5.3)	1 (1.4)	6 (5.3)	1 (0.9)	21 (4.0)	27 (5.1)	3 (0.6)	25 (3.6)	8 (1.1)
Viral upper respiratory tract infection	7 (8.2)	14 (18.7)	9 (12.2)	5 (4.4)	6 (5.5)	78 (14.9)	74 (14.1)	69 (13.1)	41 (5.9)	55 (7.8)
Nausea	6 (7.1)	4 (5.3)	2 (2.7)	8 (7.0)	6 (5.5)	21 (4.0)	23 (4.4)	26 (4.9)	30 (4.3)	22 (3.1)
Constipation	5 (5.9)	1 (1.3)	2 (2.7)	2 (1.8)	3 (2.7)	17 (3.2)	6 (1.1)	9 (1.7)	10 (1.4)	5 (0.7)
Pollakiuria	5 (5.9)	0	1 (1.4)	4 (3.5)	1 (0.9)	16 (3.1)	10 (1.9)	7 (1.3)	17 (2.4)	4 (0.6)
Diabetic ketoacidosis	4 (4.7)	5 (6.7)	2 (2.7)	3 (2.6)	3 (2.7)	21 (4.0)	30 (5.7(	5 (1.0)	25 (3.6)	7 (1.0)
Dizziness	4 (4.7)	2 (2.7)	1 (1.4)	5 (4.4)	0	13 (2.5)	9 (1.7)	9 (1.7)	10 (1.4)	4 (0.6)
Hypoglycemia	4 (4.7)	1 (1.3)	1 (1.4)	6 (5.3)	2 (1.8)	12 (2.3)	9 (1.7)	12 (2.3)	12 (1.7)	6 (0.9)
Musculoskeletal pain	4 (4.7)	1 (1.3)	1 (1.4)	0	0	9 (1.7)	7 (1.3)	12 (2.3)	0	5 (0.7)
Upper respiratory tract infection	4 (4.7)	4 (5.3)	9 (12.2)	2 (1.8)	2 (1.8)	39 (7.4)	39 (7.4)	55 (10.5)	24 (3.4)	34 (4.8)
Vomiting	3 (3.5)	1 (1.3)	1 (1.4)	3 (2.6)	1 (0.9)	16 (3.1)	11 (2.1)	15 (2.9)	13 (1.9)	14 (2.0)
Arthralgia	3 (3.5)	1 (1.3)	0	1 (0.9)	1 (0.9)	16 (3.1)	11 (2.1)	9 (1.7)	5 (0.7)	4 (0.6)
Bronchitis	3 (3.5)	1 (1.3)	2 (2.7)	2 (1.8)	1 (0.9)	14 (2.7)	13 (2.5)	16 (3.0)	9 (1.3)	12 (1.7)
Cough	3 (3.5)	5 (6.7)	2 (2.7)	1 (0.9)	2 (1.8)	12 (2.3)	25 (4.8)	12 (2.3)	5 (0.7)	10 (1.4)

	T1D-CKD Population					T1D Safety Population				
	Pooled Studies 309 and 310 52-Week			Study 312 24-Week		Pooled Studies 309 and 310 52-Week			Study 312 24-Week n	
Preferred Term, n (%)	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Limb injury	3 (3.5)	1 (1.3)	0	0	1 (0.9)	4 (0.8)	1 (0.2)	1 (0.2)	0	3 (0.4)
Back pain	2 (2.4)	5 (6.7)	4 (5.4)	1 (0.9)	3 (2.7)	14 (2.7)	20 (3.8)	11 (2.1)	8 (1.1)	8 (1.1)
Headache	2 (2.4)	3 (4.0)	0	4 (3.5)	3 (2.7)	15 (2.9)	20 (3.8)	19 (3.6)	17 (2.4)	19 (2.7)
Vulvovaginal mycotic infection	2 (2.4)	5 (6.7)	2 (2.7)	1 (0.9)	1 (0.9)	15 (2.9)	27 (5.1)	10 (1.9)	14 (2.0)	6 (0.9)
Blood creatinine increased	1 (1.2)	3 (4.0)	2 (2.7)	0	1 (0.9)	6 (1.1)	3 (0.6)	3 (0.6)	5 (0.7)	8 (1.1)
Gastroenteritis	1 (1.2)	2 (2.7)	3 (4.1)	2 (1.8)	3 (2.7)	15 (2.9)	17 (3.2)	12 (2.3)	7 (1.0)	16 (2.3)
Genital infection fungal	1 (1.2)	3 (4.0)	0	2 (1.8)	0	18 (3.4)	21 (4.0)	1 (0.2)	10 (1.4)	5 (0.7)
Ankle fracture	0	0	3 (4.1)	0	0	0	2 (0.4)	3 (0.6)	1 (0.1)*	4 (0.6)*
Pyrexia	0	3 (4.0)	1 (1.4)	1 (0.9)	1 (0.9)	10 (1.9)	13 (2.5)	10 (1.9)	2 (0.3)	5 (0.7)

CKD: chronic kidney disease; PT: preferred term; SOTA: sotagliflozin; TEAE: treatment-emergent adverse event; T1D: type 1 diabetes mellitus
*PT in Study 312 is foot fracture

7.6 Severe Adverse Events in Patients with T1D-CKD

In the pooled Studies 309 and 310 T1D-CKD population, severe AEs occurred at similar rates in the treatment groups in the placebo group. The most frequently reported severe AEs were hypoglycemia and DKA (Table 32).

Table 32: Severe Adverse Events (≥ 1 Patient in the T1D-CKD Population)

Preferred Term, n (%)	Pooled Studies 309 and 310 52-Week T1D-CKD Population			Pooled Studies 309 and 310 52-Week T1D Population		
	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)
Patients with severe TEAEs	11 (12.9)	6 (8.0)	10 (13.5)	50 (9.5)	48 (9.1)	37 (7.0)
Hypoglycemia	4 (4.7)	1 (1.3)	1 (1.4)	12 (2.3)	7 (1.3)	9 (1.7)
Diabetic ketoacidosis	3 (3.5)	3 (4.0)	0	12 (2.3)	19 (3.6)	1 (0.2)
Acute myocardial infarction	1 (1.2)	0	1 (1.4)	2 (0.4)	2 (0.4)	1 (0.2)
Atrial fibrillation	1 (1.2)	0	1 (1.4)	1 (1.2)	0	1 (1.4)
Foot deformity	1 (1.2)	0	0	1 (1.2)	0	0
Hypoglycemic unconsciousness	1 (1.2)	0	1 (1.4)	2 (0.4)	2 (0.4)	3 (0.6)
Mental status changes	1 (1.2)	0	0	1 (1.2)	0	0
Pneumonia	1 (1.2)	0	0	2 (0.4)	1 (0.2)	0
Rotavirus infection	1 (1.2)	0	0	1 (1.2)	0	0
Ankle fracture	0	0	1 (1.4)	0	0	1 (1.4)
Aortic valve incompetence	0	0	1 (1.4)	0	0	1 (1.4)
Atrioventricular block	0	0	1 (1.4)	0	0	1 (1.4)
Back pain	0	0	1 (1.4)	0	0	1 (1.4)
Coronary artery disease	0	0	1 (1.4)	0	0	1 (1.4)
Endocarditis	0	0	1 (1.4)	0	0	1 (1.4)
Fall	0	0	1 (1.4)	0	0	1 (1.4)
Glaucoma	0	1 (1.3)	0	0	1 (1.3)	0
Goitrer	0	1 (1.3)	0	0	1 (1.3)	0
Humerus fracture	0	0	1 (1.4)	0	0	1 (1.4)
Intervertebral disc disorder	0	0	1 (1.4)	0	0	1 (1.4)
Lung neoplasm malignant	0	0	1 (1.4)	0	0	1 (1.4)

Preferred Term, n (%)	Pooled Studies 309 and 310 52-Week T1D-CKD Population			Pooled Studies 309 and 310 52-Week T1D Population		
	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)
Myocardial infarction	0	0	1 (1.4)	0	0	1 (1.4)
Post procedural haemorrhage	0	0	1 (1.4)	0	0	1 (1.4)
Transient ischaemic attack	0	0	1 (1.4)	0	0	1 (1.4)

CKD: chronic kidney disease; SOTA: sotagliflozin; TEAE: treatment-emergent adverse event; T1D: type 1 diabetes mellitus

7.7 Adverse Events Leading to Study Drug Discontinuation in Patients with T1D-CKD

No TEAEs led to study drug discontinuation for more than 1 patient in any treatment group in the pooled Studies 309 and 310 T1D-CKD population (see Appendix Table 42).

In the T1D-CKD population of Study 312, the only TEAE that led to study drug discontinuation for more than 1 patient in the sotagliflozin arm was DKA (n=2; 1.8%).

7.8 Serious Adverse Events in Patients with T1D-CKD

SAEs occurred at a similar frequency across treatment groups. DKA and hypoglycemia were the only SAEs reported in more than 1 patient in either sotagliflozin treatment group (Table 33). These events are further described in Section 7.12.

Table 33: Summary of Serious Adverse Events (≥ 2 Patients in Any Treatment Group of T1D-CKD Population) in Pooled Studies 309 and 310 and in Study 312

	T1D-CKD Population					T1D Safety Population				
	Pooled Studies 309 and 310 52-Week			Study 312 24-Week		Pooled Studies 309 and 310 52-Week			Study 312 24-Week	
Preferred Term, n (%)	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Patients with any SAEs	12 (14.1)	8 (10.7)	10 (13.5)	12 (10.5)	8 (7.3)	53 (10.1)	50 (9.5)	37 (7.0)	48 (6.9)	23 (3.3)
Diabetic ketoacidosis (Investigator reported)	4 (4.7)	4 (5.3)	2 (2.7)	3 (2.6)	2 (1.8)	19 (3.6)	26 (5.0)	3 (0.6)	22 (3.1)	5 (0.7)
Hypoglycemia	2 (2.4)	1 (1.3)	0	1 (0.9)	0	5 (1.0)	5 (1.0)	5 (1.0)	3 (0.4)	1 (0.1)
Hypoglycemic unconsciousness	1 (1.2)	0	2 (2.7)	0	0	2 (0.4)	2 (0.4)	4 (0.8)	1 (0.1)	4 (0.6)

CKD: chronic kidney disease; SAE: serious adverse event; SOTA: sotagliflozin; T1D: type 1 diabetes mellitus

7.9 Deaths

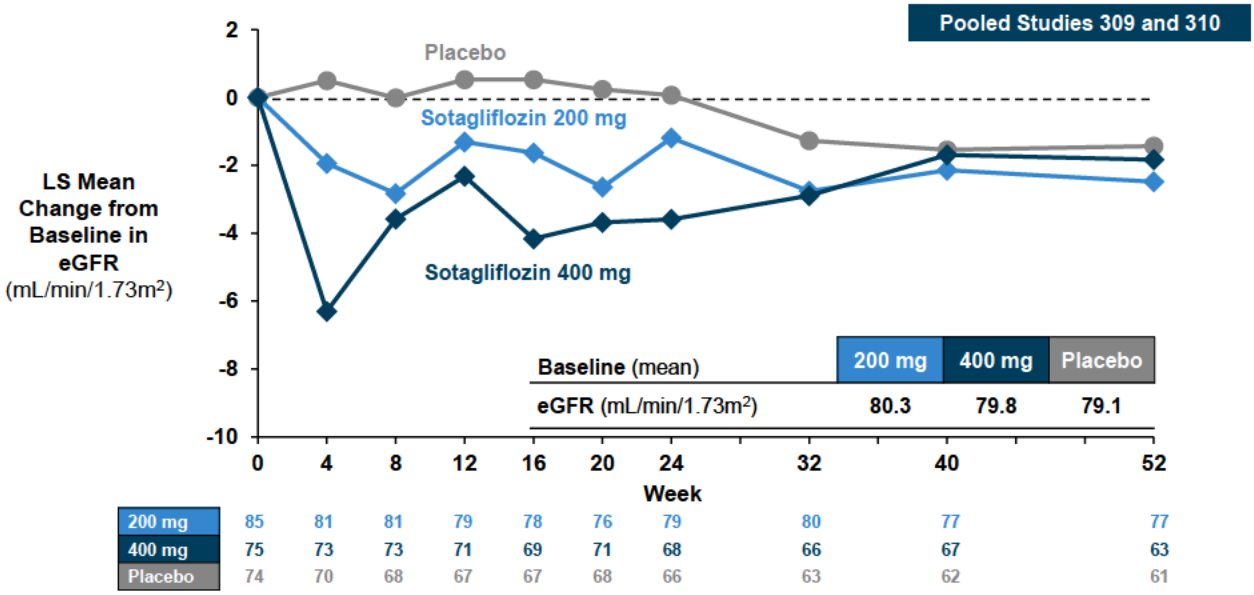
No deaths due to TEAEs occurred in either sotagliflozin treatment group in the 52-week pooled T1D-CKD population of Studies 309 and 310 or in Study 312. Two deaths occurred in the placebo group in the 52-week T1D-CKD population.

In the overall T1D population, 1 additional placebo-treated patient had TEAEs that resulted in death. Additionally, 1 patient in the sotagliflozin 400 mg treatment group died of completed suicide, which occurred on Day 55 of the study. None of the deaths were assessed as related to study treatment. One patient in the sotagliflozin 200 mg group died from T1D 473 days after last dose of study drug.

7.10 Change in eGFR

In the pooled Studies 309 and 310 T1D-CKD population, after an expected small initial decrease was observed among sotagliflozin-treated patients immediately following initiation, kidney function returned toward baseline levels at 12 weeks and remained stable through 52 weeks (Figure 36). These results suggest that there is a stabilization in kidney function decline while on treatment with sotagliflozin.

Figure 36: eGFR Change from Baseline through Week 52 in the T1D-CKD Population in Pooled Studies 309 and 310



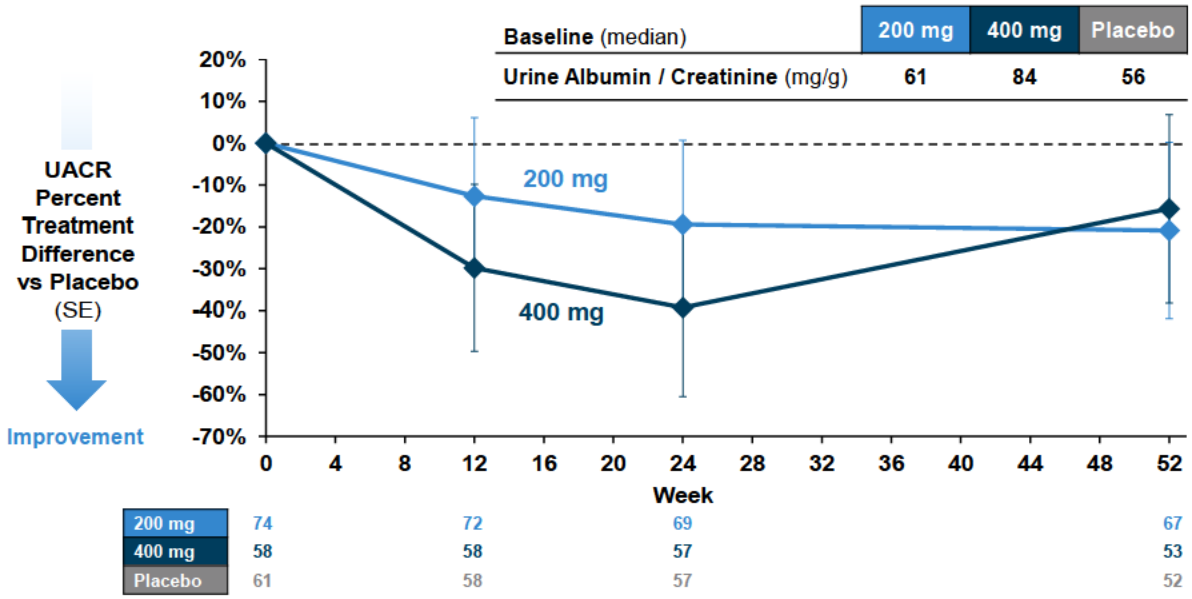
CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; LS: least squares; T1D: type 1 diabetes mellitus

7.11 Change in Albuminuria

In the patients with elevated baseline UACR (≥30 mg/g), during the 48-week follow-up period, patients treated with sotagliflozin showed improvement in albuminuria compared

with placebo patients at all time points in the pooled Studies 309 and 310 T1D-CKD population (Figure 37). The greatest benefit was observed in patients receiving sotagliflozin 400 mg, with significant reductions at Week 24.

Figure 37: Urine Albumin-to-Creatinine Ratio Change from Baseline through Week 52 in the T1D-CKD Population with Baseline UACR ≥30 mg/g in Pooled Studies 309 and 310



CKD: chronic kidney disease; SE: standard error; T1D: type 1 diabetes mellitus; UACR: urine albumin-to-creatinine ratio

7.12 Events of Interest

For Studies 309, 310, and 312, events of interest were reviewed by a treatment-blinded Clinical Endpoint Committee based on specifically identified PTs (Table 34).

In the pooled Studies 309 and 310 T1D-CKD population, events related to hypoglycemia were the most common, occurring in >95% of patients in all treatment groups. Severe hypoglycemia or hypoglycemia reported as an SAE was also common, occurring in 7.1% and 4.0% in the 200 mg and 400 mg sotagliflozin treatment groups, respectively, compared with 16.2% of patients in the placebo group. Conversely, DKA occurred more frequently in the sotagliflozin treatment groups than placebo group (5.9% in sotagliflozin 200 mg, 6.7% in sotagliflozin 400 mg, and 2.7% in placebo).

Results in the Study 312 T1D-CKD population were similar to those in the 400 mg arm of the pooled 309/310 studies.

Table 34: Overall Summary of Investigator-Reported Events of Special Interest in Pooled Studies 309 and 310 and in Study 312

	T1D-CKD Population					T1D Safety Population				
	Pooled Studies 309 and 310 52-Week			Study 312 24-Week		Pooled Studies 309 and 310 52-Week			Study 312 24-Week n	
Preferred Term, n (%)	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N =74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Documented hypoglycemia	82 (96.5)	74 (98.7)	71 (95.9)	105 (92.1)	103 (93.6)	515 (98.3)	518 (98.7)	518 (98.5)	673 (96.3)	670 (95.3)
Severe hypoglycemia and/or hypoglycemia reported as an SAE	6 (7.1)	3 (4.0)	12 (16.2)	10 (8.8)	6 (5.5)	30 (5.7)	25 (4.8)	42 (8.0)	24 (3.4)	20 (2.8)
Diabetic ketoacidosis	5 (5.9)	5 (6.7)	2 (2.7)	5 (4.4)	3 (2.7)	30 (5.7)	39 (7.4)	7 (1.3)	31 (4.4)	8 (1.1)
Urinary tract infection	12 (14.1)	3 (4.0)	6 (8.1)	6 (5.3)	6 (5.5)	37 (7.1)	29 (5.5)	32 (6.1)	25 (3.6)	27 (3.8)
Diarrhea	8 (9.4)	8 (10.7)	3 (4.1)	8 (7.0)	2 (1.8)	34 (6.5)	46 (8.8)	27 (5.1)	29 (4.1)	16 (2.3)
Genital mycotic infection	5 (5.9)	9 (12.0)	2 (2.7)	7 (6.1)	1 (0.9)	48 (9.2)	63 (12.0)	15 (2.9)	45 (6.4)	15 (2.1)
Renal event	3 (3.5)	4 (5.3)	3 (4.1)	1 (0.9)	3 (2.7)	8 (1.5)	7 (1.3)	8 (1.5)	5 (0.7)	3 (0.4)
Myocardial infarction or hospitalization for unstable angina	2 (2.4)	0	2 (2.7)	1 (0.9)	0	4 (0.8)	2 (0.4)	3 (0.6)	2 (0.3)	0
Bone fracture	2 (2.4)	2 (2.7)	5 (6.8)	1 (0.9)	2 (1.8)	15 (2.9)	10 (1.9)	18 (3.4)	4 (0.6)	5 (0.7)
Hospitalization for heart failure	1 (1.2)	0	1 (1.4)	0	0	2 (0.4)	1 (0.2)	1 (0.2)	0	0
Coronary revascularization	1 (1.2)	0	1 (1.4)	0	0	4 (0.8)	1 (0.2)	2 (0.4)	1 (0.1)	0
Volume depletion	1 (1.2)	1 (1.3)	0	1 (0.9)	6 (5.3)	14 (2.7)	6 (1.1)	5 (1.0)	13 (1.9)	2 (0.3)
Amputation	0	0	0	0	0	1 (0.2)	1 (0.2)	0	0	0
Cardiovascular death	0	0	1 (1.4)	NA	NA	0	0	2 (0.4)	NA	NA
Malignancies of special interest	0	0	0	1 (0.9)	0	2 (0.4)	2 (0.4)	1 (0.2)	1 (0.1)	2 (0.3)
Pancreatitis	0	0	0	0	0	0	1 (0.2)	0	0	0
Potential drug-induced liver injury	0	0	3 (4.1)	1 (0.9)	0	2 (0.4)	6 (1.1)	4 (0.8)	2 (0.3)	0

	T1D-CKD Population					T1D Safety Population				
	Pooled Studies 309 and 310 52-Week			Study 312 24-Week		Pooled Studies 309 and 310 52-Week			Study 312 24-Week n	
Preferred Term, n (%)	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N =74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Stroke	0	0	1 (1.4)	0	0	1 (0.2)	2 (0.4)	2 (0.4)	0	1 (0.1)
Venous thrombotic embolism	0	0	0	0	0	0	0	0	0	0

CKD: chronic kidney disease; NA: not available in preferred term in 312 CSR; SAE: serious adverse event; SOTA: sotagliflozin; T1D: type 1 diabetes mellitus
Note: Malignancies of special interest include breast cancer, renal cell cancer, Leydig cell cancer, pancreatic cancer, prostate cancer, thyroid cancer, and bladder cancer.

7.12.1 Hypoglycemia

7.12.1.1 Identification and Adjudication of Hypoglycemia Events

Hypoglycemic events were classified as severe hypoglycemia, documented hypoglycemia, and documented asymptomatic hypoglycemia according to the criteria summarized below. In cases when an event met criteria for both documented and severe hypoglycemia, both sections of the hypoglycemia-reporting electronic case report form (eCRF) were completed.

- Severe hypoglycemia occurred if the answer to any of the following 3 questions was yes:
  - Did the patient have an episode of suspected hypoglycemia treated with any form of carbohydrate or with glucagon that required the assistance of others to treat?
  - Did the patient lose consciousness during the episode?
  - Did the patient have a seizure during the episode?
- Documented hypoglycemia was defined as symptomatic or asymptomatic based on the following 2 definitions:
  - Symptomatic: An event during which typical symptoms of hypoglycemia were accompanied by a concurrent fingerstick (from self-monitoring blood glucose [SMBG]) or venous glucose result of ≤70 mg/dL (3.9 mmol/L)
  - Asymptomatic: An event not accompanied by typical symptoms of hypoglycemia but with a measured fingerstick (from SMBG) or venous glucose result of ≤70 mg/dL (3.9 mmol/L)

Severe and documented hypoglycemia was further characterized as nocturnal or diurnal using the following criteria:

- Nocturnal: Hypoglycemia that occurred between 00:00 and 05:59, regardless of whether the patient was awake or woke up because of the event
  - Nocturnal severe hypoglycemia was further characterized by sleep status: Hypoglycemia that woke the patient from sleep after having gone to bed in the evening and before getting up in the morning before administration of any insulin
- Diurnal: Hypoglycemia that occurred between 06:00 and 23:59

7.12.1.2 Documented Hypoglycemia Events

In the pooled Studies 309 and 310 T1D-CKD population, >95% of patients had an event of hypoglycemia (Table 35). Annualized event rates were lower in the sotagliflozin treatment groups (73 events per patient-year for the 200 mg sotagliflozin group and

77.5 events per patient-year for the 400 mg sotagliflozin group) than in in the placebo group (approximately 90 events per patient-year).

Table 35: Summary of Treatment-emergent Documented Hypoglycemia in Pooled Studies 309 and 310 and in Study 312

	T1D-CKD Population					T1D Safety Population				
	Pooled Studies 309 and 310 52-Week T1D-CKD Population			Study 312 24-Week T1D-CKD Population		Pooled Studies 309 and 310 52-Week			Study 312 24-Week	
Category	Sotagliflozin 200 mg (N=85)	Sotagliflozin 400 mg (N=75)	Placebo (N=74)	Sotagliflozin 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Total patient-years	78.9	68.3	64.8	46.8	46.6	480.02	477.13	474.20	303.92	298.18
Total number of treatment-emergent events	5760	5289	5825	3092	3598	39015	39937	45327	20808	23665
Patients with at least 1 event, n (%)	82 (96.5)	74 (98.7)	71 (95.9)	105 (92.1)	103 (93.6)	515 (98.3)	518 (98.7)	518 (98.5)	673 (96.3)	670 (95.3)
EAIR per 1000 patient-years	1039.2	1084.2	1095.7	2242.6	2208.4	1072.87	1085.65	1092.37	NC	NC
Events per patient per year (events per patient per day)	73.0 (0.2)	77.5 (0.2)	89.9 (0.2)	66.0 (0.2)	77.1 (0.2)	81.3 (0.2)	83.7 (0.2)	95.6 (0.3)	69.78 (0.19)	77.87 (0.21)
Number of events that were nocturnal by time of day[a]	772	625	796	NC	NC	5286	5313	5771	NC	NC
Number of events that were diurnal by time of day[b]	5009	4670	5063	NC	NC	33889	34796	39766	NC	NC
Nocturnal events (by time of day) per patient per year (per patient per day)	9.8 (0.0)	9.2 (0.0)	12.3 (0.0)	NC	NC	11.012 (0.030)	11.135 (0.030)	12.170 (0.033)	NC	NC

Diurnal events per patient per year (per patient per day)	63.5 (0.2)	68.4 (0.2)	78.1 (0.2)	NC	NC	70.599 (0.193)	72.927 (0.200)	83.859 (0.230)	NC	NC

CKD: chronic kidney disease; EAIR: exposure-adjusted incidence rate; NC: not calculated; T1D: type 1 diabetes mellitus
a. Hypoglycemic event that occurs between 0:00 am and 5:59 am.
b. Hypoglycemic event that occurs between 6:00 am and 23:59 pm.
Note: Treatment-emergent hypoglycemic events that occurred on or after the first dose of study drug with the date of last dose of study drug as the cut-off date, regardless of the onset time of the hypoglycemic event are included in the analyses.
Note: Documented hypoglycemic events for which there was a missing response to the question of "Hypoglycemic symptoms present?" in the Hypoglycemia Case Report Form were included in category of "Unknown."
Note: EAIR per 1000 patient-years of exposure is calculated as: (total number of patients who reported at least 1 event/total exposure in patient-years for all treated patients) * 1000.
Note: Events per patient per year is calculated as total number of events divided by total patient-year. Events per patient per day is calculated as total number of events divided by total patient-day.
Note: The sum of the number of events that are nocturnal by time and number of events that are diurnal by time may be more than the total number of events because the same event may have been reported by the site as both nocturnal and diurnal.

7.12.1.3 Positively Adjudicated Severe Hypoglycemia Events

In the pooled Studies 309 and 310 T1D-CKD population, the EAIR per 1000 patient-years for positively adjudicated severe hypoglycemia decreased with increased dose of sotagliflozin, with rates of 76 and 44 for the sotagliflozin 200 mg and sotagliflozin 400 mg groups, respectively (Table 36). The frequency of severe hypoglycemia was higher in the placebo group with CKD than in the sotagliflozin-treated groups. The EAIR per 1000 patient-years for positively adjudicated severe hypoglycemia was 201 for placebo.

The risk difference of EAIR (95% confidence limit) minus placebo was -124.59 in the sotagliflozin 200 mg group and -156.67 in the sotagliflozin 400 mg group. Frequency of severe hypoglycemia was reduced in both diurnal and nocturnal measurements.

The incidence of severe hypoglycemia was greater in the sotagliflozin-treated group in the 24-week T1D-CKD population of Study 312.

Overall, the risk of severe hypoglycemia is similar for the T1D-CKD population as the overall T1D population.

Table 36: Summary of Treatment-emergent Positively Adjudicated Severe Hypoglycemia in Pooled Studies 309 and 310 and in Study 312

	T1D-CKD Population					T1D Safety Population				
	Pooled Studies 309 and 310 52-Week			Study 312 24-Week		Pooled Studies 309 and 310 52-Week			Study 312 24-Week	
Category	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Total patient-years	78.90	68.25	64.80	46.82	46.64	480.02	477.13	474.20	298.18	303.92
Total number of TE positively adjudicated events	8	3	18	8	7	68	33	50	25	22
Patients with at least 1 event, n (%)	6 (7.1)	3 (4.0)	13 (17.6)	8 (7.0)	5 (4.5)	30 (5.7)	23 (4.4)	39 (7.4)	21 (3.0)	17 (2.4)
EAIR per 1000 patient-years	76.04	43.95	200.63	170.87	107.21	62.50	48.20	82.24	40	140
Relative risk of EAIR versus placebo (95% CL)	0.38 (0.13, 0.98)	0.22 (0.05, 0.72)	-	63.66 (-87.50, 214.82)	-	0.76 (0.47, 1.22)	0.59 (0.35, 0.98)	-	0.91 (0.83, 1.01)	-
Events per patient per year (events per patient per day)	0.101	0.044	0.278	0.171	0.150	0.14	0.07	0.11	0.08	0.07
Number of events that were nocturnal by time of day[a]	3	0	7	1	1	20	6	13	2	5
Number of events that were diurnal by time of day[b]	5	3	10	7	6	48	29	36	23	17
Nocturnal events (by time of day) per patient per year	0.038	0.000	0.108	0.021	0.021	0.04	0.01	0.03	NC	NC
Nocturnal events (by	0.025	0.015	0.108	0.064	0.043	0.05	0.03	0.04	NC	NC

Category	T1D-CKD Population					T1D Safety Population				
	Pooled Studies 309 and 310 52-Week			Study 312 24-Week		Pooled Studies 309 and 310 52-Week			Study 312 24-Week	
	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
sleep status) per patient per year										
Diurnal events per patient per year	0.063	0.044	0.154	0.150	0.129	0.10	0.06	0.08	NC	NC

CKD: chronic kidney disease; CL: confidence limit; EAIR: exposure-adjusted incidence rate; NC: not calculated; TE: treatment-emergent; T1D: type 1 diabetes mellitus

a. Hypoglycemic event that occurs between 0:00 am and 5:59 am.

b. Hypoglycemic event that occurs between 6:00 am and 23:59 pm.

Note: Treatment-emergent hypoglycemic events that occurred on or after the first dose of study drug with the date of last dose of study drug as the cut-off date, regardless of the onset time of the hypoglycemic event are included in the analyses. EAIR per 1000 patient-years of exposure is calculated as: (total number of patients who reported at least 1 event/total exposure in patient-years for all treated patients) * 1000. The 95% CL on EAIR per 1000 patient-years of exposure and risk difference are based on normal approximation. Stratified EAIR (stratifying on study number) and stratified risk difference with 95% CL are based on Wald's method by assigning weights to be inversely proportional to the variance of each stratum-specific estimate. Relative risk (exact 95% CL) and stratified relative risk (exact 95% CL) of EAIR between any sotagliflozin group and placebo group are obtained using StatXact procedure PROC POISSON. Events per patient per year is calculated as total number of events divided by total patient-year. Events per patient per day is calculated as total number of events divided by total patient-days. The sum of the number of events that are nocturnal by time and number of events that are diurnal by time may be more than the total number of events because the same event may have been reported by the site as both nocturnal and diurnal.

7.12.1.4 Conclusions

Most patients in the overall T1D population experienced at least one episode of hypoglycemia, patients treated with sotagliflozin demonstrated a similar incidence of severe hypoglycemia. Patients who also had CKD experienced a similar or lower incidence of severe hypoglycemia than patients in the placebo treatment arm.

Overall, treatment with sotagliflozin does not increase the incidence of severe hypoglycemia in patients with T1D and CKD.

7.12.2 Diabetic Ketoacidosis and Acidosis-Related Events

7.12.2.1 DKA Adjudication Process

A rigorous system to screen for and identify all possible DKA events was implemented during the clinical development of sotagliflozin for T1D. Potential DKA cases were identified from 3 possible sources: Investigator entry of AEs that were identified as terms suggestive of possible DKA (so-called “trigger PTs”), laboratory values suggestive of DKA/acidosis, or through additional review of AE and laboratory data by study Medical Monitors.

In addition to data mining, the program used “sick day rules” (ie, patients reporting signs and/or symptoms suspicious for DKA; the patient was instructed by the Investigator to measure blood or urine ketones and BHB levels). If the urine ketones were positive or blood BHB level was >0.6 mmol/L, the patient was asked to contact the clinical site immediately, whereupon they were instructed to increase hydration, administer insulin, and eat carbohydrates until urine ketones or BHB level normalized. If levels normalized, further assessment was not implemented, and these patients did not have an event of “Possible DKA” captured.

However, for persistent elevation of BHB levels >0.6 mmol/L, the Investigator determined if an assessment for metabolic acidosis was appropriate. If additional laboratory testing confirmed the presence of metabolic acidosis or an AE was reported for elevated BHB, a “Possible DKA” eCRF was completed and adjudication occurred.

An independent committee adjudicated all cases of possible DKA and all cases of metabolic acidosis. The criteria for each entity were based on ADA and medical literature guidelines. DKA diagnosis was based on evidence of anion-gap metabolic acidosis related to excessive ketone production in a clinical setting characterized by deficiency in insulin availability without a satisfactory alternative cause for anion-gap metabolic acidosis. Due to euglycemic DKA observed with SGLT inhibitors, absence of associated hyperglycemia documented by SMBG or plasma glucose testing did not preclude the diagnosis of DKA.

Cases were further classified as to the certainty of diagnosis as defined below:

- **Yes, with certainty**: There is sufficient evidence to support such an event.
- **Yes, probably:** The role of other factors could not be excluded (eg, underlying disease, complications, other medical events, concomitant drugs, or concurrent treatment).
- **No, unlikely:** An alternative explanation is plausible and more likely (eg, underlying disease, complications, other medical events, concomitant drugs, or concurrent treatment).
- **No, with certainty:** This is a manifestation of other clinical factors or circumstances (eg, underlying disease, complications, other medical events, concomitant drugs, or concurrent treatment).
- **Unclassifiable:** The clinical characteristics and circumstances related to the event did not allow classification.
- **Insufficient data:** The information available was inadequate to allow for classification.

7.12.2.2 Positively Adjudicated Diabetic Ketoacidosis

Positively adjudicated DKA events were greater in the sotagliflozin-treated groups than in the placebo-treated groups. The positively adjudicated DKA events for the 52-week T1D-CKD population were:

- 4 patients (4.7%) with a total of 4 events in the 200 mg sotagliflozin group
- 2 patients (2.7%) with a total of 2 events in the 400 mg sotagliflozin group
- 1 patient (1.4%) with 1 event in the placebo group

In Study 312, adjudicated DKA events for the 24-week T1D-CKD population were:

- 3 patients (2.6%) with a total of 3 events in the 400 mg sotagliflozin group
- 1 patient (0.9%) with 1 event in the placebo group

7.12.2.2.1 Summary of Each Positively Adjudicated Diabetic Ketoacidosis

A summary of the DKA events is provided in Table 37. In the sotagliflozin treatment groups, time to onset ranged from 18 to 364 days after start of treatment. Clear contributing factors were present for each event that could be identified by patients, and all events resolved. Abbreviated narratives are provided in Appendix Section 10.5.

Table 37: Overview of Positively Adjudicated Diabetic Ketoacidosis Events in T1D-CKD Population

Treatment Group	Age/Sex	Onset (days since randomized)	Peak Plasma Glucose	DKA Duration (days)	Contributing Factors	Treatment Action	Resolution
200 mg sotagliflozin	69/M	286	740 mg/dL	4	Motorcycle accident, R foot injury a few days prior to the DKA event	Drug interrupted; resumed 5 days later	Resolved
200 mg sotagliflozin	71/F	214	679 mg/dL	1	Patient had a steroid injection (dexamethasone) due to strep throat. DKA hospitalization with concomitant non-STEMI.	Drug interrupted; resumed 14 days later	Resolved
200 mg sotagliflozin	26/F	175	256 mg/dL	1	Thought secondary to rotavirus; patient had diarrhea, vomiting, nausea before admission.	Drug interrupted; resumed 5 days later	Resolved
200 mg sotagliflozin	39/M	364	347.4 mg/dL	2	Diagnosed with pneumonia	Drug withdrawn	Resolved
400 mg sotagliflozin	47/F	95	277.2 mg/dL	1	Gastrointestinal virus	No action	Resolved
400 mg sotagliflozin	27/F	281	290 mg/dL	3	Emesis before admission, didn't take rapid acting as was not eating, only basal.	Drug interrupted; resumed 4 days later	Resolved
400 mg sotagliflozin	67/M	124	384 mg/dL	4	Presented with 3 days of abdominal pain and nausea – thought possibly related to chili on hotdog eaten week prior; h/o small bowel obstruction but w/u was normal.	Drug interrupted; resumed same day	Resolved

Treatment Group	Age/Sex	Onset (days since randomized)	Peak Plasma Glucose	DKA Duration (days)	Contributing Factors	Treatment Action	Resolution
400 mg sotagliflozin	63/F	136	243 mg/dL	19	Weekend before presentation, had severe acid reflux and abdominal pain; during hospitalization, diagnosed with UTI and treated.	Drug withdrawn	Resolved
400 mg sotagliflozin	42/F	18	216 mg/dL	1	History of rheumatoid arthritis and on Enbrel	Drug withdrawn	Resolved
Placebo	54/M	189	314 mg/dL	3	PI assessment is the DKA was secondary to the exacerbation of gastro paresis for which patient was hospitalized (2d) and discharged the day prior to this event.	Drug interrupted for impaired gastric emptying; resumed 24 days later	Resolved
Placebo	29/M	9	599.4 mg/dL	4	Insulin pump “broke”	No action	Resolved

d: days; DKA: diabetic ketoacidosis; F: female; M: male; h/o: history of; PI: Principal Investigator; R: right; STEMI: ST-segment elevation myocardial infarction; UTI: urinary tract infection; w/u: work-up

7.12.2.3 Exposure-Adjusted Incidence Rate for Diabetic Ketoacidosis

In the pooled Studies 309 and 310 T1D-CKD population, the EAIR per 100 patient-years was 5.1 patient-years for the 200 mg sotagliflozin group, 2.9 patient-years for the 400 mg sotagliflozin group, and 1.5 patient-years for placebo (Table 38). Rates were not dose related.

In Study 312 in the T1D-CKD population, EAIR per 100-patient years was 6.4 for sotagliflozin 400 mg and 2.1 for placebo.

Table 38: Summary of Positively Adjudicated Acidosis-related Events through 52 Weeks of Treatment in Pooled Studies 309 and 310 and in Study 312

	T1D-CKD Population					T1D Safety Population				
	Pooled Studies 309 and 310 52-Week			Study 312 24-Week		Pooled Studies 309 and 310 52-Week			Study 312 24-Week	
Event, n (%)	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
All Positively Adjudicated DKA Events	4 (4.7)	2 (2.7)	1 (1.4)	3 (2.6)	1 (0.9)	15 (2.9)	20 (3.8)	1 (0.2)	21 (3.0)	4 (0.6)
Events per patient per year (event per patient per day)	0.051 (<0.001)	0.029 (<0.001)	0.015 (<0.001)	0.064 (<0.001)	0.021 (<0.001)	0.033 (<0.001)	0.042 (<0.001)	0.002 (<0.001)	NA	NA
EAIR per 1000 patient-years (95% CL)	50.69 (1.01,100.37)	29.30 (0.00,69.91)	15.43 (0.00,45.68)	64.08	21.44	31.25 (15.43,47.06)	41.92 (23.55,60.29)	2.11 (0.00,6.24)	70	13
Relative risk of EAIR (95% CL) versus placebo	3.28 (0.41,81.28)	1.90 (0.14,56.01)		NC	NC	14.82 (2.65,315.03)	19.88 (3.67,416.29)		NC	NC
Stratified EAIR per 1000 patient-years (95% CL)	50.51 (0.92,100.11)	28.43 (0.00,68.43)	29.32 (0.00,86.78)	NC	NC	30.05 (14.54,45.56)	41.41 (23.15,59.67)	4.22 (0.00,12.50)	NC	NC
Stratified relative risk of EAIR (95% CL) versus placebo	3.28 (0.41,81.21)	2.10 (0.16,62.66)	-	NC	NC	14.80 (2.65,314.62)	19.90 (3.67,416.86)	-	NC	NC
Severe events	3 (3.5)	2 (2.7)	0	3 (2.6)	0	11 (2.1)	15 (2.9)	0	13 (1.9)	1 (0.1)
Events leading to study drug interruption	4 (4.7)	1 (1.3)	1 (1.4)	1 (0.9)	0	10 (1.9)	9 (1.7)	1 (0.2)	11 (1.6)	1 (0.1)
All Positively Adjudicated Metabolic Acidosis Events	4 (4.7)	3 (4.0)	1 (1.4)	3 (2.6)	1 (0.9)	18 (3.4	22 (4.2)	3 (0.6)	23 (3.3)	4 (0.6)
Events per patient per year (event per patient per day)	0.051 (<0.001)	0.044 (<0.001)	0.015 (<0.001)	0.064 (<0.001)	0.021 (<0.001)	0.040 (<0.001)	0.046 (<0.001)	0.006 (<0.001)	NC	NC
EAIR per 1000 patient-years (95% CL)	50.69 (1.01,100.37)	43.95 (0.00,93.69)	15.43 (0.00,45.68)	64.08	21.44	37.50 (20.18,54.82)	46.11 (26.84,65.38)	6.33 (0.00,13.49)	NC	NC

	T1D-CKD Population					T1D Safety Population				
	Pooled Studies 309 and 310 52-Week			Study 312 24-Week		Pooled Studies 309 and 310 52-Week			Study 312 24-Week	
Event, n (%)	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Relative risk of EAIR (95% CL) versus placebo	3.28 (0.41,81.28)	2.85 (0.30,74.98)	-	NC	NC	5.93 (1.91,25.24)	7.29 (2.40,30.61)	-	NC	NC
Stratified EAIR per 1000 patient-years (95% CL)	50.51 (0.92,100.11)	34.05 (0.00,77.83)	29.32 (0.00,86.78)	NC	NC	37.07 (19.85, 54.29)	45.64 (26.47,64.81)	12.67 (0.00,27.00)	NC	NC
Stratified relative risk of EAIR (95% CL) versus placebo	3.28 (0.41,81.21)	3.27 (0.35,86.85)	-	NC	NC	5.92 (1.90,25.21)	7.30 (2.40,30.67)	-	NC	NC
Severe events	3 (3.5)	3 (4.0)	0 0	3 (2.6)	0	12 (2.3)	17 (3.2)	1 (0.2)	14 (2.0)	1 (0.1)
Events leading to study drug interruption	4 (4.7)	1 (1.3)	1 (1.4)	1 (0.9)	0	11 (2.1)	9 (1.7)	3 (0.6)	NA	NA
Events leading to study drug discontinuation	0 0	1 (1.3)	0 0	2 (1.8)	0	4 (0.8)	9 (1.7)	0	11 (1.6)	1 (0.1)

CKD: chronic kidney disease; CL: confidence limit; EAIR: exposure-adjusted incidence rate; SOTA: sotagliflozin; T1D: type 1 diabetes mellitus; NA: not available; NC: not calculated.

Note: The full datasets (up to week 52 plus 30-day follow-up in Studies 309 and 310) are used. Number of events per patient per year of exposure is calculated within a treatment group as the total number of events divided by the total exposure in patient-years for that treatment group. Number of events per patient per day of exposure is calculated similarly but using total exposure in days for that treatment group. EAIR per 1000 patient-years of exposure is calculated as: (total number of patients who reported at least 1 positively adjudicated event / total exposure in patient-years for all treated patients) * 1000. The 95% CL on EAIR per 1000 patient-years of exposure and risk difference are based on normal approximation. Stratified EAIR and stratified risk difference with 95% CL are based on Wald's method, by assigning weights to be inversely proportional to the variance of each stratum-specific estimate. Relative risk (exact 95% CL) and stratified relative risk (exact 95% CL) of EAIR between any sotagliflozin group and placebo group are obtained using StatXact procedure PROC POISSON (Breslow and Day 1987).

7.12.2.4 Risk Factors for DKA

Risk factors for DKA in T1D include acute illnesses such as infection, recent diabetes onset, insulin omission or reduction, insulin pump failure, alcohol intake, and increased strenuous activity (Peters 2020). Other nonmodifiable and modifiable risk factors that have been identified include socioeconomic disadvantages, female sex, previous DKA, nonprescription drug use, quality of diabetes care, poor mental health, and somatic comorbidities (Ehrmann 2020). Drugs that affect carbohydrate metabolism, such as corticosteroids, thiazides, sympathomimetic agents, and pentamidine may precipitate DKA (Lizzo 2023). SGLT2 inhibitor use has also been identified as a risk factor for DKA in patients with T1D or T2D (Peters 2020).

Previous reviews identified that total daily insulin dose reductions of approximately 20% or more appeared to be associated with increased risk of positively adjudicated DKA. Concomitant illness, such as infections, injuries, or surgeries, were reported in approximately 40% of the positively adjudicated DKA cases. Interruption of insulin dosing was a notable contributing factor in the development of DKA; nearly 60% of the positively adjudicated DKA cases occurred in patients using CSII, and approximately one-third of the positively adjudicated DKA cases were associated with pump-related issues affecting insulin administration.

These observations indicate that early recognition of symptoms and attention to total daily insulin dosing and to insulin pump/accessory performance can play an important role in managing the risk of DKA.

7.12.2.5 Conclusions

In the T1D-CKD population, there was an increased risk for DKA compared to placebo. All of the positively adjudicated DKA events were serious, but none led to study-drug discontinuation and there were no deaths associated with DKA in the T1D-CKD population. Appropriate patient selection, monitoring symptoms and subsequently for ketone levels, and modifying patient behaviors to decrease the risk of DKA are key factors in monitoring and managing DKA risk.

7.13 Risk Management

7.13.1 Prior Experience Among T1D-CKD with DKA and Ability to Identify and Manage Signs and Symptoms

Patients with T1D-CKD have prolonged experience in managing diabetes. This also means that they have an established history on their level of engagement in actively managing their diabetes. Education will align with best practices for mitigation of DKA, which include paying attention to total daily insulin and dose changes, understanding the factors that influence insulin levels, awareness of pump/accessory performance, and early recognition of signs and symptoms.

Further, there is evidence from the follow-up to the TN-10 study of teplizumab that early screening, education, and awareness of the risk of T1D and DKA in children (and their parents) may contribute to slowing the progression of T1D disease from Stage 2 to Stage 3 and may also delay their first event of DKA (Perdigoto 2019; Scheiner 2022).

7.13.2 Current Best Practices for DKA Management

Patients should be monitored for resolution of ketoacidosis before restarting sotagliflozin.

In temporary clinical situations that could predispose patients to ketoacidosis, such as major surgery or procedures associated with prolonged fasting, sotagliflozin should be withheld at least 3 days prior, if possible. Sotagliflozin should be resumed only when the patient is clinically stable and has resumed oral intake. If symptoms of ketoacidosis occur, patients should discontinue sotagliflozin use and seek medical attention immediately.

If ketones are elevated (blood BHB level is 0.6 mmol/L or higher, or urine ketones moderate or higher), or if early symptoms of ketosis occur, patients will be instructed to:

- Temporarily stop treatment with sotagliflozin
- Treat ketosis by eating carbohydrates, drinking fluids, and administering bolus insulin, while continuing to monitor ketone levels every 2 to 4 hours
- If using an insulin pump delivery device or system, ensure all components of the pump are working properly per manufacturer's instructions to ensure adequate insulin delivery, and correct as needed
- Seek medical advice if they do not have clear instructions to treat ketosis or if the instructions do not improve their condition
- Seek immediate emergency assessment and treatment if unable to keep down food and fluids, or if symptoms persist for more than 4 hours

7.13.3 Patient Selection Actions and Communications

Patient selection may provide the most optimal mitigation of DKA and severe hypoglycemia risk factors for patients with T1D and CKD. The following information will be provided to healthcare providers to ensure high-risk patients are not prescribed sotagliflozin:

Patients with the following characteristics would be likely candidates to consider for sotagliflozin prescription:

- Able to maintain their prescribed insulin management regimen
- A1C <10%

- No history of recurrent DKA or non-ketotic hyperosmolar state and no DKA event or non-ketotic hyperosmolar state in the last 3 months
- Does not currently use a non-FDA-approved automated insulin delivery device
- In-office blood ketone level <0.6 mmol/L
- Willingness to monitor ketones with the following specifications:
    - Blood monitoring (urine acceptable with additional counseling on drawbacks)
    - Can read and react accordingly to elevated ketone levels
    - Understanding of additional risk factors and early symptoms of possible DKA
    - Willingness to perform intensified ketone monitoring upon possible symptom recognition
    - Willingness to complete more frequent ketone monitoring if participating in (or be willing to forgo participating in) extreme athletic activities, dieting, or excessive alcohol intake
    - Willingness to complete more frequent ketone monitoring if experiencing trauma, infection, or illness
- Ability to plan to pause sotagliflozin 3 days prior to any scheduled medical procedure or surgery
- Willingness to monitor blood glucose and keep detailed records of their insulin dosing and health status
- Has not had 3 or more severe hypoglycemia events within 3 months (ie, hypoglycemia requiring third-party assistance for correction)

All patients will be educated on the signs and symptoms of ketoacidosis and instructed to discontinue sotagliflozin and seek medical attention immediately if signs and symptoms persist after corrective action or have multiple episodes of vomiting and inability to keep down fluids, have fast or heavy breathing, or are slurring words or confused. Additionally, each patient will receive a Patient Alert Card with instruction on mitigation steps and when to seek immediate attention. The Patient Alert Card instructs patients to present the card to emergency care or any healthcare provider. The Patient Alert Cards will have information for emergency providers on increased risk of DKA with sotagliflozin use and to check for ketoacidosis regardless of blood glucose level, the patient's total daily insulin dose (to aid in basing correction insulin dose), and the contact information of the prescribing physician. A QR code printed on to the card will provide a link to additional patient and physician information on DKA risk, mitigation strategies, and when to seek emergency care.

The label also contains a Patient Counseling Information, which contains the following guidance for DKA:

- Inform patients that using sotagliflozin can increase their risk of life-threatening DKA.
- Educate all patients on precipitating factors (such as infection, reduced caloric intake, ketogenic diet, surgery, insulin dose reduction, dehydration, and alcohol abuse) and symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing). Provide patients with instructions to follow sick day rules, as inability to maintain adequate food and fluid intake along with adequate insulin therapy may precipitate ketoacidosis.
- Inform patients that blood glucose may be normal even in the presence of ketoacidosis.

A Medication Guide will also be provided to patients with every filled prescription and be readily available for download. The Medication Guide summarizes the most important information the patient should know about taking sotagliflozin. This includes the risk of DKA regardless of blood glucose, specifying the risks, early warnings signs, and symptoms of ketosis. Clear information will be provided with mitigation steps to avoid DKA and instruction on when to seek immediate medical attention.

Patients may need to lower insulin dosing while taking sotagliflozin. The Medication Guide will also address the risk of severe hypoglycemia and list the signs and symptoms of hypoglycemia. The Medication Guide will provide information about the contraindications and other AEs associated with the use of sotagliflozin. Patients will be instructed to ask their prescribing healthcare provider about the safe use of the medication, and to visit the product website or call the toll-free number provided if they have questions.

7.13.4 Management Actions and Communications

Lexicon will continue to develop its relationships with opinion leaders, Investigators, professional groups, and patient advocacy organizations. As part of these relationships, the review, evaluation, and adjustment of educational materials to align with standard of care and changes in treatment protocols will be ongoing.

Specific opportunities to evaluate the mitigation strategies above include continued work with T1DX-QI and the clinics participating in the registry. Lexicon has proposed a semiannual T1D Exchange output review that would provide the frequency of DKA and severe hypoglycemia in patients with T1D taking sotagliflozin.

Study groups will be evaluating the incidence of DKA and severe hypoglycemia as part of safety monitoring as the ongoing studies progress. These evaluations will provide active insights into the risk mitigation plans as well as the possibility to assess patient burden. Pharmacovigilance of reported spontaneous DKA cases will include a

questionnaire that reviews the circumstances and root causes of the event. These large-scale ongoing trials will further allow adjustment of educational materials.

Lexicon is committed to the ongoing education of patients and providers on the management and risks of DKA. The resources proposed include but are not limited to continued commitment to professional and patient organizations on providing unbranded and frequently refreshed materials on the recognition of early warning signs of ketosis steps to correct through the STICH protocol and when to seek emergency medical attention.

Lexicon has committed to providing these materials through the American Diabetes Association, the Association of Diabetes Certified Education Specialists, and patient organizations such as beyond T1D and Taking Control of Your Diabetes.

Lexicon has also committed to reach a minimum of 12,500 adult T1D respondents in a survey that will assess confidence in understanding and recognizing DKA before and after educational materials are provided, including the patients' next step in their journey to providing change in their treatment options. Through this specific outreach, we will not only reach a large number of people with T1D, but also learn more about the confidence and understanding educational materials provide and how best to reach the broader T1D community on next steps and plans for those who receive this information. Additionally, Lexicon also employs a team of highly trained scientific and medical field-based experts who will be providing proactive education to physicians and reactive materials regarding DKA awareness and education for patients and those who treat them.

Lexicon is committed to providing patient wallet cards distributed through multiple channels to remind patients of signs and symptoms of early ketosis/DKA, when to treat, and when to seek emergency medical attention. This patient wallet card will also contain instructions for emergency healthcare providers, alerting them to the patient's prescription of sotagliflozin and that DKA cannot be diagnosed based on blood glucose levels. The card will contain a QR code for patients and providers, leading to information on how best to treat DKA regardless of blood glucose measurements.

Lexicon will also provide unbranded educational materials through wide distribution networks, including Dear Provider letters, at the prescriber pharmacy and emergency department education level.

Through patient hub services and the Lexicon-dedicated Medical Information contact center, the company will provide updated contact information on where and when to seek emergency medical attention as well as information regarding DKA irrespective of sotagliflozin treatment.

The totality of evidence on the rates of DKA in the current patient population and known steps to educate and mitigate risk through wide distribution networks will help minimize

the rates of DKA in the treated population and alert the broader T1D community on risk management for DKA and when to seek proper emergency medical attention.

Lexicon will use multiple channels of communication with key stakeholders to ensure the greatest possible reach to the most important audiences: treating healthcare providers (diabetes and endocrine specialists, advanced practice providers, pharmacy, and emergency departments), professional healthcare provider societies and associations, patient advocacy organizations, and direct-to-patient education from Lexicon. By targeting all people living with or involved in the management of T1D regardless of sotagliflozin prescription, the educational materials have the greatest opportunity to have an impact with the lowest amount of message interference between message sender and message recipient.

7.13.5 DKA Risk Mitigation Strategies in the Real World

There have been no prospective clinical trials undertaken to demonstrate that patient and provider education can eliminate DKA events in people with T1D. However, the increased DKA risk from Phase 3 clinical trials of SGLT inhibitors have not correlated to a similar increase in real-world settings. In an analysis of safety outcomes taken from the TriNetX platform with records from 96 healthcare organizations largely centered in North America and Western Europe, 196,691 adults with T1D were identified as initiating a commercially available SGLT2 inhibitors or GLP-1 receptor agonist over a 5-year period. The rate of DKA with SGLT2 inhibitor use was 3.0% compared to 1.2% in a propensity-matched group of patients with T1D using GLP-1 receptor agonists (Anson 2023). Rates of DKA events in the SGLT2 inhibitor group were consistent with the rates of DKA in the adult T1D population from 2010 through 2018 irrespective of SGLT inhibitor use (Ebrahimi 2022). The RR of DKA was statistically greater with SGLT2 inhibitor use compared to GLP-1 RAs (RR 2.08 [95% CI 1.05, 4.12] p=0.0309), but increased DKA risk and associated hospitalization was deemed not great enough to offset the increased rate of all-cause hospitalization that was significantly higher in the GLP-1 RA group (RR 0.59 [95% CI 0.46, 0.76] p=0.0001) (Anson 2023).

Following the regulatory approval and marketed use of dapagliflozin in Europe (2019-2021), retrospective observational studies and registry follow-up of reported cases of DKA in adults with T1D using dapagliflozin ranged from 0% to 2.4% (0-1.5 DKA events per 100 years) (Duran 2024; Seufert 2021; Stougaard 2022). The overall lower rates of DKA compared to those reported in Phase 3 clinical trials have been attributed to patient selection and educational materials modeled after the sotagliflozin clinical development program that followed the “STICH” protocol to monitor ketone levels and recognize early symptoms of ketosis to treat accordingly before the progression to DKA (Garg 2018).

7.14 Safety Conclusions

The safety profile of sotagliflozin in the T1D-CKD population is similar to that established in the T2D population. Results show that treatment with sotagliflozin, compared to placebo, achieves improved glycemic control without an increase in risk of severe hypoglycemia.

There were no deaths associated with DKA in the T1D-CKD population. Patients with T1D and CKD do not appear to be at increased risk for DKA based on data provided by the T1D Exchange. The DKA risk in this higher risk population is reasonable when considering appropriate patient selection that will discourage use in patients that are unable or unwilling to consistently monitor glucose, encourage monitoring of ketone levels for suspected DKA episodes, and modifying patient behaviors and consideration of events that can increase the risk for DKA via patient and provider education. These actions are expected to decrease the risk for DKA events and expedite timely interventions should an event occur.

8 BENEFIT-RISK CONCLUSIONS

Without effective glycemic control, patients with T1D remain at risk of diabetic complications, including development of CKD and progression of CKD to ESKD, CV disease, and death. Patients with T1D and CKD are at a greater risk of progression of kidney disease and of worse CV outcomes compared with the overall T1D population. These patients have a greater need to control their blood glucose to avoid hyper- and hypoglycemic episodes that contribute to morbid events, including progression of their kidney disease.

An adjunctive therapy to insulin that would enable individuals living with T1D and CKD to improve their glycemic control would be valuable to the clinical community and patients with T1D-CKD. Sotagliflozin, a dual inhibitor of SGLT1 and SGLT2, fills this unmet need, providing benefits beyond improved glycemic control alone, including reduction in risk of HF events, weight loss, reduced risk of MACE, and improved UACR.

The statistically significant primary and key secondary glycemic endpoints shown in Studies 309, 310, and 312 in an overall adult T1D population allowed for evaluation of subgroups. Of the possible subgroups identified, patients with T1D and CKD were identified as the patient group where benefits observed in the overall population would be the most valuable and clinically meaningful when also observed in the T1D-CKD subgroup. Patients with T1D and CKD receiving sotagliflozin achieved nominally significant and clinically meaningful improvement in A1C and improvements in time in target glucose range. In addition, patients gained significant reductions in body weight that will help manage other risk factors such as hypertension, CV disease, and kidney decline in this population with a greater risk for disease progression. The cumulative effect of these effects associated with sotagliflozin treatment are expected to provide near- and long-term benefit in slowing disease progression in patients with T1D and CKD.

Additionally, sotagliflozin has demonstrated benefits in reducing HF-related events in patients with T2D and CKD and is indicated for use in adults with HF, regardless of diabetes status. In addition, treatment with sotagliflozin was associated with a reduced risk of MACE, including myocardial infarction and stroke, and kidney-related outcomes in patients with T2D and CKD. It is reasonable to expect sotagliflozin to provide similar kidney-, HF-, and MACE-related benefits in adults with T1D and CKD.

A summary of sotagliflozin benefits, in terms of evidence and uncertainties, along with conclusions and reasons, is provided in Table 39.

Table 39: Sotagliflozin Benefit Summary: T1D-CKD Population

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• In 3 adult Phase 3 trials (309, 310, and 312), sotagliflozin demonstrated A1C- and BW-lowering effects in a cohort of patients with T1D and CKD to a similar degree to that observed in the entire T1D cohort. • Sotagliflozin has demonstrated CV benefits in 2 large clinical outcomes trials in adults with HF or adults with T2D, CKD, and additional risk factors, with no new risks identified. • Reductions in A1C observed with sotagliflozin in the cohort of patients with T1D and CKD are highly consistent with the A1C reductions observed during long-term follow-up in the DCCT and other studies, which demonstrated significant and sustained reductions in risk of retinopathy, renal disease progression, and CV events. • Additional benefits to patients in the sotagliflozin Phase 3 T1D program included improved patient-reported outcomes measures, improved time in range, improved UACR, reduced insulin doses, and decreased SBP. • Similar reductions relative to placebo in adjudicated SH or hypoglycemia reported as an SAE in sotagliflozin-treated patients were observed in the T1D-CKD cohort compared to the overall T1D cohort.	• The results from 3 Phase 3 studies with sotagliflozin provide evidence of A1C- and BW-lowering effects. New analyses show that these glycemic control effects were similar in the cohort of patients with T1D and CKD to those observed in the entire T1D cohort. • Evidence supporting long-term benefits of managing BW, time in range, A1C, and UACR reduce risk of kidney, eye, heart, vascular, and nerve complications in patients with T1D; improvements in which are supported by long-term studies of A1C-lowering therapies. • Statistically significant and clinically meaningful benefits due to sotagliflozin have been observed in 2 large CV outcomes studies, one in patients with T2D and CKD, and these benefits are expected to accrue to patients with T1D and CKD. • These studies and the increasing body of evidence in published reviews of the increased risk for severe complications in patients with T1D and CKD strongly suggest that the benefits of treatment with sotagliflozin for improvement in BW, insulin dose, time in range, and A1C for patients with T1D and CKD will be substantially greater than those in the overall T1D population.

A1C: hemoglobin A1C; BW: body weight; CKD: chronic kidney disease; CV: cardiovascular; DCCT: Diabetes Control and Complications Trial; HF: heart failure; SAE: serious adverse event; SH: severe hypoglycemia; T1D: type 1 diabetes mellitus; T2D: type 2 diabetes mellitus; UACR: urine albumin-to-creatinine ratio

The safety profile of sotagliflozin in the T1D-CKD population is consistent with that of the population studied for the approved HF indication. In the T1D-CKD population, sotagliflozin does not increase the risk of hypoglycemia, including severe events. As such, the time in range benefit is a result of decreases in hyperglycemia.

While the risk for DKA is increased in patients treated with sotagliflozin, this can be managed with patient selection and education. The risks of DKA in patients with T1D with sotagliflozin and other SGLT inhibitors have been described and strategies have been developed for the safe implementation of these drugs when used in this group of patients. Lexicon has prepared a detailed and comprehensive Risk Management Plan to help healthcare providers and patients on sotagliflozin manage the risk of DKA and take actions to most appropriately treat DKA events.

Furthermore, patients with T1D-CKD typically have decades of experience in managing their diabetes and have experience with the tools and techniques to avoid unexpected glucose excursions and manage those events should they occur. This disease history also helps clinicians select appropriate patients that have the willingness and ability to closely manage their disease and not select those patients who are unlikely to be responsive to carefully prepared communication and education measures.

Based on the results of new analyses of the T1D-CKD cohort, as well as results from other relevant studies with sotagliflozin, it is clear that the benefit-risk profile for sotagliflozin in patients with T1D and CKD is favorable and supports the approval of sotagliflozin as an adjunct to insulin therapy to improve glycemic control for adults with T1D and CKD.

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10 APPENDICES

10.1 Studies 309, 310, and 312 Study Design Details

Design Overview

Three Phase 3 studies in the sotagliflozin T1D program included Studies 309, 310, and 312. Studies 309 and 310, which were conducted in North America and in Europe and Israel, respectively, included intensive insulin optimization, and evaluated 200 mg versus 400 mg versus placebo. The third Phase 3 study, Study 312, was conducted globally, without insulin optimization.

All 3 Phase 3 studies included a Screening Period of up to 2 weeks, which was followed by a 2-week Run-in period. During the Single-blind placebo Run-in Period, all patients were to take placebo tablets once daily before the first meal of the day. The placebo tablets were identical to sotagliflozin tablets in appearance. In order to qualify for randomization, patients must have had ≥80% compliance during the Single-blind placebo Run-in Period. In addition, patients had to demonstrate compliance with SMBG testing and compliance with entering required data in the study diary.

In this Phase 3 program, a placebo control was used to allow for an unbiased assessment of treatment effects and safety data, consistent with FDA and European Medicines Agency (EMA) guidances (EMA 2012; FDA 2008). The comparison with placebo was chosen because patients continued their use of prescribed insulin therapy, and because the patients' glycemic status was monitored and adjustments were made to the patients' insulin dose throughout the study as needed based on prespecified glycemic targets. Furthermore, use of a placebo control was appropriate because insulin is considered standard of care and an appropriate comparator is not available for T1D treatment. Pramlintide is the only approved non-insulin therapy marketed in the US. Its use is limited due to nausea, and a black box warning for severe hypoglycemia. Pramlintide (Symlin®) is not approved outside the US (AstraZeneca 2016).

A wide range of screening A1C (from 7.0% to 11.0%) in all 3 Phase 3 studies allowed evaluation of sotagliflozin's efficacy and safety in a broad population of patients with T1D. Patients with screening eGFR ≥45 mL/min/1.73m^2 were allowed to participate in Phase 3 studies based on supporting data from Study 107, which showed safe use of sotagliflozin in these patients.

In all three Phase 3 studies, patients received diet and exercise counseling according to nutritional recommendations for a healthy lifestyle consistent with ADA (ADA 2015) and European Association for the Study of Diabetes (EASD) guidelines (EASD 2013), or similar local guidelines with a goal of weight maintenance for the study duration. Patients were also educated on the use of the glucose meter provided during the study and the use of the study diary to record insulin doses, SMBG, and data related to hypoglycemic events. A BHB meter and testing strips and urine ketone test strips were

provided to all patients to allow testing of urine/blood ketones with the occurrence of symptoms suggestive of ketosis/DKA, eg, nonspecific gastrointestinal symptoms, malaise, not feeling well. A Clinical Endpoint Committee, Data Monitoring Committee, and T1D Steering Committee provided oversight in Studies 309, 310, and 312. An IDMC was in place for Studies 309 and 310.

Insulin Optimization

In order to evaluate the efficacy of sotagliflozin beyond what can be provided by insulin alone, all patients in Studies 309 and 310 entered a rigorous 6-week insulin optimization period prior to randomization, with the objective of improving glycemic control using insulin alone. Patients were maintained on optimized insulin after being randomized to 1 of 2 doses of sotagliflozin (200 mg or 400 mg) or placebo. During insulin optimization, insulin adjustment was assessed by an IDMC of independent experts from Week -5 to Week 24 (time of primary and secondary endpoint assessment). To be eligible for inclusion in both studies, the screening (pre-optimization) A1C was required to be ≥7.0%. This A1C inclusion criterion was not repeated after optimization; therefore, the study population included approximately 20% patients with A1C <7.0% at Baseline.

Sample Size

Separately for both Studies 309 and 310, the sample size estimate was based on satisfying design assumptions and statistical testing requirements for the primary efficacy endpoint. The final sample size was estimated as 250 randomized patients per treatment group (750 total) for each study.

For Study 312, the sample size was based on satisfying assumptions made for the primary efficacy endpoint of net clinical benefit and to provide a suitable number of patients so that a reliable estimate of treatment group differences in severe hypoglycemia could be made. Based on these considerations, 700 randomized patients were required per treatment group or 1400 total patients.

The statistical analyses for all Phase 3 studies were performed on the modified intent-to-treat (mITT) population, defined as all randomly assigned patients who received at least 1 dose of study drug. In Studies 309 and 310, the primary efficacy analysis was performed using an MMRM based on the restricted maximum likelihood method for estimation, with fixed and categorical effects of treatment, insulin delivery (MDI, CSII), Week -2 A1C (≤8.5%, >8.5%), time (study week), baseline A1C-by-time interaction, and a treatment-by-time interaction. Sensitivity analyses of the MMRM were conducted using multiple imputation methods, and specifically, pattern mixture models and tipping point analyses. Assessments of net benefit in all 3 studies were performed using a Cochran-Mantel-Haenszel test stratified by the randomization factors and with missing observations imputed as nonresponders. Control of the Type I error in testing the primary and secondary efficacy endpoints for Studies 309 and 310 was maintained by use of a Bonferroni-based, tree-structured gatekeeping multiple comparison

procedure. In Study 312, a prespecified hierarchical testing sequence was used to maintain control of the Type I error.

Analysis Population

Modified intent-to-treat (mITT) population: Included all randomly assigned patients who received at least 1 dose of study drug. The mITT patients were analyzed according to their randomized treatment.

10.2 Studies 309 and 310 Disposition and Baseline Characteristics (Randomized Population)

Table 40: Summary of Patient Disposition for Studies 309 and 310 (Randomized Population)

Disposition, n (%):	Study 309			Study 310		
	SOTA 200 mg (N=263)	SOTA 400 mg (N=262)	Placebo (N=268)	SOTA 200 mg (N=261)	SOTA 400 mg (N=263)	Placebo (N=258)
Randomized	263 (100)	262 (100)	268 (100)	261 (100)	263 (100)	258 (100)
mITT population	263 (100)	262 (100)	268 (100)	261 (100)	263 (100)	258 (100)
Completed 24 weeks	240 (91.3)	236 (90.1)	235 (87.7)	239 (91.6)	240 (91.3)	236 (91.5)
Completed 52 weeks	228 (86.7)	221 (84.4)	218 (81.3)	226 (86.6)	227 (86.3)	225 (87.2)

mITT: modified intent-to-treat; SOTA: sotagliflozin

Table 41: Summary of Patient Demographics and Baseline Characteristics for Studies 309 and 310 (mITT Population)

Disposition	Study 309			Study 310		
	SOTA 200 mg (N=263)	SOTA 400 mg (N=262)	Placebo (N=268)	SOTA 200 mg (N=261)	SOTA 400 mg (N=263)	Placebo (N=258)
Mean (SD) age at study entry (years)	46.6 (13.48)	46.4 (13.12)	45.2 (12.72)	42.3 (13.59)	41.7 (13.23)	39.7 (13.42)
Female, n (%)	137 (52.1)	142 (54.2)	131 (48.9)	122 (46.7)	130 (49.4)	124 (48.1)
Race, n (%)						
White	241 (91.6)	246 (93.9)	244 (91.0)	252 (96.6)	250 (95.1)	250 (96.9)
Black	11 (4.2)	8 (3.1)	9 (3.4)	0	0	1 (0.4)
BMI (kg/m^2), mean (SD)	29.81 (5.686)	29.63 (5.297)	29.55 (5.188)	27.97 (5.275)	27.85 (4.921)	27.50 (5.170)
<18.5	0	0	0	3 (1.1)	2 (0.8)	0
18.5 to <25	60 (22.8)	51 (19.5)	53 (19.8)	79 (30.3)	74 (28.1)	88 (34.1)
25 to <30	82 (31.2)	97 (37.0)	101 (37.7)	95 (36.4)	109 (41.4)	98 (38.0)
≥30	121 (46.0)	114 (43.5)	114 (42.5)	84 (32.2)	78 (29.7)	72 (27.9)
Insulin delivery method, n (%)						
CSII	156 (59.3)	157 (59.9)	160 (59.7)	68 (26.1)	67 (25.5)	66 (25.6)
Non-CSII	107 (40.7)	105 (40.1)	108 (40.3)	193 (73.9)	196 (74.5)	192 (74.4)
Mean (SD) A1C (%)	7.61 (0.735)	7.56 (0.724)	7.54 (0.712)	7.74 (0.806)	7.71 (0.819)	7.79 (0.881)
Mean (SD) total daily insulin dose (IU/kg)	0.72 (0.386)	0.72 (0.335)	0.74 (0.357)	0.73 (0.277)	0.74 (0.267)	0.75 (0.295)

A1C: hemoglobin A1C: BMI: body-mass index; CSII: continuous subcutaneous insulin infusion; mITT: modified intent-to-treat; SD: standard deviation; SOTA: sotagliflozin

10.3 Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation in Studies 309, 310 and 312

Table 42: Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (≥ 1 Patient in the T1D-CKD Population)

	T1D-CKD Population					T1D Safety Population				
	Pooled Studies 309 and 310 52-Week			Study 312 24-Week		Pooled Studies 309 and 310 52-Week			Study 312 24-Week	
Preferred Term, n (%)	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Patients with TEAEs leading to study drug discontinuation	3 (3.5)	4 (5.3)	4 (5.4)	8 (7.0)	4 (3.6)	23 (4.4)	35 (6.7)	20 (3.8)	44 (6.3)	16 (2.3)
Constipation	1 (1.2)	0	0	0	0	2 (0.4)	0	2 (0.4)	0	1 (0.1)
Genital infection fungal	1 (1.2)	0	0	0	0				2 (0.3)	0
Hypoglycaemia	1 (1.2)	0	0	0	0	1 (0.2)	0	2 (0.4)	2 (0.3)	0
Aortic valve incompetence	0	0	1 (1.4)	NA	NA	0	0	1 (0.2)	NA	NA
Blood creatinine increased	0	1 (1.3)	0	0	0	0	1 (0.2)	0	1 (0.1)	0
Diabetic ketoacidosis	0	1 (1.3)	0	2 (1.8)	0	4 (0.8)	10 (1.9)	0	10 (1.4)	1 (0.1)
Diarrhea	0	1 (1.3)	0	1 (0.9)	0	2 (0.4)	3 (0.6)	2 (0.4)	3 (0.4)	0
Diverticulitis	0	0	0	0	1 (0.9)	0	0	0	0	1 (0.9)
Gastritis	0	0	0	1 (0.9)	0	0	0	0	2 (0.3)	0
Headache	0	0	0	1 (0.9)	1 (0.9)	0	0	0	1 (0.1)	1 (0.1)
Hepatic pain	0	0	1 (1.4)	0	0	0	0	1 (0.2)	0	0
Hepatic enzyme increased	0	0	0	1 (0.9)	0	0	1 (0.2)	0	3 (0.4)	0
Hypotension	0	1 (1.3)	0	0	0	0	1 (0.2)	0	1 (0.1)	0
Lung neoplasm malignant	0	0	1 (1.4)	0	0	0	0	1 (0.2)	0	0
Myalgia	0	0	0	1 (0.9)	0	0	0	0	1 (0.1)	0
Rash	0	0	1 (1.4)	0	0	0	0	1 (0.2)	0	0
Renal Failure	0	0	0	0	1 (0.9)	0	0	0	0	1 (0.9)
Urinary tract infection	0	0	0	0	1 (0.9)	3 (0.6)	0	0	0	2 (0.3)

Preferred Term, n (%)	T1D-CKD Population					T1D Safety Population				
	Pooled Studies 309 and 310 52-Week			Study 312 24-Week		Pooled Studies 309 and 310 52-Week			Study 312 24-Week	
	SOTA 200 mg (N=85)	SOTA 400 mg (N=75)	Placebo (N=74)	SOTA 400 mg (N=114)	Placebo (N=110)	SOTA 200 mg (N=524)	SOTA 400 mg (N=525)	Placebo (N=526)	SOTA 400 mg (N=699)	Placebo (N=703)
Wrist fracture	0	0	0	1 (0.9)	0	0	0	0	1 (0.9)	0

CKD: chronic kidney disease; NA: Not Available as a preferred term in 312 dataset; SOTA: sotagliflozin; TEAE: treatment-emergent adverse event; T1D: type 1 diabetes mellitus

10.4 SCORED Patient Demographics (ITT)

Table 43: SCORED: Summary of Demographics in the Overall Population

	Randomized Population	
	Sotagliflozin (N=5292)	**Placebo (N=5292)**
Age at study entry (years), mean (SD)	68.4 (8.38)	68.2 (8.44)
Sex, n (%)		
Male	2945 (55.7)	2885 (54.5)
Female	2347 (44.3)	2407 (45.5)
Race, n (%)		
White	4383 (82.8)	4329 (81.8)
Black or African American	176 (3.3)	187 (3.5)
Asian	317 (6.0)	365 (6.9)
American Indian or Alaska Native	205 (3.9)	216 (4.1)
Native Hawaiian or other Pacific Islander	25 (0.5)	15 (0.3)
Multiple	129 (2.4)	114 (2.2)
Not reported	29 (0.5)	27 (0.5)
Unknown	25 (0.5)	32 (0.6)
BMI (kg/m^2)		
Mean (SD)	32.58 (6.285)	32.44 (6.252)

BMI: body mass index; SD: standard deviation

Table 44: SCORED: Summary of Baseline Characteristics in the Overall Population

	Randomized Population	
	Sotagliflozin (N=5292)	Placebo n=5292
Baseline A1C (%) categories, n (%)		
<8.0	1965 (37.1)	2011 (38.0)
≥8.0 to <9.0	1576 (29.8)	1516 (28.6)
≥9.0 to <10.0	893 (16.9)	863 (16.3)
≥10.0	855 (16.2)	898 (17.0)
A1C (%)		
Mean (SD)	8.689 (1.4493)	8.701 (1.4626)
Baseline eGFR (mL/min/1.73m²)		
Mean (SD)	44.1392 (9.54592)	44.2795 (9.53944)
≥45	2526 (47.7)	2590 (48.9)
Baseline UACR (mg/g)		
Median (min, max)	79.5000 0.000, 14429.925	84.0750 0.000, 17291.500
Baseline UACR (mg/g) categories, n (%)[a]		
<30 (normal)	1709 (32.3)	1741 (32.9)
≥30 to 300 (microalbuminuria)	1905 (36.0)	1891 (35.7)
≥300 (macroalbuminuria)	1676 (31.7)	1658 (31.3)
Baseline SBP (mm Hg)		
Mean (SD)	137.85 (16.730)	137.68 (16.740)

A1C: hemoglobin A1C; eGFR: estimated glomerular filtration rate; Max: maximum; Min: minimum; SBP: systolic blood pressure; SD: standard deviation; UACR: urine albumin-to-creatinine ratio
[a] Baseline UACR is defined as the average of all spot urine values assessed by the central laboratory from screening up to and including randomization. However, if the 24-urine value during screening indicates the patient is ≥300 mg/g, the patient is included in the macroalbuminuria category.

10.5 Abbreviated Patient Narratives for DKA Events in Studies 309, 310, and 312

10.5.1 Sotagliflozin 200 mg

A 69-year-old male (white, not Hispanic or Latino) patient with T1D experienced an SAE of DKA of severe severity during the Double-blind Treatment Period.

The patient was diagnosed with T1D at age 37 years. Relevant medical history included diabetic retinopathy, hyperlipidemia, and peripheral neuropathy. Other concurrent

conditions included hypertension and benign prostatic hypertrophy. There was no known history of DKA.

Concomitant medications at the onset of the event included acetylsalicylic acid, dutasteride, hyzaar, and simvastatin. The patient received insulin lispro and insulin glargine via subcutaneous injection as treatment for T1D.

The patient's A1C at Baseline was 7.1%. The patient's BHB at Baseline was 0.26 mmol/L.

On Study Day 286, the patient experienced an SAE of DKA of severe severity. This was a life-threatening event as it required hospitalization. The patient was incoherent and had shortness of breath and required intubation. The patient's blood glucose was in the 700-mg/dL range and he was placed on insulin drip and treated with aggressive fluid resuscitation. He was also started on norepinephrine for his hypotension. Study drug was temporarily discontinued and was resumed; the event did not reappear. The SAE of DKA was considered resolved 4 days later on Study Day 290, and the patient was discharged in stable condition with discharge diagnosis of DKA.

The patient received the last dose of study medication 2 months later. No precipitating factor for the DKA event was identified.

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A 71-year-old female (white, not Hispanic or Latino) patient with T1D experienced SAEs of acute myocardial infarction, DKA, and atrial fibrillation, all of severe severity during the Double-blind Treatment Period.

The patient was diagnosed with T1D at age 30 years. Relevant medical history included retinopathy, coronary artery bypass, hypertension, hyperlipidemia, and cerebrovascular accident. The patient had no prior history of DKA.

Concomitant medications at the onset of the SAEs included acetylsalicylic acid, benazepril with hydrochlorothiazide, citalopram hydrobromide, multivitamins, simvastatin, and miconazole nitrate. The patient’s concomitant medications included insulin glulisine via insulin pump as T1D treatment.

The patient’s A1C at Baseline was 7.8%. The patient’s BHB at Baseline was 0.22 mmol/L.

On Study Day 209, the patient experienced an AE of mild pharyngitis streptococcal and received penicillin. Dexamethasone injection was administered on Study Day 213.

On Study Day 214, the patient experienced an SAE of acute myocardial infarction of severe severity and an SAE of DKA of severe severity. Both events required hospitalization. The Investigator reported that the DKA was due to the systemic corticosteroids that were administered to the patient, prior to the event. Study drug was interrupted on Study Day 214 because of the SAE of DKA. The AE of DKA was

considered resolved 1 day later on Study Day 215. The Investigator considered the event of DKA as not related to study drug.

The AEs of acute myocardial infarction and atrial fibrillation were considered resolved 5 days later on Study Day 219. The patient was discharged from the hospital on the same day. The Investigator considered the events of acute myocardial infarction and atrial fibrillation as not related to study drug. The study drug was resumed on Study Day 225 and continued for 5 more months.

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A 26-year-old female (white, not Hispanic or Latino) patient with T1D experienced SAEs of DKA and rotavirus infection, both of severe severity, during the Double-blind Treatment Period.

The patient was diagnosed with T1D at age 13 years. Relevant medical history included hypothyroidism and hypercholesterolemia. The patient did not have a history of DKA.

Concomitant medications at the onset of the SAEs included levothyroxine sodium, colecalciferol, Yasminelle (ethinyl estradiol / drospirenone), and cetirizine hydrochloride. The patient received insulin lispro and insulin glargine via subcutaneous injection for the treatment of T1D.

The patient's A1C at Baseline was 8.2%. The patient's BHB on at Baseline was 0.43 mmol/L.

On Study Day 175, the patient experienced an SAE of DKA of severe severity and an SAE of rotavirus infection of severe severity. The events required hospitalization. During the episode of DKA, the patient's blood glucose was not very high (200 mg/dL to 260 mg/dL) but was consistently elevated. Serum ketones were positive, the highest BHB was measured at 6.1 mmol/L, the lowest serum bicarbonate was 13.3 mEq/L, the lowest pH measured was 7.30, and the lowest serum creatinine was 0.6 mg/mL.

The study drug was interrupted. The SAE of DKA considered resolved 1 day later, Study Day 176. The SAE of rotavirus infection was considered resolved 3 days later on Study Day 178 and the patient was discharged the same day. The Investigator considered the event of DKA as possibly related to study drug and caused by the rotavirus infection. Study drug was resumed on Study Day 179.

The patient received the last dose of study drug 6 months later.

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A 39-year-old male (white, not Hispanic or Latino) patient with T1D experienced SAEs of pneumonia of severe severity and DKA of moderate severity during the Double-blind Treatment Period.

The patient was diagnosed with T1D at age 4 years. Relevant medical history included diabetic neuropathy and diabetic retinopathy. Concurrent condition was

gastroesophageal reflux disease. The patient also had influenza in 2016. Concomitant medications at the onset of the events included cetirizine, pantoprazole sodium sesquihydrate, and thioctic acid. The patient received insulin glargine and insulin lispro via subcutaneous injection as T1D treatment.

The patient's A1C at Baseline was 8.0%. The patient's BHB at Baseline was 0.19 mmol/L.

The patient began the Double-blind Treatment Period with sotagliflozin 200 mg. On Study Day 363, the patient experienced an SAE of pneumonia of severe severity. This event required hospitalization. Prior to hospitalization, the patient reported having taken amoxicillin/clavulanic acid for 3 to 4 days at home for his cough. He was then admitted for treatment of febrile pneumonia. Blood glucose was 15 mmol/L; he had a decompensated metabolic acidosis (pH: 6.989). Nausea and fever resolved and the patient's condition cleared.

On Study Day 364, the patient experienced an SAE of DKA of moderate severity; the patient was placed in the intensive care unit (ICU) for continued treatment with alkalization, and continuous intravenous insulin therapy. Study drug was stopped and not resumed. The SAE of DKA resolved 2 days later on Study Day 366. The Investigator considered the event of DKA as not related to study drug. Per the Investigator's assessment, the triad of hyperglycemia, ketonemia, and high anion gap was not demonstrated. There was no known history of chronic ethanol abuse or recent binge drinking. At the time of acidosis, hyperglycemia was present.

Study drug was not changed in response to the SAE of pneumonia. The SAE of pneumonia resolved 10 days later on Study Day 373. The Investigator considered the event of pneumonia as not related to study drug.

The patient received the last dose of study drug on Study Day 363.

10.5.2 Sotagliflozin 400 mg

A 47-year-old female (white, not Hispanic or Latino) patient with T1D experienced an SAE of DKA of severe severity during the Double-blind Treatment Period.

The patient was diagnosed with T1D at age 9 years. Concurrent conditions included hypothyroidism, obesity, hypertension, and dyslipidemia. Concomitant medications at the onset of the event included Co-ramipril, levothyroxine sodium, and rosuvastatin calcium. The patient received insulin aspart administered via insulin pump for the treatment of T1D.

The patient's A1C at Baseline was 8.3%. The patient's BHB at Baseline was 0.18 mmol/L.

On Study Day 95, the patient experienced an SAE of DKA of severe severity. The patient also experienced an AE of gastrointestinal viral infection of mild severity the same day. No action was taken with the study drug because of the SAE of DKA. The

SAE of DKA resolved 1 day later on Study Day 96 and she was sent home from the emergency room (ER). The Investigator considered the event of DKA as possibly related to study drug.

The patient received the last dose of study drug on Study Day 373 and completed the study.

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A 27-year-old female (white, not Hispanic or Latino) patient with T1D experienced an SAE of DKA of severe severity during the Double-blind Treatment Period.

The patient was diagnosed with T1D at age 9 years. Concurrent condition was insomnia. The patient had no prior history of DKA. The patient was not on any concomitant medications at the onset of the event. The patient received insulin aspart and insulin glargine administered subcutaneously via injection for the treatment of T1D.

The patient's A1C at Baseline was 7.6%. The patient's BHB at Baseline was 0.24 mmol/L.

On Study Day 281, the patient had severe vomiting and went to the ER; her glucose was 180 mg/dL. The patient had no fever, no chills, no urinary symptoms, no chest pains, and no diarrhea. DKA was suspected and the patent was admitted to the ICU, pH was 7.04. In response to the event, study drug was stopped temporarily.

The Investigator considered the event of DKA as possibly related to study drug.

The patient resumed study drug and completed the study 3 months later.

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A 67-year-old male (black or African American, not Hispanic or Latino) patient with T1D experienced SAEs of rhabdomyolysis of moderate severity, DKA of severe severity, and DKA of moderate severity during the Double-blind Treatment Period.

The patient was diagnosed with T1D at age 34 years. Relevant medical history included hypertension, hypercholesterolemia, and DKA. Concurrent conditions included CKD, fracture (not otherwise specified), arthritis, back pain, sinusitis, diarrhea (intermittent), constipation (intermittent), and irritable bowel syndrome. The patient also had small intestinal obstruction, hernia repair, knee arthroplasty, tendon operation, pneumonia, thoracotomy, cholecystectomy, and appendectomy.

Concomitant medications at the onset of the events included lubiprostone, acetylsalicylic acid, doxazosin mesilate, multivitamins, oxycodone/paracetamol, and quinapril hydrochloride. The patient received insulin lispro via subcutaneous injection as treatment for T1D.

The patient's A1C at Baseline was 8.6%. The patient's BHB at Baseline was <0.10 mmol/L.

On Study Day 121, the patient experienced an SAE of rhabdomyolysis of moderate severity. This event required hospitalization. The patient had an episode of abdominal pain and reported blood glucose in the 120-mg/dL range. Subsequent blood glucose checks revealed elevated blood glucose as high as 400 mg/dL and he had an episode of vomiting. The patient was diagnosed with rhabdomyolysis with acute kidney injury and DKA. This first event of DKA was severe in severity. According to the Investigator, rhabdomyolysis and DKA caused the acute kidney failure and the acute kidney failure was not a separate event. Per Investigator, the patient's rhabdomyolysis was caused by dehydration due to DKA, vomiting, and excessive urination. Study drug was interrupted for the SAEs of rhabdomyolysis and DKA. The SAEs of rhabdomyolysis and DKA resolved on Study Day 128. The Investigator considered the event of rhabdomyolysis as not related to study drug and the event of DKA as unlikely related to study drug.

On Study Day 193, the patient experienced the second SAE of DKA that was moderate in severity. This event required hospitalization. Ketones were 1.7 and serum bicarbonate was 22.4 mEq/L, and highest anion gap was 15.0 mEq/L. The SAE of DKA resolved 2 days later on Study Day 195 and the patient was discharged the same day. The Investigator considered the event of DKA as not related to study drug. This episode of DKA was evaluated by the Clinical Endpoint Committee, which determined that criteria for a DKA event and criteria for metabolic acidosis were not met.

The patient received the last dose of study drug on Study Day 168.

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A 63-year-old female (white, not Hispanic or Latino) patient with T1D experienced an SAE of DKA of severe severity during the Double-blind Treatment Period.

The patient was diagnosed with T1D at age 36 years. Relevant medical history included DKA, diabetic neuropathy, and diabetic retinopathy. Concurrent conditions included hypersensitivity (environmental irritants), drug hypersensitivity, polyarthritis, nephrolithiasis, and goiter. The patient also had a tonsillectomy, hysterectomy, breast operation, and renal colic.

Concomitant medications at the onset of the event included lactobacillus acidophilus, colecalciferol, losartan potassium, meloxicam, fluticasone propionate, ketoprofen/lidocaine, multivitamins, vaccinium macrocarpon, loratadine, tamsulosin hydrochloride, solifenacin succinate, cyanobalamin, and paracetamol. The patient received insulin lispro via insulin pump as treatment for T1D.

The patient’s A1C at Baseline was 9.3%. The patient's BHB at Baseline was 0.63 mmol/L.

At the last visit prior to the event, at Week 16 (approximately 1 month prior to SAE of DKA), the patient’s A1C was 8.4%, fasting glucose was 176 mg/dL, and BHB was 1.74 mmol/L. Due to the elevated BHB, the patient was instructed by the Investigator to take

a bolus of insulin to correct the hyperglycemia, check her blood BHB, and contact the site every 2 hours until BHB fell below 0.6 mmol/L. At 20:21, after following the Investigator's instructions, the patient's BHB was 0.2 mmol/L. The patient denied any symptoms related to this event.

On Study Day 136, the patient experienced an SAE of DKA of severe severity. This event required hospitalization and led to discontinuation of study drug. The next day, the patient developed fever, inability to maintain oral intake, generalized weakness, gastrointestinal symptoms, and upper chest pain. On Study Day 138, the patient's symptoms persisted, her BHB was >3 mmol/L; she presented to the ER. The patient was rehydrated and treated for acute acid reflux and abdominal pain and was discharged the same day. On Study Day 139, the patient developed a burning sensation during urination and urinary urgency, and urine was positive for ketones. Evaluation on Study Day 140 showed mild acidosis and she returned to ER and was admitted to the ICU. She was discharged from hospital on Study Day 142. The SAE of DKA was considered resolved on Study Day 155.

According to hospital physicians and the Investigator, the DKA could have been possibly triggered by a urinary tract infection. The Investigator also believed that the DKA could have been caused by starvation and a lack of insulin.

The patient received the last dose of study drug on Study Day 139.

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A 42-year-old female (white, not Hispanic or Latino) patient with T1D experienced an SAE of DKA of severe severity during the Double-blind Treatment Period.

The patient was diagnosed with T1D at age 5 years. Concurrent medical history included rheumatoid arthritis, anxiety, periarthritis (left shoulder), hypothyroidism, and urinary tract infection. The patient also had an appendectomy, hip arthroplasty (left), and vulvovaginal mycotic infection. The patient experienced 1 episode of DKA 5 years ago.

Concomitant medications at the onset of the event included anovlar, methotrexate, paroxetine, etanercept, levothyroxine, lorazepam, pravastatin, and vitamin D. The patient received insulin lispro administered via insulin pump for the treatment of T1D.

The patient's A1C at Baseline was 7.9%. The patient's BHB at Baseline was <0.10 mmol/L.

On Study Day 18, the patient experienced an SAE of DKA of severe severity. The event required hospitalization and led to discontinuation of study drug. The patient presented to the ED with an episode of emesis. She had checked her blood glucose, which was 197 mg/dL, and her ketones were at 5.9 (reference range: <4.0). On admission, pH was 7.28. The patient was clinically stable and admitted to the internal medicine service for further monitoring and treatment. The patient denied changes to her diet, medications,

or insulin pump functionality. She denied contact with anyone who was sick and did not have any symptoms of urinary tract infection, infections symptoms, or myocardial symptoms on admission.

Study drug was withdrawn on Study Day 18 because of the SAE of DKA. The SAE of DKA resolved 1 day later and the patient was discharged the same day. The Investigator considered the event of DKA as related to study drug.

10.5.3 Placebo

A 54-year-old male (white, not Hispanic or Latino) patient with T1D experienced SAEs of impaired gastric emptying and DKA, both of moderate severity during the Double-blind Treatment Period.

The patient was diagnosed with T1D at age 40 years. Relevant medical history included gastroesophageal reflux disease, impaired gastric emptying, and irritable bowel syndrome. Concurrent conditions included coronary artery disease, coronary artery bypass, hypertension, hyperlipidemia, and depression.

Concomitant medications at the onset of the events included acetylsalicylic acid, carvedilol, gabapentin, omeprazole, sertraline, and simvastatin. The patient received insulin lispro via insulin pump as T1D treatment.

The patient's A1C at Baseline was 7.2%. The patient's BHB at Baseline was <0.10 mmol/L.

On Study Day 186, the patient experienced an SAE of impaired gastric emptying (exacerbation of gastroparesis) of moderate severity. This event required hospitalization. On Study Day 189, the patient experienced an SAE of DKA of moderate severity. This event prolonged hospitalization. The patient experienced gastrointestinal symptoms (nausea and vomiting), with a constantly elevated blood glucose. The SAEs resolved on Study Day 192 and were considered unlikely related to study drug.

Study drug was drug interrupted for 24 days because of the SAE of impaired gastric emptying and was then resumed. The last dose of study drug was Study Day 364 and the patient completed the study.

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A 29-year-old male (white, not Hispanic or Latino) patient with T1D experienced an SAE of DKA of mild severity during the Double-blind Treatment Period.

The patient was diagnosed with T1D at age 3 years. Relevant medical history included DKA, diabetic retinopathy, and hypercholesterolemia. Concurrent conditions included substance use (cocaine), and recent hospitalization for acute kidney injury (<1 month before first dose of Study Drug). Concomitant medication at the onset of the event was perindopril erbumine. The patient received insulin aspart via insulin pump as treatment for T1D.

On Study Day 9, the patient experienced an SAE of DKA of mild severity. This event required hospitalization. His insulin pump had stopped working.

Study drug was not changed due to the SAE of DKA. The SAE of DKA resolved on Study Day 13 and the patient was discharged the same day. The Investigator considered the event of DKA as not related to study drug.

The patient received the last dose of study drug on Study Day 34.