FDA Briefing Document

NDA# 210934

Drug name: sotagliflozin

Applicant: Lexicon Pharmaceuticals, Inc.

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

10/31/24

Division of Diabetes, Lipids, and Obesity (DDLO)

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)

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Glossary

A1C	hemoglobin A1C
AC	Advisory Committee
ACEi	angiotensin-converting enzyme inhibitor
ADA	American Diabetes Association
ANCOVA	analysis of covariance
ARB	angiotensin II receptor blocker
AUC	area under the concentration curve
BHB	beta-hydroxybutyrate
BMI	body mass index
BW	body weight
CDER	Center for Drug Evaluation and Research
CEC	Clinical Event Committee
CFB	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
CKD	chronic kidney disease
CREDENCE	Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy
CRL	Complete Response Letter
CSG	Collaborative Study Group
CSII	continuous subcutaneous insulin infusion
CV	cardiovascular
CVOT	cardiovascular outcomes trial
DAPA-CKD	Dapagliflozin in Patients with Chronic Kidney Disease
DCCT	Diabetes Control and Complications Trial
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DTSQ	Diabetes Treatment Satisfaction Questionnaire
eCRF	electronic case report form
EDIC	Epidemiology of Diabetes Interventions and Complications
eGFR	estimated glomerular filtration rate

EMDAC	Endocrinologic and Metabolic Disease Advisory Committee
EMPA-KIDNEY	Study of Heart and Kidney Protection with Empagliflozin
ESRD	end stage renal disease
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FDRR	formal dispute resolution request
FIDELIO-DKD	Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease
GLP-1	glucagon-like peptide 1
HF	heart failure
HHF	hospitalization for heart failure
HR	hazard ratio
ICD	International Classification of Diseases
IDNT	Irbesartan Diabetic Nephropathy Trial
IND	investigational new drug
IR	incidence rate
IRD	incidence rate difference
ITT	intention-to-treat
KDIGO	Kidney Disease: Improving Global Outcomes
LSMean	least-squares mean
MACE	major adverse cardiovascular event
MAR	missing at random
MDI	multiple daily injection
MI	myocardial infarction
MMRM	mixed model repeated measures
NDA	new drug application
NNH	number needed to harm
NNT	number needed to treat
NOOH	notice of opportunity for hearing
OCHEN	Office of Hematology, Cardiology, Endocrinology and Nephrology
ODE2	Office of Drug Evaluation 2
OND	Office of New Drugs

PD	pharmacodynamic
PERL	Preventing Early Renal Loss in Diabetes
PK	pharmacokinetic
PPV	positive predictive value
PS	propensity-score
RAS	renin-angiotensin system
RENAAL	Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan
SBP	systolic blood pressure
SCORED	Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk
SD	standard deviation
SE	standard error
SGLT	sodium-glucose co-transporter
SGLT2i	sodium-glucose co-transporter 2 inhibitor
SMBG	self-monitoring of blood glucose
Sota	sotagliflozin
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
UACR	urine albumin-creatinine ratio
UGCR	urine glucose-to-creatinine ratio
UGE	urinary glucose excretion
UHFV	urgent heart failure visit
USPI	United States Prescribing Information

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the Advisory Committee Meeting

The Food and Drug Administration (FDA) has convened this Advisory Committee (AC) meeting to discuss New Drug Application (NDA) 210934 for sotagliflozin tablets (dosed at 200 mg or 400 mg daily) as Zynquista, proposed as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus (T1D) and chronic kidney disease (CKD). For the purposes of this application, the Applicant defines CKD as an estimated glomerular filtration rate (eGFR) of 45 to <60 mL/min/1.73 m^2 or eGFR ≥60 mL/min/1.73 m^2 and urine albumin-creatinine ratio (UACR) ≥30 mg/g.

The current application is a revision of the original NDA submission, which proposed sotagliflozin as an adjunct to insulin therapy to improve glycemic control in adults with T1D. The original submission received a Complete Response because FDA determined that the risk of diabetic ketoacidosis (DKA) outweighed the benefits for the proposed indication and patient population. FDA seeks advice from the AC on whether the data in the revised NDA support an overall favorable benefit-risk assessment for sotagliflozin for the revised indication that proposes to limit the population to patients with T1D and CKD.

1.2 Context for Issues to Be Discussed at the AC Meeting

Type 1 diabetes mellitus (T1D) is characterized by progressive, autoimmune destruction of pancreatic β-cells. Insulin therapies remain the mainstay for glycemic control in patients with T1D. The goal of therapy is to reduce hemoglobin A1c (A1C) while avoiding hypoglycemia. The landmark Diabetes Control and Complications Trial (DCCT) established that improvement in glycemic control reduces the risk of long-term microvascular disease (retinopathy, nephropathy, and neuropathy). Using current treatment options, however, fewer than one quarter of adult patients with T1D are able to achieve recommended glycemic targets (Nathan 2021).

CKD secondary to diabetes is present in 20 to 40% of patients with diabetes. Although CKD may be present at the time of diagnosis in patients with type 2 diabetes (T2D), CKD typically presents in patients with T1D only after a disease duration of 5 to 15 years. CKD can progress to end-stage kidney disease requiring dialysis or kidney transplantation. In addition, the presence of CKD increases cardiovascular risk in patients with T1D. The *Standards of Care* published by the American Diabetes Association (ADA) recommends use of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) for patients with T1D who have hypertension and albuminuria to reduce the progression of CKD and to reduce the risk of major adverse cardiovascular events (MACE). Despite the widespread adoption of renin-angiotensin system (RAS) inhibitors, the risk of progression of CKD remains a significant issue for patients with T1D and comorbid CKD. Although some additional pharmacotherapies have a demonstrated benefit in reducing the risk of progression of CKD in other populations (finerenone, canagliflozin, dapagliflozin, and empagliflozin in patients with T2D and CKD; dapagliflozin and empagliflozin in patients with CKD without diabetes mellitus), these agents have not been evaluated in cardiorenal outcome trials of patients with T1D (American Diabetes Association Professional Practice 2024).

Both dapagliflozin and empagliflozin have approved indications in adults with CKD at risk of progression, which encompass adults with T1D and CKD (see Section 2.1 for discussion of the approvals of these indications). Nonetheless, in the few years since the addition of these indications to the USPIs, treatment guidelines from ADA and other professional organizations have not been modified to recommend dapagliflozin or empagliflozin for patients with T1D and CKD.

1.3 Brief Description of Issues for Discussion at the AC

The FDA is seeking advice from the AC on several issues related to the benefit-risk assessment of sotagliflozin, including the evidence and uncertainties regarding the magnitude of benefits likely to accrue to patients with T1D and mild-to-moderate CKD treated with sotagliflozin and the evidence and uncertainty regarding the magnitude of DKA risk incurred by such patients. The FDA also seeks the perspective of the committee regarding proposals by the Applicant to apply evidence of benefits in patients with T2D to patients with T1D.

1.4 Draft Points for Consideration

- Discuss the adequacy of the existing clinical trial data to support a conclusion that sotagliflozin improves glycemic control across the range of eGFRs (45 mL/min/1.73 m^2 to >90 mL/min/1.73 m^2) included in the indication proposed by the Applicant. Discuss the evidence and uncertainties regarding the magnitude and durability of the treatment effect established for patients with T1D and eGFRs in the following ranges: 45 to <60 mL/min/1.73 m^2, 60 to <90 mL/min/1.73 m^2, and ≥90 mL/min/1.73 m^2. Discuss the evidence and uncertainties regarding the magnitude of clinical benefit conferred by the estimated reduction in A1C in the revised proposed population, especially with regard to intermediate and long-term renal benefits.
- Discuss the adequacy of the existing data to support a conclusion that the magnitude of the DKA risk in patients with T1D and CKD treated with sotagliflozin can be assumed to be similar to that observed in patients with T1D in the overall TANDEM program. Discuss the evidence and uncertainties regarding such an inference for patients with T1D and eGFRs in the following ranges: 45 to <60 mL/min/1.73 m^2, 60 to <90 mL/min/1.73 m^2, and ≥90 mL/min/1.73 m^2.
- Discuss your view of the scientific rationale justifying extrapolation of the demonstrated benefit of sotagliflozin to reduce the risk of cardiovascular (CV) death, hospitalization for heart failure (HHF), and urgent heart failure visit (UHFV) in patients with T2D, CKD, and other cardiovascular (CV) risk factors to a population of patients with T1D, CKD, and other risk factors. Discuss other potential benefits of sotagliflozin that would be scientifically justified to extrapolate to a population of patients with T1D and CKD, if demonstrated in patients with T2D and CKD. Discuss the evidence and uncertainties regarding the magnitude of clinical benefit related to any of these additional benefits that might accrue to patients with T1D and mild-to-moderate CKD without other CV risk factors.
- Discuss the overall benefit-risk assessment for sotagliflozin as an adjunct to insulin to improve glycemic control in patients with T1D and CKD as defined by the Applicant. Address how to consider the increased risk of DKA against the benefit of an A1C improvement. Discuss any other advantage or disadvantage of sotagliflozin therapy that should be considered in the benefit-risk assessment for the proposed indication. Discuss how uncertainties regarding individual components of the benefit-risk assessment should be factored into the overall assessment of benefit-risk.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1D) is characterized by progressive, autoimmune destruction of pancreatic β-cells, usually leading to severe endogenous insulin deficiency. The primary activity of insulin is regulation of glucose metabolism: insulin lowers blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.[1] Exogenous insulin is typically required for survival in T1D. In the United States (U.S.), the prevalence of T1D is estimated to be 1.7 million adults (CDC 2024) over the age of 20 years and 244,000 children or adolescents younger than 20 years. This corresponds to 5.7% of all U.S. adults diagnosed with diabetes. The global T1D prevalence is 5.9 per 10,000 individuals and its incidence has risen in the past half-century to 15 per 100,000 individuals per year globally (Holt et al. 2021). On average, 50,000 individuals are diagnosed with T1D each year in the U.S.

The severe insulin deficiency that characterizes patients with T1D classically presents as a triad of thirst and polydipsia, polyuria, and weight loss. A relative or absolute insulin deficiency (coinciding with concomitant increases in glucagon, cortisol, epinephrine, and growth hormone) can also result in DKA; a florid DKA event is sometimes the first presentation of T1D. Without treatment with exogenous insulin, the life expectancy of patients with T1D is measured in months (Goldenberg et al. 2016; Holt et al. 2021). The discovery of insulin and subsequent advent of exogenous insulin therapy in the 1920s significantly mitigated the acute morbidity and mortality associated with a new T1D diagnosis, but the association between T1D and long-term complications (including impaired vision, renal failure, amputations, myocardial infarctions, and stroke) and shortened life expectancy quickly became evident. DCCT demonstrated that insulin regimens targeted to achieve more intensive glycemic control reduced the risk of long-term microvascular complications (retinopathy, nephropathy, neuropathy) when compared to conventional insulin regimens designed to avoid acute clinical symptoms of hypoglycemia and hyperglycemia. The results of DCCT are the basis for modern approaches to the management of patients with T1D, which focus on optimizing glycemic control. The ADA treatment guidelines recommend treating most adult patients to a goal A1C of <7%, if achievable without significant hypoglycemia.

In addition to regular human insulin, insulin analogs have been developed and are commonly used by patients with T1D. Insulin analog options include: rapid-acting insulins for mealtime, and long-acting insulin analogs for basal coverage (via multiple daily injections [MDI]). Continuous subcutaneous insulin infusions (CSII, also known as insulin pumps) use rapid-acting insulin analogs for continuous basal insulin with mealtime boluses. In addition to subcutaneous routes of administration, inhaled insulin is also an option. Pramlintide, a synthetic analog of human amylin, is an additional anti-diabetic agent approved as an adjunctive treatment in patients with T1D who use mealtime insulin therapy (Holt et al. 2021).[2] Finally, the use of some devices (e.g., continuous glucose monitors, hybrid closed loop pumps) has been

[1] See the Humulin R United States Prescribing Information (USPI) at: https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=b60e8dd0-1d48-4dc9-87fd-e14675255e8c.
[2] See the pramlintide USPI at: https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=4aea30ff-eb0d-45c1-b114-3127966328ff.

demonstrated to further improve glycemic control (Beck et al. 2017; Brown et al. 2019; Pratley et al. 2020).

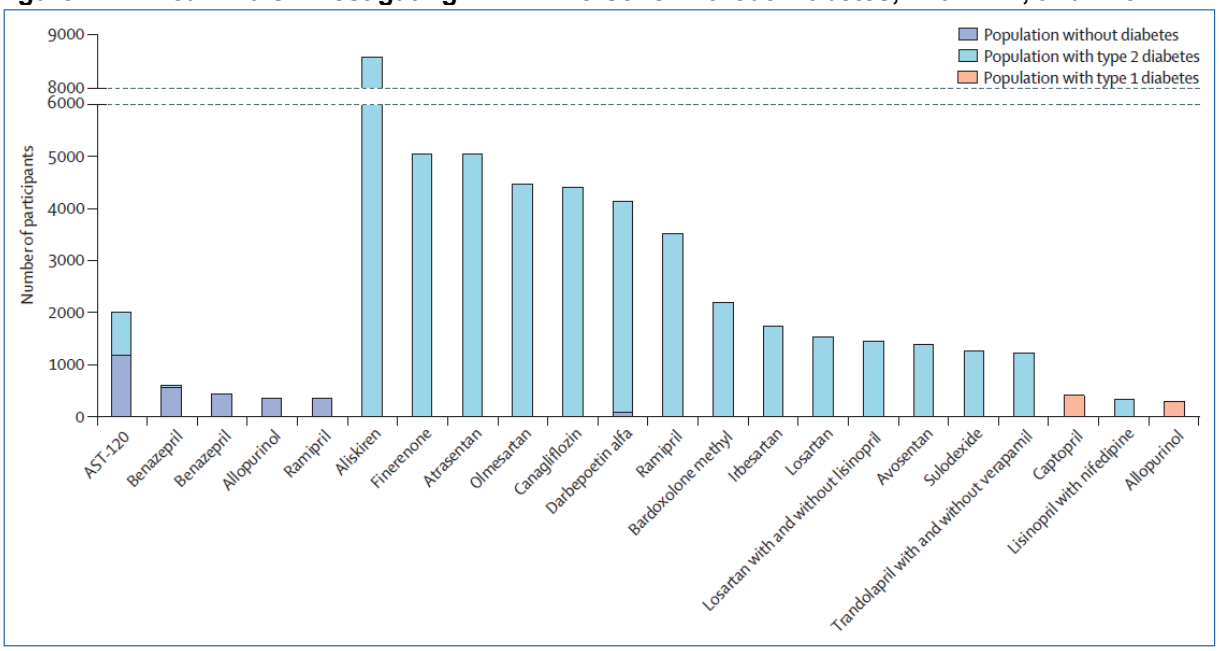
Chronic Kidney Disease (CKD)

CKD is a progressive condition characterized by structural and functional changes to the kidney due to various causes; it is typically defined as a reduction in kidney function (i.e., reduced eGFR) and/or markers of kidney damage (albuminuria, hematuria, or abnormalities detected through laboratory testing or imaging) that are present for at least 3 months. There are many causes of CKD (e.g., diabetes, glomerulonephritis, and cystic kidney diseases) (Kalantar-Zadeh et al. 2021). CKD secondary to diabetes is present in 20 to 40% of patients with diabetes. Although CKD may be present at the time of diagnosis in patients with T2D, CKD typically presents in patients with T1D only after a disease duration of 5 to 15 years. CKD secondary to T1D can progress to end stage kidney disease requiring dialysis or kidney transplantation. In addition, the presence of CKD increases cardiovascular risk in patients with T1D (American Diabetes Association Professional Practice 2024).

In addition to the ADA standards of care, treatment guidelines have been issued jointly by the ADA and Kidney Disease: Improving Global Outcomes (KDIGO). According to the consensus report from ADA and KDIGO, patients with T1D and CKD should "optimize nutrition, exercise, smoking cessation, and weight, upon which are layered evidence-based pharmacologic therapies aimed at preserving organ function and other therapies selected to attain intermediate targets for glycemia, blood pressure, and lipids." Similar to the ADA, the only pharmacologic therapies recommended for patients with T1D and CKD in the consensus ADA/KDIGO guidelines are RAS inhibitors (to reduce the progression of CKD and to reduce the risk of MACE) and statins (to reduce the risk of MACE). In the same consensus treatment guidelines, additional pharmacologic therapies are recommended for some patients with T2D and CKD, including some sodium-glucose co-transporter 2 (SGLT2) inhibitors, some glucagon-like peptide 1 (GLP-1) receptor agonists, and some nonsteroidal mineralocorticoid receptor antagonists (de Boer et al. 2022).

Significantly fewer therapies have been evaluated in patients with T1D and CKD compared to patients with T2D and CKD or patients with CKD without diabetes (Heerspink et al. 2023) (see Figure 1). Figure 1 notably omits important clinical trials of dapagliflozin (Heerspink et al. 2021) and empagliflozin (Group et al. 2023) (conducted in patients with CKD and T2D and in patients with CKD without diabetes, but not in patients with CKD and T1D), sotagliflozin (Bhatt et al. 2021) (conducted in patients with CKD and T2D) and semaglutide (Perkovic et al. 2024) (conducted in patients with CKD and T2D), but it nonetheless illustrates the striking differences in evidence generation across these three groups of patients with CKD. To date, indications for drugs approved by FDA for treatment of CKD have been based on trials conducted with the drug and have reflected the populations studied in the trials (see Figure 1 and Table 1).

Figure 1. Clinical Trials Investigating CKD in Persons Without Diabetes, With T1D, and With T2D



Source: Heerspink et al. (2023).

Table 1. FDA-Approved Drugs Indicated to Treat Patients With CKD and the Study Supporting the Indication

Drug	Trial	Indication
Captopril	Collaborative Study Group (CSG) Captopril Trial (Lewis et al. 1993)	For the treatment of diabetic nephropathy (proteinuria >500 mg/day) in patients with type 1 insulin-dependent diabetes mellitus and retinopathy
Irbesartan	Irbesartan Diabetic Nephropathy Trial (IDNT) (Lewis et al. 2001)	For the treatment of diabetic nephropathy in hypertensive patients with type 2 diabetes, an elevated serum creatinine, and proteinuria
Losartan	Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) (Brenner et al. 2001)	For the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and a history of hypertension
Finerenone	Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) (Bakris et al. 2020)	To reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes
Canagliflozin	Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) (Perkovic et al. 2019)	To reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day
Dapagliflozin	Dapagliflozin in Patients with Chronic Kidney Disease	To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and

Drug	Trial	Indication
	(DAPA-CKD) (Wheeler et al. 2021)	hospitalization for heart failure in adults with chronic kidney disease at risk of progression
Empagliflozin	Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) (Group et al. 2023)	To reduce the risk of sustained decline in eGFR, end-stage kidney disease, cardiovascular death and hospitalization in adults with chronic kidney disease at risk of progression
Sotagliflozin	Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) (Bhatt et al. 2021)	To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visits in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors

Source: Compiled by FDA staff.

The studies that supported indications for dapagliflozin and empagliflozin for the treatment of patients with CKD included patients with CKD and T2D and patients with CKD without diabetes. The trials excluded patients with T1D, with CKD secondary to polycystic kidney disease, or with a recent history of immunosuppressive therapy for kidney disease. The exclusion criterion for T1D in EMPA-KIDNEY was added in a protocol amendment after 68 participants with T1D had been enrolled (34 randomized to empagliflozin and 34 randomized to placebo); participants with T1D who were already recruited prior to the amendment could remain in the study.

FDA approved the supplemental NDA submissions of DAPA-CKD (NDA 202293/S-024) and EMPA-KIDNEY (NDA 204629/S-040) on April 30, 2021, and September 21, 2023, for dapagliflozin (marketed as Farxiga) and empagliflozin (marketed as Jardiance), respectively. In each case, FDA determined that the demonstrated benefits applied to patients with CKD (and not just patients with T2D and CKD). This benefit, therefore, extends to non-diabetic patients with CKD and patients with T1D and CKD. As noted in a commentary piece published in the Lancet subsequent to the approval of NDA 204629/S-040, "No new drug or therapy has been shown to slow the progression of CKD to kidney failure in the past two decades… Dapagliflozin is the first SGLT2 inhibitor to be approved by any regulatory agency for patients with CKD irrespective of diabetes status." (Jafar 2021).

The FDA-approved labeling of Farxiga (dapagliflozin) and Jardiance (empagliflozin) reflects FDA's determination that the benefits observed in DAPA-CKD and EMPA-KIDNEY apply to patients with T1D and CKD at risk of progression: the USPIs include indications "to reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, and HHF in adults with CKD at risk of progression" and "to reduce the risk of sustained decline in eGFR, end-stage kidney disease, CV death, and HHF in adults with CKD at risk of progression", respectively. The limitations of use of each drug state that they are not recommended for the treatment of CKD in patients with polycystic kidney disease or with a recent history of immunosuppressive therapy for kidney disease, as they are not expected to be effective in these populations, but they do not include a limitation of use recommending against the treatment of CKD in patients with T1D. Like sotagliflozin marketed as Inpefa, they do include a limitation of use recommending against their use to improve glycemic control in patients with T1D. The USPIs for dapagliflozin and empagliflozin also include detailed information about the severity of CKD among the participants of DAPA-CKD and EMPA-KIDNEY, respectively, to give patients and providers adequate

context to understand the indication statement (i.e., in adults with CKD at risk of progression). Notwithstanding the FDA approvals, treatment guidelines published by professional societies have yet to recommend either product for use in patients with T1D and CKD.

2.2 Pertinent Drug Development and Regulatory History

2.2.1 Sotagliflozin Overview

Sotagliflozin is an orally bioavailable, small molecule belonging to the broader class of sodium-glucose cotransporter 2 (SGLT2) inhibitors, which lower blood glucose levels by increasing urinary excretion of glucose. Sotagliflozin inhibits both SGLT1 and SGLT2.[3] Sotagliflozin does not directly alter the underlying pathophysiology of T1D.

The efficacy and safety of sotagliflozin for glycemic control in T1D was evaluated in three Phase 3 clinical trials, also referred to as the TANDEM program:

- Trials 309 and 310: These were randomized, double-blind, placebo-controlled, parallel-group trials involving a total of 1,049 participants (524 on 200 mg, 525 on 400 mg, and 526 on placebo) across both studies. The trials assessed glycemic control (A1C), weight, and insulin requirements in patients with T1D over a 24-week core period, followed by a 28-week extension. The combined follow-up for these studies was approximately 902 patient-years.
- Trial 312: This trial involved 1,402 participants (699 on 400 mg and 703 on placebo) and focused solely on the 400 mg dose to demonstrate its superiority in reducing A1C levels without increasing the risk of severe hypoglycemia or DKA. The follow-up for this trial was approximately 605 patient-years.

NDA 210934 was initially submitted on March 22, 2018, seeking the following indication: "ZYNQUISTA is indicated as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus." The original submission was not approved, because the FDA determined that the overall benefit-risk assessment for patients with T1D was not favorable because of the risk of DKA relative to the benefits demonstrated.

The Applicant resubmitted NDA 210934 on June 20, 2024, with the revised indication "ZYNQUISTA is indicated as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus and chronic kidney disease."

In this resubmission, the Applicant has included post hoc analyses of the TANDEM clinical development program, selecting only participants with a baseline measurement of eGFR between 45 and <60 mL/min/1.73 m^2 or a baseline measurement of eGFR ≥60 mL/min/1.73 m^2 and UACR≥30 mg/g (renal parameters consistent with a definition of mild-to-moderate CKD). The Applicant describes this group of participants as the TANDEM-CKD subpopulation. The Applicant has also included a post hoc analysis of the effect of sotagliflozin on A1C using data collected in SCORED, a large cardiovascular outcomes trial (CVOT) conducted in patients with T2D and moderate-to-severe CKD; the post hoc analysis was conducted using the data collected from the SCORED participants whose eGFR was at least 45 mL/min/1.73m^2. The Applicant asserts that the available data support a conclusion that sotagliflozin is effective for the reduction of A1C in patients with T1D and eGFR between 45 and <60 mL/min/1.73 m^2 or a baseline measurement of eGFR ≥60 mL/min/1.73 m^2 and UACR ≥30 mg/g.

The Applicant asserts that similar improvements in glycemic control confer greater benefits to patients with T1D and CKD than to those with T1D without CKD. The scientific basis for this assertion is discussed

[3] The in vitro 50% inhibitory concentration [IC_{50}] is 36.3nM for SGLT1 and 1.8nM for SGLT2.

in Section 3.4. The Applicant also references potential benefits to patients with T1D and CKD independent of improved glycemic control (reduced risk of MACE, HHF, and CKD progression) based on new data generated in a large CVOT conducted in patients with T2D and moderate-to-severe CKD and other cardiovascular risk factors and a second large CVOT conducted in patients with T2D and heart failure (HF). The scientific basis for this assertion is discussed in Section 3.5. The Applicant asserts that the risks of sotagliflozin, including the risk of DKA, are similar in patients with T1D and CKD and in those with T1D without CKD; see Section 4.1.2 for discussion of the risk of DKA. The Applicant proposes a glycemic control indication in a revised population of patients with T1D and CKD.

2.2.2 Pertinent Regulatory History

Sotagliflozin was developed as an adjunct to insulin therapy to improve glycemic control in adults with T1D and was submitted as NDA 210934 on March 22, 2018. The FDA sought the advice of the Endocrinologic and Metabolic Drug Advisory Committee (EMDAC) in an AC meeting on January 17, 2019 (The 2019 FDA Briefing Document is located in Section 7.7); the committee voted eight to eight on the question of whether the overall benefits outweighed the risks.

On March 22, 2019, the FDA issued a Complete Response Letter (CRL), which provided FDA's assessment that the demonstrated improvement in glycemic control did not outweigh the observed increased risk of DKA with use of sotagliflozin in patients with T1D.

Separately, sotagliflozin was developed for multiple cardiorenal indications in adults with T2D under Investigational New Drug (IND) 102191 and IND 135095 and was submitted as NDA 216203 on December 30, 2021. Sotagliflozin (Inpefa) was approved on May 27, 2022, under NDA 216203 to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visits in adults with heart failure or adults with T2D and CKD and other cardiovascular risk factors.

This section summarizes only new regulatory history related to the glycemic control indication in patients with T1D following the January 17, 2019 EMDAC meeting. Refer to the January 17, 2019, Advisory Committee FDA Briefing Document for a summary of the regulatory history prior to this meeting.

Complete Response Letter for NDA 210934

The Office of Drug Evaluation 2 (ODE2), now the Office of Hematology, Cardiology, Endocrinology and Nephrology, OCHEN) issued a CRL to NDA 210934 on March 22, 2019.

The basis for the CRL was an unfavorable benefit-risk assessment because an increased risk of DKA, despite implementation of DKA risk mitigation strategies (i.e., patient instructions for ketone monitoring, teaching on recognizing signs and symptoms for DKA risk, precautionary measures such as hydration) outweighed the benefits of the demonstrated improvements in glycemic control.

As potential paths forward, the ODE2 recommended that the Applicant submit prospectively collected clinical data that provide evidence of additional clinical benefits of sotagliflozin other than A1C reduction and/or identify strategies to reduce the risk of DKA. ODE2 provided the following specific recommendations: (1) identify and evaluate the effect of sotagliflozin on other efficacy outcomes beyond A1C reduction through assessments that directly measure how a patient feels, functions, or survives, (2) develop and evaluate the effectiveness of DKA risk mitigation strategies (e.g., ketone monitoring, adequate insulinization instructions for patients), and (3) identify and prospectively study a group of patients in whom the benefit of the drug may outweigh its risks.

End-of-Review (Post-Action) Meeting

The Applicant requested and was granted an End-of-Review meeting, which was held on June 5, 2019, to discuss the CRL and a path forward for resubmission. During the meeting, the Applicant expressed its view that the FDA's benefit-risk assessment did not give adequate consideration to benefits other than A1C (e.g., body weight, time in range, blood pressure). The Applicant also expressed its view that FDA weighed the risk of DKA too heavily and the risk of hypoglycemia (which favored sotagliflozin, according to some metrics) too lightly. The FDA review division did not concur with the Applicant and provided detailed responses to the Applicant's assertions.

OND-Level Formal Dispute Resolution Request

The Applicant submitted a formal dispute resolution request (FDRR) to OND on September 3, 2019, concerning the CRL issued on March 22, 2019. In the OND FDRR, given the higher DKA risk with 400 mg, the Applicant proposed restricting their NDA approval to only sotagliflozin 200 mg. The Applicant also reasserted their view of the FDA's consideration of other benefits. The Applicant further asserted that proposed DKA mitigation strategies were efficacious. On November 29, 2019, OND denied the FDRR, concluding that the other benefits were not substantial enough to change the overall benefit-risk assessment and that the assertion regarding DKA mitigation strategies was not adequately supported by evidence.

CDER-Level Formal Dispute Resolution Request

The Applicant submitted an FDRR to CDER on December 19, 2019, appealing the finding of the Office of New Drugs (OND). On March 22, 2020, CDER denied the second FDRR in correspondence dated March 11, 2020, reaffirming the reasoning provided in OND's denial in the prior FDRR.

Notice of Opportunity for Hearing (NOOH)

The Applicant submitted a request for an opportunity for a hearing under 21 CFR 314.110(b)(3), to discuss grounds for denying approval of the NDA. In response, CDER issued a Notice of Opportunity for Hearing (NOOH) under 21 CFR 314.200, proposing to refuse to approve NDA 210934, which was published in the Federal Register on March 3, 2021. The Applicant submitted a written notice of participation and request for a hearing on March 5, 2021, followed on April 30, 2021 by information to justify a hearing.

On August 5, 2021, Lexicon and CDER jointly requested that the Office of the Commissioner hold the NOOH in abeyance until September 27, 2021, to allow for discussion between the parties. CDER/OCHEN requested that Lexicon submit a Type A meeting request, and any additional data about sotagliflozin's safety and efficacy that are currently not included in the NDA. In a letter dated August 6, 2021, the Office of the Commissioner granted the joint request. By joint request, the abeyance was later extended until October 27, 2021, and November 26, 2021.

Communications During the 2021 Abeyance

The Applicant requested and was granted a type A meeting, which was held on September 14, 2021. The Applicant proposed to cite data from SCORED (a cardiorenal outcomes trial conducted in adult patients with T2D, CKD, and other CV risk factors) and SOLOIST-WHF (a cardiorenal outcomes trial conducted in adult patients with T2D and HF), arguing that the evidence of cardiorenal benefits collected in these studies constitutes additional evidence of benefit relevant to patients with T1D. In addition, the Applicant proposed new risk mitigation strategies to mitigate the risk of DKA. The FDA expressed that it

was not immediately evident how the benefits demonstrated in cardiorenal outcome trials conducted in patients with T2D and high CV risk are relevant to patients with T1D without established CV disease. The FDA and the Applicant discussed the possibility of a CVOT in patients with T1D. The FDA also noted the lack of evidence supporting the effectiveness of their revised risk mitigation strategies. The FDA reiterated its position in a December 21, 2021 General Advice letter, stating in reference to the SCORED and SOLOIST data "We believe that information supporting your position about the applicability of these data to patients with T1D may be appropriate for review in an NDA submission… If you include the data from SCORED and SOLOIST as part of a resubmission to address the March 22, 2019, CRL, you will need to provide adequate scientific justification that the cardiovascular benefits demonstrated in T2D patients would also be expected to apply to T1D patients for this information to be considered in the overall benefit-risk assessment in the NDA resubmission review."

Subsequently, the Applicant requested that the Office of the Commissioner set a schedule for a hearing regarding the NDA. The Office of the Commissioner established the hearing schedule. On June 30, 2022, CDER submitted a proposed order denying the hearing request. On November 18, 2022, the Applicant submitted a response to CDER's proposed order denying the hearing request, and CDER submitted a reply to the Applicant's response on January 31, 2023.

At the request of the Applicant, the Applicant and CDER submitted a joint request to the Office of the Commissioner for a second abeyance, which was granted on September 19, 2023.

Communications During the 2023 to 2024 Abeyance

The Applicant requested and was granted a type A meeting, which was held on December 4, 2023. The Applicant proposed a revised glycemic control indication in adults with T1D and CKD, based on data from the sotagliflozin T1D developmental program (Trials 309, 310, and 312) and on data from the two aforementioned CVOTs conducted in patients with T2D and high CV risk (SCORED and SOLOIST). The FDA indicated its willingness to review a resubmission of NDA 210934 and that approvability would include consideration of benefit and risk for its proposed use. The FDA recommended that the Applicant provide a rationale for their proposed CKD population, with statistically and clinically meaningful evidence of glycemic control. The FDA acknowledged that the new data from SOLOIST-HF and SCORED likely have some relevance to comparable patients with T1D, though FDA also noted that the definition of CKD used in SCORED differed from that proposed for the revised glycemic control indication: SCORED studied participants with moderate-to-severe CKD, whereas the current resubmission proposes a glycemic control indication in patients with mild-to-moderate CKD. The FDA also clarified that it considered the evidence of renal benefits of sotagliflozin to be exploratory and that a resubmission that relied on potential, but not demonstrated, renal benefits may be challenging. The FDA indicated that extrapolation of the demonstrated HHF benefits in a population that more closely resembles SCORED (e.g., patients with T1D, eGFR 25 to 60 mL/min/1.73 m^2, and other CV risk factors) would be more amenable to scientific justification, but emphasized that a resubmission proposing a glycemic control indication would still need to demonstrate evidence of an A1C-lowering effect in the relevant eGFR range. The FDA also inquired whether the Applicant had considered proposing to revise the existing indication for Inpefa (NDA 216203) to encompass all patients with diabetes mellitus (DM) (i.e., both T1D and T2D), CKD, and other CV risk factors based on the data from SCORED and the safety data from the sotagliflozin T1D program.

The Applicant requested and was granted a second Type A meeting to continue discussion of their proposal to resubmit NDA 210934 with a revised glycemic control indication in patients with T1D and CKD. FDA issued preliminary written responses to questions from the Applicant on March 1, 2024. FDA acknowledged that a resubmission would be a reasonable vehicle to further consider the Applicant's premise that improved glycemic control may confer greater benefit to patients with T1D and CKD than to patients with T1D without CKD. The FDA reiterated that the NDA resubmission would need to provide meaningful evidence of efficacy across the entire range of kidney function in the proposed CKD population. FDA also recommended a risk assessment for DKA in the proposed population of patients with T1D and CKD. The meeting was canceled by the Applicant, who determined that the preliminary written responses were adequate and no further discussion was required.

The Applicant resubmitted NDA 210934 on June 20, 2024, proposing the revised indication for sotagliflozin (Zynquista) as an adjunct to insulin therapy to improve glycemic control in adults with T1D and CKD. For the purposes of this proposal, the Applicant defines CKD as an eGFR of 45 to <60 mL/min/1.73 m^2 or an eGFR ≥60 mL/min/1.73 m^2 and UACR ≥30 mg/g; FDA considers this definition compatible with mild-to-moderate CKD.

3 Clinical Pharmacology of Sotagliflozin in Chronic Kidney Disease

Pharmacokinetics (PK)

Sotagliflozin is primarily eliminated by the kidneys, and renal impairment alters the pharmacokinetics (PK) of sotagliflozin. In a dedicated renal impairment study, the PK exposure or area under the concentration curve (AUC) of sotagliflozin in participants with mild (eGFR 60 to 89 mL/min/1.73 m^2) and moderate (eGFR 30 to 59 mL/min/1.73 m^2) renal impairment was 1.72- and 2.21-fold higher, respectively, compared to matched participants with normal renal function (eGFR >90 mL/min/1.73 m^2).

Inspection of population pharmacokinetic estimates of individual PK exposures from the studies 309 and 310 show the effect of renal impairment is less pronounced: dose-adjusted AUC is approximately 1.4-fold higher in participants with eGFR <60 mL/min/1.73 m^2 compared to participants with eGFR ≥90 mL/min/1.73 m^2 (Table 30 in Section 7.6). It was also noted that within the same eGFR category, participants with microalbuminuria tended to have slightly lower PK exposures than those without.

Pharmacodynamics (PD)

The kidney is responsible for the glucose-lowering effect of sotagliflozin. Renal SGLT2 is the primary transporter responsible for glucose reabsorption from renal filtrate in the renal proximal tubule. Sotagliflozin binds and inhibits SGLT2. Inhibition of SGLT2 prevents glucose reabsorption and leads to increased urinary glucose excretion (UGE). However, as renal function declines, the effect of sotagliflozin on UGE is reduced, diminishing its glucose-lowering effect. Available SGLT2 inhibitors approved for glycemic control are not recommended for this use in patients with an eGFR below a certain threshold (30 or 45 mL/min/1.73 m^2, depending on the specific SGLT2 inhibitor product). A dedicated renal impairment study of sotagliflozin in patients with T2D showed 24-hour UGE is approximately 50% lower in participants with eGFR <45 mL/min/1.73 m^2 compared to participants with eGFR ≥45 mL/min/1.73 m^2. No clinical pharmacology data were submitted investigating 24-hour UGE with a wider eGFR range.

In clinical studies, sotagliflozin-related glucosuria can be assessed using the urine glucose-to-creatinine ratio (UGCR), a direct measure of urine glucose excretion in a spot urine sample. Inspection of routinely

collected UGCR during the TANDEM study suggests the pharmacodynamic effect is present, but attenuated, in lower eGFR categories (Figure 11 in Section 7.6).

Sotagliflozin also binds and inhibits SGLT1 with lower potency. SGLT1 is expressed in the small intestine and transports glucose across the intestinal mucosa from the gut. The Applicant conducted a clinical pharmacology study which demonstrated a modest reduction in the rate but not the extent of glucose absorption following coadministration of sotagliflozin 400 mg and oral glucose solution. Based on the local action in the gut, the SGLT1 inhibitory effect on glucose absorption likely only affects the meal coadministered with sotagliflozin. The extent to which SGLT1 inhibition contributes to the overall efficacy and safety profile of sotagliflozin is unknown.

Safety and Efficacy

Only 8.5% of participants (N=149) in the TANDEM population had a baseline eGFR of 45 to <60 mL/min/1.73 m^2 or a baseline eGFR ≥60 mL/min/1.73 m^2 and UACR ≥30 mg/g with evaluable PK data. This precluded a robust clinical pharmacology assessment of safety and efficacy specific to the proposed population for the revised indication. However, FDA's exploratory exposure-response analyses for the overall TANDEM population, discussed at the 2019 EMDAC, suggested a "flat" dose-response relationship for glycemic control within the range of PK exposures observed in participants randomized to either the 200 mg or 400 mg dose of sotagliflozin. In contrast, a strong dose- and exposure-response relationship was identified for DKA. For general clinical pharmacology information, refer to the FDA Briefing Document in Section 7.7.

3.1 Sources of Data for Glycemic Efficacy

The following is a brief introduction of the designs and endpoints of the clinical trials of sotagliflozin for glycemic control in patients with T1D (the TANDEM program). Refer to the 2019 FDA Briefing Document in Section 7.7 for additional information.

Data from the overall TANDEM population demonstrate substantial evidence of effectiveness for reduction of A1C in patients with T1D. The magnitude of A1C reduction in the revised population of patients with T1D and CKD is estimated in the resubmission by post hoc analyses of a subgroup of patients from the TANDEM program. The subgroup included participants who met the following criteria at baseline: eGFR 45 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2 or an eGFR ≥60 mL/min/1.73 m^2 with a UACR ≥30 mg/g.

In addition, the Applicant proposed to examine glycemic data incidentally collected in SCORED, a phase 3 cardiorenal outcomes trial conducted in patients with T2D and moderate-to-severe CKD and other CV risk factors.

Study Designs and Endpoints in the TANDEM Program

Trials 309 and 310 were multicenter, randomized (1:1:1), double-blind, placebo-controlled, parallel-group trials stratified by baseline A1C (≤8.5% versus >8.5%) and insulin delivery method (MDI versus CSII). The primary objective for both trials was to demonstrate the superiority of either sotagliflozin 200 mg or 400 mg versus placebo on A1C reduction at Week 24 among adult participants with T1D and inadequate glycemic control with insulin therapy. For both trials, the primary endpoint was the change

from baseline (CFB) in A1C at Week 24.[4] The Bonferroni procedure with evenly split alpha was used to assess the two doses of sotagliflozin against placebo, and within each sotagliflozin dose, a gatekeeping strategy was applied to the primary and key secondary endpoint assessments.

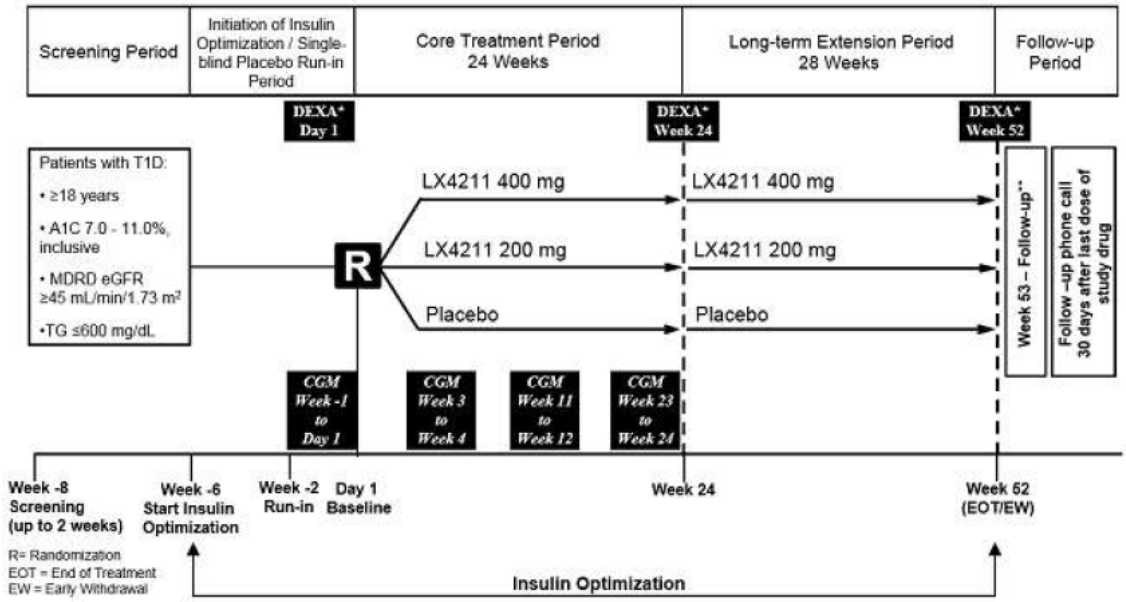
Trial 312 was a multicenter, randomized (1:1), double-blind, placebo-controlled, parallel-group trial stratified on baseline body mass index (BMI;<25 kg/m^2 versus ≥25 kg/m^2), baseline A1C (≤9.0% versus >9.0%), and insulin delivery method (MDI versus CSII). The primary objective of the trial was to demonstrate the superiority of sotagliflozin 400 mg versus placebo in the composite of achieving A1C <7.0% at Week 24 and experiencing no episode of severe hypoglycemia and no episode of DKA from randomization to Week 24, among adult participants with T1D and inadequate glycemic control with insulin therapy. The primary endpoint was achievement (yes/no) of A1C <7.0% at Week 24 with no episode of severe hypoglycemia and no episode of DKA from randomization to Week 24.[5]

Eligibility for each trial in the TANDEM program was determined at screening (up to 8 weeks prior to randomization). For the three trials, eligible participants must have been on insulin therapy, have had a screening A1C between 7.0% and 11.0% (inclusive), a screening eGFR >45 mL/min/1.73 m^2, and had no history of DKA or severe hypoglycemia within 1 month prior to screening. Trials 309 (in the United States and Canada) and 310 (in Europe and Israel) had identical designs, and hence were pooled for the efficacy and safety analyses. Trial 312 was analyzed separately, because it differed from Trials 309 and 310 in that it 1) did not have an insulin optimization period, 2) only studied the sotagliflozin 400 mg dose, and 3) had a shorter treatment period of 24 weeks compared to 52 weeks. Figure 2 and Figure 3 show the trial designs.

[4] Key secondary endpoints include achievement (Yes/No) of A1C <7% at Week 24 with no episode of severe hypoglycemia and no episode of DKA from randomization to Week 24, CFB (both absolute and percent) in body weight at Week 24, CFB in mean daily bolus insulin at Week 24, and CFB in FPG at Week 24, CFB in diabetes treatment satisfaction at Week 24 measured by Diabetes Treatment Satisfaction Questionnaire status version (DTSQs), and CFB in diabetes distress at Week 24 measured by DDS2.

[5] Key secondary endpoints include CFB in A1C at Week 24, CFB (both absolute and percent) in body weight at Week 24, CFB in systolic blood pressure at Week 24, and CFB in mean daily bolus insulin at Week 24.

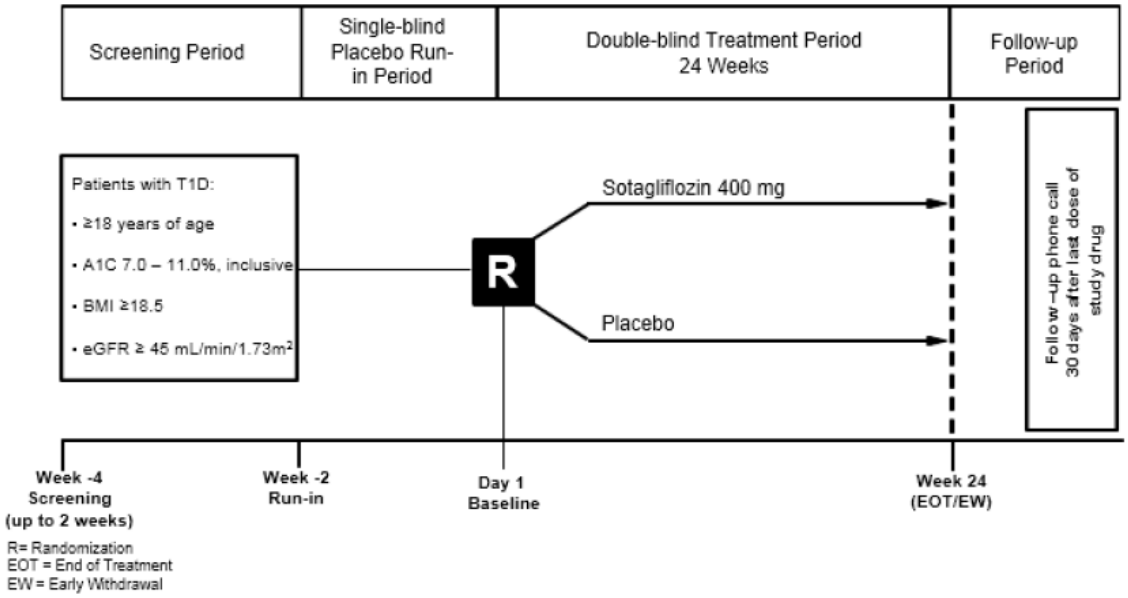
Figure 2. Schema for Trials 309 and 310



Source: Figure 9.1-1, Clinical Study Report for Trial 309.

Abbreviations: A1C, hemoglobin A1C; CGM, continuous glucose monitor; eGFR, estimated glomerular filtration rate; EOT, end of treatment; MDRD, modification of diet in renal disease; T1D, type 1 diabetes

Figure 3. Schema for Trial 312



Source: Figure 9.1-1, Clinical Study Report for Study 312.

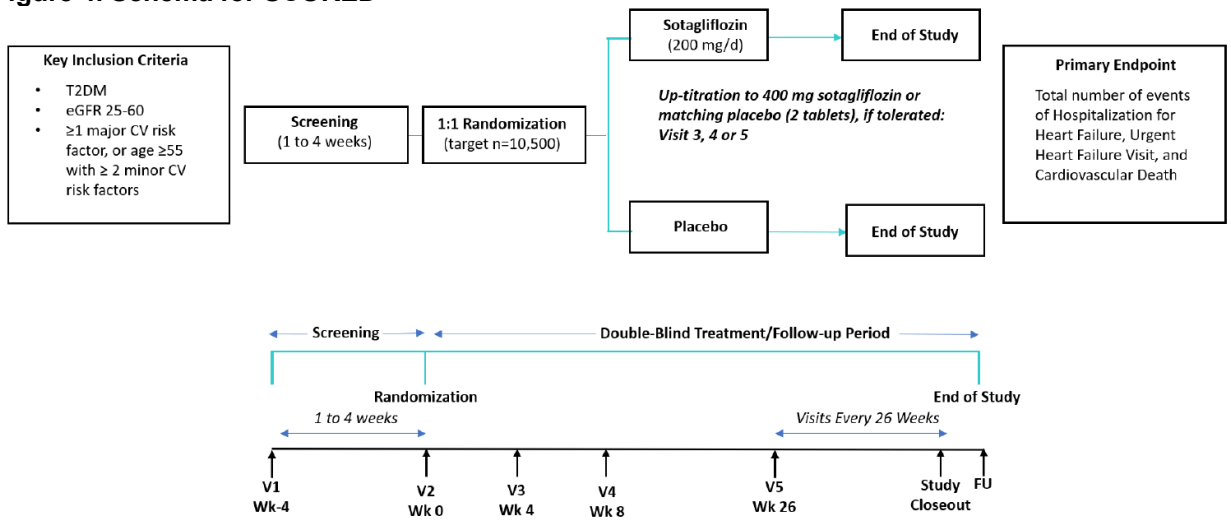
Abbreviations: A1C, hemoglobin A1C; BMI, body mass index; eGFR, estimated glomerular filtration rate; EOT, end of treatment; T1D, type 1 diabetes

Study Designs and Endpoints in SCORED (T2D)

SCORED was a cardiorenal outcome trial of sotagliflozin in patients with T2D, CKD (eGFR 25 to 60 mL/min/1.73 m^2), and other CV risk factors (N=10,584). SCORED was a randomized, double-blind, placebo-controlled trial. The primary endpoint of SCORED was a composite endpoint of CV death, HHF, and urgent visit for heart failure (UVHF). Secondary endpoints of SCORED included composite endpoints

intended to evaluate the effect of sotagliflozin on major adverse cardiovascular events (MACE) and progression of CKD in patients with T2D, moderate-to-severe CKD (baseline eGFR 25 to 60 mL/min/1.73 m^2), and other CV risk factors. Although SCORED was not a glycemic control trial, its collection of glycemic data (including A1C) was robust. The Applicant submitted a post hoc analysis of glycemic data collected in SCORED, selecting only participants meeting the TANDEM-CKD population eligibility criteria.

Figure 4. Schema for SCORED



T2DM, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); CV, cardiovascular; FU, follow-up; V, visit; Wk, week.
Source: Figure 1, Clinical Study Report for SCORED (NDA216203, SDN0001).

3.2 FDA's Approach to the Assessment of Glycemic Efficacy

TANDEM Trials (T1D)

The FDA's review of the original NDA submission concluded that the TANDEM program demonstrated substantial evidence of effectiveness for improving glycemic control in patients with T1D.

The Applicant's approach to estimating a treatment effect of sotagliflozin on A1C in patients with T1D and CKD comprised analyzing all TANDEM participants who met their proposed definition of CKD as a single group. One disadvantage of this approach is that it assumes sotagliflozin has the same effect on A1C reduction across the range of eGFRs captured by this definition. However, as described in Section 3, sotagliflozin is expected to have less effect in patients with more severely reduced eGFRs. A second disadvantage of this approach is that it disregards informative data from patients whose UACR is less than 30 mg/g.

The FDA's review of the NDA resubmission focused on its own analyses in patients with T1D from Trials 309, 310, and 312 to estimate the treatment effect of sotagliflozin on A1C in the revised population of patients with T1D and CKD, in addition to considering those of the Applicant. The FDA used a different subgrouping strategy: (a) eGFR ≥90 mL/min/1.73 m^2; (b) eGFR > 60 ml/min/1.73 m^2 to <90 mL/min/1.73 m^2; (c) eGFR <60 mL/min/1.73 m^2. FDA believes this is scientifically justified because eGFR but not UACR is linked to glycosuria. The FDA chose this approach because it includes all informative data collected in TANDEM and provides treatment estimates according to eGFR subgroup

(rather than a single treatment estimate that reflects an average across all patients with CKD). Because all three TANDEM trials excluded subjects with eGFR < 45 mL/min/1.73m^2, the subgroup of eGFR < 60 mL/min/1.73 m^2 functionally represents a population with eGFR ≥ 45 mL/min/1.73m^2 to < 60 mL/min/1.73 m^2.[6]

Both sets of efficacy analyses pooled Trials 309 (North America) and 310 (Europe) due to their identical 52-week durations, treatment arms, and randomization schemes. Trial 312 was analyzed and presented separately, because it was of shorter duration, did not include a 200 mg treatment arm, and did not include an insulin optimization run-in period. Both the FDA and the Applicant used a modified intention to treat approach (i.e., including all randomized participants who had taken at least one dose of study drug).

Acknowledging the post-hoc nature of Applicant's and FDA's subgrouping strategy, additional approaches to key efficacy analyses are presented in Section 7.4.

The FDA's efficacy assessment focused on change from baseline (CFB) in A1C at Week 24 and Week 52 (for Pooled Trials 309/310 only). Other efficacy endpoints assessed in the T1D-CKD population include CFB in body weight (BW) and systolic blood pressure (SBP) at Week 24.

The FDA used an analysis of covariance (ANCOVA) model adjusted for treatment, stratification factors, trial effect (for Pooled Trials 309/310 only) and baseline A1C. Missing endpoint values were handled via multiple imputation (MI) based on the placebo-washout method (Wang et al. 2023). The FDA adopted a different analysis approach from the Applicant's model, which was based on a mixed model repeated measures (MMRM) approach[7,.8]

SCORED (T2D)

FDA does not agree that the glycemic data from SCORED meaningfully informs the magnitude or durability of A1C reduction in a population of patients with T1D and mild-to-moderate CKD due to several limitations. First, the SCORED trial was not designed to assess glycemic control. Key design elements (e.g., glycemic rescue criteria, fixed baseline antihyperglycemic therapy) were not conducive to the evaluation of glycemic control. In addition, SCORED does not include any participants with eGFR >60 mL/min/1.73 m^2. Most importantly, SCORED is a trial conducted in patients with T2D rather than T1D. For instance, given that patients with T1D would be expected to titrate their insulin in response to the addition of an noninsulin antihyperglycemic agent, the net effect of the noninsulin antihyperglycemic agent would be expected to be lower than in patients with T2D (who do not

[6] Although the protocols for all 3 TANDEM trials excluded participants with eGFR < 45 ml/min/1.73 m^2, a total of 7 participants with eGFR < 45 ml/min/1.73 m^2 were nonetheless enrolled (3 participants in Pooled Trials 309/310 and 3 participants in Trial 312). These 7 participants are also included in the eGFR < 60 ml/min/1.73 m^2 subgroup analyses.

[7] The MMRM model used an unstructured covariance structure, and was adjusted for treatment, time (study week), stratification factor treatment-by-time interaction, and baseline value-by-time interaction. The model for the 309/310 pool also included a study effect. The stratification factors include insulin delivery method at Screening (MDI versus CSII), and A1C at Screening (≤8.5% versus >8.5%); for Trial 312, the adjusted stratification factors consist of BMI at Screening (<25 kg/m^2 versus ≥25 kg/m^2), A1C at Screening (≤9.0 % versus >9.0 %) and use of CSII at Screening (yes versus no).

[8] The FDA prefers an ANCOVA model and MI-based imputation method, since it does not assume data are missing at random (MAR) like the MMRM approach. The MAR assumption indicates that missing data are unrelated to the treatment effect (i.e., the status of participants with missing endpoint values were comparable to similar participants from the same treatment arms with observed endpoint values), which is an unrealistic assumption for most clinical trials.

frequently adjust insulin doses based on routine glucose monitoring, even among those patients with T2D who use insulin).

3.3 Glycemic Efficacy Data

The baseline demographic characteristics were organized by eGFR subgroups and are presented in Table 2 for Pooled Trials 309/310, and for Trial 312. Participants with eGFR <60 mL/min/1.73 m^2 were older and had a longer duration of T1D than participants from the other two eGFR subgroups. Refer to Section 7.3 for demographic information summarized by treatment arm for each subgroup of Pooled Trials 309/310 and Trial 312.

Table 2. Demographics and Baseline Characteristics—Pooled Trials 309 and 310 and Trial 312, mITT Population

	Pooled Trials 309 and 310				Trial 312			
Mean (SD) or N (%)	**eGFR <60 N=71**	**60≤eGFR <90 N=774**	**eGFR ≥90 N=730**	**Total N=1575**	**eGFR <60 N=74**	**60≤eGFR <90 N=612**	**eGFR ≥90 N=716**	**Total N=1402**
Age (years)	57.3 (11.0)	48.0 (12.0)	37.8 (12.4)	43.7 (13.5)	57.3 (12.0)	47.9 (12.5)	37.0 (12.8)	42.8 (14.1)
Male sex	26 (37)	347 (45)	416 (57)	789 (50)	30 (41)	263 (43)	404 (56)	697 (50)
Race								
White	68 (96)	734 (95)	681 (93)	1483 (94)	63 (85)	567 (93)	610 (85)	1240 (88)
Black or African American	0	7 (1)	22 (3)	29 (2)	4 (5)	7 (1)	35 (5)	46 (3)
Am. Indian or Alaska Native	0	0	1 (0)	1 (0)	0	2 (0)	4 (1)	6 (0)
Asian	0	7 (1)	9 (1)	16 (1)	1 (1)	3 (0)	8 (1)	12 (1)
Native Hawaiian or other Pacific Islander	0	3 (0)	1 (0)	4 (0)	0	1 (0)	0	1 (0)
Other	3 (4)	23 (3)	16 (2)	42 (3)	4 (5)	23 (4)	41 (6)	68 (5)
North America (US + Canada)	45 (63)	430 (56)	318 (44)	793 (50)	40 (54)	280 (46)	259 (36)	579 (41)
Insulin delivery method - CSII	30 (42)	357 (46)	287 (39)	674 (43)	32 (43)	247 (40)	276 (39)	555 (40)
Duration of T1D (years)	31.4 (12.7)	23.8 (12.4)	17.9 (10.9)	21.4 (12.3)	25.7 (14.2)	22.7 (13.1)	17.2 (10.4)	20.0 (12.2)
A1C (%)	7.8 (0.8)	7.6 (0.7)	7.7 (0.8)	7.7 (0.8)	8.4 (1.0)	8.1 (0.9)	8.3 (1.0)	8.2 (0.9)
Total daily insulin (IU)	54.6 (28.8)	61.5 (34.6)	66.0 (36.9)	63.3 (35.5)	51.6 (24.5)	55.9 (29.3)	59.7 (27.7)	57.6 (28.4)
Basal daily insulin (IU)	28.5 (14.3)	31.5 (18.9)	32.8 (18.0)	32.0 (18.3)	27.4 (15.3)	28.2 (15.1)	30.9 (16.6)	29.6 (15.9)
Bolus daily insulin (IU)	26.1 (18.0)	29.9 (20.0)	33.3 (23.6)	31.3 (21.8)	24.2 (14.2)	27.6 (19.4)	28.8 (17.1)	28.0 (18.0)
Systolic blood pressure (mmHg)	127.5 (18.8)	122.1 (14.6)	120.5 (14.1)	121.6 (14.6)	129.2 (14.4)	122.7 (15.5)	120.4 (14.4)	121.9 (15.0)
Diastolic blood pressure (mmHg)	74.6 (8.9)	75.9 (8.8)	77.0 (9.0)	76.4 (8.9)	76.8 (9.6)	76.1 (9.4)	76.9 (8.4)	76.5 (8.9)
Fasting plasma glucose (mg/dL)	166.8 (80.7)	158.6 (69.7)	156.0 (65.0)	157.7 (68.1)	160.0 (84.9)	167.1 (70.4)	162.3 (68.6)	164.3 (70.3)
eGFR (mL/min/1.73m^2)	53.4 (4.4)	77.7 (8.0)	105.6 (12.7)	89.5 (18.8)	53.9 (4.6)	78.4 (7.7)	107.5 (15.8)	92.0 (20.9)
UACR (mg/g)	200.5 (664.2)	32.3 (156.7)	28.5 (138.5)	38.1 (204.3)	311.3 (922.3)	38.8 (177.1)	37.0 (172.3)	52.6 (279.4)

Source: Statistical Reviewer's analysis; adsl.xpt, adlb.xpt.

Abbreviations: A1C, hemoglobin A1C; CSII, continuous subcutaneous insulin infusion; eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat population; T1D, type 1 diabetes mellitus; UACR, urine albumin-to-creatinine ratio

The analysis results across different eGFR subgroups with respect to A1C change from baseline at Week 24 are presented in Table 3 for Pooled Trials 309/310 and Table 4 for Trial 312; a similar set of results at Week 52 are presented in Table 5 for Pooled Trials 309/310. Analyses based on additional subgrouping strategies are shown in Section 7.1.

The FDA has the following observations regarding the magnitude of treatment effect estimated in the different eGFR subgroups (i.e., <60 mL/min/1.73 m^2, 60 mL/min/1.73 m^2≤eGFR <90 mL/min/1.73 m^2, and ≥90 mL/min/1.73 m^2) (see Table 3, Table 4, and Table 5):

- The magnitudes of the estimated treatment effect observed for the subgroups of eGFR ≥90 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2≤eGFR <90 mL/min/1.73 m^2 are generally consistent with those of the overall population.
- The magnitude of the estimated treatment effect for the subgroup of eGFR <60 mL/min/1.73 m^2 is smaller (based on inspection of the point estimate) compared to the other subgroups and the 95% CI of treatment difference was wide and includes 0.
- The subgroups with eGFR ≥90 mL/min/1.73 m^2 and with 60 mL/min/1.73 m^2≤eGFR <90 mL/min/1.73 m^2 had comparable sample sizes, but the sample size for the subgroup with eGFR <60 mL/min/1.73 m^2 was only around one tenth of the former two groups. The limited sample size for participants with eGFR <60 mL/min/1.73 m^2 brings additional uncertainties to the treatment effect estimates and may preclude meaningful interpretation of the analysis results.
- For all the subgroups, the placebo-adjusted treatment effect at Week 52 was numerically lower than that at Week 24, suggesting that the drug effect may not be maintained for an extended treatment period.

The FDA also conducted eGFR-based subgroup analyses for secondary endpoints using the same subgrouping approach. We considered two unique benefits not related to glycemic control, which were change from baseline to week 24 in body weight (BW) and systolic blood pressure (SBP). The effect observed BW and SBP in the subgroups of eGFR ≥90 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2≤eGFR <90 mL/min/1.73 m^2 are generally consistent with those of the overall population. The effect observed in the subgroup of eGFR <60 mL/min/1.73 m^2 is also similar (based on inspection of the point estimate) compared to the other subgroups, but small sample size and low precision prevent any meaningful conclusion about this population. The analyses for BW and SBP are presented in Section 7.4 (for BW, see Table 22 and Table 23; for SBP, see Table 24 and Table 25).

Table 3. Change From Baseline in A1C (%) at Week 24—Pooled Trials 309/310

		Treatment Arm		
Subgroup	**Variable**	**Sota 200 mg**	**Sota 400 mg**	**Placebo**
Overall population	Sample size	524	525	526
	Baseline, mean (SD)	7.68 (0.77)	7.64 (0.78)	7.66 (0.81)
	Missing endpoint values, n (%)	40 (7.6)	42 (8.0)	41 (7.8)
	Change from baseline, LSMean (SE)	-0.38 (0.03)	-0.41 (0.03)	-0.04 (0.03)
	Difference from placebo, LSMean (95% CI)	**-0.34 (-0.41, -0.27)**	**-0.37 (-0.44, -0.30)**	

Subgroup	Variable	Treatment Arm		
		Sota 200 mg	Sota 400 mg	Placebo
eGFR ≥90	Sample size	232	241	257
	Baseline, mean (SD)	7.72 (0.78)	7.66 (0.82)	7.77 (0.88)
	Missing endpoint values, n (%)	21 (9.1)	18 (7.5)	16 (6.2)
	Change from baseline, LSMean (SE)	-0.33 (0.04)	-0.33 (0.04)	-0.05 (0.04)
	Difference from placebo, LSMean (95% CI)	**-0.28 (-0.39, -0.17)**	**-0.28 (-0.39, -0.17)**	
60≤eGFR <90	Sample size	270	259	245
	Baseline, mean (SD)	7.63 (0.78)	7.60 (0.72)	7.54 (0.70)
	Missing endpoint values, n (%)	19 (7.0)	23 (8.9)	23 (9.4)
	Change from baseline, LSMean (SE)	-0.40 (0.04)	-0.47 (0.04)	-0.00 (0.04)
	Difference from placebo, LSMean (95% CI)	**-0.39 (-0.50, -0.30)**	**-0.46 (-0.56, -0.36)**	
eGFR <60	Sample size	22	25	24
	Baseline, mean (SD)	7.82 (0.64)	7.85 (0.88)	7.74 (0.89)
	Missing endpoint values, n (%)	0	1 (4.0)	2 (8.3)
	Change from baseline, LSMean (SE)	-0.58 (0.13)	-0.53 (0.12)	-0.31 (0.13)
	Difference from placebo, LSMean (95% CI)	**-0.27 (-0.64, 0.11)**	**-0.21 (-0.57, 0.14)**	

Source: Statistical Reviewer's analysis.

Abbreviations: A1C, hemoglobin A1C; CI, confidence interval; eGFR, estimated glomerular filtration rate; LSMean, least-squares mean; SE, standard error; Sota, sotagliflozin

Table 4. Change From Baseline in A1C (%) at Week 24—Trial 312

Subgroup	Variable	Treatment Arm	
		Sota 400 mg	Placebo
Overall population	Sample size	699	703
	Baseline, mean (SD)	8.26 (0.96)	8.21 (0.92)
	Missing endpoint values, n (%)	72 (10.3)	75 (10.7)
	Change from baseline, LSMean (SE)	-0.76 (0.03)	-0.32 (0.03)
	Difference from placebo, LSMean (95% CI)	**-0.44 (-0.52, -0.36)**	
eGFR ≥90	Sample size	355	361
	Baseline, mean (SD)	8.35 (1.02)	8.29 (0.92)
	Missing endpoint values, n (%)	41 (11.5)	46 (12.7)
	Change from baseline, LSMean (SE)	-0.79 (0.04)	-0.31 (0.04)
	Difference from placebo, LSMean (95% CI)	**-0.48 (-0.60, -0.35)**	
60≤eGFR <90	Sample size	312	300
	Baseline, mean (SD)	8.13 (0.88)	8.11 (0.91)
	Missing endpoint values, n (%)	25 (8.0)	24 (8.0)
	Change from baseline, LSMean (SE)	-0.75 (0.04)	-0.31 (0.04)
	Difference from placebo, LSMean (95% CI)	**-0.43 (-0.54, -0.32)**	
eGFR <60	Sample size	32	42
	Baseline, mean (SD)	8.49 (1.05)	8.25 (0.94)
	Missing endpoint values, n (%)	6 (18.8)	5 (11.9)
	Change from baseline, LSMean (SE)	-0.64 (0.16)	-0.47 (0.14)
	Difference from placebo, LSMean (95% CI)	**-0.17 (-0.58, 0.25)**	

Source: Statistical Reviewer's analysis.

Abbreviations: A1C, hemoglobin A1C; CI, confidence interval; eGFR, estimated glomerular filtration rate; LSMean, least-squares mean; SE, standard error; Sota, sotagliflozin

Table 5. Change From Baseline in A1C (%) at Week 52—Pooled Trials 309/310

		Treatment Arm		
Subgroup	**Variable**	**Sota 200 mg**	**Sota 400 mg**	**Placebo**
Overall population	Sample size	524	525	526
	Baseline, mean (SD)	7.68 (0.77)	7.64 (0.78)	7.66 (0.81)
	Missing endpoint values, n (%)	64 (12.2)	71 (13.5)	78 (14.8)
	Change from baseline, LSMean (SE)	-0.21 (0.03)	-0.29 (0.03)	0.02 (0.03)
	Difference from placebo, LSMean (95% CI)	**-0.22 (-0.31, -0.13)**	**-0.31 (-0.39, -0.22)**	
eGFR ≥90	Sample size	232	241	257
	Baseline, mean (SD)	7.72 (0.78)	7.66 (0.82)	7.77 (0.88)
	Missing endpoint values, n (%)	34 (14.7)	29 (12.0)	35 (13.6)
	Change from baseline, LSMean (SE)	-0.12 (0.05)	-0.25 (0.05)	0.05 (0.05)
	Difference from placebo, LSMean (95% CI)	**-0.17 (-0.31, -0.02)**	**-0.30 (-0.44, -0.16)**	
60≤eGFR <90	Sample size	270	259	245
	Baseline, mean (SD)	7.63 (0.78)	7.60 (0.72)	7.54 (0.70)
	Missing endpoint values, n (%)	30 (11.1)	39 (15.1)	38 (15.5)
	Change from baseline, LSMean (SE)	-0.26 (0.04)	-0.33 (0.04)	0.01 (0.04)
	Difference from placebo, LSMean (95% CI)	**-0.27 (-0.39, -0.16)**	**-0.34 (-0.46, -0.22)**	
eGFR <60	Sample size	22	25	24
	Baseline, mean (SD)	7.82 (0.64)	7.85 (0.88)	7.74 (0.89)
	Missing endpoint values, n (%)	0	3 (12.0)	5 (20.8)
	Change from baseline, LSMean (SE)	-0.47 (0.13)	-0.20 (0.13)	-0.29 (0.14)
	Difference from placebo, LSMean (95% CI)	**-0.17 (-0.55, 0.21)**	**0.09 (-0.28, 0.46)**	

Source: Statistical Reviewer's analysis.

Abbreviations: A1C, hemoglobin A1C; CI, confidence interval; eGFR, estimated glomerular filtration rate; LSMean, least-squares mean; SE, standard error; Sota, sotagliflozin

Given the concerns about post hoc analyses and multiplicity, available data do not support definitive conclusions about the magnitude of treatment effect on A1C in patients with T1D and CKD. However, it appears that the treatment effect on A1C in patients with T1D and eGFR ≥60 mL/min/1.73 m^2 may approximate the treatment effect observed in the overall population (i.e., around 0.3 to 0.4%) established in the review of the original NDA. The treatment effect on A1C in patients with T1D and eGFR <60 mL/min/1.73 m^2 is also uncertain but appears smaller in magnitude. Finally, issues raised in the original submission regarding the durability of the treatment effect beyond 24 weeks and the lack of convincing evidence of additional A1C benefit from the 400 mg dose compared to the 200 mg dose apply to the reanalyses conducted in the subpopulation of patients with T1D and CKD.

Similarly, the available data cannot support definitive conclusions about the magnitude of effect on BW and SBP in the revised population. However, it appears that sotagliflozin has a modest effect on each, similar to the effects observed in the original NDA.

3.4 Assessment of the Microvascular (Kidney) Benefits Associated With Improved Glycemic Control in Patients With T1D and CKD

To quantify the effect of a modest reduction in A1C on long-term renal outcomes, FDA considered available evidence from published studies in T1D: the DCCT and its follow-up EDIC study, and the Preventing Early Renal Loss in Diabetes (PERL) trial.

DCCT established that improvements in blood glucose control, as measured by reduction in A1C, significantly reduced the risk of microvascular complications (e.g., retinopathy, nephropathy, neuropathy) in patients with T1D. Intensive glucose control, comprised three or more daily insulin injections combined with SMBG four times daily and strict glycemic targets, was associated with an average A1C of approximately 7.3%, whereas conventional glucose control (one or two daily insulin injections in combination with less frequent monitoring and no specific glycemic targets) was associated with an A1C of 9.2%. The roughly 2% difference in A1C between the two groups was maintained for approximately 6.5 years (the average follow-up period of the trial). Analyses of outcomes observed during DCCT demonstrated that each 10% relative reduction in A1C was associated with a 40 to 45% reduction in the relative risk of sustained retinopathy progression (DCCTRG 1995). The sustained improvement in A1C also resulted in an absolute risk difference for microalbuminuria of 7% at 6.5 years; during EDIC that absolute risk difference remained constant over a total follow-up time of 25 years. Smaller risk differences were observed for the more severe renal outcomes: macroalbuminuria, eGFR <60 mL/min/1.73 m^2, and end stage renal disease (ESRD).

DCCT/EDIC demonstrates that large improvements in A1C sustained over many years can result in significant renal benefits that do not manifest until decades later. However, estimating the magnitude of the long-term renal benefit of sotagliflozin in patients with long-standing T1D and mild-to-moderate CKD based on data from DCCT/EDIC is challenging. DCCT/EDIC was conducted in a cohort of young patients (mean baseline age, 27 years) with recently diagnosed T1D (mean baseline duration of disease, 6 years) who had baseline A1C of 9 to 10% and no evidence of CKD at trial entry and who did not routinely receive treatment with RAS inhibition over the course of follow-up according to modern standards; in contrast, modern patients with T1D and CKD are likely to present with significantly lower A1C, longer history of disease, and will likely be managed with RAS inhibition. Moreover, the intervention in DCCT/EDIC resulted in a 1.9% absolute improvement in A1C sustained for more than 6 years, whereas data from TANDEM suggest that sotagliflozin may result in a 0.3% reduction in A1C which may attenuate after Week 24. Overall, the data from DCCT/EDIC alone are insufficient to estimate the magnitude of the long-term renal benefits of a modest improvement in A1C in patients with mild-to-moderate CKD (which is important for benefit-risk assessment in the setting of a serious risk).

Conducted from February 2014 to August 2019, the PERL trial investigated whether urate lowering therapy with allopurinol delays the progression of CKD in patients with T1D. Enrollment criteria required all participants to have a history of albuminuria or evidence of a decline in eGFR of at least 3 mL/min/1.73 m^2/year for the past 3 to 5 years. Although PERL failed to demonstrate that allopurinol delays the progression of CKD, it provides relevant data on renal function decline over time in patients with T1D and mild-to-moderate CKD at risk of progression. The enrolled population (n=530) in the PERL trial had a mean eGFR of 75 mL/min/1.73 m^2, a median UACR of 41 mg/g, mean baseline A1C of 8.2%, mean age of 51 years, with a mean duration of T1D of 35 years. In addition, PERL participants were medically optimized with RAS inhibitors for blood pressure control. An average eGFR decline of -2.5 mL/min/1.73 m^2/year was observed in the placebo-treated arm over the 3 year treatment period.

A follow-up analysis of data from the PERL trial (Shah et al. 2024) failed to demonstrate an association between glycemic control and eGFR decline in participants without microalbuminuria. In participants with microalbuminuria, worse glycemic control was associated with greater declines in eGFR: the observed eGFR declines across the strata of A1C <7.5%, A1C 7.5 to 8.5%, and A1C >8.5% were -1.03, -1.69, and -2.60 mL/min/1.73 m^2/year, respectively (P-trend =0.03). The association was

stronger in participants with macroalbuminuria: the observed eGFR decline rates across the same A1C strata were -3.0, -3.5, and -6.3 mL/min/1.73 m^2, respectively (P-trend =0.002). Using mixed-effects linear regression, in an unadjusted analysis, the association between poorer glycemic control and more rapid eGFR decline in the overall PERL population was -0.87 mL/min/1.73 m^2/year per A1C (%) unit increment (SE =0.14, p<0.001). After adjusting for potential confounding variables (albumin excretion rate, serum uric acid, mean SBP, mean DBP, age), the effect diminished to -0.54 mL/min/1.73 m^2 per year per A1C (%) unit increment (SE 0.15, p=0.002).

An observational study of a cohort of 349 participants with T1D (the Joslin Proteinuria Cohort) suggests that the relationship between glycemic control and progression of CKD is more pronounced among patients with macroalbuminuria. Participants were recruited from patients receiving long-term care at the Joslin Clinic who were diagnosed with proteinuria (UACR ≥ 250 mg/g for men and UACR ≥ 350 mg/g for women). At study entry, participants had a median UACR of 687 mg/g and a median eGFR of 85, a median duration of T1D of 24 years, and a median age of 38 years; 69.5% of participants were receiving treatment with a RAS inhibitor at study entry. Median A1C over the 5-year interval prior to study enrollment was 9.3%. Participants were followed for a median of 5.1 years, with some participants having more than 15 years of follow up; median postbaseline A1C was 8.7%. 40 participants did not return to clinic but were followed for events of ESRD or death; they were defined as "nonattenders". During the follow-up period, a total of 77 events of ESRD were observed among the 349 study participants. The study authors defined participants who experienced ESRD within 3 years of study entry as "rapid progressors". After excluding the 30 events observed among the rapid progressors, a multivariate Cox regression analysis of the remaining 47 events using the variables of prebaseline A1C and change between pre- and postbaseline A1C yielded an ESRD hazard ratio of 0.76 (95% CI 0.63 to 0.91) for a 1% point improvement in postbaseline A1C. However, the potential for confounding in this retrospective observational analysis is significant (Skupien et al. 2014).

In summary, DCCT/EDIC and PERL trials suggest a relationship between A1C reduction and rate of eGFR decline in patients with T1D, including patients with T1D and mild-to-moderate CKD. The data from PERL suggest that the effect of a 0.3% reduction in A1C maintained over 10 years might translate to a preservation of 1.6 mL/min/1.73 m^2 of eGFR in a population of patients with T1D and mild-to-moderate CKD. Because of the lack of long-term follow-up data, the results of PERL do not exclude the possibility that a modest improvement in A1C maintained over decades might ultimately manifest in more clinically significant kidney benefits. The results of the observational study of the Joslin Proteinuria Cohort suggests that a similar reduction in A1C might have greater benefit in patients with macroalbuminuria and a history of poor glycemic control.

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

The Applicant has proposed that observations regarding the effects of sotagliflozin in patients with T2D, moderate-to-severe CKD, and other risk factors may inform the benefit-risk assessment of sotagliflozin in patients with T1D and mild-to-moderate CKD. The Applicant has cited results of SCORED, a large cardiorenal outcomes trial, asserting that sotagliflozin has additional benefits not necessarily mediated through glycemic control. Specifically, the Applicant states that the results of SCORED suggest benefits on reducing the risk of HHF, MACE, and progression of CKD (Table 6). During the review of NDA 216203 (Inpefa), FDA determined that SCORED demonstrated a reduced risk for the composite endpoint of CV death, hospitalization for heart failure (HHF), and UHFV in patients with T2D, CKD, and other CV risk factors. Although additional endpoints of clinical interest were pre-specified and showed nominally

significant p-values, they were considered exploratory because formal testing was not indicated according to the statistical analysis plan.[9]

In the current submission, the Applicant has asserted that it is reasonable to extrapolate benefits suggested by SCORED to patients with T1D and CKD. However, during the review of NDA 216203, the Applicant did not propose an indication for Inpefa that encompassed all patients with diabetes mellitus, CKD, and other CV risk factors.

Table 6. Secondary Endpoint Results (Investigator-Reported)—ITT Population, SCORED

Endpoint	Placebo N=5292 [n (rate per 100 PY)]	Sotagliflozin N=5292 [n (rate per 100 PY)]	Hazard Ratio (95% CI)	p-value
Total occurrences of CV death, HHF or UVHF (primary)[b]	530 (7.5)	400 (5.6)	0.75 (0.63, 0.88)	0.0004
Total occurrences of HHF and UVHF[b]	360 (5.1)	245 (3.5)	0.67 (0.55, 0.82)	0.0001
Time to CV death[a]	170 (3.2)	155 (2.9)	0.90 (0.73, 1.12)	0.3566
Total occurrences of CV death, HHF, nonfatal MI, or nonfatal stroke[b]	680 (9.6)	504 (7.1)	0.73 (0.64, 0.84)	<0.0001[c]
Total occurrences of CV death, HHF, UVHF, or HF while hospitalized[b]	589 (8.3)	453 (6.4)	0.76 (0.65, 0.89)	0.0005[c]
Renal composite[d]	65 (1.2)	43 (0.8)	0.65 (0.45, 0.96)	0.0303[c]
Time to all-cause mortality[a]	246 (4.6)	246 (4.6)	0.99 (0.83, 1.18)	0.9256[c]
Total occurrences of CV death, nonfatal MI, or non-fatal stroke[b]	384 (5.4)	306 (4.3)	0.79 (0.67, 0.93)	0.0047[c]

Source: Curated from Table 11 and Table 13 of the Integrated Review for INPEFA available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/216203Orig1s000TOC.cfm.
Endpoints are presented in order of hierarchical testing.
[a] Time-to-event analysis; results are number of patients with an event (percentage of patients with an event)
[b] Total occurrences analysis; results are total number of events (event rate per 100 patient-years); event rate is calculated as the cumulative number of events ÷ [cumulative duration at risk (years) ÷ 100].
[c] Nominal p-value.
[d] Time to first occurrence of the composite of sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days).
Abbreviations: CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; ITT, intent-to-treat; MI, myocardial infarction; No, number; PY, patient-years; UVHF, urgent visit for heart failure

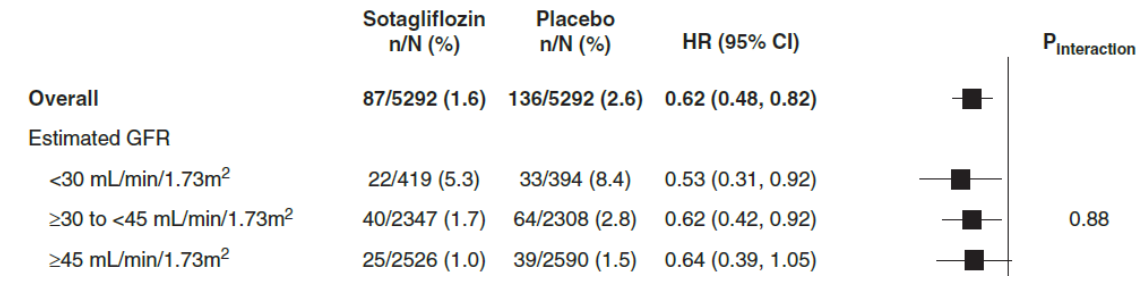
The approved USPI for Inpefa includes a subgroup analysis conducted in SCORED participants with baseline eGFR of 45 to <60 mL/min/1.73 m^2 for the primary endpoint that supported approval (see Figure 6 in the Inpefa USPI). The relative measure of benefit appears consistent across the eGFR subgroups of <30 mL/min/1.73 m^2, 30 to 45 mL/min/1.73 m^2, ≥45 to ≤60 mL/min/1.73 m^2 (HR 0.68, 0.75,

[9] For the listed secondary endpoints, only the first secondary endpoint was less than 0.05. Secondary endpoints were pre-specified and planned to be tested hierarchically in a pre-specified order at a 2-sided 0.05 alpha level. Hypothesis testing for later tests was conditioned on a success of primary endpoint tested at the 2-sided 0.05 alpha level. Because the second endpoint failed hypothesis testing, subsequent p-values were considered nominal only.

and 0.76, respectively). However, the absolute measure of benefit across these same subgroups is inversely correlated with eGFR: the estimated event rate difference is 4.7 events/100 PY, 2.2 events/100 PY, and 1.2 events/100 PY, respectively. The risk difference observed in SCORED participants with eGFR 45 to <60 mL/min/1.73 m^2 corresponds to a number needed to treat (NNT) of 83 patients per year to avoid one event of HHF, CV death, or UHFV.

Reduced risk for progression of CKD is not an approved indication in the Inpefa USPI. Nonetheless, the Applicant cited a published analysis of observed kidney outcomes in SCORED by eGFR subgroups (<30 mL/min/1.73 m^2, 30 to 45 mL/min/1.73 m^2, 45 to ≤60 mL/min/1.73 m^2) (Sridhar et al. 2024). The analysis used a post hoc ascertainment strategy to identify composite renal events which did not rely on blinded adjudication but rather relied on incidentally collected laboratory values. This analysis included a larger number of composite renal events than were considered in FDA's review of the Inpefa NDA. Similar to HHF, this analysis suggests that the relative risk differences are similar across eGFR subgroups, but the absolute risk differences are smaller among subgroups with higher eGFR. The data presented in Figure 5 correspond to a NNT of approximately 250 patients per year for sotagliflozin to prevent one additional event of a 50% decline in eGFR or kidney failure (defined as eGFR <15 mL/min/1.73 m^2), maintenance dialysis, or kidney transplant among patients with T2D, baseline eGFR 45 to ≤60 mL/min/1.73 m^2, and other CV risk factors.[10]

Figure 5. Forest Plot With eGFR Subgroups for the Composite of First Event of 50% Decline in eGFR or Kidney Failure Defined as eGFR <15 mL/min/1.73 m^2, Maintenance Dialysis, or Kidney Transplant Using Laboratory Data



Source: Clinical Overview from NDA 210934 (SDN0070), Figure 4. The Applicant referenced Sridhar et al. (2024).
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio

Reduced risk of MACE is also not an approved indication in the Inpefa USPI and the Applicant did not submit any reanalysis of the MACE data from SCORED according to eGFR subgroup to supplement their assertion that these data are relevant. However, for the entire SCORED population, the NNT based on the data presented in Table 6 to prevent one additional event of myocardial infarction, stroke, or CV death is approximately 90 patients per year with T2D, eGFR 20 to 60 mL/min/1.73 m^2, and other CV risk factors.

The FDA has the following uncertainties regarding the Applicant's proposal to infer benefits in patients with T1D and mild-to-moderate CKD based on the results of SCORED:

- SCORED did not demonstrate a statistically significant benefit on prespecified renal composite or MACE endpoints.

[10] Estimation of NNT per year also based on the mean duration of exposure to sotagliflozin in SCORED (16 months).

- It is unclear that one can extrapolate benefits observed in patients with T2D, moderate-to-severe CKD, and other CV risk factors to a population of patients with T1D and moderate-to-severe CKD.
- In terms of absolute risk reduction, it is unclear that the magnitudes of benefits in patients with T1D and moderate-to-severe CKD would be similar to magnitudes of benefits in patients with T1D and mild-to-moderate CKD.
- The relevance of non-glycemic benefits to support an indication for improved glycemic control [rather than indication(s) describing the particular non-glycemic benefit(s)] is unclear.

4 Safety Issues

4.1 Safety Summary

The safety of sotagliflozin has been well characterized in patients with T2D in the two large cardiorenal outcomes trials (SCORED, conducted in patients with T2D, moderate-to-severe CKD, and other CV risk factors; SOLOIST, conducted in patients with T2D and heart failure) that supported the approval of NDA 216203 (sotagliflozin 200 mg and 400 mg, as Inpefa). In addition, the safety database from the TANDEM program (conducted in patients with T1D) informed the labeling of Inpefa. Overall, the safety profile of sotagliflozin was similar in patients with T1D and patients with T2D, with two notable exceptions: 1) patients randomized to sotagliflozin experienced fewer hypoglycemia events than patients randomized to placebo in the TANDEM program, but not in SCORED (hypoglycemia events were balanced across treatment arms) or SOLOIST (patients randomized to sotagliflozin experienced more events of hypoglycemia), 2) patients randomized to sotagliflozin experienced a significantly increased dose-dependent risk of DKA in the TANDEM program, but not in SCORED or SOLOIST. As described in the 2019 sotagliflozin EMDAC FDA briefing document for NDA 210934, patients randomized to sotagliflozin subsequently reduced their baseline total daily insulin dose over the duration of the study (i.e., they reduced their insulin dose in the course of usual titrations based on routine monitoring in response to the glucose-lowering effect of sotagliflozin). The reduction in total daily insulin use likely explains the findings that sotagliflozin reduces hypoglycemia risk in patients with T1D and that sotagliflozin increases DKA risk in patients with T1D substantially more than in patients with T2D.

The Inpefa USPI warns of an observed dose-dependent increased risk of DKA in patients with T1D. The Inpefa USPI also addresses the following risks (which are class effects): volume depletion, urosepsis and pyelonephritis, hypoglycemia with concomitant use of insulin and insulin secretagogues, necrotizing fasciitis of the perineum (Fournier's gangrene), and genital mycotic infections. The most common adverse reactions reported in the Inpefa USPI are urinary tract infection, volume depletion, diarrhea, hypoglycemia, dizziness, and genital mycotic infections, again similar to the SGLT2i class, except for diarrhea which is likely linked to the SGLT1 activity of sotagliflozin.

The safety of sotagliflozin in the overall TANDEM program was previously presented in the 2019 sotagliflozin EMDAC FDA briefing document for NDA 210934.

FDA reanalyzed the TANDEM safety database to assess whether similar patterns of adverse reactions were observed across eGFR subgroups. The subgroup analyses used the same subgrouping strategy as defined in Section 3.2: (a) eGFR ≥90 mL/min/1.73 m^2; (b) 60≤eGFR <90 mL/min/1.73 m^2; (c) eGFR <60 mL/min/1.73 m^2. FDA focused its safety review for the current NDA resubmission on hypoglycemia and DKA, both because of the findings in the original review of the TANDEM program and because hypoglycemia and DKA are the two most common reasons for hospitalization among patients with T1D.

Because of the limitations of the available clinical data from the TANDEM program, FDA also considered other sources of information outside of the TANDEM program to inform its assessment of DKA risk in patients with T1D and CKD.

A selection of adverse events of special interest that were discussed at the 2019 EMDAC were reanalyzed (using identical preferred term queries) by eGFR category according to the same subgrouping strategy defined in Section 3.2. The results of these analyses are provided in section 7.2. No meaningful relationship with eGFR and these adverse drug reactions was identified. The new analyses of hypoglycemia and DKA are discussed separately in the sections immediately below.

4.1.1 Hypoglycemia

Hypoglycemia is a common occurrence in patients with T1D. Most hypoglycemic events are treated by the patient or by receiving assistance from other(s), and do not necessarily lead to an emergency room visit or hospitalization. However, some events can be life-threatening. Additionally, fear of hypoglycemia may discourage patients from achieving optimal glycemic control.

ADA categorizes hypoglycemic events according to severity (ElSayed et al. 2023):

- Level 1: Blood glucose levels less than 70 milligrams/deciliter (mg/dL) (3.9 millimoles/liter [mmol/L]) and greater than or equal to 54 mg/dL (3 mmol/L). This threshold is an alert value at which patients should take action to avoid continued decline in blood glucose.
- Level 2: Blood glucose levels less than 54 mg/dL regardless of the presence of hypoglycemia symptoms. At this threshold, adrenergic and/or neuroglycopenic symptoms typically begin.
- Level 3 (severe hypoglycemia): characterized by a severely altered mental and/or physical functioning, which if untreated may result in loss of consciousness, seizures, coma, or ultimately death. Hypoglycemia reversal necessitates the assistance of another person. Glucose measurements may not be available during an event, but neurological recovery attributable to the restoration of blood glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

The draft FDA guidance for industry, *Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products* (May 2023) recommends level 3 and level 2 hypoglycemia as acceptable endpoints in support of claims related to improvement in glycemic control and/or iatrogenic hypoglycemia risk reduction. Level 3 hypoglycemia is a direct measurement of how a participant feels, functions, or survives and is therefore a clinical endpoint. FDA considers level 2 hypoglycemia to be a surrogate endpoint for neuroglycopenia-related adverse events (e.g., cognitive impairment, incoordination) acceptable for traditional approval (i.e., as opposed to accelerated approval). Although the TANDEM trials systematically collected hypoglycemia data and prespecified various hypoglycemia safety endpoints, they did not include endpoints intended to demonstrate reduction in hypoglycemia (by any definition) in the formal testing hierarchy. The original submission of NDA 210934 was reviewed prior to issuance of this guidance; for the current resubmission FDA reanalyzed the hypoglycemia data according to the new recommended definitions of hypoglycemia in the guidance.

Participants were excluded from the TANDEM trials if they experienced severe hypoglycemia within one month of screening. During the studies, participants were given glucometers and instructed to record every hypoglycemia event regardless of severity in a study diary. Investigators recommended a 5-point SMBG profile least 3 days in the week prior to a study visit, with at least one 8-point SMBG profile closer

to visit day. SMBG was also recommended prior to critical activities such as driving, before exercise, and with more frequency during acute illness.

The TANDEM program employed a dedicated hypoglycemia electronic case report form (eCRF), which contained different sections for documented hypoglycemic events and severe hypoglycemic events. Study-provided glucometer data (web-based glucose meter data, glucometer memory review, or meter download) was routinely collected and used to corroborate the study diary and/or hypoglycemia reports. Unless the severe hypoglycemic event was also a serious adverse event, reports were only reported in hypoglycemia eCRF. A blinded Clinical Event Committee (CEC) adjudicated all potential severe hypoglycemia events.

Documented hypoglycemia was defined as an occurrence of an SMBG or venous glucose result of ≤70 mg/dL, regardless of whether the event was accompanied by typical symptoms of hypoglycemia. Events of documented hypoglycemia were categorized as "symptomatic" or "asymptomatic" and also categorized by severity, using blood glucose thresholds of ≤55 mg/dL and < 70 mg/dL. Importantly, the decision to use ≤55 mg/dL as the threshold in the TANDEM program to identify clinically significant hypoglycemic events was made prior to the ADA's adoption of <54 mg/dL as the definition of a Level 2 hypoglycemia and prior to the publication of the FDA draft guidance for industry (May 2023). FDA considers the Applicant's prespecified threshold of ≤55 mg/dL as sufficiently consistent with FDA's preferred definition of Level 2 hypoglycemia for purposes related to the review of NDA 210934. Similarly, FDA determined that the definition used for severe hypoglycemia events in the dedicated hypoglycemia eCRF is consistent with the FDA's preferred definition of Level 3 hypoglycemia for purposes related to the review of NDA 210934. Hereafter, FDA refers to events captured on the dedicated hypoglycemia eCRF as documented hypoglycemia ≤ 55 mg/dL and severe hypoglycemia as Level 2 and Level 3 events, respectively.

FDA analysis of hypoglycemia events focused on both the incidence of hypoglycemia and total number of hypoglycemia events, adjusted by exposure to the investigational product. Level 2 and Level 3 hypoglycemia events were evaluated over 52 weeks for Pooled Trials 309 and 310 and over 24 weeks for Trial 312.

Level 3 Hypoglycemic Events

In Pooled trials 309 and 310, numerically more participants randomized to placebo experienced at least one Level 3 hypoglycemia event compared to patients randomized to sotagliflozin. In Trial 312, slightly fewer patients randomized to placebo experienced at least one Level 3 hypoglycemia event compared to patients randomized to sotagliflozin. However, patients randomized to sotagliflozin experienced a larger total number of Level 3 hypoglycemia events compared to patients randomized to placebo; this finding was driven by a relatively small number of participants, including one participant randomized to sotagliflozin 200 mg who experienced 18 Level 3 events. There were too few Level 3 events observed among the various eGFR subgroups to conclude whether the pattern observed in the overall TANDEM population was due to chance or drug effect (see Table 7).

Table 7. Summary of Positively Adjudicated Level 3 Hypoglycemia in the TANDEM Program

Group	Statistic	Studies 309 and 310 (52 Weeks)			Study 312 (24 Weeks)	
		Placebo	Sota 200 mg	Sota 400 mg	Placebo	Sota 400 mg
Overall T1D population	N	526	524	525	703	699
	n (%) [events]	39 (7.4) [50]	30 (5.7) [68]	23 (4.4) [33]	17 (2.4) [22]	21 (3.0) [25]
eGFR <60 mL/min/1.73m^2	N	24	22	25	42	32
	n (%) [events]	3 (12.5) [4]	3 (13.6) [3]	2 (8.0) [2]	1 (2.4) [1]	3 (9.4) [3]
eGFR 60 – 89 mL/min/1.73m^2	N	245	270	259	300	312
	n (%) [events]	22 (9.0) [30]	16 (5.9) [45]	13 (5.0) [19]	9 (3.0) [13]	9 (2.9) [12]
eGFR ≥90 mL/min/1.73m^2	N	257	232	241	361	355
	n (%) [events]	14 (5.4) [16]	11 (4.7) [20]	8 (3.3) [12]	7 (1.9) [8]	9 (2.5) [10]

Source: Curated from Response to Information Request to NDA210934 (SDN 81)
Abbreviations: n, number of participants with event; N, number of participants; %, percentage of participants with event

Level 2 Hypoglycemic Events

In the overall population of the TANDEM trials, participants randomized to sotagliflozin experienced fewer Level 2 events compared to participants randomized to placebo. Although almost all participants experienced at least one Level 2 hypoglycemia event, the total number of Level 2 hypoglycemia events was reduced by 14 to 24% in the sotagliflozin treatment groups, based on the point estimates. Although the TANDEM program did not include any endpoint related to hypoglycemia in the formal testing hierarchy, given the large number of Level 2 events reported, the observation appears relatively robust. In addition, the finding is biologically plausible: the risk of hypoglycemia in patients with T1D is attributable to their exogeneous insulin use and the participants in TANDEM randomized to sotagliflozin commonly reduced their use of exogeneous insulin. Refer to the 2019 FDA EMDAC briefing document in Section 7.7 for more details. To confirm that the treatment effect of sotagliflozin on Level 2 hypoglycemia events was consistent across the relevant eGFR subgroups, FDA reanalyzed the Level 2 hypoglycemia data using the same strategy employed for its assessment of glycemic control. The results of the subgroup analyses were generally consistent with one another and supported a conclusion that the participants in the TANDEM program with mild-to-moderate CKD who were randomized to sotagliflozin also experienced fewer Level 2 hypoglycemia events than those randomized to placebo.

Table 8. Summary of Level 2 Hypoglycemia in the TANDEM Program

Group	Statistic	Studies 309 and 310 (52 Weeks)			Study 312 (24 Weeks)	
		Placebo	Sota 200 mg	Sota 400 mg	Placebo	Sota 400 mg
Overall T1D population	N	526	524	525	703	699
	n Events (event rate)	8995 (18.12)	7129 (14.94)	7133 (15.65)	4682 (15.41)	3512 (11.78)
	Relative risk (95% CI)	-	0.82 (0.79, 0.86)	0.86 (0.83, 0.90)	-	0.76 (0.73, 0.80)
eGFR <60 mL/min/1.73m^2	N	24	22	25	42	32
	n Events (event rate)	428 (25.67)	341 (15.57)	355 (21.25)	248 (13.91)	143 (11.14)
	Relative risk (95% CI)	-	0.66 (0.53, 0.78)	0.91 (0.75, 1.05)	-	0.80 (0.65, 0.98)
eGFR 60 – 89 mL/min/1.73m^2	N	245	270	259	300	312
	n Events (event rate)	3987 (19.71)	3744 (15.85)	3480 (16.05)	2048 (15.42)	1670 (12.51)
	Relative risk (95% CI)	-	0.78 (0.75, 0.84)	0.80 (0.76, 0.86)	-	0.81 (0.76, 0.87)
eGFR ≥90 mL/min/1.73m^2	N	257	232	241	361	355
	n Events (event rate)	4580 (15.14)	3044 (13.36)	3298 (13.95)	2386 (15.57)	1699 (11.19)
	Relative risk (95% CI)	-	0.87 (0.82, 0.94)	0.92 (0.86, 0.99)	-	0.72 (0.68, 0.76)

Source: Curated from Response to Information Request to NDA210934 (SDN 81)
Event rate is calculated as total number of events divided by total exposure. Total exposure is calculated as the time from first to last dose of study drug. The units of event rate are events per patient-year.
Relative risk (95% CI) was calculated using an exact Poisson distribution, and stratified by study by assigning weights to be inversely proportional to the variance of each stratum-specific estimate.
Abbreviations: n, number of events; CI, confidence interval

As stated above, FDA considers Level 2 hypoglycemia to be a surrogate endpoint for neuroglycopenia-related adverse events. Interpretation of the hypoglycemia data in the NDA resubmission, however, presents some challenges. Although the observation of a reduction in Level 2 hypoglycemia events was numerically robust and biologically plausible, the endpoint was not prespecified or subjected to formal statistical testing. Moreover, the magnitude of benefit conferred by an observed reduction in Level 2 hypoglycemia events captured by SMBG is difficult to quantify. Event ascertainment using SMBG has important limitations. Although SMBG has the advantage of identifying Level 2 hypoglycemia events more accurately than continuous glucose monitors due to its superior performance at lower glucose levels, SMBG likely fails to capture many Level 2 hypoglycemia events and therefore underestimates the absolute number of Level 2 hypoglycemia events avoided by participants randomized to sotagliflozin. Although one cannot reliably calculate the absolute risk reduction for Level 2 hypoglycemia events from the available data, a reasonable estimate of the relative risk reduction of Level 2 hypoglycemia associated with sotagliflozin in the TANDEM program is perhaps 20%. However, it nonetheless constitutes an advantage of treatment with sotagliflozin that may merit consideration with respect to an overall benefit-risk assessment for a proposed glycemic control indication.

4.1.2 Diabetic Ketoacidosis (DKA)

DKA is an acute, serious, life-threatening metabolic complication that requires immediate medical intervention. Between 2 to 3% of patients with T1D are hospitalized annually in the United States with this complication, and in-hospital mortality estimates range from 0.4 to 3% (Benoit et al. 2018; Ramphul and Joynauth 2020; Thomas et al. 2020).

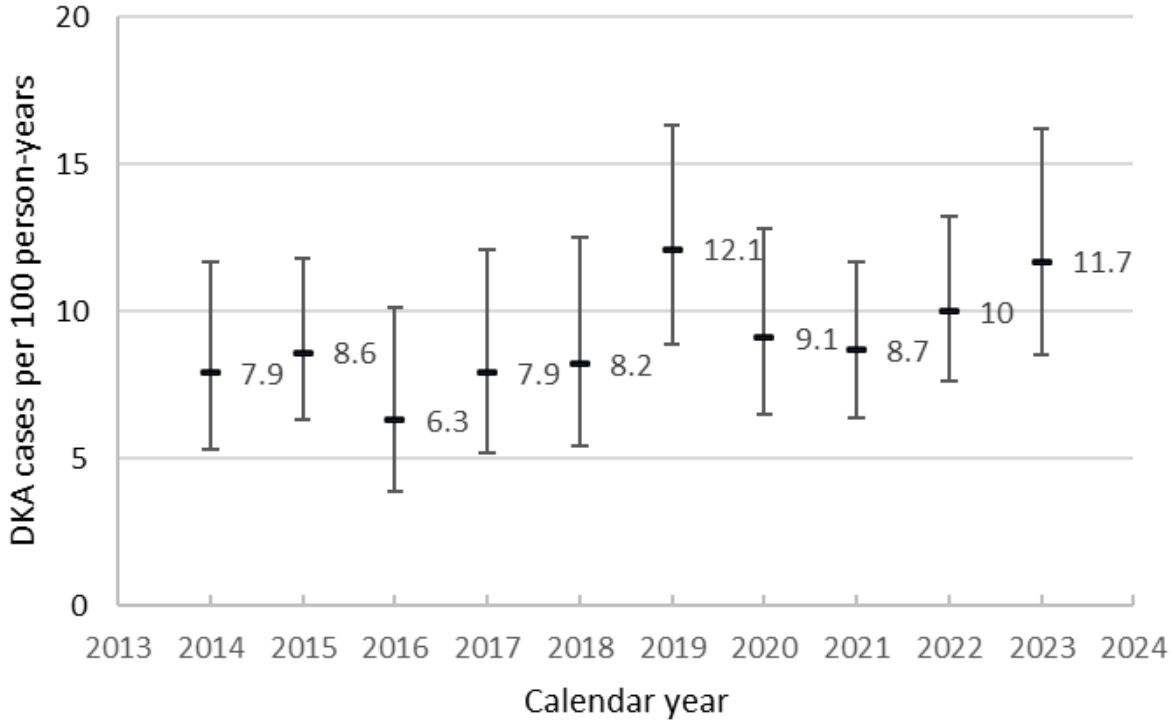
A DKA risk has been demonstrated in randomized clinical trials of multiple SGLT2 inhibitors in patients with T1D and cases of ketoacidosis in both patients with T1D and patients with T2D have been reported to the FDA Adverse Event Reporting System database. Although DKA traditionally presents with hyperglycemia, DKA events associated with SGLT2 inhibitor use sometimes present as euglycemic (normal blood glucose concentration) DKA. All approved SGLT2 inhibitors (including sotagliflozin marketed as Inpefa) have a similar Warning and Precaution[11] in their USPIs regarding the risk of DKA. FDA issued a Drug Safety Communication on December 4, 2015 (FDA 2022) to alert patients and prescribers of revisions to the prescribing information for SGLT2 inhibitors to include the risk of DKA.

The FDA analyzed data available through Sentinel for calendar years 2013 to 2024 to estimate DKA rates among patients with T1D who initiated SGLT2 inhibitors off label (Taylor et al. 2015). Notwithstanding the FDA Drug Safety Communications, revised labeling of SGLT2 inhibitors, and efforts of the diabetes community to develop risk mitigation strategies (Danne et al. 2019; Goldenberg et al. 2019) (e.g., the STOP protocol, the STICH protocol), the occurrence of DKA among patients with T1D who initiate use of SGLT2 inhibitors off label does not appear to have declined (Figure 6)[12] over that same period of time. A full report of this analysis is available in Section 7.5.

[11] The language in the Inpefa Warnings and Precautions includes the following: “In patients with type 1 diabetes mellitus, Inpefa significantly increases the risk of diabetic ketoacidosis, a life-threatening event, beyond the background rate. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was markedly increased in patients who received sodium glucose transporter 2 (SGLT2) inhibitors compared to patients who received placebo".

[12] Results for 2013 and 2024 were not presented because data were not available for the entire year.

Figure 6. Incidence Rate of DKA by Calendar Year Among Initiators of SGLT-2 Inhibitors With T1D



Source: FDA Review staff.
Error bars indication 95% CIs
Abbreviations: DKA, diabetic ketoacidosis; SGLT-2, sodium-glucose transport protein 2; T1D, type 1 diabetes

The proposed mechanism(s) through which SGLT2 inhibitors cause the increased risk of DKA include 1) decreased exogenous insulin use and increased endogenous glucagon release to compensate for reduced glycemia secondary to increased urinary excretion of glucose and 2) increased glucagon production and secretion due to direct action on pancreatic alpha cells (Bonner et al. 2015; Taylor et al. 2015). Decreased insulinemia and increased glucagonemia each contribute to ketogenesis. Thus, available evidence suggests that SGLT2 inhibitors can cause ketogenesis both through their effect on glucosuria and independent of their effect on glucosuria.

The Applicant has asserted the estimates of DKA risk in the overall TANDEM population are transportable to the revised population of patients with T1D and mild-to-moderate CKD. However, the assertion relies on multiple assumptions, including that CKD is not associated with DKA risk and the interaction between sotagliflozin and DKA risk is the same across all levels of kidney function. To probe the Applicant's assertion, the FDA first evaluated available data from the TANDEM program to determine whether subgroup analyses conducted in the TANDEM population suffice to support a conclusion that the increased risk of DKA in participants with mild-to-moderate CKD was similar to the increased risk of DKA observed in the overall TANDEM population. Next, FDA considered epidemiologic studies to elucidate whether the presence of CKD is a predictor of DKA events (i.e., whether CKD is associated with DKA, either causally or non-causally). Finally, FDA investigated available clinical pharmacology data from the TANDEM program in the context of the available information regarding the mechanisms through which sotagliflozin increases DKA risk in an attempt to assess the effect of sotagliflozin on ketogenesis in patients with T1D and mild-to-moderate CKD.

Assessment of DKA Risk in Patients With T1D and CKD Based on FDA Reanalysis of TANDEM

DKA Event Ascertainment in the TANDEM Program

In the TANDEM program, adverse events potentially indicative of DKA were first identified through prespecified criteria, including clinical symptoms, laboratory results, and insulin use patterns. The investigator-reporting of some clinical data (e.g., certain MedDRA preferred terms) triggered a dedicated DKA case report form to collect additional data. These events were then reviewed by an independent CEC to confirm the diagnosis of DKA, with prespecified diagnostic criteria. DKA was adjudicated by the CEC based on the following diagnostic criteria: elevated blood or urine ketones (2+ on standard urine dipsticks or plasma BHB >3.0 mmol/L), metabolic acidosis (decreased serum HCO_3^-, increased anion gap, or decreased blood pH), and associated hyperglycemia (if observed).

Statistical Analysis of Adjudicated DKA (Overall TANDEM Population)

During review of the original submission of NDA 210934 conducted in 2019, analyses of DKA events were conducted separately in the Pooled Trials 309/310, Trials 309/310/312, and Trial 312. These analyses of Trials 309/310 and 309/310/312 were stratified by trial using the Mantel-Haenszel method to account for differences in the trial design. Active treatment doses (sotagliflozin 200 mg and 400 mg) were analyzed in combination and individually against the placebo in Trials 309/310. Trial 312 did not study sotagliflozin 200 mg.

To address treatment discontinuation, all analyses employed a while-on-treatment approach that censored participants 30 days after treatment discontinuation, at the time of DKA event or at the end of the trial, whichever occurred first. The incident rate difference (IRD) was estimated using the first DKA event and the corresponding number needed to harm (NNH) was estimated as the reciprocal of IRD. Hazard ratio (HR) was estimated using a Cox proportional hazards model, stratified by trial, with actual treatment as the only covariate. HRs were presented for Trials 309/310 only.

The key results from the 2019 analyses are described as follows:

- In Trials 309/310 (Table 9), a numerically higher incidence of DKA was observed in the sotagliflozin treatment arm compared to placebo. Thirty-five of 1049 (3.40 per 100 PY) participants on sotagliflozin and 1 of 526 (0.19 per 100 PY) on placebo experienced DKA. Thus, an additional 3.21 DKA events per 100 PYs of exposure were associated with sotagliflozin (IRD 3.21 [2.02, 4.40]). The estimated NNH to observe an additional DKA event in sotagliflozin treated patients was 31 PYs [23, 49].
- In Trial 312 (Table 10), 21 of 699 (6 per 100 PY) participants on sotagliflozin 400 mg and 4 of 703 (1.11 per 100 PY) on placebo experienced DKA, which led to an IRD (95% CI) of 4.89 [2.10, 7.68] and an estimated NNH of 20 [13, 48].
- In the three trials combined (Trials 309/310/312, data not shown), 56 of 1748 (4.06 per 100 PY) participants on sotagliflozin and 5 of 1229 (0.57 per 100 PY) on placebo experienced DKA. The IRD was 3.78 [2.55, 5.01] and the estimated NNH was 26 [20, 39].

In Trials 309/310 (Table 9), when analyzed by sotagliflozin dose, the incidence of DKA numerically increased in a dose-dependent manner: the incidence rate (IR) of DKA was 2.90 and 3.91 in the sotagliflozin 200 mg and 400 mg arms, respectively. The IRDs of sotagliflozin 200 mg and 400 mg compared with placebo were 2.71 (1.19, 4.23), and 3.72 (1.97, 5.48), respectively. The corresponding estimated NNHs were 37 (24, 84), and 27 (18, 51).

Statistical Analysis of Adjudicated DKA (by eGFR Subgroup)

In the subgroup analysis, we present IRD and NNH as the comparative measure.

A nominal treatment difference not favoring sotagliflozin was observed in each eGFR subgroup in pooled Trials 309/310 (Table 9). No remarkable trends in DKA risk were identified among different eGFR categories based on inspection of the point estimates. However, the 95% CIs for all three subgroups are wide and overlapping, making it difficult to draw definitive conclusions. Similar observations are noted from Trial 312 (Table 10).

Table 9. CEC-Adjudicated DKA by eGFR Subgroup in the T1D Population—Pooled Trials 309/310

	Statistic	Placebo	200 mg	400 mg	All Sotagliflozin
Overall T1D population	n/N	1/526	15/524	20/525	35/1049
	IR (100 PY)	0.19	2.90	3.91	3.40
	HR*	Reference	14.97 (1.8, 113.3)	20.20 (2.71, 150.5)	17.57 (2.41, 128.2)
	IRD (100 PY)**		2.71 (1.19, 4.23)	3.72 (1.97, 5.48)	3.21 (2.02, 4.40)
	NNH		37 (24, 84)	27 (18, 51)	31 (23, 49)
eGFR <60 mL/min/1.73 m^2	n/N	0/24	2/22	1/25	3/47
	IR (100 PY)	0	8.75	4.12	6.37
	IRD (100 PY)**	Reference	8.44 (-3.26, 20.13)	3.94 (-3.79, 11.67)	6.03 (-0.79, 12.86)
	NNH		12 (5, NA)	25 (9, NA)	17 (8, NA)
eGFR 60-89 mL/min/1.73 m^2	n/N	1/245	5/270	7/259	12/529
	IR (100 PY)	0.42	1.87	2.79	2.31
	IRD (100 PY)**	Reference	1.44 (-0.37, 3.25)	2.41 (0.17, 4.65)	1.91 (0.36, 3.45)
	NNH		70 (31, NA)	42 (22, 588)	52 (29, 275)
eGFR ≥90 mL/min/1.73 m^2	n/N	0/257	8/232	12/241	20/473
	IR (100 PY)	0	3.54	5.08	4.33
	IRD (100 PY)**	Reference	3.52 (1.08, 5.96)	5.08 (2.21, 7.97)	4.32 (2.43, 6.22)
	NNH		28 (17, 93)	20 (13, 45)	23 (16, 41)

Source: Reviewer's analysis.

* A Cox proportional hazards model stratified by trial was used for the Trials 309/310 with actual treatment as the only covariate.

** Mantel-Haenszel method to account for design differences; confidence interval of each estimate was calculated using the Greenland and Robins method from the metainc R package.

Abbreviations: HR, hazard ratio; IR, incidence rate; IRD, incidence rate difference; n, number of participants with event; N, number of participants; NA, not available; NNH, number needed to harm

Table 10. CEC-Adjudicated DKA by eGFR Subgroup in the T1D Population—Trial 312

	Statistic	Placebo	400 mg
Overall T1D population	n/N	4/703	21/699
	IR (100 PY)	1.11	6.00
	IRD (100 PY)	Reference	4.89 (2.10, 7.68)
	NNH		20 (13, 48)
eGFR <60 mL/min/1.73 m^2	n/N	0/42	1/32
	IR (100 PY)	0	6.59
	IRD (100 PY)	Reference	6.58 (-6.32, 19.47)
	NNH		15 (5, NA)
60 ≤ eGFR <90 mL/min/1.73 m^2	n/N	1/300	7/312
	IR (100 PY)	0.64	4.44
	IRD (100 PY)	Reference	3.79 (0.28, 7.30)
	NNH		26 (14, 357)
eGFR ≥90 mL/min/1.73 m^2	n/N	3/361	13/355
	IR (100 PY)	1.66	7.34
	IRD (100 PY)	Reference	5.69 (1.28, 10.10)
	NNH		18 (10, 78)

Source: Reviewer's analysis.

* A Cox proportional hazards model stratified by trial was used for the Trials 309/310 with actual treatment as the only covariate.

Abbreviations: HR, hazard ratio; IR, incidence rate; IRD, incidence rate difference; n, number of participants with event; N, number of participants; NA, not available; NNH, number needed to harm

Discussion of Analyses of DKA Events in the TANDEM Program

In participants with baseline eGFR 45 to <60 mL/min/1.73 m^2 or eGFR ≥60 mL/min/1.73 m^2 and UACR ≥30 mg/g, there were only seven incident DKA events observed. An analysis of DKA conducted in this subgroup would therefore not support meaningful conclusions on a T1D with CKD population. Although FDA's subgrouping approach allowed for the use of more data, the FDA analysis of data from the TANDEM program supports only three observations, each of limited value regarding the DKA risk associated with sotagliflozin in patients with T1D and CKD:

- A nominal treatment difference not favoring sotagliflozin was observed in each eGFR subgroup in Pooled Trials 309/310.
- Based on the lower bound of the 95% CIs, the amount of DKA risk ruled out for the ≥60 mL/min/1.73 m^2 to <90 mL/min/1.73 m^2 subgroup is similar to the risk ruled out from the overall TANDEM population.
- The group of participants with an eGFR <60 mL/min/1.73 m^2 had particularly limited data. However, the point estimate and lower bound of 95% CI of DKA risk in this population are concerning, and it is not reassuring that 3 events occurred among 47 participants randomized to sotagliflozin compared to no events among the 42 participants randomized to placebo.

Beyond these three observations, FDA analyses of data from the TANDEM program do not support meaningful conclusions about the risk of DKA associated with sotagliflozin in patients with T1D and CKD compared to the risk of DKA associated with sotagliflozin in patients with T1D without CKD.

Epidemiologic Investigations of the Association Between CKD and DKA

Epidemiologic studies may provide some insight into whether CKD is a risk factor for DKA and also to whether the presence of CKD may correlate with other risk factors for DKA (i.e., would serve as a predictor of DKA events). Evidence of either would raise uncertainties about whether the estimate of the magnitude of increased DKA risk from the overall TANDEM program are generalizable to patients with T1D and CKD. FDA considered three epidemiology studies that may help elucidate the risk of DKA in patients with T1D and CKD: one study was identified in the published literature (Thomas et al. 2020) (the Finnish Diabetic Nephropathy Study), one study was conducted by FDA through Sentinel to support the review of the current NDA submission (the FDA Sentinel Analysis), and one study was conducted by the Applicant using data from the T1D Exchange.

The Finnish Diabetic Nephropathy Study (FinnDiane)

FinnDiane was a registry study that investigated the risk of hospitalization for DKA in 4,758 adults with T1D[13] enrolled between 1994 and 2015 in Finland. At baseline, the mean age was 38.0 years and 547 (11% of 4,758) participants had eGFR <60 mL/min/1.73 m^2. During a median follow-up of 14.4 (IQR, 10.6 to 16.6) years, 969 nonfatal or fatal DKA events were ascertained from discharge records of 461 participants in the Finnish Care Registry for Health Care, corresponding to 1.5 DKA events per 100 PY. Compared with participants with a baseline eGFR of ≥60 mL/min/1.73 m^2, participants with baseline eGFR <60 mL/min/1.73 m^2 had an adjusted 1.71 (95% CI 1.26 to 2.67)-fold risk for hospitalization for DKA events, adjusted for prior history of hospitalization for DKA, insulin pump use, smoking, weekly alcohol consumption, serial A1C, A1C variability over time, high density lipoprotein level, and triglyceride level. Age at baseline was balanced and not included in the model. The authors concluded that CKD is a predictor for DKA events in patients with T1D and noted that "This is a particularly important observation, as many studies of the potential vasculoprotective effects of SGLT2 inhibitors in patients with T1D are now in planning stages, and individual with severely increased albumin excretion rates and/or reduced eGFR are the recruitment targets because of their high rate of renal and cardiovascular complications. It is now clear that this population also has an increased risk of hospitalization for DKA, making the use of SGLT2 inhibitors in this setting problematic." (Thomas et al. 2020).

FDA Sentinel Analysis

FDA analyzed summary data gathered from six Sentinel data partners from 2013 to 2024 to estimate the background rate of DKA across CKD stages in the T1D population. DKA was defined as having an inpatient or emergency department diagnosis with an ICD-9-CM code of 250.1x or an ICD-10-CM code of E1x.1x in any diagnosis position (Bobo et al. 2011).[14] T1D and CKD stage were identified using an adaptation of published and validated algorithms (Klompas et al. 2013; Friberg et al. 2018; Schroeder et

[13] Authors defined T1D as insulin dependence and C-peptide <0.30nmol/L, age at onset of diabetes <40 years, and insulin treatment initiated within 1 year of diagnosis.
[14] This algorithm had a PPV of 88.9% among children and youth.

al. 2018).[15] Table 11 presents the incidence rate of DKA by CKD stage in the T1D population; the data suggest an increasing incidence rate of DKA with advancing CKD stage. In an ongoing investigation, FDA is using propensity-score based approaches to assess whether CKD is an independent risk factor for DKA or whether confounding variables correlated with CKD explain the association between CKD and DKA observed in the Sentinel data. The descriptive data from the Sentinel distributed database suggest that patients with T1D with a diagnosis of advanced CKD have a greater risk of experiencing DKA than patients with T1D without a diagnosis of CKD. A full report on the initial results of the Sentinel data query can be found in Section 7.5.

Table 11. Incidence of DKA by CKD Stage in the T1D Population in the Sentinel Database

CKD Stage	Patients, n	DKA Cases, n	At-Risk Person-Years	Incidence Rate (95% CI) per 100 Person-Years
Stage 1 or 2	612,800	17,689	169,588	10.4 (10.3, 10.6)
Stage 3	40,091	1,496	10,610.4	14.1 (13.4, 14.8)
Stage 4 or 5	37,958	2,446	9,094.4	26.9 (25.9, 28.0)

Source: FDA Review staff.
Stage 1 or 2: eGFR ≥60 mL/min/1.73 m^2; Stage 3: eGFR 30-59 mL/min/1.73 m^2; Stage 4 or 5: eGFR <30 mL/min/1.73 m^2
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; DKA, diabetic ketoacidosis; T1D, type 1 diabetes

Applicant's Post-hoc Analysis of the T1D Exchange Database

In the Applicant's descriptive analyses using data from the T1D Exchange multicenter, electronic medical record database, 1,558 participants with T1D and CKD and 47,620 participants with T1D and without CKD were identified between 2015 and 2023. During a mean 4.6 years (T1D without CKD) and 5.2 years (T1D with CKD) of follow-up, DKA events were identified in 117 of the 1,558 participants with T1D and CKD, as well as in 3,652 of the 47,620 participants with T1D and without CKD, corresponding to an incidence rate of 2.9 and 3.2 events per 100 PY, respectively. The T1D-Exchange analysis and the Sentinel analysis have incongruent results: whereas the Sentinel data suggest that patients with T1D who have a diagnosis of advanced CKD have a greater risk of experiencing DKA than patients with T1D who do not have a diagnosis of advanced CKD, the T1D Exchange data do not. It is notable that the reported overall incidence rates (i.e., irrespective of CKD status) are substantially lower in the T1D Exchange analysis than in the Sentinel analysis, suggesting differences between the two data sources with respect to event ascertainment or study populations or both. It is unclear whether and how these differences may explain the incongruent results. Furthermore, *a priori* defined protocol and statistical analysis plan for T1D Exchange analysis are unavailable and the analysis lacks information on the underlying study population and data completeness, which limit the interpretation. The Applicant also created propensity-score (PS) matched cohorts of 1,201 T1D participants with CKD and 3,603 T1D participants without CKD. Baseline characteristics were generally balanced between-groups. In the PS-matched cohorts, the DKA rate was numerically greater in participants with T1D with CKD (2.6 cases per 100 PY) than in participants without CKD (2.1 cases per 100 PY for T1D participants without CKD).

[15] T1D definition required a plurality (>50%) of diabetes diagnosis codes during the baseline period was specific to T1D, having at least one prescription for a short- or rapid-acting insulin, and no dispensing of noninsulin antidiabetic drug (other than metformin) during the baseline period. CKD stage was categorized using a claims-based algorithm developed in registry data and validated against eGFR.

Discussion of Epidemiological Studies

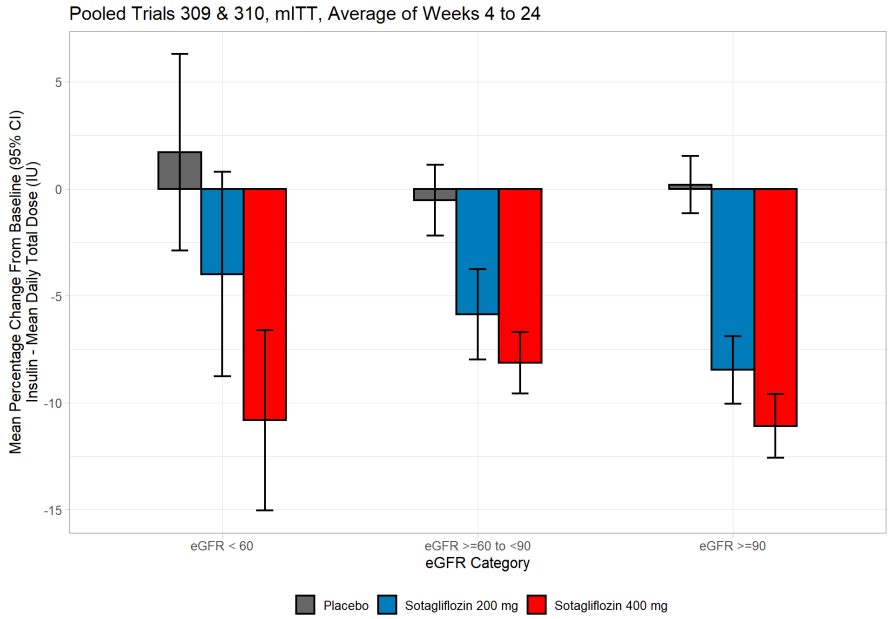
Overall, available sources of information (literature review, investigations of real-world data) increase the uncertainty about the generalizability of estimates of DKA risk from the overall TANDEM population to patients with T1D and CKD: in aggregate, they suggest that CKD may have some association with DKA events. However, the contributing role of CKD in the association between sotagliflozin and DKA remains unclear. Further, it is unknown whether and how CKD modifies the effect of sotagliflozin on the risk of DKA.

Other Information to Further Inform DKA Risk in Patients With T1D and CKD

As discussed in the clinical pharmacology summary (Section 3), eGFR is an important covariate for sotagliflozin exposure. In Trials 309 and 310, participants with an eGFR <60 mL/min/1.73 m^2 had a mean AUC 1.4-fold higher than participants with eGFR ≥90 mL/min/1.73 m^2. Considering only the positive exposure- and dose- response relationship for DKA and the PK data showing increased exposures with reduced eGFR, patients with T1D and CKD could theoretically have greater DKA risk. However, eGFR is also an important covariate for sotagliflozin-induced glucosuria. Studies 309 and 310 demonstrated a clear relationship between eGFR level and UGCR, with lower UGCR in participants with lower eGFR (Figure 11 in Section 7.6). As previously discussed, the glycosuria induced by sotagliflozin can be expected to result in decreased exogenous insulin use and increased glucagon secretion in patients with T1D, both of which may contribute to increased DKA risk. Considering only this relationship, patients with CKD who have lower UGCR may theoretically experience a smaller increase in DKA risk (and also a reduced A1C benefit) compared to patients without CKD. Because the increase in DKA risk attributable to direct actions of sotagliflozin on pancreatic alpha cells would not be affected by kidney function, it remains unclear whether sotagliflozin would have a differential effect on ketogenesis in patients with T1D and mild-to-moderate CKD compared to patients with T1D without CKD.

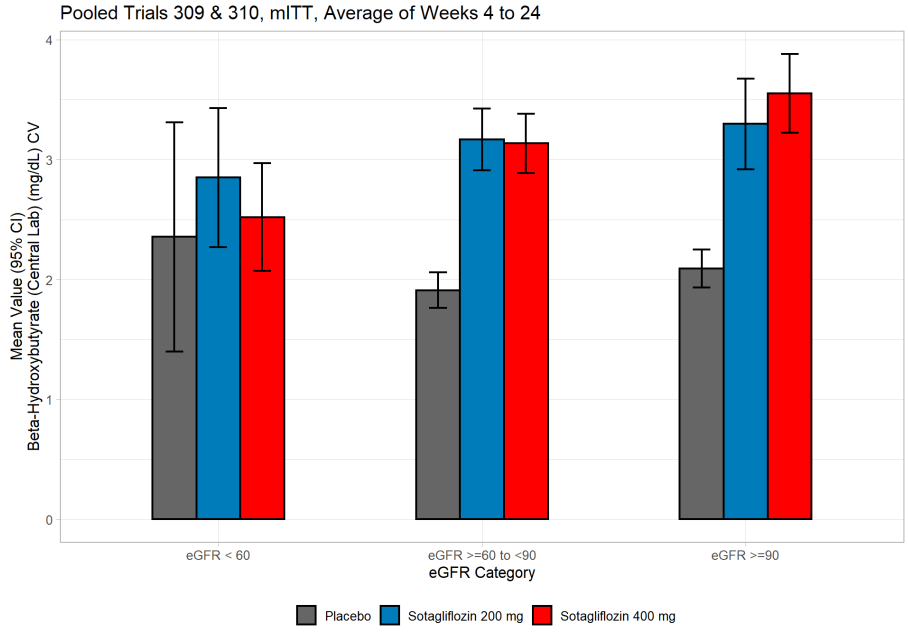
Glucagon data was not routinely measured in TANDEM, which precluded direct exploration of whether sotagliflozin has differential effect on glucagon levels in patients with T1D and CKD compared to patients with T1D without CKD. However, routinely collected insulin dose and BHB measurements in TANDEM participants may offer other insight into sotagliflozin-induced ketogenesis among patients with T1D and mild-to-moderate CKD. The data suggest that lower eGFR is not associated with a smaller percentage reduction in total daily insulin use; however, the data suggest lower eGFR is associated with a smaller absolute increase in routinely-measured BHB levels (Figure 7 and Figure 8). The small sample sizes, especially for the subgroup with eGFR <60 mL/min/1.73 m^2, preclude definitive conclusions regarding whether sotagliflozin has a differential effect on ketogenesis in patients with T1D and mild-to-moderate CKD compared to patients with T1D without CKD. Finally, given that non-physiologic explanations may explain the association between CKD and DKA observed in the epidemiology studies, a conclusion that sotagliflozin does not cause greater ketogenesis in patients with T1D and mild-to-moderate CKD would not preclude the possibility that patients with T1D selected for treatment with sotagliflozin on the basis of CKD status would not experience DKA at a higher rate than the overall TANDEM population.

Figure 7. Total Daily Insulin Dose Reduction, Averaged Over the Core Treatment Period (24 Weeks)—Pooled Trials 309 and 310



Source: FDA Review Staff, NDA210934, SDN0001 (adsl.xpt, adlb.xpt).
Parameter values were measured at baseline and every 4 weeks during the trial. The average on-study value for each participant was used to calculate the descriptive statistics shown.
Error bars represent 95% CI
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat

Figure 8. BHB Levels, Averaged Over the Core Treatment Period (24 weeks)—Pooled Trials 309 and 310



Source: FDA Review Staff, NDA210934, SDN0001 (adsl.xpt, adlb.xpt).
Parameter values were measured at baseline and every 4 weeks during the trial. The average on-study value for each participant was used to calculate the descriptive statistics shown.
Error bars represent 95% CI
Abbreviations: CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat

5 Integrated Benefit and Risk Assessment

The Applicant has proposed a revised indication for sotagliflozin as an adjunct to insulin therapy to improve glycemic control in adults with T1D and CKD. For the purposes of this proposal, the Applicant defines CKD as an eGFR of 45 to <60 mL/min/1.73 m^2 or an eGFR ≥60 mL/min/1.73 m^2 and UACR ≥30 mg/g. Considerations for the overall benefit-risk assessment for the proposed indication include:

- The magnitude (and durability) of improvement in glycemic control, based on post hoc estimates of difference from placebo in CFB of A1C in the TANDEM program:
  - CFB A1C in participants with eGFR > 90 mL/min/1.73 m2.
  - CFB A1C in participants with eGFR > 60 mL/min/1.73 m2 to ≤ 90 mL/min/1.73 m2.
  - CFB A1C in participants with eGFR ≤ 60 mL/min/1.73 m2.
- Additional advantages in the overall TANDEM population and reasonably confirmed within the revised proposed population:
  - Difference from placebo in CFB body weight in each eGFR subgroup.
  - Difference from placebo in CFB SBP in each eGFR subgroup.
  - Reduced risk of hypoglycemia in each eGFR subgroup.
- Potential additional benefits suggested by results of cardiorenal outcome trials conducted in patients with T2D and high cardiovascular risk (SCORED and SOLOIST).
- Significantly increased risk of DKA in the overall TANDEM program and uncertainties regarding the magnitude of the increased risk of DKA in the revised proposed population.

Given that the Applicant has proposed both the 200 mg and 400 mg doses of sotagliflozin for the revised indication, the benefit-risk assessment also addresses whether the evidence and uncertainties for these issues differs for sotagliflozin dosed at 200 mg and at 400 mg. The evidence and uncertainties for each of these considerations is summarized below. For details, refer to the efficacy and/or safety section of the Briefing Document for the analyses pertinent to each issue.

Improvement in Glycemic Control

During the review of the original submission of NDA 210934, FDA concluded that the TANDEM program constitutes substantial evidence of effectiveness for sotagliflozin as an adjunct to insulin therapy for the improvement of glycemic control in patients with T1D based on the differences compared to placebo in CFB A1C in Trials 309, 310, and 312. The magnitude of the effect of sotagliflozin on A1C in the overall TANDEM population was approximately -0.35% to -0.45% at Week 24, and -0.2% to -0.3% at Week 52.

Given the mechanism of action of sotagliflozin and the known inverse relationship between eGFR and the magnitude of glucosuria, uncertainty exists about whether sotagliflozin would have the same magnitude of effect on A1C in patients with reduced eGFR as it demonstrated in the overall TANDEM population. The analyses conducted by the FDA provide reasonable reassurance that sotagliflozin is effective with respect to improved glycemic control in patients with T1D and eGFR ≥60 mL/min/1.73 m^2, with a similar magnitude of effect to that in patients with T1D without CKD. The analyses are considerably less reassuring with respect to patients with T1D and an eGFR <60 mL/min/1.73 m^2: the estimates of efficacy were numerically small and had confidence intervals too broad for any statistical conclusions.

The results for difference in CFB A1C at Week 52 raise uncertainties regarding the durability of the observed effect. The Applicant proposes that the glycemic data collected in the cardiorenal outcome studies (SCORED and SOLOIST) address the uncertainty regarding durability. However, it is not clear that the persistent pharmacodynamic effect on A1C in patients with T2D fully addresses concerns about durability, given the differences between patients with T1D and those with T2D (e.g., all patients with T1D continuously titrate their daily insulin doses in response to ongoing and frequent blood glucose monitoring).

The intermediate-term effect of improvements in glycemic control on renal function in patients with T1D and CKD may be best informed by the data from the PERL study. As discussed in Section 3.3, data from PERL suggest that the effect of a 0.3% reduction in A1C maintained over 10 years might translate to a preservation of 1.6 mL/min/1.73 m^2 of eGFR in patients with mild-to-moderate CKD, though considerable uncertainty exists around that estimate. Given the absence of long-term follow-up data, PERL does not exclude the possibility that relatively small improvements in A1C could yield more clinically significant benefits over time. Observational data from the Joslin Proteinuria Cohort suggests a modest but durable improvement in A1C might confer greater clinical benefits to patients with T1D and macroalbuminuria and poor baseline glycemic control.

Consideration of Additional Advantages Related to Body Weight, Blood Pressure, and Hypoglycemia

Body Weight

During the review of the original submission of NDA 210934, the FDA concluded that small differences numerically favoring the sotagliflozin treatment arm were observed in the TANDEM program for the endpoint of CFB in body weight. Reanalysis of the body weight endpoint yielded similar small differences between participants randomized to sotagliflozin versus placebo among the various subgroups of populations with reduced eGFR. Although it is not unreasonable to assert that the small difference in CFB in body weight should be considered an advantage of the sotagliflozin intervention, the magnitude of the difference does not suggest a clinical benefit that would contribute significantly to the overall benefit-risk assessment.

Blood Pressure

Similarly, during the review of the original submission of NDA 210934, FDA concluded that small differences numerically favoring the sotagliflozin treatment arm were observed in the TANDEM program for the endpoint of CFB in SBP. Reanalysis of the SBP endpoint by eGFR subgroups yielded similar small differences between participants randomized to sotagliflozin versus placebo among the various subgroups of populations with reduced eGFR. The small differences in SBP could be considered an advantage of the sotagliflozin intervention, but the magnitude of the difference observed in participants does not suggest a clinical benefit that would contribute significantly to the overall benefit-risk assessment, particularly given that not all patients require additional BP lowering.

Hypoglycemia

Reanalyses of the hypoglycemia data from the TANDEM program showed a consistent pattern across the various eGFR subgroups and the overall TANDEM population: although the data did not show a treatment effect of sotagliflozin on Level 3 hypoglycemia events, the data indicated that TANDEM participants (with and without CKD) randomized to sotagliflozin experienced approximately 20% fewer Level 2 hypoglycemia events relative to participants randomized to placebo. A 20% relative risk

reduction for Level 2 events may merit consideration with respect to an overall benefit-risk assessment for the proposed glycemic control indication.

Proposed Additional Advantages Related to Daily Insulin Doses and Time in Range

The Applicant has described differences observed in the overall TANDEM population and also in their TANDEM-CKD subgroup related to daily insulin doses (total, basal, bolus), and time in range (TIR). The FDA does not consider these differences to constitute an additional benefit per se. For instance, the FDA acknowledges that reduced daily insulin doses could reduce the risk of hypoglycemia events or result in lower body weight. However, those potential benefits are best considered through direct assessment of the clinical endpoint (e.g., level 2 hypoglycemia, body weight). Similarly, the FDA does not believe that TIR has been validated as a tool to measure an additional benefit of improved glycemic control not adequately captured by consideration of the A1C endpoint and the hypoglycemia endpoint.

Proposed Additional Benefits Suggested by SCORED and SOLOIST

The Applicant has proposed that data from large cardiorenal outcomes studies of sotagliflozin conducted in patients with T2D and high cardiovascular risk are relevant to the proposed population of patients with T1D and CKD. The FDA previously reviewed the data from SCORED and SOLOIST in the context of NDA 216203 (sotagliflozin marketed as Inpefa).

Reduced Risk of Hospitalization for Heart Failure

Based on the results of SOLOIST and SCORED, the FDA approved sotagliflozin as Inpefa to reduce the risk of CV death, hospitalization for heart failure, and urgent heart failure visit in adults with:

- Heart failure or
- T2D, CKD, and other cardiovascular risk factors.

Although all the participants in SOLOIST had T2D, FDA determined that it was scientifically justified to extrapolate the benefit of reduced risk of CV death, HHF, and urgent heart failure visit to all patients with HF (i.e., patients with HF with and without DM). The risk difference observed in SCORED participants with eGFR 45 to <60 mL/min/1.73 m^2 corresponds to a NNT of 83 patients per year to avoid one event of HHF, CV death, or UHFV. During the review of NDA 216203 (Inpefa), the Applicant did not propose a broader indication encompassing all patients with DM, CKD, and other CV risk factors. While uncertainties exist, it may be scientifically justified to extrapolate the heart failure benefit to patients with T1D, CKD, and other CV risk factors (i.e., to encompass all patients with DM, CKD, and other CV risk factors). However, an additional uncertainty is whether benefits in patients with T1D, moderate-to-severe CKD, and other CV risk factors would extend to patients with T1D and mild-to-moderate CKD. Finally, the relevance of a benefit on HHF to the proposed glycemic control indication is unclear.

Reduced Risk for Progression of CKD

Based on the Applicant's post-hoc analysis of non-adjudicated renal composite events observed in SCORED, the estimated NNT is 250 patients per year for sotagliflozin to prevent one additional event of 50% decline in eGFR or kidney failure (defined as eGFR <15 mL/min/1.73 m^2, maintenance dialysis or kidney transplant) among patients with T2D, baseline eGFR 45 to ≤60 mL/min/1.73 m^2, and other CV risk factors. The FDA has not concluded that data from SCORED constitute evidence of a demonstrated benefit of sotagliflozin for the reduction of the risk of progression of CKD in patients with T2D, moderate-to-severe CKD, and other CV risk factors. In addition to the significant uncertainties reflected

in that conclusion, further uncertainties exist regarding whether it would be scientifically justified to extrapolate a demonstrated benefit in reducing the risk of progression of CKD in patients with T2D and moderate-to-severe CKD and other CV risk factors to patients with T1D and moderate-to-severe CKD and other CV risk factors. Finally, further uncertainties exist regarding whether such benefits in patients with T1D and moderate-to-severe CKD and other CV risk factors would extend to patients with T1D and mild-to-moderate CKD.

Reduced Risk for MACE

For the entire SCORED population, the estimated NNT to prevent one additional event of myocardial infarction, stroke, or CV death is approximately 90 patients per year with T2D, eGFR 20 to 60 mL/min/1.73 m^2, and other CV risk factors. The FDA has not concluded that data from SCORED constitute evidence of a demonstrated benefit of sotagliflozin for the reduction of the risk of MACE in patients with T2D, moderate-to-severe CKD, and other CV risk factors. In addition to the significant uncertainties reflected in that conclusion, further uncertainties exist regarding whether it would be scientifically justified to extrapolate a demonstrated benefit in reducing the risk of MACE in patients with T2D, moderate-to-severe CKD, and other CV risk factors to patients with T1D, moderate-to-severe CKD and other risk factors. Further uncertainties exist regarding whether such benefits in patients with T1D and moderate-to-severe CKD and other CV risk factors would extend to patients with T1D and mild-to-moderate CKD.

Increased Risk of DKA

During the original review of the TANDEM program for NDA 210934, a significantly increased risk of DKA among patients with T1D randomized to sotagliflozin was identified, despite the DKA risk mitigation strategies employed during the conduct of the TANDEM trials. The NNH (i.e., the number of patients with T1D who needed to be treated with sotagliflozin to result in one additional DKA event) was estimated to be 26 (95% CI, 20, 39) for the overall TANDEM population. Based on Trials 309/310 (which randomized patients to placebo, 200 mg sotagliflozin, or 400 mg sotagliflozin), the NNH for the 200 mg dose was estimated to be 37 (95% CI, 24, 84), and the NNH for the 400 mg dose was estimated to be 27 (95% CI, 18, 51). During the original review (and throughout the subsequent FDRR processes), the FDA concluded that the increased risk of DKA in patients with T1D outweighed the benefits demonstrated in patients with T1D in TANDEM. Various risk mitigation strategies have been proposed, but their effectiveness has not been demonstrated in prospective studies (Garg et al. 2018; Danne et al. 2019; Goldenberg et al. 2019; Teng et al. 2021).

In the resubmission of NDA 210934 supporting a revised glycemic control indication in patients with T1D and CKD, the Applicant asserts that it is reasonable to estimate the increased risk of DKA from exposure to sotagliflozin in patients with T1D and CKD based on the data from the TANDEM program. The assertion has limited support from clinical trial data given the small size of the TANDEM subgroup with CKD (especially with eGFR <60 mL/min/1.73 m^2). The available epidemiologic data increase the uncertainty about the generalizability of estimates of DKA risk from the overall TANDEM population to patients with T1D and CKD: in aggregate, they suggest that CKD may have some association with DKA events. However, the contributing role of CKD in the association between sotagliflozin and DKA remains unclear. Further, it is unknown whether and how CKD modifies the effect of sotagliflozin on the risk of DKA. The available clinical pharmacology data and other mechanistic data do not, in aggregate, support conclusions about the magnitude of increased risk for DKA with use of sotagliflozin in patients with T1D

and mild-to-moderate CKD compared to patients with T1D without CKD. Overall, in the absence of additional clinical data, one cannot exclude the possibility that patients with T1D and mild-to-moderate CKD treated with sotagliflozin could have an increased risk of DKA compared to the risk observed in the overall TANDEM program.

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7 Appendix

7.1 Additional Statistical DKA Analyses

Table 12. CEC-Adjudicated DKA by eGFR Subgroup in the T1D Population—Pooled Trials 309, 310, and 312

Trial	Statistic	Placebo	All Sotagliflozin
Overall T1D population	n/N	5/1229	56/1748
	IR (100 PY)	0.57	4.06
	HR	Reference	7.93 (3.16, 19.9)
	IRD (100 PY)**		3.78 (2.55, 5.01)
	NNH		26(20, 39)
eGFR <60 mL/min/1.73 m^2	n/N	0/66	4/79
	IR (100 PY)	0	6.42
	IRD (100 PY)**	Reference	6.23 (-0.17, 12.64)
	NNH		16 (8, NA)
eGFR 60-89 mL/min/1.73 m^2	n/N	2/545	19/841
	IR (100 PY)	0.51	2.81
	IRD (100 PY)**	Reference	2.52 (0.97, 4.06)
	NNH		40 (25, 103)
eGFR ≥90 mL/min/1.73 m^2	n/N	3/618	33/828
	IR (100 PY)	0.69	5.16
	IRD (100 PY)**	Reference	4.80 (2.82, 6.78)
	NNH		21 (15, 35)

Source: Reviewer's analysis.

** Mantel-Haenszel method to account for design differences; confidence interval of each estimate was calculated using the Greenland and Robins method from the metainc R package.

Abbreviations: n, number of participants with event; N, number of participants; IR, incidence rate; HR, hazard ratio; IRD, incidence rate difference; NNH, number needed to harm; NA, not available

Adjudicated DKA Events in the Applicant's Subgroup

In the NDA resubmission, the Applicant requested sotagliflozin approval in a pooled subgroup of TANDEM trials participants with eGFR 45≤eGFR <60 mL/min/1.73 m^2 or eGFR ≥60 mL/min/1.73 m^2 and UACR ≥30 mg/g. Within this pooled subgroup of TANDEM participants (n=458) there were seven adjudicated DKA events.

Similar to the original NDA submission, the primary analysis was conducted separately for the Pooled Trials 309/310, Trial 312, and combined Trials 309/310/312. Analyses of combined trials were stratified by trial to account for differences in trial design. The secondary analysis by individual treatment dose was conducted in combined Trials 309/310. The subgroup analyses was defined by either eGFR <60 mL/min/1.73 m^2 or eGFR ≥60 mL/min/1.73 m^2 due to the sparsity of DKA events and smaller sample size.

The key results are as follows:

- In pooled Trials 309/310 (Table 13), a higher incidence of DKA was observed in the sotagliflozin treatment arm compared with the placebo treatment arm. The IRD was 2.44 (-1.66, 6.53) additional events per 100 PYs of exposure associated with sotagliflozin. The corresponding estimated NNH was 41 (15, NA).

- In Trial 312, 3 of 114 (5.4 per 100 PY) participants on sotagliflozin 400 mg and 1 of 110 (1.82 per 100 PY) on placebo experienced DKA, for an IRD (95% CI) of 3.58 (-3.49, 10.65). The estimated NNH was 28 (9, NA).
- The combined TANDEM trials (309/310/312, data not shown), 9 of 274 (4.22 per 100PY) participants on sotagliflozin and 2 of 184 (1.60 per 100 PY) on placebo experienced DKA. The IRD was 2.85 (-0.81, 6.51) and the estimated NNH was 35 (15, NA).

A secondary analysis of individual treatment doses was conducted in pooled Trials 309/310 (Table 13). The IRDs of sotagliflozin 200 mg and 400 mg compared with placebo were 3.31 (-2.12, 8.75), and 1.52 (-3.11, 6.15), respectively, which did not support a drug dose-strength dependent increase in DKA risk. The corresponding estimated NNHs were 30 (11, NA), and 41 (15, NA).

Table 13. CEC-Adjudicated DKA in the T1D-CKD Population—Pooled Trials 309 and 310

	309/310 Pooled				312	
Metric	**Placebo**	**200 mg**	**400 mg**	**All Sotagliflozin**	**Placebo**	**400 mg**
n/N	1/74	4/85	2/75	6/160	1/110	3/114
IR (100 PY)	1.43	4.74	2.74	3.81	1.82	5.40
IRD (100 PY)**	Reference	3.31 (-2.12, 8.75)	1.52 (-3.11, 6.15)	2.44 (-1.66, 6.53)	Reference	3.58 (-3.49, 10.65)
NNH		30 (11, NA)	66 (16, NA)	41 (15, NA)		28 (9, NA)

Source: Reviewer's analysis.

** Mantel-Haenszel method to account for design differences; confidence interval of each estimate was calculated using the Greenland and Robins (1985) method from the *metainc* R package.

Abbreviations: n, number of participants with event; N, number of participants; IR, incidence rate; HR, hazard ratio; IRD, incidence rate difference; NA, not applicable; NNH, number needed to harm

Additional Safety Analysis Results Based on the Complete Breakdown of Subgroups

This section presents additional safety analysis results based on the complete breakdown of subgroups (i.e., Subgroups A to E listed below, which incorporated both eGFR and UACR thresholds), as well as the T1D-CKD population defined by the Applicant (Subgroup f).

A. eGFR ≥90 mL/min, with UACR ≥30 mg/g or UACR <30 mg/g.
B. 60≤eGFR <90 mL/min, with UACR ≥30 mg/g or UACR <30 mg/g.
C. eGFR <60 mL/min.
D. eGFR <60 mL/min, or eGFR ≥60 mL/min with UACR ≥30 mg/g.[16]
E. eGFR ≥90 mL/min, with either UACR ≥30 mg/g or UACR <30 mg/g.

[16] The T1D-CKD subgroup as defined by the Applicant (i.e., eGFR: 45 to <60 mL/min, or eGFR ≥60 mL/min with UACR ≥30 mg/g) slightly differed from Subgroup f. Despite the study eligibility criterion which required enrolled participants with a screening eGFR ≥45 mL/min, all three studies accidentally included participants with a screening eGFR <45 mL/min (three participants from Pooled Trials 309/310, and four participants from Trial 312). For easy presentation and interpretation, our analyses for the T1D-CKD subgroup also included these seven accidentally enrolled participants with screening eGFR <45 mL/min.

Table 14. CEC-Adjudicated DKA by Sotagliflozin Dose and eGFR Subgroup in the T1D Population—Pooled Trials 309 and 310

eGFR	UACR	Statistic	Placebo	200 mg	400 mg	All Sotagliflozin
eGFR ≥90 mL/min	All	n/N	0/257	8/232	12/241	20/473
		IR (100 PY)	0	3.54	5.08	4.33
		IRD (100 PY)**	Reference	3.52 (1.08, 5.96)	5.08 (2.21, 7.97)	4.32 (2.43, 6.22)
	UACR ≥30	n/N	0/23	1/25	1/27	2/52
		IR (100 PY)	0	(4.10)	(3.74)	(3.92)
		IRD (100 PY)**	Reference	3.4 (-3.03, 10.27)	3.09 (-2.97, 9.15)	3.05 (-1.18, 7.27)
	UACR <30	n/N	0/231	7/199	11/208	18/407
		IR (100 PY)	0	3.61	5.42	4.53
		IRD(100 PY)**	Reference	3.52 (0.91, 6.13)	5.41 (2.21, 8.61)	4.49 (2.41, 6.57)
eGFR 60-89 mL/min	All	n/N	1/245	5/270	7/259	12/529
		IR (100 PY)	0.42	1.87	2.79	2.31
		IRD (100 PY)**	Reference	1.44 (-0.37, 3.25)	2.41 (0.17, 4.65)	1.91 (0.36, 3.45)
	UACR ≥30	n/N	1/29	1/38	0/24	1/62
		IR (100 PY)	3.69	2.70	0	1.66
		IRD (100 PY)**	Reference	-0.93 (-11.25, 9.39)	-3.23 (-9.57, 3.10)	-2.04 (-10.24, 6.17)
	UACR <30	n/N	0/207	4/229	7/227	11/456
		IR (100 PY)	0	1.76	3.18	2.46
		IRD (100 PY)**	Reference	1.75 (0.03, 3.47)	3.20 (0.83, 5.57)	2.48 (1.01, 3.94)
eGFR <60 mL/min (original submission)	All	n/N	0/24	2/22	1/25	3/47
		IR (100 PY)	0	8.75	4.12	6.37
		IRD (100 PY)**	Reference	8.44 (-3.26, 20.13)	3.94 (-3.79, 11.67)	6.03 (-0.79, 12.86)

Source: Reviewer's analysis.

** Mantel-Haenszel method to account for design differences; confidence interval of each estimate was calculated using the Greenland and Robins method in the *metainc* R package

Abbreviations: n, number of participants with event; N, number of participants; IR, incidence rate; HR, hazard ratio; IRD, incidence rate difference; NNH, number needed to harm

Table 15. CEC-Adjudicated DKA by eGFR Subgroup in the T1D Population—Pooled Trials 309, 310, and 312

eGFR	UACR	Statistic	Placebo	All Sotagliflozin
eGFR ≥90 mL/min	All	n/N	3/618	33/828
		IR (100 PY)	0.69	5.16
		IRD (100 PY)**	Reference	4.80 (2.82, 6.78)
	UACR ≥30	n/N	0/59	2/92
		IR (100 PY)	0	2.83
		IRD (100 PY)**	Reference	1.86 (-0.72, 4.45)
	UACR <30	n/N	3/541	31/707
		IR (100 PY)	0.78	5.66
		IRD (100 PY)**	Reference	5.25 (3.01, 7.49)

eGFR	UACR	Statistic	Placebo	All Sotagliflozin
eGFR 60-89 mL/min	All	n/N	2/545	19/841
		IR (100 PY)	0.51	2.81
		IRD (100 PY)**	Reference	2.52 (0.97, 4.06)
	UACR ≥30	n/N	2/64	3/105
		IR (100 PY)	4.43	3.68
		IRD (100 PY)**	Reference	-0.03 (-7.97, 7.92)
	UACR <30	n/N	0/461	15/714
		IR (100 PY)	0	(2.59)
		IRD (100 PY)**	Reference	2.66 (1.28, 4.04)
eGFR <60 mL/min (original submission)	All	n/N	0/66	4/79
		IR (100 PY)	0	6.42
		IRD (100 PY)**	Reference	6.23 (-0.17, 12.64)

Source: Reviewer's analysis.

Abbreviations: CEC, Clinical Events Committee; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IR, incidence rate; IRD, incidence rate difference; n, number of participants with event; N, number of participants; NNH, number needed to harm; PY, person-years; T1D, type 1 diabetes mellitus; UACR, urine albumin-creatinine ratio

7.2 Additional Safety Analyses Based on eGFR Subgroups

Table 16. Adverse Events of Special Interest in Pooled Trials 309 and 310 (52 Weeks)

		Placebo	Sotagliflozin 200 mg		Sotagliflozin 400 mg	
		n/N (%)	n/N (%)	Risk Difference (95% CI)	n/N (%)	Risk Difference (95% CI)
Diabetic ketoacidosis**	eGFR <60	1/24 (4.2)	3/22 (13.6)	9.5 (-9.0, 30.2)	3/25 (12.0)	7.8 (-10.2, 26.8)
	eGFR ≥60 and <90	6/245 (2.4)	25/270 (9.3)	6.8 (2.9, 11.2)	29/259 (11.2)	8.7 (4.6, 13.4)
	eGFR ≥90	7/257 (2.7)	23/232 (9.9)	7.2 (3.1, 12.0)	41/241 (17.0)	14.3 (9.4, 19.8)
Genital mycotic infections	eGFR <60	0/24	4/22 (18.2)	18.2 (2.8, 38.8)	4/25 (16.0)	16.0 (0.9, 34.9)
	eGFR ≥60 and <90	9/245 (3.7)	26/270 (9.6)	6.0 (1.7, 10.5)	31/259 (12.0)	8.3 (3.8, 13.2)
	eGFR ≥90	6/257 (2.3)	22/232 (9.5)	7.1 (3.2, 11.9)	33/241 (13.7)	11.4 (6.9, 16.5)
Renal events	eGFR <60	2/24 (8.3)	1/22 (4.5)	-3.8 (-22.4, 15.0)	3/25 (12.0)	3.7 (-16.1, 23.4)
	eGFR ≥60 and <90	3/245 (1.2)	8/270 (3.0)	1.7 (-0.9, 4.7)	1/259 (0.4)	-0.8 (-3.2, 1.0)
	eGFR ≥90	2/257 (0.8)	5/232 (2.2)	1.4 (-0.9, 4.3)	3/241 (1.2)	0.5 (-1.7, 2.9)
Urinary tract infections	eGFR <60	1/24 (4.2)	7/22 (31.8)	27.7 (6.3, 49.7)	1/25 (4.0)	-0.2 (-17.1, 16.2)
	eGFR ≥60 and <90	24/245 (9.8)	20/270 (7.4)	-2.4 (-7.5, 2.5)	13/259 (5.0)	-4.8 (-9.7, -0.2)
	eGFR ≥90	9/257 (3.5)	11/232 (4.7)	1.2 (-2.4, 5.2)	16/241 (6.6)	3.1 (-0.7, 7.4)
Volume depletion	eGFR <60	0/24	2/22 (9.1)	9.1 (-5.7, 28.1)	1/25 (4.0)	4.0 (-10.3, 19.8)
	eGFR ≥60 and <90	5/245 (2.0)	10/270 (3.7)	1.7 (-1.4, 4.9)	6/259 (2.3)	0.3 (-2.7, 3.2)
	eGFR ≥90	2/257 (0.8)	7/232 (3.0)	2.2 (-0.2, 5.4)	8/241 (3.3)	2.5 (0.1, 5.7)

Source: FDA Review team

** Note that the DKA query is distinct from adjudicated DKA events, as it only includes investigator-reported terms associated with DKA (PTs: acetonemia, acidosis, blood ketone body increased, ketoacidosis, ketosis, and diabetic ketoacidosis)

Genital mycotic infections PT list: balanitis candida, balanoposthitis, candida infection, genital burning sensation, genital candidiasis, genital discomfort, genital infection, genital infection fungal, pruritis genital, vaginal discharge, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal discomfort, vulvovaginal dryness, vulvovaginal mycotic infection, vulvovaginal pruritis, vulvovaginitis

Renal events PT list: acute kidney injury, blood creatinine increased, blood urea increased, blood urea nitrogen/creatinine ratio increased, glomerular filtration rate decreased, renal impairment, urine output increased

Urinary tract infections PT list: bacterial prostatitis, cystitis, cystitis glandularis, dysuria, genitourinary tract infection, prostatitis, pyuria, urethritis, urinary tract infection, urinary tract infection fungal, white blood cells urine positive, bacterial prostatitis

Volume depletion PT list: included MedDRA PTs: blood urea nitrogen/creatinine ratio increased, dehydration, heart rate increased, hypotension, hypovolaemia, orthostatic hypotension, presyncope, syncope, thirst

For a participant experiencing multiple events within an AESI category, they are counted as one participant.

Abbreviations: AESI, adverse event of special interest; CI, confidence interval; CEC, Clinical Events Committee; eGFR, estimated glomerular filtration rate; PT Medical Dictionary for Regulatory Activities preferred term

7.3 Additional Demographic Tables

This section presents demographic tables for for the Pooled Trial 309/310 and Trial 312 populations by treatment arm and eGFR category.

Table 17. Baseline Demographics— Pooled Trials 309/310, mITT Population

	309/310 Pool								
	eGFR <60 mL/min/1.73m^2			60 ≤eGFR <90 mL/min/1.73m^2			eGFR ≥90 mL/min/1.73m^2		
	Placebo	200 mg	400 mg	Placebo	200 mg	400 mg	Placebo	200 mg	400 mg
Variable	**N=24**	**N=22**	**N=25**	**N=245**	**N=270**	**N=259**	**N=257**	**N=232**	**N=241**
Age (years)	56.1 (12.1)	58.8 (11.4)	57.1 (9.7)	46.8 (12.1)	48.9 (11.6)	48.2 (12.4)	37.2 (12.2)	37.9 (13.0)	38.3 (12.1)
Male sex	8 (33)	9 (41)	9 (36)	109 (44)	123 (46)	115 (44)	154 (60)	133 (57)	129 (54)
Race									
White	23 (96)	21 (95)	24 (96)	231 (94)	257 (95)	246 (95)	240 (93)	215 (93)	226 (94)
Black or African American	0	0	0	2 (1)	2 (1)	3 (1)	8 (3)	9 (4)	5 (2)
American Indian or Alaska Native	0	0	0	0	0	0	0	1 (0)	0
Asian	0	0	0	1 (0)	3 (1)	3 (1)	3 (1)	4 (2)	2 (1)
Native Hawaiian or other Pacific Islander	0	0	0	2 (1)	1 (0)	0	0	1 (0)	0
Other	1 (4)	1 (5)	1 (4)	9 (4)	7 (3)	7 (3)	6 (2)	2 (1)	8 (3)
Missing	0	0	0	0	0	0	0	0	0
BMI ≥30 kg/m2	12 (50)	8 (36)	13 (52)	104 (42)	113 (42)	94 (36)	70 (27)	84 (36)	85 (35)
North America (US + Canada)	15 (62)	14 (64)	16 (64)	141 (58)	146 (54)	143 (55)	112 (44)	103 (44)	103 (43)
Insulin delivery method - CSII	7 (29)	11 (50)	12 (48)	118 (48)	117 (43)	122 (47)	101 (39)	96 (41)	90 (37)
Duration of T1D (years)	30.6 (12.4)	34.8 (10.8)	29.2 (14.2)	23.7 (12.2)	24.1 (12.6)	23.7 (12.4)	17.9 (10.7)	17.5 (10.8)	18.3 (11.2)
A1C (%)	7.7 (0.9)	7.8 (0.6)	7.9 (0.9)	7.5 (0.7)	7.6 (0.8)	7.6 (0.7)	7.8 (0.9)	7.7 (0.8)	7.7 (0.8)
Total daily insulin (IU)	53.3 (36.0)	53.7 (29.0)	56.8 (20.9)	65.9 (39.2)	60.2 (35.5)	58.7 (28.2)	63.9 (33.9)	66.5 (38.1)	67.8 (38.7)
Basal daily insulin (IU)	26.7 (14.2)	29.8 (17.1)	29.0 (12.0)	33.4 (20.0)	30.8 (20.6)	30.6 (15.8)	32.1 (15.1)	33.6 (20.6)	32.6 (18.4)
Bolus daily insulin (IU)	26.6 (24.5)	23.9 (14.8)	27.7 (13.0)	32.6 (23.2)	29.4 (19.3)	28.0 (17.1)	31.8 (23.4)	32.8 (22.7)	35.2 (24.7)
Systolic blood pressure (mmHg)	128.5 (20.5)	128.4 (12.7)	126.0 (21.9)	122.5 (14.2)	122.0 (15.2)	121.8 (14.2)	120.9 (14.1)	120.3 (14.8)	120.3 (13.4)
Diastolic blood pressure (mmHg)	74.8 (8.5)	75.0 (8.6)	74.1 (9.8)	76.5 (8.5)	76.2 (9.2)	74.9 (8.6)	76.4 (8.2)	77.9 (10.0)	76.9 (8.8)
Fasting plasma glucose (mg/dL)	183.5 (89.4)	169.5 (90.6)	148.4 (59.5)	158.0 (65.3)	160.6 (72.5)	156.9 (71.0)	153.6 (61.6)	156.9 (69.0)	157.7 (64.9)
eGFR (mL/min/1.73m2)	52.9 (4.3)	52.6 (4.2)	54.5 (4.5)	77.9 (8.2)	77.3 (8.2)	77.9 (7.6)	105.3 (11.6)	106.7 (13.7)	104.8 (12.7)
UACR (mg/g)	305.5 (1069.7)	104.0 (177.7)	183.4 (339.9)	33.1 (133.9)	35.5 (175.3)	28.0 (156.1)	19.5 (80.1)	32.7 (134.1)	34.3 (184.9)

Source: Statistical Reviewer's analysis; adsl.xpt, adlb.xpt.

Abbreviations: A1C, hemoglobin A1C; ACR, urine albumin-to-creatinine ratio; BMI, body mass index; CSII, continuous subcutaneous insulin infusion; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; IQR, interquartile range; MDI, multiple daily injection; mITT, modified intent-to-treat population; SD, standard deviation; T1D, type 1 diabetes mellitus

Table 18. Baseline Demographics— Trial 312, mITT Population

	eGFR <60 mL/min		60≤eGFR <90 mL/min		eGFR ≥90 mL/min	
	Placebo	400 mg	Placebo	400 mg	Placebo	400 mg
Variable	**N=42**	**N=32**	**N=300**	**N=312**	**N=361**	**N=355**
Age (years)	56.5 (11.5)	58.2 (12.6)	46.7 (12.5)	49.1 (12.4)	37.2 (13.2)	36.8 (12.5)
Male sex	20 (48)	10 (31)	120 (40)	143 (46)	199 (55)	205 (58)
Race						
White	36 (86)	27 (84)	273 (91)	294 (94)	312 (86)	298 (84)
Black or African American	3 (7)	1 (3)	5 (2)	2 (1)	14 (4)	21 (6)
American Indian or Alaska Native	0	0	2 (1)	0	3 (1)	1 (0)
Asian	1 (2)	0	1 (0)	2 (1)	3 (1)	5 (1)
Native Hawaiian or other Pacific Islander	0	0	0	1 (0)	0	0
Other	1 (2)	3 (9)	14 (5)	9 (3)	22 (6)	19 (5)
BMI ≥30 kg/m2	11 (26)	15 (47)	109 (36)	102 (33)	98 (27)	119 (34)
North America (US + Canada)	23 (55)	17 (53)	146 (49)	134 (43)	133 (37)	126 (35)
Insulin delivery method - CSII	20 (48)	12 (38)	127 (42)	120 (38)	133 (37)	143 (40)
Duration of T1D (years)	26.2 (14.3)	25.0 (14.2)	21.8 (12.7)	23.4 (13.5)	17.0 (10.5)	17.4 (10.3)
A1C (%)	8.3 (0.9)	8.5 (1.0)	8.1 (0.9)	8.1 (0.9)	8.3 (0.9)	8.3 (1.0)
Total daily insulin (IU)	52.1 (27.5)	51.0 (20.3)	57.7 (31.2)	54.1 (27.3)	59.6 (27.4)	59.9 (28.2)
Basal daily insulin (IU)	26.7 (14.6)	28.3 (16.4)	28.6 (14.9)	27.9 (15.2)	30.8 (16.1)	31.1 (17.1)
Bolus daily insulin (IU)	25.3 (15.6)	22.7 (12.2)	29.1 (21.4)	26.2 (17.2)	28.8 (17.2)	28.8 (17.0)
Systolic blood pressure (mmHg)	128.2 (14.2)	130.6 (14.8)	122.3 (15.5)	123.0 (15.5)	120.6 (14.2)	120.2 (14.8)
Diastolic blood pressure (mmHg)	76.0 (10.0)	77.9 (9.0)	76.4 (9.4)	75.9 (9.3)	77.1 (8.6)	76.7 (8.3)
Fasting plasma glucose (mg/dL)	156.6 (83.1)	164.4 (88.3)	166.5 (67.5)	167.6 (73.2)	161.7 (68.7)	162.9 (68.6)
eGFR (mL/min/1.73m2)	53.8 (5.1)	54.1 (3.8)	78.6 (7.6)	78.3 (7.8)	108.5 (17.0)	106.5 (14.4)
UACR (mg/g)	330.2 (900.4)	285.7 (965.7)	32.1 (141.9)	45.1 (205.4)	30.3 (130.0)	43.9 (206.7)

Source: Statistical Reviewer's analysis; adsl.xpt, adlb.xpt.

Abbreviations: A1C, hemoglobin A1C; ACR, urine albumin-to-creatinine ratio; BMI, body mass index; CSII, continuous subcutaneous insulin infusion; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; IQR, interquartile range; MDI, multiple daily injection; mITT, modified intent-to-treat population; SD, standard deviation; T1D, type 1 diabetes mellitus

7.4 Additional Efficacy Analyses

Table 19 displays the results from additional efficacy analysis results on A1C (%) CFB based on the complete breakdown of subgroups (i.e., Subgroups a to e listed below, which incorporated both eGFR and UACR thresholds), as well as the T1D-CKD population defined by the Applicant (Subgroup f).

a. eGFR ≥90 mL/min, with UACR ≥30 mg/g
b. eGFR ≥90 mL/min, with UACR <30 mg/g
c. 60≤eGFR <90 mL/min, with UACR ≥30 mg/g
d. 60≤eGFR <90 mL/min, with UACR <30 mg/g
e. eGFR <60 mL/min
f. eGFR <60 mL/min, or eGFR ≥60 mL/min with UACR ≥30 mg/g[17]

Table 19. Change From Baseline in A1C (%) at Week 24—Pooled Trials 309/310 (Complete Version)

Subgroup	Population	Sota 200 mg	Sota 400 mg	Placebo
Overall population	Sample size	524	525	526
	Baseline, mean (SD)	7.68 (0.77)	7.64 (0.78)	7.66 (0.81)
	Missing primary endpoint, n (%)	40 (7.6%)	42 (8.0%)	41 (7.8%)
	Change from baseline, LSMean[1] (SE)	-0.38 (0.03)	-0.41 (0.03)	-0.04 (0.03)
	Difference from placebo, LSMean[1] (CI)	**-0.34 (-0.41, -0.27)**	**-0.37 (-0.44, -0.30)**	
T1D-CKD population	Sample size	85	76	76
	Baseline, mean (SD)	7.70 (0.83)	7.91 (0.80)	7.80 (0.88)
	Missing primary endpoint, n (%)	5 (5.9%)	4 (5.3%)	8 (10.5%)
	Change from baseline, LSMean[1] (SE)	-0.40 (0.07)	-0.40 (0.08)	-0.08 (0.08)
	Difference from placebo, LSMean[1] (CI)	**-0.32 (-0.53, -0.12)**	**-0.32 (-0.53, -0.11)**	
eGFR <60	Sample size	22	25	24
	Baseline, mean (SD)	7.82 (0.64)	7.85 (0.88)	7.74 (0.89)
	Missing primary endpoint, n (%)	0	1 (4.0%)	2 (8.3%)
	Change from baseline, LSMean[1] (SE)	-0.58 (0.13)	-0.53 (0.12)	-0.31 (0.13)
	Difference from placebo, LSMean[1] (CI)	**-0.27 (-0.64, 0.11)**	**-0.21 (-0.57, 0.14)**	
60≤eGFR <90 and UACR ≥30	Sample size	38	24	29
	Baseline, mean (SD)	7.55 (0.94)	7.95 (0.69)	7.82 (0.93)
	Missing primary endpoint, n (%)	2 (5.3%)	1 (4.2%)	4 (13.8%)
	Change from baseline, LSMean[1] (SE)	-0.37 (0.11)	-0.49 (0.14)	0.13 (0.13)
	Difference from placebo, LSMean[1] (CI)	**-0.50 (-0.83, -0.17)**	**-0.62 (-0.98, -0.25)**	

[17] The T1D-CKD subgroup as defined by the Applicant (i.e., eGFR: 45 to < 60 mL/min/1.73m^2, or eGFR ≥60 mL/min/1.73m^2 with UACR ≥30 mg/g) slightly differed from Subgroup f. We note that 7 participants (i.e., 3 participants from the pooled studies 309/310 and 4 participants from Study 312) had baseline eGFR < 45. FDA analyses for the T1D-CKD subgroup included these 7 participants.

Subgroup	Population	Sota 200 mg	Sota 400 mg	Placebo
60≤eGFR <90 and UACR <30	Sample size	229	227	207
	Baseline, mean (SD)	7.64 (0.75)	7.55 (0.72)	7.50 (0.64)
	Missing primary endpoint, n (%)	16 (7.0%)	21 (9.3%)	18 (8.7%)
	Change from baseline, LSMean[1] (SE)	-0.41 (0.04)	-0.46 (0.04)	-0.03 (0.04)
	Difference from placebo, LSMean[1] (CI)	**-0.38 (-0.49, -0.28)**	**-0.44 (-0.54, -0.33)**	
eGFR ≥90 and UACR ≥30	Sample size	25	27	23
	Baseline, mean (SD)	7.80 (0.80)	7.94 (0.83)	7.82 (0.82)
	Missing primary endpoint, n (%)	3 (12.0%)	2 (7.4%)	2 (8.7%)
	Change from baseline, LSMean[1] (SE)	-0.27 (0.14)	-0.18 (0.13)	-0.13 (0.15)
	Difference from placebo, LSMean[1] (CI)	**-0.14 (-0.54, 0.26)**	**-0.04 (-0.44, 0.35)**	
eGFR ≥90 and UACR <30	Sample size	199	208	231
	Baseline, mean (SD)	7.69 (0.78)	7.61 (0.80)	7.76 (0.87)
	Missing primary endpoint, n (%)	17(8.5%)	16 (7.7%)	14 (6.1%)
	Change from baseline, LSMean[1] (SE)	-0.35 (0.04)	-0.34 (0.04)	-0.04 (0.04)
	Difference from placebo, LSMean[1] (CI)	**-0.31 (-0.42, -0.19)**	**-0.30 (-0.41, -0.18)**	

Source: Statistical Reviewer's analysis.

Abbreviations: A1C, hemoglobin A1C; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LS, least squares; SE, standard error; Sota, sotagliflozin; T1D, type 1 diabetes mellitus

Table 20. Change From Baseline in A1C (%) at Week 52—Pooled Trials 309/310 (Complete Version)

Subgroup	Population	Sota 200 mg	Sota 400 mg	Placebo
Overall population	Sample size	524	525	526
	Baseline, mean (SD)	7.68 (0.77)	7.64 (0.78)	7.66 (0.81)
	Missing primary endpoint, n (%)	64 (12.2)	71 (13.5)	78 (14.8)
	Change from baseline, LSMean[1] (SE)	-0.21 (0.03)	-0.29 (0.03)	0.02 (0.03)
	Difference from placebo, LSMean[1] (CI)	**-0.22 (-0.31, -0.13)**	**-0.31 (-0.39, -0.22)**	
T1D-CKD population	Sample size	85	76	76
	Baseline, mean (SD)	7.70 (0.83)	7.91 (0.80)	7.80 (0.88)
	Missing primary endpoint, n (%)	8 (9.4)	9 (11.8)	13 (17.1)
	Change from baseline, LSMean[1] (SE)	-0.18 (0.08)	-0.19 (0.09)	-0.11 (0.08)
	Difference from placebo, LSMean[1] (CI)	**-0.07 (-0.29, 0.16)**	**-0.08 (-0.32, 0.15)**	
eGFR <60	Sample size	22	25	24
	Baseline, mean (SD)	7.82 (0.64)	7.85 (0.88)	7.74 (0.89)
	Missing primary endpoint, n (%)	0	3 (12.0)	5 (20.8)
	Change from baseline, LSMean[1] (SE)	-0.47 (0.13)	-0.20 (0.13)	-0.29 (0.14)
	Difference from placebo, LSMean[1] (CI)	**-0.17 (-0.55, 0.21)**	**0.09 (-0.28, 0.46)**	

Subgroup	Population	Sota 200 mg	Sota 400 mg	Placebo
60≤eGFR <90 and UACR ≥30	Sample size	38	24	29
	Baseline, mean (SD)	7.55 (0.94)	7.95 (0.69)	7.82 (0.93)
	Missing primary endpoint, n (%)	5 (13.2)	4 (16.7)	4 (13.8)
	Change from baseline, LSMean[1] (SE)	-0.04 (0.13)	-0.15 (0.17)	-0.01 (0.15)
	Difference from placebo, LSMean[1] (CI)	**-0.03 (-0.42, 0.36)**	**-0.14 (-0.58, 0.29)**	
60≤eGFR <90 and UACR <30	Sample size	229	227	207
	Baseline, mean (SD)	7.64 (0.75)	7.55 (0.72)	7.50 (0.64)
	Missing primary endpoint, n (%)	24 (10.4)	34 (15.0)	33 (15.9)
	Change from baseline, LSMean[1] (SE)	-0.30 (0.04)	-0.34 (0.04)	0.03 (0.05)
	Difference from placebo, LSMean[1] (CI)	**-0.33 (-0.45, -0.20)**	**-0.37 (-0.50, -0.25)**	
eGFR ≥90, and UACR ≥30	Sample size	25	27	23
	Baseline, mean (SD)	7.80 (0.80)	7.94 (0.83)	7.82 (0.82)
	Missing primary endpoint, n (%)	3 (12.0)	2 (7.4)	4 (17.4)
	Change from baseline, LSMean[1] (SE)	-0.11 (0.15)	-0.24 (0.14)	-0.06 (0.16)
	Difference from placebo, LSMean[1] (CI)	**-0.05 (-0.49, 0.40)**	**-0.18 (-0.61, 0.25)**	
eGFR ≥90, and UACR <30	Sample size	199	208	231
	Baseline, mean (SD)	7.69 (0.78)	7.61 (0.80)	7.76 (0.87)
	Missing primary endpoint, n (%)	29 (14.6)	27 (13.0)	31 (13.4)
	Change from baseline, LSMean[1] (SE)	-0.11 (0.06)	-0.24 (0.06)	0.07 (0.05)
	Difference from placebo, LSMean[1] (CI)	**-0.18 (-0.33, -0.03)**	**-0.31 (-0.46, -0.16)**	

Source: Statistical Reviewer's analysis.

Abbreviations: A1C, hemoglobin A1C; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LS, least squares; SE, standard error; Sota, sotagliflozin; T1D, type 1 diabetes mellitus

Table 21. Change From Baseline in A1C (%) at Week 24—Trial 312 (Complete Version)

Subgroup	Variable	Sota 400 mg	Placebo
Overall population	Sample size	699	703
	Baseline, mean (SD)	8.26 (0.96)	8.21 (0.92)
	Missing primary endpoint, n (%)	72 (10.3)	75 (10.7)
	Change from baseline, LSMean[1] (SE)	-0.76 (0.03)	-0.32 (0.03)
	Difference from placebo, LSMean[1] (CI)	**-0.44 (-0.52, -0.36)**	
T1D-CKD population	Sample size	115	113
	Baseline, mean (SD)	8.71 (1.22)	8.26 (0.97)
	Missing primary endpoint, n (%)	16 (13.9)	15 (13.3)
	Change from baseline, LSMean[1] (SE)	-0.79 (0.08)	-0.37 (0.08)
	Difference from placebo, LSMean[1] (CI)	**-0.41 (-0.65, -0.19)**	
eGFR <60	Sample size	32	42
	Baseline, mean (SD)	8.49 (1.05)	8.25 (0.94)
	Missing primary endpoint, n (%)	6 (18.8)	5 (11.9)
	Change from baseline, LSMean[1] (SE)	-0.64 (0.16)	-0.47 (0.14)
	Difference from placebo, LSMean[1] (CI)	**-0.17 (-0.58, 0.25)**	

Subgroup	Variable	Sota 400 mg	Placebo
60≤eGFR <90 and UACR ≥30	Sample size	43	35
	Baseline, mean (SD)	8.62 (0.92)	8.06 (1.03)
	Missing primary endpoint, n (%)	4 (9.3%)	3 (8.6%)
	Change from baseline, LSMean[1] (SE)	-0.80 (0.14)	-0.24 (0.15)
	Difference from placebo, LSMean[1] (CI)	**-0.57 (-0.98, -0.15)**	
60≤eGFR <90 and UACR <30	Sample size	258	254
	Baseline, mean (SD)	8.02 (0.82)	8.12 (0.90)
	Missing primary endpoint, n (%)	21 (8.1)	21 (8.3)
	Change from baseline, LSMean[1] (SE)	-0.74 (0.04)	-0.31 (0.04)
	Difference from placebo, LSMean[1] (CI)	**-0.43 (-0.54, -0.31)**	
eGFR ≥90 and UACR ≥30	Sample size	40	36
	Baseline, mean (SD)	9.01 (1.55)	8.60 (0.94)
	Missing primary endpoint, n (%)	6 (15.0)	7 (19.4)
	Change from baseline, LSMean[1] (SE)	-0.93 (0.14)	-0.39 (0.15)
	Difference from placebo, LSMean[1] (CI)	**-0.54 (-0.93, -0.14)**	
eGFR ≥90 and UACR <30	Sample size	300	310
	Baseline, mean (SD)	8.28 (0.90)	8.26 (0.91)
	Missing primary endpoint, n (%)	31 (10.3)	37 (11.9)
	Change from baseline, LSMean[1] (SE)	-0.77 (0.05)	-0.31 (0.05)
	Difference from placebo, LSMean[1] (CI)	**-0.46 (-059, -0.33)**	

Source: Statistical Reviewer's analysis.

Abbreviations: A1C, hemoglobin A1C; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LS, least squares; SE, standard error; Sota, sotagliflozin; T1D, type 1 diabetes mellitus

Table *22*. Body Weight (kg) Change From Baseline at Week 24—Pooled Trials

		Treatment Arm		
Subgroup	**Variable**	**Sota 200 mg**	**Sota 400 mg**	**Placebo**
Overall population	Sample size	524	525	526
	Baseline, mean (SD)	84.5 (18.1)	84.2 (18.1)	84.2 (17.6)
	Missing endpoint values, n (%)	39 (7.4)	42 (8.0)	42 (8.0)
	Change from baseline, LSMean (SE)	-1.61 (0.14)	-2.32 (0.14)	0.42 (0.13)
	Difference from placebo, LSMean (95% CI)	**-2.03 (-2.41, -1.66)**	**-2.74 (-3.12, -2.37)**	
eGFR ≥90	Sample size	232	241	257
	Baseline, mean (SD)	84.1 (18.4)	83.8 (18.9)	82.7 (17.7)
	Missing endpoint values, n (%)	20 (8.6)	18 (7.5)	17 (6.6)
	Change from baseline, LSMean (SE)	-1.3 (0.22)	-2.23 (0.21)	0.61 (0.2)
	Difference from placebo, LSMean (95% CI)	**-1.91 (-2.48, -1.33)**	**-2.84 (-3.41, -2.28)**	
60≤eGFR <90	Sample size	270	259	245
	Baseline, mean (SD)	85.1 (17.8)	84.2 (17.4)	86.0 (17.6)
	Missing endpoint values, n (%)	19 (7.0)	23 (8.9)	23 (9.4)
	Change from baseline, LSMean (SE)	-1.84 (0.18)	-2.3 (0.19)	0.25 (0.19)
	Difference from placebo, LSMean (95% CI)	**-2.09 (-2.62, -1.57)**	**-2.56 (-3.09, -2.02)**	

		Treatment Arm		
Subgroup	**Variable**	**Sota 200 mg**	**Sota 400 mg**	**Placebo**
eGFR <60	Sample size	22	25	24
	Baseline, mean (SD)	80.3 (19.3)	88.7 (17.3)	82.5 (13.4)
	Missing endpoint values, n (%)	0	1 (4.0)	2 (8.3)
	Change from baseline, LSMean (SE)	-1.97 (0.51)	-3.22 (0.49)	-0.11 (0.51)
	Difference from placebo, LSMean (95% CI)	**-1.86 (-3.28, -0.44)**	**-3.12 (-4.51, -1.72)**	

Source: Statistical Reviewer's analysis.

Abbreviations: A1C, hemoglobin A1C; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LS, least squares; SE, standard error; Sota, sotagliflozin; T1D, type 1 diabetes mellitus

Table 23. Body Weight (kg) Change From Baseline at Week 24—Trial 312

		Treatment Arm	
Subgroup	**Variable**	**Sota 400 mg**	**Placebo**
Overall population	Sample size	699	703
	Baseline, mean (SD)	82.4 (17.1)	81.5 (17.0)
	Missing endpoint values, n (%)	69 (9.9)	70 (10.0)
	Change from baseline, LSMean (SE)	-2.02 (0.12)	0.72 (0.12)
	Difference from placebo, LSMean (95% CI)	**-2.75 (-3.08, -2.41)**	
eGFR ≥90	Sample size	355	361
	Baseline, mean (SD)	81.7 (17.7)	80.5 (16.8)
	Missing endpoint values, n (%)	38 (10.7)	42 (11.6)
	Change from baseline, LSMean (SE)	-1.97 (0.17)	0.93 (0.17)
	Difference from placebo, LSMean (95% CI)	**-2.90 (-3.38, -2.41)**	
60≤eGFR <90	Sample size	312	300
	Baseline, mean (SD)	82.9 (16.2)	83.1 (17.5)
	Missing endpoint values, n (%)	26 (8.3)	23 (7.7)
	Change from baseline, LSMean (SE)	-2.05 (0.17)	0.48 (0.17)
	Difference from placebo, LSMean (95% CI)	**-2.53 (-3.01, -2.05)**	
eGFR <60	Sample size	32	42
	Baseline, mean (SD)	85.3 (19.1)	79.3 (15.3)
	Missing endpoint values, n (%)	5 (15.6)	5 (11.9)
	Change from baseline, LSMean (SE)	-2.37 (0.57)	0.68 (0.49)
	Difference from placebo, LSMean (95% CI)	**-3.05 (-4.54, -1.56)**	

Source: Statistical Reviewer's analysis.

Abbreviations: A1C, hemoglobin A1C; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LS, least squares; SE, standard error; Sota, sotagliflozin; T1D, type 1 diabetes mellitus

Table 24. Systolic Blood Pressure (mmHg) Change at Week 24—Pooled Trials

		Treatment Arm		
Subgroup	**Variable**	**Sota 200 mg**	**Sota 400 mg**	**Placebo**
Overall population	Sample size	524	525	526
	Baseline, mean (SD)	121.5 (15.0)	121.3 (14.3)	122.0 (14.5)
	Missing endpoint values, n (%)	39 (7.4)	42 (8.0)	41 (7.8)
	Change from baseline, LSMean (SE)	-2.66 (0.47)	-3.41 (0.46)	-0.76 (0.46)
	Difference from placebo, LSMean (95% CI)	**-1.90 (-3.18, -0.62)**	**-2.66 (-3.93, -1.38)**	

		Treatment Arm		
Subgroup	**Variable**	**Sota 200 mg**	**Sota 400 mg**	**Placebo**
eGFR ≥90	Sample size	232	241	257
	Baseline, mean (SD)	120.3 (14.8)	120.3 (13.4)	120.9 (14.1)
	Missing endpoint values, n (%)	20 (8.6)	17 (7.1)	17 (6.6)
	Change from baseline, LSMean (SE)	-3.71 (0.66)	-3.32 (0.64)	-1.18 (0.61)
	Difference from placebo, LSMean (95% CI)	**-2.53 (-4.31, -0.75)**	**-2.14 (-3.86, -0.42)**	
60≤eGFR <90	Sample size	270	259	245
	Baseline, mean (SD)	122.0 (15.2)	121.8 (14.2)	122.5 (14.2)
	Missing endpoint values, n (%)	19 (7.0)	24 (9.3)	22 (9.0)
	Change from baseline, LSMean (SE)	-1.83 (0.66)	-3.84 (0.67)	-0.36 (0.70)
	Difference from placebo, LSMean (95% CI)	**-1.47 (-3.35, 0.4)**	**-3.48 (-5.39, -1.58)**	
eGFR <60	Sample size	22	25	24
	Baseline, mean (SD)	128.4 (12.7)	126.0 (21.9)	128.5 (20.5)
	Missing endpoint values, n (%)	0	1 (4.0)	2 (8.3)
	Change from baseline, LSMean (SE)	-1.84 (2.79)	-0.02 (2.63)	-0.03 (2.74)
	Difference from placebo, LSMean (95% CI)	**-1.81 (-9.54, 5.93)**	**0.01 (-7.49, 7.51)**	

Source: Statistical Reviewer's analysis.

Abbreviations: A1C, hemoglobin A1C; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LS, least squares; SE, standard error; Sota, sotagliflozin; T1D, type 1 diabetes mellitus

Table 25. Systolic Blood Pressure (mmHg) Change at Week 24—Trial 312

		Treatment Arm	
Subgroup	**Variable**	**Sota 400 mg**	**Placebo**
Overall population	Sample size	699	703
	Baseline, mean (SD)	122.0 (15.3)	121.8 (14.8)
	Missing endpoint values, n (%)	67 (9.6)	69 (9.8)
	Change from baseline, LSMean (SE)	-1.97 (0.43)	0.98 (0.43)
	Difference from placebo, LSMean (95% CI)	**-2.96 (-4.15, -1.76)**	
eGFR ≥90	Sample size	355	361
	Baseline, mean (SD)	120.2 (14.8)	120.6 (14.2)
	Missing endpoint values, n (%)	37 (10.4)	42 (11.6)
	Change from baseline, LSMean (SE)	-1.56 (0.57)	1.30 (0.57)
	Difference from placebo, LSMean (95% CI)	**-2.86 (-4.45, -1.28)**	
60≤eGFR <90	Sample size	312	300
	Baseline, mean (SD)	123.0 (15.5)	122.3 (15.5)
	Missing endpoint values, n (%)	25 (8.0)	22 (7.3)
	Change from baseline, LSMean (SE)	-2.55 (0.64)	0.05 (0.65)
	Difference from placebo, LSMean (95% CI)	**-2.59 (-4.40, -0.79)**	
eGFR <60	Sample size	32	42
	Baseline, mean (SD)	130.6 (14.8)	128.2 (14.2)
	Missing endpoint values, n (%)	5 (15.6)	5 (11.9)
	Change from baseline, LSMean (SE)	-0.40 (2.98)	4.60 (2.46)
	Difference from placebo, LSMean (95% CI)	**-5.00 (-12.27, 2.27)**	

Source: Statistical Reviewer's analysis.

Abbreviations: A1C, hemoglobin A1C; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LS, least squares; SE, standard error; Sota, sotagliflozin; T1D, type 1 diabetes mellitus

7.5 Postmarketing Experience: Rates of DKA in Patients With T1D Exposed to SGLT-2 Inhibitors: Update of the 2019 Sentinel Analysis

Objectives

To provide context on the DKA risk in patients with T1D, the current analyses query the Sentinel claims database to estimate (1) the rate of DKA following exposure to SGLT-2 inhibitors among patients with T1D, overall and by calendar year from 2013 to 2024, and (2) the background rate of DKA across CKD stages in the T1D population.

Methods

This descriptive analysis was conducted in six data partners of FDA's Sentinel system,[18] with data from March 1, 2013 (approval of canagliflozin) until February 29, 2024 (varied by data partner). Study drug cohorts included new users of SGLT-2 inhibitors and new users of sitagliptin[19], who had a 365-day baseline period, continuous medical and pharmacy benefits, and no prior dispensing records of either SGLT-2 inhibitors or sitagliptin. We created exposure episodes using days of supply, allowing for a gap between dispensings of up to 10 days, with a 10-day extension at the end of an episode.

Exposure episodes were censored at the first occurrence of the following: DKA event, end of SGLT-2 inhibitor or sitagliptin supply (up to 365 days), death, disenrollment, or end of available data.

T1D was defined by a broad definition and a narrow definition using an adaptation of a published and validated algorithm (Klompas et al. 2013; Schroeder et al. 2018).[20] The T1D-broad definition required a plurality (>50%) of diabetes diagnosis codes during the baseline period was specific to T1D,[21] and the T1D-narrow definition additionally required at least one prescription for a short- or rapid-acting insulin and no dispensing of noninsulin antidiabetic drug (other than metformin) during the baseline period. CKD stage was categorized using a claims-based algorithm that was validated against eGFR (Friberg et al. 2018).

Diabetic ketoacidosis (DKA) was defined as having an inpatient or emergency department diagnosis with an ICD-9-CM code of 250.1x or an ICD-10-CM code of E1x.1x in any diagnosis position (Bobo et al. 2011).[22]

Incidence rates of DKA were calculated using the numbers of the first DKA events observed during exposure in the numerator and cumulative person-years of exposure in the denominator. Analyses were stratified by age (<12, 12 to 18, 19 to 24, 25 to 44, 45 to 64, and ≥65 years), sex (male or female), and calendar year, and in the T1D population, by CKD stage. Cohort-specific baseline characteristics included

[18] Participating data partners include CVS Health/Aetna, Medicaid, Medicare, Carelon, Humana, and Optum.
[19] SGLT-2 inhibitors consisted of bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and sotagliflozin. Dipeptidyl-peptidase-4 (DPP-4) inhibitor sitagliptin served as a control exposure, for which off-label use among T1D patients was not expected to be substantive, to track the performance of algorithms used to categorize diabetes type and to provide context for findings of SGLT-2 inhibitors without testing a prespecified hypothesis.
[20] For the T1D-broad algorithm, Klompas et al. (1) measured sensitivity of 63% and positive predictive value (PPV) of 94%. For the same algorithm, Schroeder et al. (2) measured PPV of 96.4% in a different cohort.
[21] Diagnosis codes for diabetes were ascertained between 365 days and 5 days before cohort entry, to account for potential miscoding associated with the off-label prescription of an SGLT-2 inhibitor. The baseline period ranged from 365 before to 1 day before cohort entry for all other purposes.
[22] This algorithm had a PPV of 88.9% among children and youth.

age, sex, history of antidiabetic drug use, use of insulin pumps, and diagnosis of DKA during the baseline period.

Results

The study sample consisted of 2,271,283 new users of SGLT-2i and 1,598,255 new users of sitagliptin. Among the new users of SGLT-2 inhibitors, 17,915 (0.79%) met the criteria for T1D-broad and 8,942 (0.39%) met the criteria for T1D-narrow. Across the calendar year from 2014 to 2023,[23] the proportion of new users of SGLT-2 inhibitors who met the criteria for T1D decreased consistently, from 2.2% in 2014 to 0.5% in 2023 for T1D-broad and from 1.1% in 2014 to 0.3% in 2023 for T1D-narrow (Table 26). For initiators of sitagliptin, 8,749 (0.55%) and 2,141 (0.13%) met the criteria for T1D-broad and T1D-narrow, respectively; and the proportion of those who met the criteria for T1D was constant across the calendar year (ranging from 0.4% to 0.7% for T1D-broad and 0.1% for T1D-narrow).

Especially for SGLT-2 inhibitors, the proportion of new users who met the criteria for T1D-broad or T1D-narrow (Table 26) were highly age-dependent. For instance, among patients who initiated SGLT-2 inhibitors between 19 and 24 years of age, 6.3% met the criteria for T1D-broad and 4.4% met the criteria for T1D-narrow. By contrast, among SGLT-2 initiators ≥65 years of age, 0.49% met the criteria for T1D-broad and 0.19% met the criteria for T1D-narrow. Rates for T1D were lower in users of sitagliptin across all age categories.

Table 26. Number and Proportion of Initiators of SGLT-2 Inhibitors or Sitagliptin Who Met the Criteria for T1D

	SGLT-2 Inhibitor			Sitagliptin		
Variable	Overall (n=2,271,283)	T1D-Broad (n=17,915)	T1D-Narrow (n=8,942)	Overall (n=1,598,255)	T1D-Broad (n=8,749)	T1D-Narrow (n=2,141)
Age (years)						
<19	1,884	178 (9.4)	117 (6.2)	1,210	(Redacted)	(Redacted)
19-24	7,434	470 (6.3)	326 (4.4)	4,600	144 (3.1)	73 (1.6)
25-44	203,916	4,040 (2.0)	2,604 (1.3)	121,664	1,152 (0.9)	501 (0.4)
45-64	865,512	7,350 (0.8)	3,628 (0.4)	529,542	2,940 (0.6)	734 (0.1)
≥65	1,192,537	5,877 (0.49)	2,267 (0.19)	941,239	4,446 (0.5)	795 (0.1)
Sex						
Female	1,049,592	8,789 (0.84)	4,537 (0.43)	852,011	4,587 (0.44)	1,186 (0.11)
Male	1,221,691	9,126 (0.75)	4,405 (0.36)	746,244	4,162 (0.56)	955 (0.08)
Calendar year						
2013	13,710	339 (2.45)	135 (0.98)	126,655	1,089 (0.85)	187 (0.15)
2014	69,222	1,505 (2.17)	751 (1.08)	172,673	1,241 (0.72)	242 (0.14)
2015	110,759	1,976 (1.78)	1,063 (0.96)	173,798	1,176 (0.68)	245 (0.14)
2016	110,577	1,327 (1.20)	662 (0.60)	179,240	955 (0.53)	227 (0.13)
2017	144,429	1,398 (0.97)	661 (0.46)	203,007	1,042 (0.51)	270 (0.13)
2018	146,960	1,310 (0.89)	621 (0.42)	186,980	947 (0.51)	261 (0.14)
2019	203,016	1,644 (0.81)	824 (0.41)	166,323	722 (0.43)	224 (0.13)
2020	248,808	1,675 (0.67)	825 (0.33)	138,323	608 (0.39)	187 (0.14)
2021	401,238	2,503 (0.62)	1,234 (0.31)	130,475	513 (0.38)	167 (0.13)
2022	388,358	2,049 (0.53)	1,081 (0.28)	69,068	260 (0.38)	79 (0.11)
2023	418,541	2,111 (0.50)	1,046 (0.25)	49,421	185 (0.37)	(Redacted)
2024	15,665	78 (0.50)	39 (0.25)	2,292	11 (0.48)	(Redacted)

Source: FDA Review staff.

Abbreviations: SGLT-2, sodium-glucose transport protein 2; T1D, type 1 diabetes mellitus

[23] Results for 2013 and 2024 were not presented because data were not available for the entire years.

Baseline Patient Characteristics

Among initiators of SGLT-2 inhibitors who met the criteria for T1D, the largest subgroup comprised the age category of 45 to 64 years (T1D-broad: n=7,350; T1D-narrow: n=3,628) with mean (±standard deviation) ages of 55.7 (±13.2) years (T1D-broad) and 52.3 (±13.5) years (T1D-narrow). Few exposed patients with T1D were ≤25 years of age (T1D-broad: n=648, 3.6%; T1D-narrow: n=443, 5.0%). Females comprised 49% of initiators of SGLT-2 inhibitors who met the criteria for T1D-broad, and 51% of those who met the criteria for T1D-narrow.

Table 27 lists baseline noninsulin antidiabetic drug use and insulin use for initiators of SGLT-2 inhibitors or sitagliptin with T1D-narrow and T1D-broad. Consistent with our criteria for T2D-narrow, these patients did not use noninsulin antidiabetic drugs other than metformin during the baseline period. The use of metformin was more prevalent among patients who met the broad T1D definition compared with the narrow definition (39.3% versus 25.2%). Comparing initiators of SGLT-2 inhibitors and initiators of sitagliptin with T1D, the latter were more likely to have used metformin, sulfonylureas, and thiazolidinedione during the baseline period but were less likely to have used glucagon-like peptide (GLP)-1 analogs.

Among initiators of SGLT2 inhibitors, the baseline use of short- or rapid-acting insulin (100% versus 65.3%), long- or intermediate acting insulin (64.4% versus 57.1%), and insulin pump (25.7% versus 16.3%) tended to be more common among patients who met the criteria for T1D-narrow compared with T1D-broad. Similar patterns of baseline insulin use were observed among initiators of sitagliptin.

Table 27. Baseline Use of Noninsulin Antidiabetic Drugs and Insulin Products

		SGLT-2 Inhibitors		Sitagliptin	
Variable		T1D-Narrow (n=8,942)	T1D-Broad (n=17,915)	T1D-Narrow (n=2,141)	T1D-Broad (n=8,749)
Non-insulin Antidiabetic drugs	Metformin	25.2%	39.3%	40.3%	53.4%
	Sulfonylurea	0	11.6%	0	27.9%
	Thiazolidinedione	0	4.3%	0	5.2%
	DPP-4 inhibitors*	0	3.4%	0	6.9%
	GLP1 analogs	0	16.3%	0	4.5%
	SGLT-2 inhibitors	0	0	0	0
Insulin products	Short- or rapid-acting insulin	100%	65.3%	100%	34.7%
	Long- or intermediate-acting insulin	64.4%	57.1%	83.7%	48.9%
	Combination insulin	2.2%	5.5%	6.7%	8.8%
	Insulin pump	25.7%	16.3%	5.4%	1.8%

Source: FDA Review staff.

GLP1 RA glucagon-like peptide-1 analogs.

* DPP-4 inhibitors other than sitagliptin.

Abbreviations: DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SGLT-2, sodium-glucose transport protein 2; T1D, type 1 diabetes mellitus

Diabetic Ketoacidosis

During the baseline period, 6.1% and 9.2% of initiators of SLGT-2 inhibitors who met the criteria for T1D-broad and T1D-narrow, respectively, had a DKA event. Among the sitagliptin initiators, 3.1% and 9.1% of those with T1D-broad and T1D-narrow, respectively, had a DKA event.

Table 28 presents unadjusted rates of DKA during exposure to SGLT-2 inhibitors.[24] Among initiators of SGLT-2 inhibitors who met the criteria for T1D-narrow and T1D-broad, the rates of DKA decreased with increasing age and females had higher rates of DKA than males.

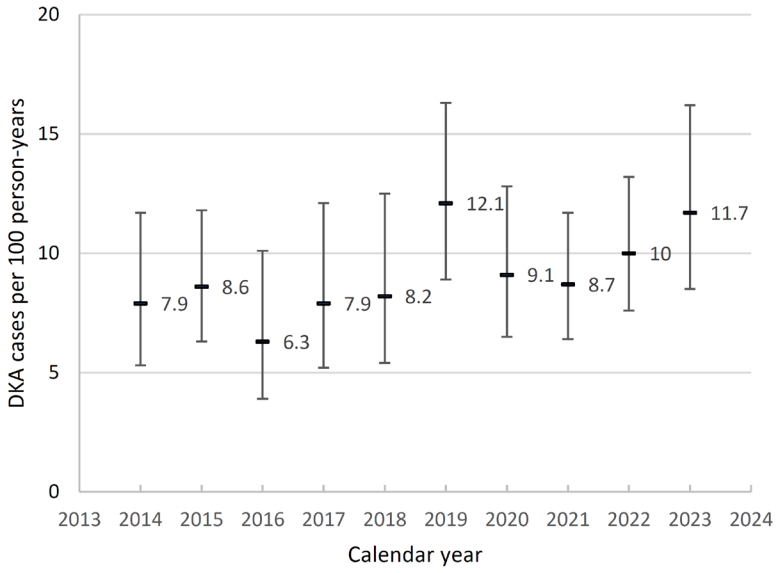
Table 28. DKA Rate in New Users of SGLT-2 Inhibitors

	DKA Rate (95% CI), Cases per 100 Person-Years	
Characteristic	**T1D-Narrow**	**T1D-Broad**
Overall	9.2 (8.3, 10.2)	6.1 (5.6, 6.7)
Age (years)		
19-24	19.0 (12.1, 29.7)	17.0 (11.6, 25.0)
25-44	11.6 (9.7, 13.9)	9.6 (8.2, 11.3)
45-64	8.2 (6.9, 9.7)	5.3 (4.5, 6.1)
≥65	6.7 (5.3, 8.6)	4.0 (3.3, 4.9)
Female	11.3 (9.8, 13.0)	7.7 (6.8, 8.7)
Male	7.3 (6.1, 8.6)	4.7 (4.1, 5.4)

Source: FDA Review staff.
Abbreviations: CI, confidence interval; DKA, diabetic ketoacidosis; SGLT-2, sodium-glucose transport protein 2; T1D, type 1 diabetes mellitus

Across the calendar year from 2014 to 2023,[25] the rates of DKA among initiators of SGLT-2 inhibitors with T1D-narrow ranged from 6.3 (95% CI, 3.9 to 10.1) per 100 PY in 2016 to 12.1 (95% CI, 8.9 to 16.3) per 100 PY in 2019 (Figure 9). For initiators of SGLT-2 inhibitors with T1D-broad, the rate of DKA ranged from 4.6 (95% CI, 3.1-6.8) per 100 PY in 2016 and 8.3 (95% CI, 6.2 to 10.9) per 100 PY in 2023 (Figure 10). The widely overlapping 95% CIs suggested that the rates of DKA did not change substantially across the calendar year.

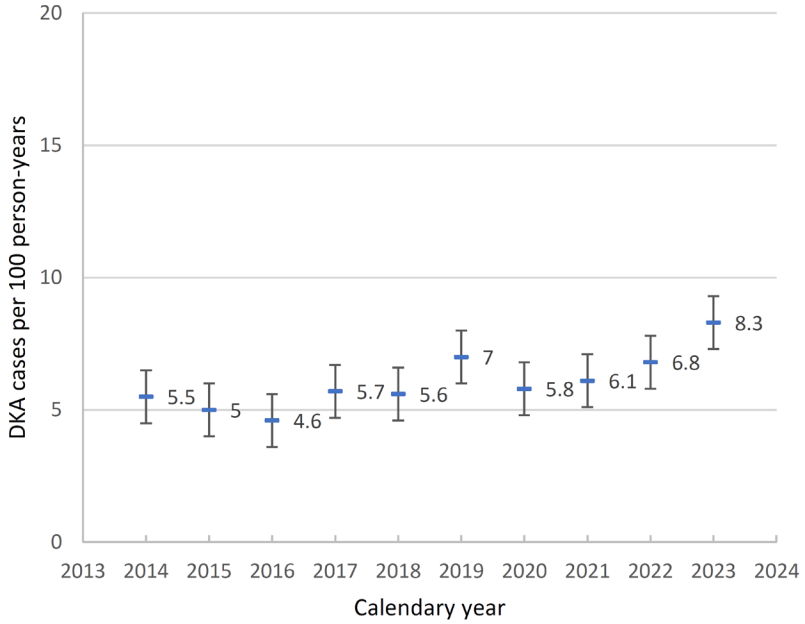
Figure 9. DKA Rate by Calendar Year Among Initiators of SGLT-2 Inhibitors With T1D-Narrow



Source: FDA Review staff.
Abbreviations: DKA, diabetic ketoacidosis; SGLT-2, sodium-glucose transport protein 2; T1D, type 1 diabetes mellitus

[24] These rates were not adjusted for patient characteristics.
[25] Results for 2013 and 2024 were not presented because data were not available for the entire calendar year.

Figure 10. DKA Rate by Calendar Year Among Initiators of SGLT-2 Inhibitors With T1D-Broad



Source: FDA Review staff.
Abbreviations: DKA, diabetic ketoacidosis; SGLT-2, sodium-glucose transport protein 2; T1D, type 1 diabetes mellitus

DKA Rate by CKD in the T1D Population

Among the 690,849 participants with T1D-narrow, 88.7% had a CKD stage 1 or 2, 5.8% had CKD stage 3, and 5.5% had CKD stage 4 or 5. Table 29 presents the rates of DKA across CKD stages in the T1D population. The crude incidence rates of DKA increased with advancing CKD stage.

Table 29. DKA Rate (Cases per 100 PY) by CKD Stage in the T1D Population in Six Sentinel Data Partners

CKD Stage	Patients, n	DKA Cases, n	At-Risk PY	DKA Rate (95% CI), Cases per 100 PY
Stage 1 or 2	612,800	17,689	169,588	10.4 (10.3, 10.6)
Stage 3	40,091	1,496	10,610.4	14.1 (13.4, 14.8)
Stage 4 or 5	37,958	2,446	9,094.4	26.9 (25.9, 28.0)

Source: FDA Review staff.
Stage 1 or 2: eGFR ≥60 mL/min/1.72 m^2; Stage 3: eGFR 30-59 mL/min/1.72 m^2; Stage 4 or 5: eGFR <30 mL/min/1.72 m^2
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; DKA, diabetic ketoacidosis; PY, person-years; T1D, type 1 diabetes mellitus

Discussion

This analysis of 2.27 million new users of SGLT-2 inhibitors found that new users of SGLT-2 inhibitors who met T1D criteria were less than 1% and decreased consistently over time from 2014 to 2023. Overall, 0.39% of new users of SGLT-2 inhibitors met the criteria for T1D-narrow and 0.78% met the criteria for T1D-broad.

Among patients who used SGLT-2 inhibitors off-label, the overall rate of DKA was 6.1 per 100 PY among patients with T1D-broad and 9.2 per 100 PY for patients with T1D-narrow. Rates of DKA were highest for younger patients (e.g., 14.2 per 100 PY among patients 25 to 44 years of age who met the criteria for T1D-narrow), and females had a higher rate than males. While the use of SGLT-2 inhibitors in patients with T1D decreased consistently from 2014 to 2023 (2.2% to 0.5% for T1D-broad and 1.1% to 0.3% for

T1D-narrow), the incidence rates of DKA among patients with T1D who initiate use of SGLT2 inhibitors off label appears to have not declined over the same period (Figure 9 and Figure 10).

We observed that the proportion of off-label use of sitagliptin for T1D was, as expected, lower than that of SGLT-2 inhibitors. Also, incidence rates of DKA in sitagliptin users appeared to be numerically lower than SGLT-2 inhibitors users among patients who met the criteria for T1D-broad but comparable among patients who met the criteria for T1D-narrow. It is unclear whether the DKA rates observed in sitagliptin users who met the criteria for T1D-narrow reflect pharmacologic properties, different patient characteristics (compared with SGLT-2 inhibitor users, sitagliptin users with T1D-narrow tended to be older, female, were more likely to have used metformin or long- or intermediate-acting insulin, and were substantially less likely to have used an insulin pump during the baseline period), or random error.

In a T1D-narrow population, the majority (88.7%) had CKD stage 1 or 2 and 11.3% had CKD stage 3 or above. The crude DKA rate increased with advancing CKD stage, suggesting that patients with T1D who have CKD have an elevated background risk for DKA. In an ongoing investigation, we are using propensity-score based approaches to assess whether CKD is an independent risk factor for DKA in the Sentinel data.

The strengths of this analysis include the large size and diverse nature of the database. The Sentinel system includes large commercial data partners, Medicare and Medicaid. However, the present analysis is not nationally representative because it underrepresents uninsured patients. Additionally, the incidence rates of DKA may differ in databases with different patient characteristics including different prevalences of T1D due to age.

Inherent to claims-based analyses, possible limitations arise from the use of diagnostic codes to categorize patients into those with T1D and to ascertain events of DKA. It is possible that both the T1D-narrow and, to a lesser degree, the T1D-broad cohorts missed some patients with T1D, thus underestimating patients with off-label use of SGLT2 inhibitors. Also, the T1D-broad cohort may inadvertently have included some patients with T2D. Similarly, although we used a validated algorithm to ascertain DKA, in the absence of adjudication, we may have missed some events while possibly including others that were false positives.

In summary, the off-label use of SGLT-2 inhibitors in patients who met the study criteria for T1D was not widespread in the overall study population, but the proportion of off-label use was higher in younger patients. Among patients who used SGLT-2 inhibitors off-label, the risk of DKA was notable, especially among those <45 years of age. Of note, although the off-label use of SGLT-2 inhibitors in patients with T1D decreased from 2014 to 2023, the rate of DKA following exposure to SGLT-2 inhibitors in the T1D population did not change substantially over time.

7.6 Additional Clinical Pharmacology Information

Pharmacokinetics in CKD

The FDA conducted subgroup PK analyses to compare the PK exposures in participants with T1D stratified by eGFR and UACR and the Applicant's defined non-CKD and CKD T1D participants. There was increased sotagliflozin exposure for eGFR <60 mL/min/1.73 m^2 compared to eGFR groups with lesser degrees of renal impairment (i.e., eGFR >90 mL/min/1.73 m^2, 60 to 89 mL/min/1.73 m^2). There was also a consistently lower sotagliflozin exposure in participants with UACR ≥30 mg/g compared to those with UACR <30 mg/g for each eGFR subcategory. The mechanism underlying this observation is unclear.

Table 30. Dose-Normalized Population PK Model-Predicted Sotagliflozin Area Under the Curve at Steady State in Participants With T1D (Trials 309 and 310) by eGFR and UACR

Variable	Geometric Mean AUC ± SD (ng·h/mL/mg)	Subgroup	Geometric Mean AUC ± SD (ng·h/mL/mg)
eGFR <60 mL/min/1.73 m^2 N=46	5.73±1.58	UACR <30 N=27	5.75±1.52*
		UACR ≥30 N=19	5.70±1.69*
eGFR ≥60 to <90 mL/min/1.73 m^2 N=492	4.44±1.62	UACR <30 N=436	4.56±1.62
		UACR ≥30 N=56	3.66±1.60*
eGFR ≥90 mL/min/1.73 m^2 N=438	4.08±1.66	UACR <30 N=390	4.11±1.64
		UACR ≥30 N=48	3.85±1.79*

Source: Reviewer's analysis.

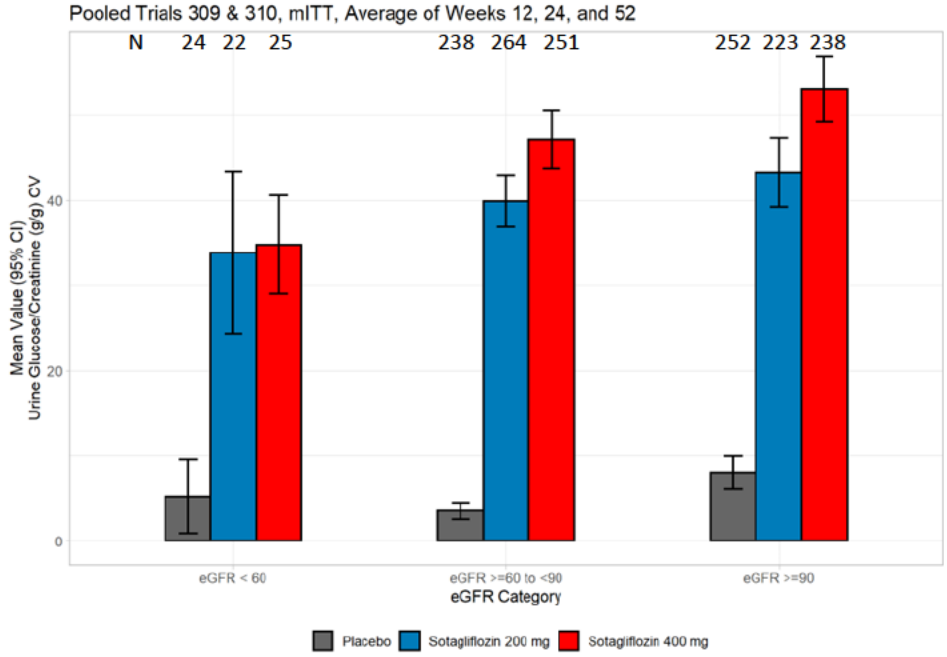
* Applicant's defined CKD population.

Abbreviations: AUC, area under the concentration-time curve; eGFR, estimated glomerular filtration rate; PK, pharmacokinetics; T1D, type 1 diabetes mellitus; UACR, urine albumin-creatinine ratio

Pharmacodynamics in CKD

Longitudinal analysis of UGCR with data from the TANDEM trials (309 and 310) was evaluated to assess the durability of glycosuria response with sotagliflozin treatment. UGCR was routinely drawn at 12, 24, and 52 weeks. Inspection of longitudinal plots revealed a sustained and consistent treatment difference at the population level, starting at the first treatment-emergent measurement (data not shown). Hence, data were summarized at the patient level, and plotted by treatment arm and eGFR category (Figure 11). There appears to be a modest dose-response relationship, which is more pronounced in the higher eGFR categories. There is a modest decrease in UGCR among the lower eGFR categories. These observations are consistent with the observations in A1C.

Figure 11. Average Urine Glucose/Creatinine Ratio at Weeks 12, 24, and 52—Pooled Trials 309 and 310



Source: Clinical Data Scientist.
The medians (ranges) of baseline eGFR in participants with eGFR <60, ≥60 to <90, and ≥90 mL/min/1.73 m^2 are 53.2 (40.3-59.8), 78.7 (60-89.9) and 102.8 (90-170.7) mL/min/1.73 m^2, respectively.
Abbreviations: CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat

7.7 2019 FDA EMDAC Briefing Document

Attachment: FDA Briefing Document, Endocrinologic and Metabolic Drugs Advisory Committee Meeting, January 17, 2019

FDA Briefing Document

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

January 17, 2019

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought New Drug Application (NDA) 210934 for sotagliflozin to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Division Director Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medication Error Prevention and Risk Management
M E M O R A N D U M

Date:	January 17, 2019
From:	Lisa Yanoff, M.D. Director (Acting), Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, CDER, FDA
To:	Chair, Members and Invited Guests Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)
Subject	Overview of the January 17, 2019 EMDAC meeting

This document provides the briefing material for the January 17, 2019 meeting of the Endocrinology and Metabolic Drugs Advisory Committee to discuss data in support of sotagliflozin (New Drug Application 210934) submitted on March 22, 2018. The application seeks marketing approval for sotagliflozin as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus (T1DM).

T1DM is a serious medical condition caused by T-cell mediated autoimmune destruction of the pancreatic beta cells. The resulting loss of pancreatic beta cells leads to impaired insulin production and secretion, and impaired glucose metabolism. The mainstay of medical therapy for T1DM is exogenous insulin, which is required for survival. Also approved for T1DM is an adjunctive therapy, pramlintide, an amylin-mimetic. Both exogenous insulin and pramlintide can help improve glycemic control, but they do not alter the underlying pathophysiology of T1DM.

Acute life-threatening complications of T1DM include profound hyperglycemia and diabetic ketoacidosis due to insulin deficiency. Chronic complications of T1DM include macrovascular/cardiovascular disease and microvascular disease, e.g. retinopathy, nephropathy,

and neuropathy. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive insulin therapy and consequent tight glycemic control resulted in a reduction in the onset and progression of microvascular complications[1,2,3]. Based on these data, patients with T1DM are generally recommended to use multiple daily injections (MDI) of insulin, including "basal" or long-acting insulin, along with "prandial" or short-acting insulin taken before each meal, to achieve their glycemic goals. An insulin pump, using a continuous subcutaneous infusion (CSII) of short-acting insulin, may also be used to achieve glycemic control.

FDA recognizes there is an unmet need for patients with T1DM to help achieve glycemic goals and improve quality of life and treatment satisfaction. At the same time, the additional risk(s) incurred by an adjunct therapy need to be carefully considered relative to the benefits the therapy provides. During development of pramlintide, an antihyperglycemic agent that is approved for T1DM, an increased risk of severe hypoglycemia in combination with insulin relative to insulin alone was observed. Further assessment identified a patient population and method of use that lowered the risk of severe hypoglycemia to an incidence comparable to insulin alone, providing a favorable benefit risk profile, and supporting an approval decision.[1]

Sotagliflozin is an orally administered inhibitor of both sodium-glucose co-transporter 1 (SGLT1) and sodium-glucose co-transporter 2 (SGLT2) that is being developed as an adjunct to insulin for patients with type 1 diabetes mellitus (T1DM). Sotagliflozin does not alter the underlying pathophysiology of T1DM but lowers plasma glucose by increasing urinary glucose excretion. This application does not intend to market sotagliflozin for type 2 diabetes mellitus (T2DM), and none of the currently approved SGLT2 inhibitors carry an indication for patients with T1DM. Two doses of sotagliflozin were studied in the phase 3 program and are proposed for marketing by the applicant. The Clinical Pharmacology Summary, in addition to providing an overview of the pharmacokinetic and pharmacodynamic characteristics of sotagliflozin, shows exploratory dose-response analyses that attempt to provide insight into the clinical trial results such as the similar glycemic lowering effect of the two doses yet higher rate of DKA with the higher dose.

While it is established that patients with diabetes are at increased risk for both microvascular and macrovascular complications, drugs for the treatment of diabetes are typically approved based on hemoglobin A1c (HbA1c). HbA1c is formed by irreversible attachment of glucose to hemoglobin, is directly proportional to the ambient glucose concentration, and correlates with average blood glucose over the preceding 2 to 3 months. In the diabetes control and complications trial (DCCT) there was a 43% reduction in microvascular risk for every 10% decrease in A1c. Based on the robust body of evidence, reduction in HbA1c is considered to be a reliable biomarker for glycemic lowering and reduction in the onset and progression of microvascular complications and is an accepted surrogate endpoint for regulator decision making for T1DM. Other glucose based endpoints used by the sponsor in the sotagliflozin development program include "glycemic variability" and "time-in-range." While these endpoints are valued by patients and may relate to at least short-term improvements in quality of life and treatment satisfaction, these do not have an established relationship with long-term macrovascular and microvascular complications and have not been validated for use in regulatory decision making for antidiabetic drugs.

[1]https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/21332_Symlin%20Injection_medr.PDF

Potential benefits of sotagliflozin, e.g. improved glycemic control through lowering of HbA1c, reduction in hypoglycemia (particularly severe hypoglycemia), and reduction in body weight were evaluated in three phase 3 clinical trials, the results of which are presented in this document in the Summary of Efficacy. Body weight reduction may be viewed as a clinical benefit for some patients, and a reduction in severe hypoglycemia, defined generally as requiring assistance from another person because of neuroglycopenia (which can include altered mental status, loss of consciousness, or seizure) would be viewed as an important clinical benefit. Other definitions of hypoglycemia have uncertain clinical relevance.

A serious adverse event for sotagliflozin is the consistent and clinically meaningful increase in the risk of diabetic ketoacidosis (DKA) compared to placebo observed in all three phase 3 clinical trials (the reader will find details of these analyses in the Summary of Safety). DKA occurs due to insulin deficiency (either relative or absolute) and subsequent ketogenesis. SGLT2 inhibitors appear to increase the risk of DKA. The mechanisms are beginning to be explored, but likely both indirect effects (through insulin dose reduction and volume contraction) and direct effects (through ketogenesis) are implicated. The applicant had previously identified metabolic acidosis, including DKA, as an adverse event of special interest based on the known safety concern included in the Warnings and Precautions section of the labeling for approved SGLT2 inhibitors in T2DM patients; therefore, events of DKA were rigorously collected and analyzed providing reliable analysis results. While all patients with type 1 diabetes may to some degree be at risk for DKA, sotagliflozin therapy clearly increases that risk, and the risk may be unpredictable (please see the Safety Summary for the full discussion). In addition, we explored spontaneous postmarketing reports of DKA among patients with T1DM using SGLT2, and we queried the Sentinel database to evaluate the rate of DKA among patients with T1DM exposed to SGLT2 inhibitors in real world data sources; results of both investigations are discussed in the section on Postmarketing Experience. Additional safety risks of sotagliflozin include genital mycotic infections and renal impairment and are discussed in full in the Safety Summary.

To partially assess the overall benefit-risk of sotagliflozin, the applicant pre-specified a composite endpoint of HbA1c<7% with no episodes of severe hypoglycemia or diabetic ketoacidosis. This endpoint attempts to incorporate benefit and risk into a single composite, but we have concerns about the clinical significance of the chosen composite. For one, the composite uses a responder rate for glycemic efficacy (achieving or not achieving HbA1c <7%), and for example, puts equal weight on a lowering from 7.5% to 6.9% as on a lowering from 9.5% to 6.9%. More broadly, we believe that there are additional clinical benefits and risks of importance beyond those captured in the composite endpoint. In general, FDA is interested in approaches to assessing the benefit risk profile, including various qualitative and quantitative methods, as these can inform an approval decision; however, such assessments must start with a clinically meaningful way to frame both benefits and risks.

Draft Points to Consider

- Discuss the benefits claimed by the applicant, e.g. glycemic control, effects on body weight and risk for hypoglycemia, for patients with type 1 diabetes. Comment on the

strength of the statistical evidence and clinical meaningfulness of each of these claimed benefits.

- Discuss your level of concern about the observed risk of DKA in adult patients in the sotagliflozin clinical studies and DKA risk associated with sotagliflozin use in a real-world setting.

- Comment on any relevant differences in efficacy and/or safety observed between the two proposed doses of sotagliflozin (200 mg and 400 mg).

- Consider the clinical meaningfulness of the composite endpoint used by the applicant (HbA1c<7% with no episodes of severe hypoglycemia or diabetic ketoacidosis). If you would recommend an alternative strategy, please explain your rationale.

- Discuss whether the benefits of sotagliflozin outweigh the risks for patients with type 1 diabetes. What specific benefits and risks factored into your decision; what was your approach and rationale for how were they weighed against each other?

Clinical Pharmacology Summary

The clinical pharmacology section summarizes mechanism of action, proposed dosing regimen, pharmacokinetics (PK) characteristics including absorption, distribution, metabolism and excretion, pharmacodynamics (PD), e.g. post-prandial glucose (PPG) excursion and urinary glucose excretion (UGE), drug-drug interactions (DDI), specific population considerations, and dose/exposure-response for efficacy and safety towards the proposed dosing regimen for sotagliflozin in patients with type 1 diabetes on a background of insulin use.

Sotagliflozin (also known as LX4211) is an oral, dual inhibitor of sodium glucose co-transporter 1 (SGLT1) (50% inhibitory concentration [IC50] = 36.3 nM) and sodium glucose co-transporter 2 (SGLT2) (IC50=1.8 nM) with more selectivity towards SGLT2. Local inhibition of SGLT1 in the gut presumably delays and reduces glucose absorption in the proximal intestine, while systemic inhibition of SGLT2 in the proximal renal tubule reduces renal glucose reabsorption.

The drug product is a film-coated oral tablet containing 200 mg of sotagliflozin, formulated for immediate release. The proposed dosing regimen is 200 mg once daily, before the first meal of the day. The dose may be increased to 400 mg once daily in patients tolerating 200 mg once daily dose.

Key Clinical Pharmacology Characteristics of Sotagliflozin

The table below summarizes the key clinical pharmacology characteristics of sotagliflozin. For more detailed information see *Appendix A: Supplemental Clinical Pharmacology Information*.

Table 1. Highlights of the Clinical Pharmacology of Sotagliflozin

Absorption	• Tmax: 1.25-4.5 hours • Food effect: Cmax↑149%, AUC↑50%
Distribution	• High protein binding (>93%)
Metabolism	• Metabolized by UGT1A9 (primarily) and CYP3A4 • Sotagliflozin-3-O-glucuronide (M19) is the main metabolite (94.3% in plasma) with >275-fold lower inhibitory activity for SGLT1 and SGLT2 than sotagliflozin.
Elimination	• Sotagliflozin – Metabolism; Metabolites - Renal elimination, Elimination $t_{1/2}$: 21-35 hours
Dose proportionality	• Cmax and AUC are dose proportional in dose range of 200-400 mg

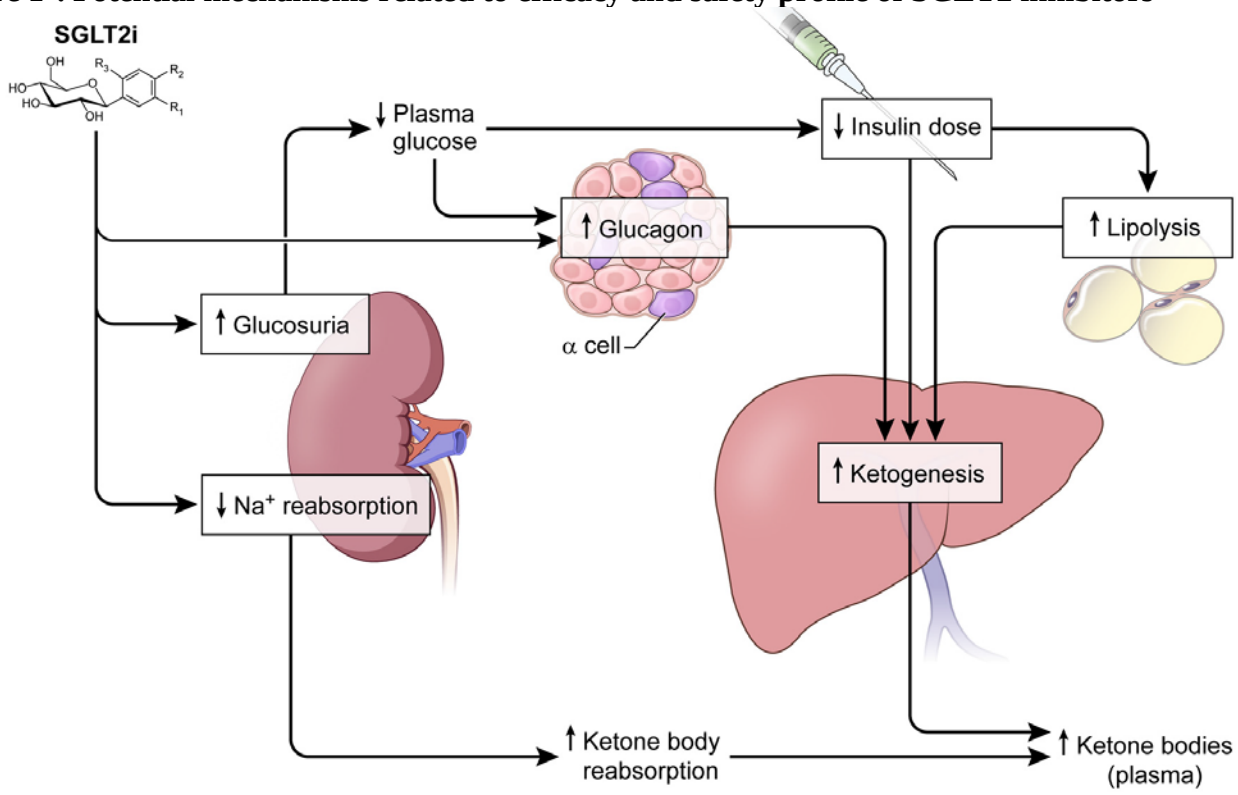
Steady state	• Steady state achieved after 5 days with once daily dosing with 1.5-2-fold accumulation
Drug-Drug Interaction (DDI)	No clinically meaningful DDI • Sotagliflozin: weak inhibitor of P-gp and BCRP • M19: inhibit CYP3A4 and CYP2D6; induce CYP3A4
QTc Prolongation	No QTc prolongation
Specific population	From PK perspective: • No dose adjustment for patients with eGFR≥45 ml/min/1.73m^2; available safety/efficacy data in the eGFR 45-60 takes precedence for additional considerations. • No dose adjustment for patients with mild hepatic impairment; not recommended for use in patients with moderate and severe hepatic impairment in the context of observed PK changes
Tmax-time to maximum concentration; Cmax-maximum concentration; AUC-area under the concentration-time curve; UGT1A9- uridine 5'-diphospho-glucuronosyltransferase 1A9; CYP3A4-cytochrome P450 3A4; t1/2-half life; P-gp: P-glycoprotein; BCRP-breast cancer resistance protein; CYP2D6- cytochrome P450 2D6; QTc-QT corrected; eGFR-estimated glomerular filtration rate; PK-pharmacokinetic(s)	

Source: table generated by Clinical Pharmacology reviewer

Pharmacodynamics

While the understanding of exclusive pharmacodynamic effects of SGLT1 inhibition are still evolving, potential pharmacodynamic effects of SGLT2 inhibition as they may relate to the efficacy and safety profile of these drugs are described in the Figure 8 below. SGLT2 inhibitors appear to be directly ketogenic, potentially through a reduction in renal clearance of ketones, as well as direct effects on the pancreatic alpha cells, which causes increased secretion of glucagon, thereby increasing ketone body production further.

Figure 1[2]. Potential mechanisms related to efficacy and safety profile of SGLT2 inhibitors



The data from studies conducted for sotagliflozin in healthy subjects and T1DM shows that sotagliflozin reduces renal glucose reabsorption by inhibiting SGLT2, while sotagliflozin-mediated SGLT1 inhibition appears to delay the absorption of glucose rather than reducing the extent of glucose absorption post-meal. Therefore, the clinical relevance of 2-hour PPG reduction with sotagliflozin as reported in T1DM is not well understood.

<u>Effect of single oral dose of sotagliflozin on postprandial glucose (PPG) and urinary glucose excretion (UGE) in healthy subjects</u>

In a PD study in healthy subjects using stable isotope tracer methods, following a radio-labelled glucose drink within 15 minutes after the administration of sotagliflozin, the rate of oral glucose appearance with sotagliflozin is significantly lower than placebo during the first 1 and 2 hours, but was comparable over 0-5 hour time interval between sotagliflozin and placebo groups. Regarding UGE, sotagliflozin produced significantly higher $UGE_{0\text{-}24\ hours}$ as compared to placebo.

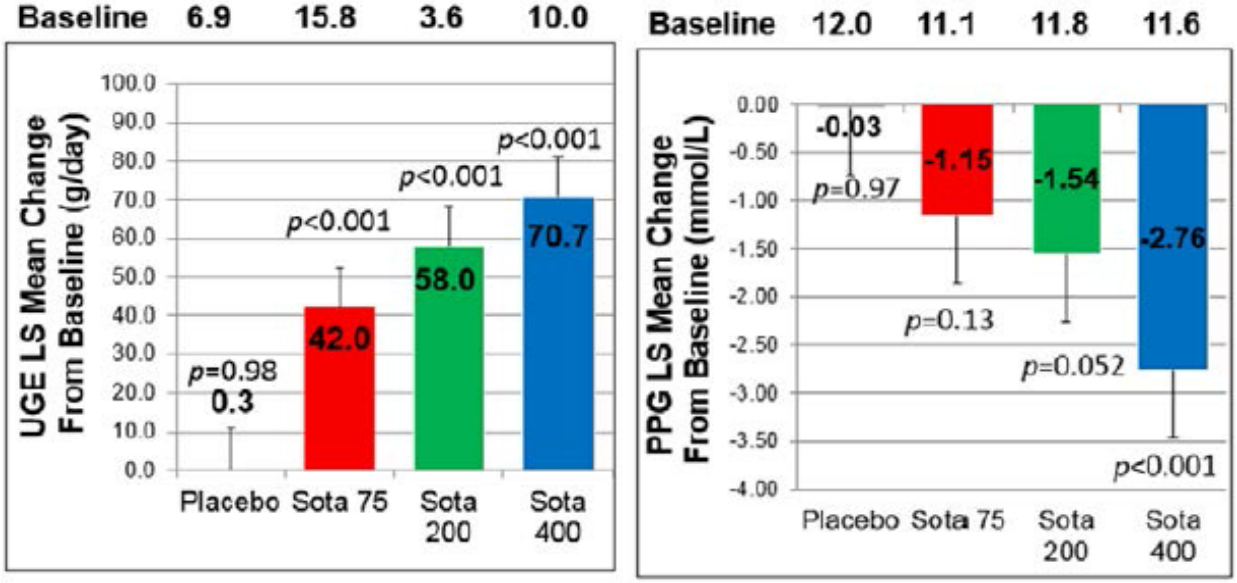
<u>Effect of sotagliflozin on PPG and UGE in T1DM</u>

In a dose-ranging study in T1DM, following the administration of sotagliflozin at 75 mg, 200 mg, or 400 mg once daily doses, the reduction in 2-hour PPG from baseline in sotagliflozin groups was statistically significant in the sotagliflozin 400 mg group as

[2] Figure adapted from Simeon I. Taylor, Jenny E. Blau, and Kristina I. Rother. SGLT2 Inhibitors May Predispose to Ketoacidosis. J Clin Endocrinol Metab, August 2015, 100(8):2849–2852.

compared to placebo after 12 weeks (-2.76 mg/dL; p<0.001) (Figure 22). The change from baseline in UGE at Week 12 was statistically significant in all 3 sotagliflozin dosing groups as compared to placebo: 75 mg (42.0 g/day, p <0.001); 200 mg (58.0 g/day, p <0.001), and 400 mg (70.7 g/day, p <0.001).

Figure 2. LS mean change from baseline in urinary glucose excretion (g/day) and 2-hour postprandial glucose (mg/dL) at Week 12



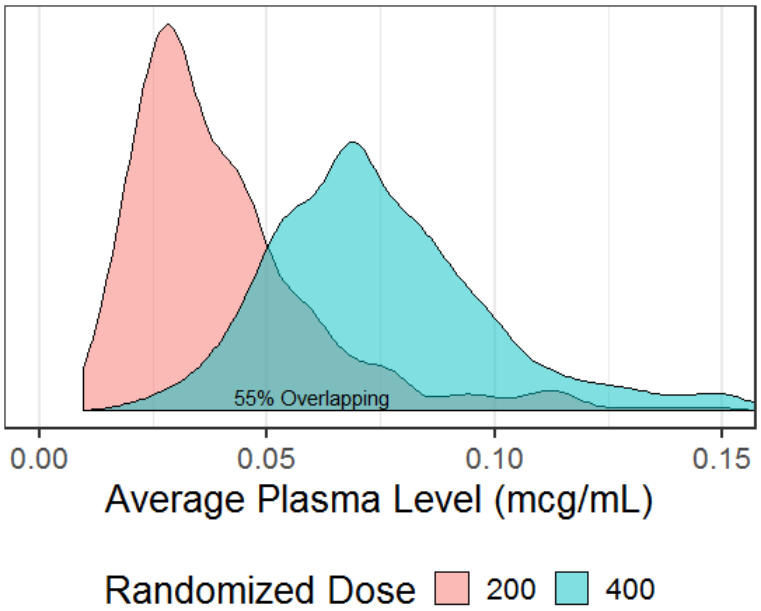
(Source: adapted from Figure 33 of Summary of Clinical Efficacy)

Exposure-Response Relationships

Due to patient-to-patient variability in its pharmacokinetics, average plasma concentrations[3] in patients treated with 200 mg sotagliflozin and 400 mg sotagliflozin have approximately 55% overlap (Figure 3.3). In other words, approximately half of subjects receiving a 200 mg dose had average plasma concentrations that were the same as half of subjects receiving a 400 mg dose. Therefore, FDA performed exploratory exposure-response analyses to explore the relationship between sotagliflozin exposure (i.e. instead of actual dose administered) and efficacy, safety, and key pharmacodynamic endpoints. All subsequent analyses described in this section include pooled data from clinical studies 309 and 310 (see Clinical Summary for a description of these studies). Note that no pharmacokinetic data were collected in study 312.

Figure 3. Distribution of Average Plasma Concentrations, Separated by Dose

[3] Calculated as steady state AUC divided by 24 hours

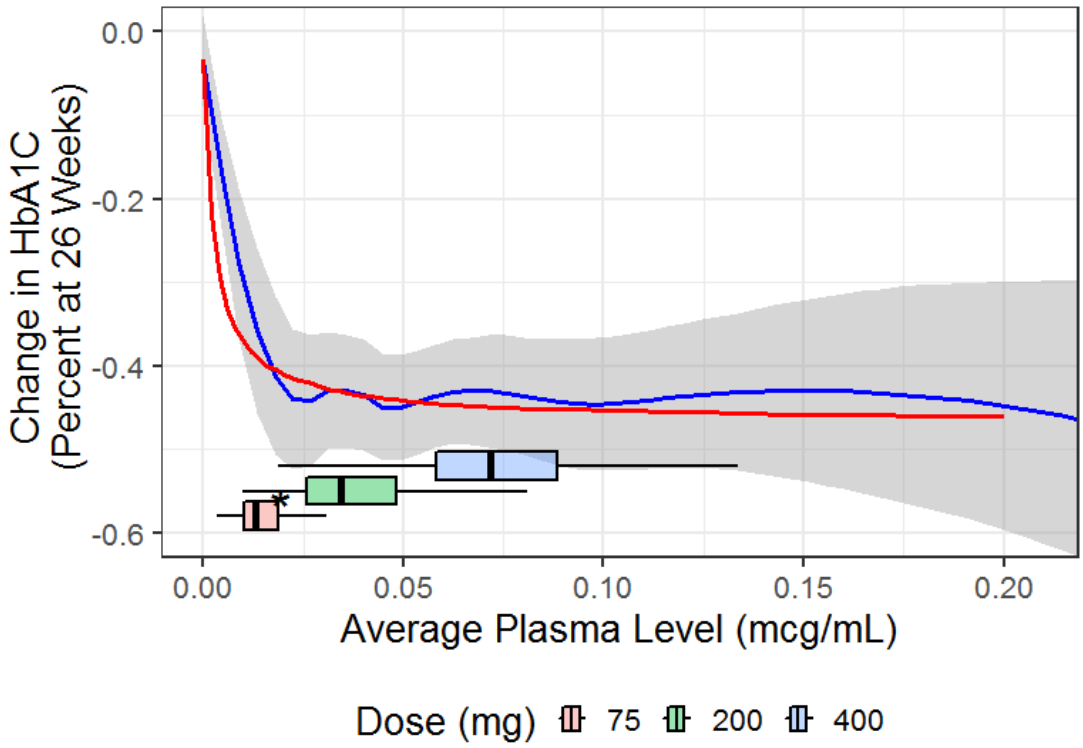


Source: Reviewer's Supplementary Analysis using final-pk-tbl.txt. Includes only subjects with pharmacokinetic data.

HbA1c Exposure-Response

The observed relationship between the change from baseline in HbA1c at 26 weeks and sotagliflozin plasma level (exposure) is presented in Figure 11. Among those treated with sotagliflozin, there were no significant trends in HbA1c reduction throughout the observed range of sotagliflozin plasma levels with 200 and 400 mg dose. The exposure-response relationship was primarily driven by the difference between placebo and treated groups (the average placebo A1c response (y axis) is at the x=0 (where AUC = 0)).

Figure 4. Exposure-Response for HbA1c In Studies 309 and 310



***** *The boxplot represents population PK predicted distribution of exposures for 75 mg. The red line represents model prediction a sigmoidal Emax model. The blue line represents a loess regression with a smoothing factor of 0.4. Gray bands indicate 95% confidence interval for the loess-estimated mean value.*
Source: Reviewer's Supplementary Analysis using final-pd-tbl.txt.

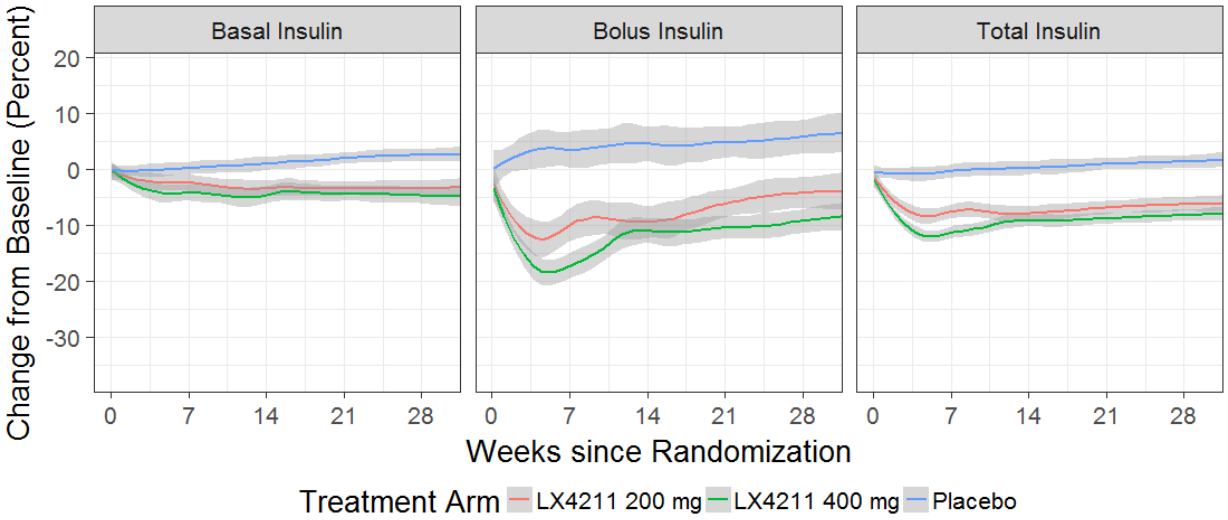
The observed relationship between sotagliflozin exposure and HbA1c reduction may be explained by the reduction in insulin dose that is often needed to prevent hypoglycemia in the face of the glucose lowering effect of sotagliflozin through SGLT-2-mediated urinary glucose excretion. This potential explanation is further explored in the following sections for urinary glucose excretion and insulin dose reductions.

Dose/Exposure-Response in Insulin Dose Reduction

The time profiles of change in basal, bolus, and total insulin dose are presented in Figure 55, separated by sotagliflozin dose. There is a numeric increase in insulin use in the placebo arms, and a dose-dependent reduction in insulin use in the sotagliflozin arms, most evident in the bolus insulin dosing. There is an apparent exposure-response relationship for the time-averaged[4] insulin reduction, with greater insulin reduction associated with higher sotagliflozin exposure (Figure 12).

[4] Calculated as Area under the Effect Curve for Insulin Reduction, divided by length of measurement. All insulin treatment data recorded less than 200 days following randomization was used.

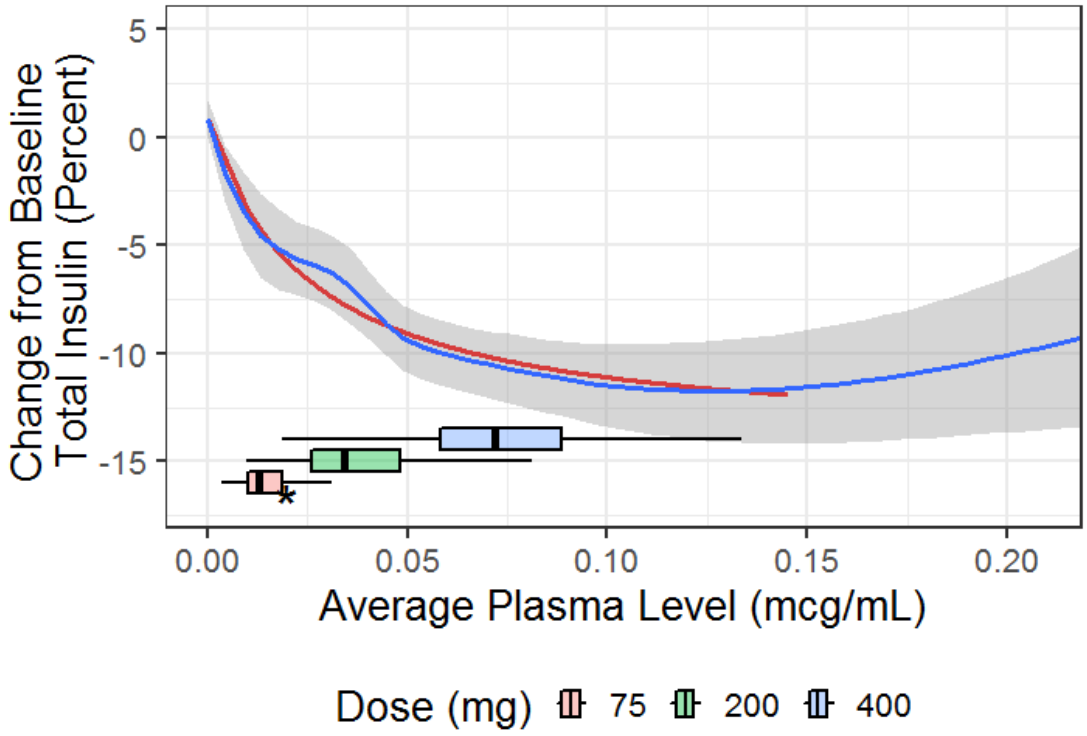
Figure 5. Changes in Insulin Dose versus Time, Separated by Sotagliflozin Dose (Studies 309 and 310)



Source: Reviewer's Supplementary Analysis, using adbhb.xpt in the submitted Integrated Summary of Safety. Smoothing was conducted using a loess regression with a smoothing factor of 0.4. Gray bands indicate 95% confidence interval for the loess-estimated mean value.

The stronger relationship with bolus insulin change compared to basal insulin to exposure is likely explained by the study design because in studies 309 and 310, if insulin dose reduction was warranted, the protocol suggested a reduction in bolus rather than basal insulin dose.

Figure 6. Exposure-Response Relationship for Total Insulin Dose Reduction, with Model Fit Overlay (Studies 309 and 310)

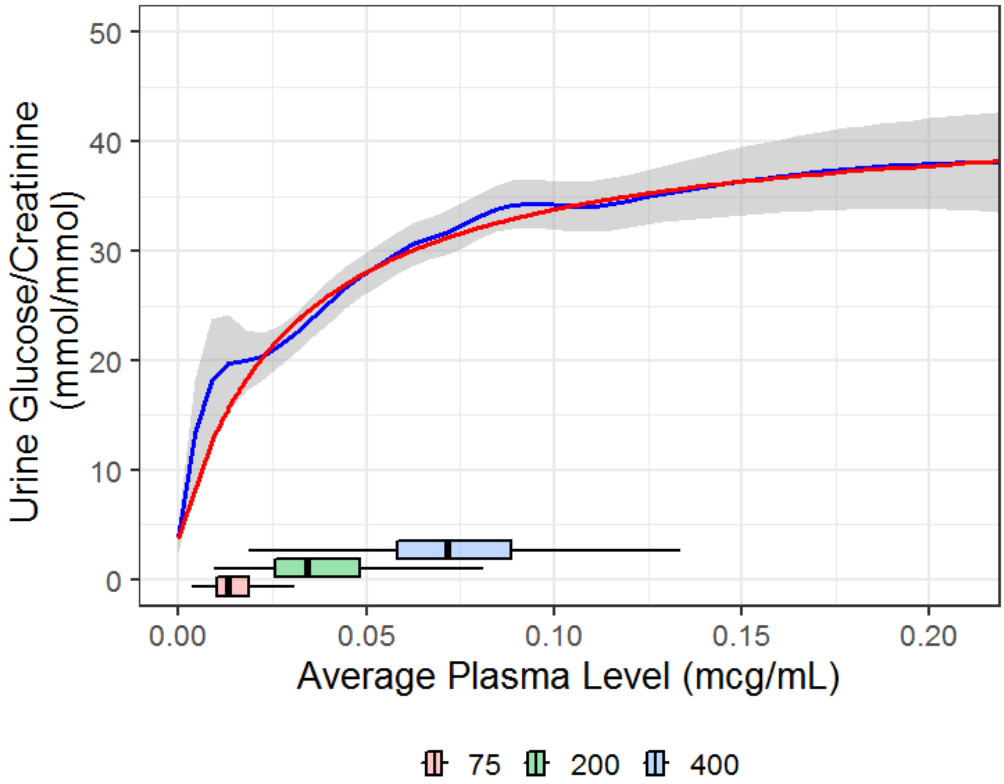


Source: Reviewer's Supplementary Analysis, using adbhb.xpt and final-pk-tbl.txt. ***** *The boxplot represents population PK predicted distribution of exposures for 75 mg. The red line represents model prediction from a sigmoidal Emax model. The model was predicted omitting the top 2% of exposures. The blue line represents a loess regression with a smoothing factor of 0.4. Gray bands indicate 95% confidence interval for the loess-estimated mean value.*

Exposure-Response in Urinary Glucose Excretion (UGE)

Urine Glucose to Urine Creatinine Ratio (UGCR) was reported as a marker for urinary glucose excretion (UGE). The relationship between UGCR and sotagliflozin plasma levels are shown in Figure 14. Consistent with dose-response, higher UGCR is associated with increasing sotagliflozin plasma level.

Figure 7. Exposure-Response Relationship for Urinary Glucose Excretion (Studies 309 and 310)



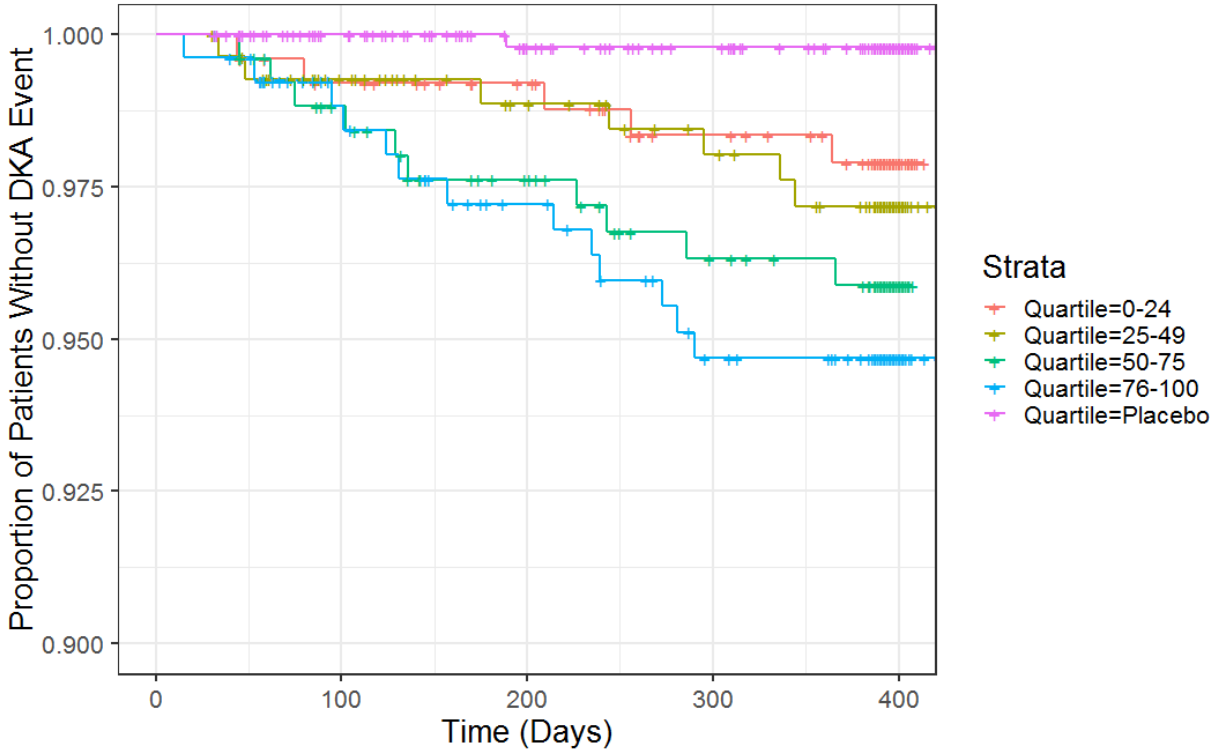
Source: Reviewer's Supplementary Analysis, using adlb.xpt (from ISS) and using final-pk-tbl.txt. Only subjects with suitable pharmacokinetic and urinary glucose excretion data are included in this analysis. The red line represents model prediction from a sigmoidal Emax model. The blue line represents a loess regression with a smoothing factor of 0.4. Gray bands indicate 95% confidence interval for the loess-estimated mean value.

The exposure-response data for UGCR and insulin reduction provide supportive evidence for the homeostatic mechanism described above. The 200 mg sotagliflozin dose results in plasma levels which are near the half-maximal effect of both insulin dose reduction and UGCR. These competing mechanisms may contribute to the lack of robust dose-response and exposure-response for HbA1c reduction.

Exposure-Response for Diabetic Ketoacidosis (DKA)

The distribution of 'time-to-DKA' by quartiles of sotagliflozin exposure was explored using the Kaplan-Meier method (Figure 8). There is a separation between subjects grouped into each quartile of exposure, where higher exposure appears to have higher risk and shorter time to DKA, particularly with the highest two quartiles. Placebo appears to have lower risk than any quartile of sotagliflozin exposure.

Figure 8. Kaplan-Meier Curves for CEC Adjudicated Time-to-DKA Event Stratified by Quartiles of Sotagliflozin Exposure (Studies 309 and 310)



Source: Reviewer's Analysis using aette.xpt, and inal-pk-tbl.txt, with FDA adjudicated Events Added

The distribution of potential baseline risk factors, e.g. lower BMI, younger age, history of DKA, use of insulin pump, lower HbA1c at baseline, appears to be reasonably balanced across the exposure quartiles (Table 2), except that a higher percentage of patients with lower sotagliflozin exposure had a history of DKA. For a complete discussion on DKA risk factors, refer to the summary of safety.

Table 2. Distribution of baseline risk factors by exposure quartiles (Studies 309 and 310)

Groups		Mean BMI	Mean Age (Years)	Percent with History of DKA	Percent using Insulin Pump	Mean HbA1c at BL	Time Averaged Change from Baseline in Insulin Dose to 200 Days
Sotagliflozin Exposure Quartiles	**0-24**	30.7	41.3	4.3	40	7.76	-6.61%
	25-49	29.2	45.1	4.7	44	7.68	-8.33%
	50-75	28.3	44.3	1.9	44	7.59	-9.86%
	76-100	27.1	46.3	1.9	43	7.61	-9.69%
Placebo		28.5	42.5	2.3	43	7.66	0.845%

Source: Reviewer's Analysis using adsl.xpt, aette.xpt, and inal-pk-tbl.txt.
BL: Baseline

Safety and Efficacy: Executive Summary and Conclusions

Three phase 3 studies were submitted to support the proposed indication. Studies 309 and 310 were designed to assess the safety and efficacy of sotagliflozin 200 mg and 400 mg once daily (qd) compared to placebo. The primary endpoint for studies 309 and 310 was change from baseline to week 24 in A1C. Study 312 was an efficacy and safety study to assess the proportion of subjects with A1C<7.0% at week 24 and no episode of severe hypoglycemia and no episode of diabetic ketoacidosis (DKA) from randomization to week 24 (which the applicant defined as net benefit) with sotagliflozin 400 mg vs. placebo.

Superiority was achieved for the primary endpoint in all three studies. A statistically significant treatment effect of ~ 0.2 - 0.4% reduction of A1C from baseline in subjects taking sotagliflozin 200 mg and 400 mg compared to subjects taking placebo was observed. Aligned with the primary efficacy findings, more subjects achieved HbA1c<7% in the both sotagliflozin groups than in placebo. In terms of risk, there were more DKA events in the sotagliflozin groups than in the placebo groups. Severe hypoglycemia overall did not show a significant difference between sotagliflozin and placebo.

For consideration of anti-hyperglycemic efficacy for the treatment of diabetes, the FDA relies on the use of the validated surrogate endpoint, HbA1c. As discussed above, while the primary endpoint for studies 309 and 310 was change from baseline to week 24 in A1c, study 312 had a composite primary endpoint which included the proportion of subjects with A1c < 7.0% at week 24 and no episode of severe hypoglycemia and no episode of diabetic ketoacidosis (DKA) from randomization to week 24 in A1c. The primary composite endpoint for study 312 achieved statistical significance; however, this was primarily driven by the HbA1c reduction calling into question the clinical relevance of the results of analyses based on the composite in informing the overall benefit risk assessment. As noted above, more subjects in the sotagliflozin arms experienced DKA compared to placebo, and most DKA events occurred among subjects who did not achieve A1C <7% at the end of treatment.

Two doses of sotagliflozin (200 mg and 400 mg) were studied in comparison to placebo in the three Phase 3 studies. No formal testing was performed comparing the two doses to each other, but there was a slight trend towards greater efficacy in terms of glycemic control for the 400 mg dose in comparison to the 200 mg dose, as well as greater reductions in body weight with the 400 mg dose. It may be useful to consider these results in the context of the overlapping exposure between the two doses (see Exposure-Response Relationships in Clinical Pharmacology Summary). In addition, there was also a trend towards a higher number of events of DKA with the 400 mg dose in comparison to the 200 mg dose.

DKA was the most notable and concerning adverse reaction associated with sotagliflozin. Our analyses concluded the following:

- Sotagliflozin was associated with an approximately 8-fold increase in DKA risk vs. placebo (95% CI: [3.1, 19.9]). The estimated number needed to harm (NNH) was approximately 26 patient-years of exposure to sotagliflozin to observe 1 additional DKA event (95% CI: [20.1, 38.5]).

- Subgroup analyses showed a consistently elevated DKA risk associated with sotagliflozin, with estimated hazard ratios ranging from 4 to 11, and NNH ranging from 11 to 37.
- The risk of DKA associated with sotagliflozin was consistently observed across subgroups.
- The observed risk of DKA was highest, independently of treatment, in subjects with the following characteristics: prior DKA history, young age, high baseline A1c, and CSII insulin delivery method, i.e. pump use.
- Sensitivity analyses by including pre-DKA and additional FDA-adjudicated DKA events (data not shown in these background materials) did not change the general conclusion.

Summary of Efficacy

Study Designs and Endpoints

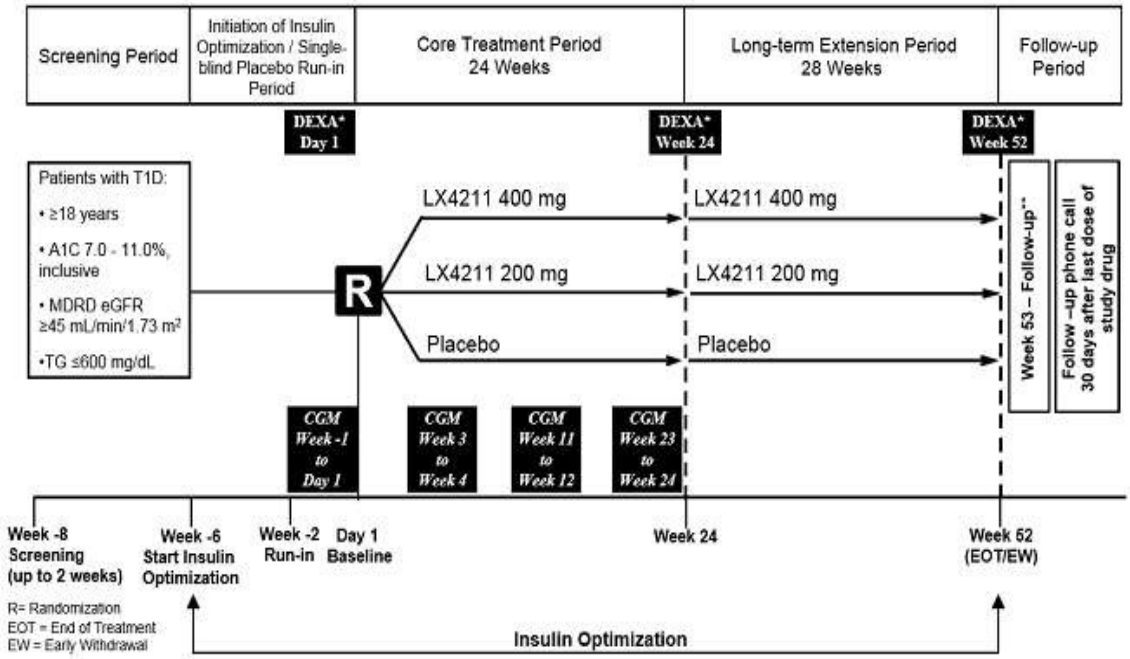
Studies 309 and 310

Studies 309 and 310 had identical study designs- multicenter, randomized, double-blind, placebo-controlled, parallel-group studies in adult patients with T1DM with inadequate glycemic control (HbA1c 7.0-11.0%, inclusive) treated with insulin (either MDI or CSII). Patients were to have no history of diabetic ketoacidosis (DKA) or severe hypoglycemic within 1 month prior to screening and eGFR>45 ml/min/1.73 m^2.

Prior to randomization, patients entered an insulin optimization period at week minus 6. At week 0 patients who met the enrollment criteria were randomized in a 1:1:1 fashion to sotagliflozin 200 mg, 400 mg, or placebo for a 24-week core treatment period, followed by a 28-week double-blinded extension period. Randomization was stratified by baseline A1c (<8.5, >8.5) and method of insulin delivery (pump or injections).

The primary objective was to demonstrate superiority of either 200 mg or 400 mg of sotagliflozin versus placebo (on a background of insulin) on HbA1c reduction at Week 24. The key secondary objective was to evaluate a composite of the proportion of patients with HbA1c<7% and no episode of severe hypoglycemia and no episode of DKA at Week 24. Study 309 was conducted in the US and Canada; 310 was conducted in Europe and Israel. There were continuous glucose monitor (CGM) and dual-energy X-ray absorptiometry (DEXA) for bone density substudies for a subset of patients.

Figure 9. Study Design for Study 309 and 310



Source: Figure 9.1-1 from Applicant's clinical study report

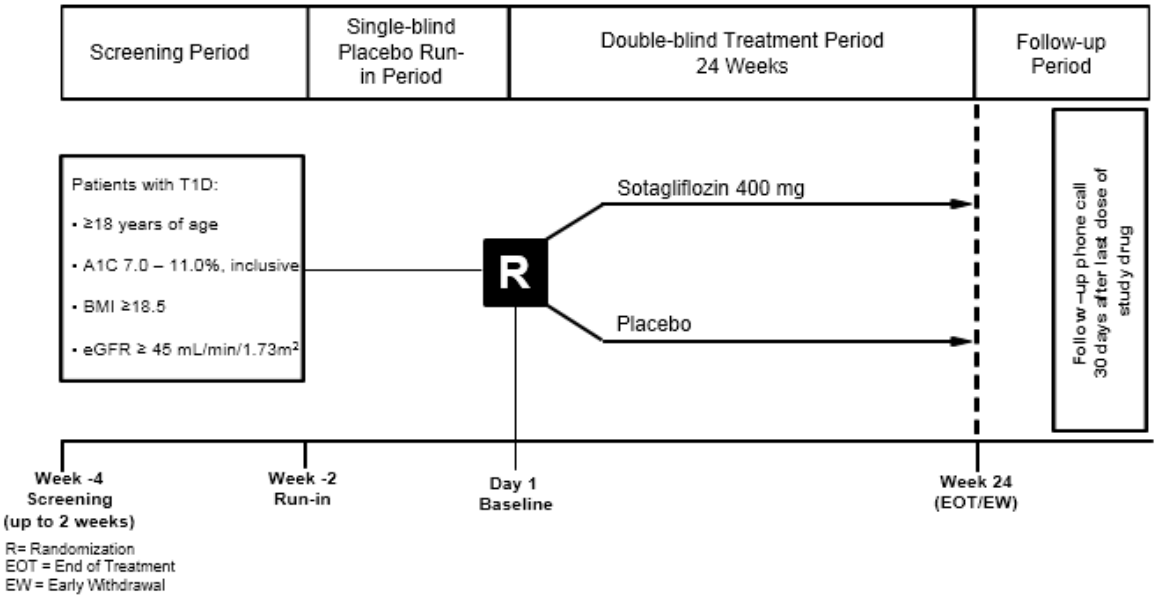
Study 312

Study 312 was also a multi-center, randomized 1:1, double-blind, placebo-controlled, parallel-group study in adult patients with T1DM with inadequate glycemic control with insulin therapy, and the inclusion and exclusion criteria were the same as for Studies 309 and 310. Study 312 differed from Studies 309 and 310 as there was no insulin optimization period, only the sotagliflozin 400 mg dose was studied, and the length of the study was 24 weeks not 52 weeks.

The primary objective for Study 312 was to demonstrate superiority of 400 mg of sotagliflozin versus placebo in the composite of the proportion of patients with HbA1c < 7.0% at Week 24 and no episode of severe hypoglycemia and no episode of diabetic ketoacidosis after randomization. The key secondary objective was to evaluate the change from baseline of sotagliflozin versus placebo on HbA1c, and body weight. Study 312 was conducted globally, and included 33 sites in the US. In a subgroup of patients, there was a satiety sub-study.

Given their identical study design, Studies 309 and 310 were pooled for purposes of efficacy (EFF-1 pool) and safety (SAF-1). Study 312 is presented separately.

Figure 10. Study Design for Study 312



Source: Figure 9.1-1 from Applicant's clinical study report

Glycemic management during the trials

The glycemic goals recommended for patients included treating HbA1c to a target of <7.0%, fasting plasma glucose between 80-130 mg/dL, and 2-hour postprandial glucose of <180 mg/dL. If glycemic goals were not met, Investigators were instructed to assess the need for a change in insulin dosing. Insulin titration algorithms for both MDI and CSII were provided to the Investigators to serve as a reference, but could be modified based on the Investigator's clinical assessment. Adjustments to insulin of more than 10% were not recommended. For further details, please see Appendix B: Insulin Dose Adjustment Guidelines.

For the first dose of study drug, patients were instructed to decrease their usual mealtime bolus insulin by 30% on Day 1 only. Subsequent adjustments to insulin were to be made by the Investigator.

Patient Disposition

Patient disposition for the EFF-1 pool (309 and 310) is displayed below in Table 3. The overall percentage of patients who were lost-to-follow up was approximately 0.4% for both trials. The amount of missing data in these trials was moderate (approximately 7-8% for both trials). The applicant collected data after treatment discontinuation. This helped reduce the amount of missing data.

Table 3. Disposition of Patients in EFF-1 (Studies 309 and 310)

	SOTA 200 mg n (%)	SOTA 400 mg n (%)	All SOTA n (%)	Placebo n (%)
Number of patients randomized/mITT Population	524	525	1049	526
Number of patients who received study drug	524 (100)	525 (100)	1049 (100)	526 (100)
Number of patients who completed 24 weeks	479 (91.4)	476 (90.7)	955 (91.0)	471 (89.5)
Number of patients who discontinued during CTP	45 (8.6)	49 (9.3)	94 (9.0)	55 (10.5)
Number of patients who completed 52 weeks	454 (86.6)	448 (85.3)	902 (86.0)	443 (84.2)
Number of patients who discontinued during LTE	25 (4.8)	28 (5.3)	53 (5.1)	28 (5.3)
Number of patients who discontinued the study	70 (13.4)	77 (14.7)	147 (14.0)	83 (15.85)

Source: adapted from Applicant's Table 1.1.2.1 from Integrated Summary of Efficacy

Subject disposition for Study 312 is displayed below in Table 4. The amount of missing data for Study 312 was approximately 10%, and was similar to EFF-1.

Table 4. Disposition of Patients in Study 312

	SOTA 400 mg n (%)	Placebo n (%)
Number of patients randomized/mITT Population	700	705
Number of patients who received study drug	699 (99.9)	703 (99.7)
Number of patients who completed study	605 (86.4)	624 (88.5)
Number of patients who discontinued the study	95 (13.6)	81 (11.5)

Source: adapted from Applicant's Table 10.1.1-2 from Clinical Study Report for Study 312

Patient Demographics

The demographic characteristics of patients in EFF-1 are summarized in Table 5. Baseline demographics were well-balanced between treatment groups. There was also no meaningful difference in baseline insulin dosing in U/kg or insulin delivery method across treatment groups. For further details on study demographics, see *Appendix C: Demographics Table for EFF-1*.

Table 5. Patient Demographics for EFF-1 (Studies 309 and 310)

Subgroup	SOTA 200 mg (N=524) n (%)	SOTA 400 mg (N=525) n (%)	SOTA ALL (N=1049) n (%)	Placebo (N=526) n (%)
Sex				
Female	259 (49.4)	272 (51.8)	531 (50.6)	255 (48.5)
Male	265 (50.6)	253 (48.2)	518 (49.4)	271 (51.5)
Age (years)				
Mean (SD)	44.4 (13.7)	44.0 (13.4)	44.2 (13.5)	42.5 (13.3)
Race				
Asian	7 (1.3)	5 (1.0)	12 (1.1)	4 (0.8)
Black	11 (2.1)	8 (1.5)	19 (1.8)	10 (1.9)

Subgroup	SOTA 200 mg (N=524) n (%)	SOTA 400 mg (N=525) n (%)	SOTA ALL (N=1049) n (%)	Placebo (N=526) n (%)
Native American	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)
Other	10 (1.9)	16 (3.0)	26 (2.5)	16 (3.0)
Pacific Islander	2 (0.4)	0 (0.0)	2 (0.2)	2 (0.4)
White	493 (94.1)	496 (94.5)	989 (94.3)	494 (93.9)
Region				
Asia	16 (3.1)	16 (3.0)	32 (3.1)	17 (3.2)
Canada	63 (12.0)	50 (9.5)	113 (10.8)	57 (10.8)
Europe	245 (46.8)	247 (47.0)	492 (46.9)	241 (45.8)
United States	200 (38.2)	212 (40.4)	412 (39.3)	211 (40.1)
Insulin Delivery				
CSII	224 (42.7)	224 (42.7)	448 (42.7)	226 (43.0)
MDI	300 (57.3)	301 (57.3)	601 (57.3)	300 (57.0)
HbA1c at Baseline (%)				
Mean (SD)	7.68 (0.773)	7.64 (0.776)	7.66 (0.774)	7.66 (0.808)
HbA1c Category				
<= 8.5%	423 (80.7)	425 (81.0)	848 (80.8)	422 (80.2)
> 8.5%	101 (19.3)	100 (19.0)	201 (19.2)	104 (19.8)
Duration of T1DM (yrs)				
Mean (SD)	21.6 (12.5)	21.5 (12.3)	21.5 (12.4)	21.2 (12.0)
BMI Category (kg/m^2)				
< 18.5	3 (0.6)	2 (0.4)	5 (0.5)	0 (0.0)
>= 30	205 (39.1)	192 (36.6)	397 (37.8)	186 (35.4)
>=18.5 to <25	139 (26.5)	125 (23.8)	264 (25.2)	141 (26.8)
>=25 to <30	177 (33.8)	206 (39.2)	383 (36.5)	199 (37.8)
Total Insulin Dose (U/kg)				
Mean (SD)	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)
eGFR by Category				
< 60	22 (4.2)	25 (4.8)	47 (4.5)	24 (4.6)
>= 90	232 (44.3)	241 (45.9)	473 (45.1)	257 (48.9)
>=60 to <90	270 (51.5)	259 (49.3)	529 (50.4)	245 (46.6)

Source: generated by the reviewer using ADLB datasets and adapted from data from Applicant's Table 10 from Summary of Clinical Efficacy

The demographic characteristics of patients in Study 312 are summarized in Table 6. As with EFF-1, baseline demographics were well balanced between treatment groups. For further details on study demographics, see *Appendix D: Demographics for Study 312*.

Table 6. Patient Demographics for Study 312

Subgroup	SOTA 400 mg (N=699) n (%)	Placebo (N=703) n (%)	Total (N=1402) n (%)
Sex			
Female	341 (48.8)	364 (51.8)	705 (50.3)
Male	358 (51.2)	339 (48.2)	697 (49.7)
Age (years)			
Mean	43.3 (14.2)	42.4 (14.0)	42.8 (14.0)
Age Group (years)			
Under 65 (AGE < 65)	644 (92.1)	657 (93.5)	1301 (92.8)
Over 65 (65 <= AGE)	55 (7.9)	46 (6.5)	101 (7.2)
Race			
Asian	7 (1.0)	5 (0.7)	12 (0.9)
Black	24 (3.4)	22 (3.1)	46 (3.3)
Native American	1 (0.1)	5 (0.7)	6 (0.4)
Other	47 (6.7)	50 (7.1)	97 (6.9)
Pacific Islander	1 (0.1)	0 (0.0)	1 (0.1)
White	619 (88.6)	621 (88.3)	1240 (88.4)
Region			
Africa	49 (7.0)	49 (7.0)	98 (7.0)
Asia	22 (3.1)	17 (2.4)	39 (2.8)
Canada	84 (12.0)	88 (12.5)	172 (12.3)
Europe	261 (37.3)	237 (33.7)	498 (35.5)
Other	63 (9.0)	69 (9.8)	132 (9.4)
South America	27 (3.9)	29 (4.1)	56 (4.0)
United States	193 (27.6)	214 (30.4)	407 (29.0)
Insulin Delivery Method			
MDI	424 (60.7)	423 (60.2)	847 (60.4)
CSII	275 (39.3)	280 (39.8)	555 (39.6)
HbA1c at Baseline (%)			
Mean	8.26 (0.965)	8.21 (0.921)	8.23 (0.943)
A1C Category			
<=8.5%	423 (60.5)	417 (59.3)	840 (59.9)
>8.5%	276 (39.5)	284 (40.4)	560 (39.9)

Subgroup	SOTA 400 mg (N=699) n (%)	Placebo (N=703) n (%)	Total (N=1402) n (%)
Missing	0 (0.0)	2 (0.3)	2 (0.1)
Duration of T1DM (yrs)			
Mean	20.5 (12.4)	19.6 (12.1)	20.0 (12.2)
BMI Category (kg/m^2)			
< 18.5	3 (0.4)	1 (0.1)	4 (0.3)
>= 30	236 (33.8)	218 (31.0)	454 (32.4)
>=18.5 to <25	201 (28.8)	205 (29.2)	406 (29.0)
>=25 to <30	259 (37.1)	279 (39.7)	538 (38.4)
Total Insulin U/kg			
Mean (SD)	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)
eGFR Category			
< 60	32 (4.6)	42 (6.0)	74 (5.3)
>= 90	355 (50.8)	361 (51.4)	716 (51.1)
>=60 to <90	312 (44.6)	300 (42.7)	612 (43.7)

Source: generated by the reviewer using ADLB datasets and adapted from Applicant's Table 11.2.1-1 from clinical study report

Statistical Efficacy

Statistical Methodologies

All analyses were performed using the modified intent-to-treat population (mITT), which was defined as all randomized subjects who had taken at least one dose of the study drug. The primary efficacy analyses were performed on the 24-week core treatment period. The long-term extension (LTE) period was used to support the primary efficacy analyses for studies 309 and 310.

Studies 309 and 310

The applicant's pre-specified analysis of the primary endpoint, change from baseline to week 24 in HbA1c, was performed using a mixed-effect model with repeated measures (MMRM) under the restricted maximum likelihood method for estimation. The model included randomization strata of insulin delivery method (MDI, CSII), randomization strata of week -2 HbA1c ($\leq$ 8.5%, > 8.5%), time (study weeks), treatment-by-time interaction, and baseline HbA1c-by-time interaction.

During review, we requested from the applicant that additional missing data analysis be conducted. MMRM assumes the data are missing at random (MAR), this treats the behavior of missing data for those patients who are off-treatment to be the same as that of observed data for those patients who are on-treatment in the same treatment arm. We asked the applicant to address missing data on the efficacy endpoints by having the missing data from subjects who do not

adhere to therapy imputed from a model based on the data from those subjects on the same treatment arm that also do not adhere to therapy but have the measurement for the efficacy endpoints (retrieved drop-out). The applicant was asked to explore other methods, such as wash-out to address missing values if there was insufficient retrieved drop-out data.

The secondary endpoints were as follows:

- Proportion of subjects with HbA1c <7% at week 24 and no episode of severe hypoglycemia, and no episode of DKA (severe hypoglycemia and DKA occurrence over the cumulative randomized double-blind 24-week Core Treatment Period) (Applicant defined Net benefit at week 24)
- Change from baseline in body weight at Week 24
- Change from baseline in mean daily bolus insulin at week 24
- Change from baseline FPG at week 24
- Change from baseline in diabetes treatment satisfaction as measured by DTSQs scores at Week 24
- Change from baseline in Diabetes Distress as measured by DDS2 scores at Week 24

The continuous secondary efficacy endpoints were analyzed in the same manner as the primary efficacy endpoint with the corresponding baseline value-by-time covariate specific for that secondary endpoint to be used in the model. Binary efficacy endpoints were analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by the different levels of the randomization stratification factors of insulin delivery method (MDI, CSII) and week -2 HbA1c (≤8.5%, >8.5%).

The applicant used a pattern mixture model (PMM) with control (placebo) based imputation to assess missing data. The applicant also conducted multiple imputation based on using jump-to-reference method, copy-to-reference and a one-dimensional tipping point analysis. See the reviewer's comments above.

Multiplicity in statistical testing of the efficacy variables in study 309 and 310 occurred from 2 main sources: (a) testing of the primary endpoint and multiple secondary endpoints, and (b) testing of 2 sotagliflozin dose groups against placebo for each endpoint. These considerations yielded sequential tests that can be grouped into 7 families (Table 7): each family had two parallel tests corresponding to two sotagliflozin doses vs. placebo for the specific endpoint. Each of two parallel tests corresponding to two sotagliflozin doses (200mg and 400 mg) vs. placebo use an equal weight Bonferroni procedure so that the per comparison error rate = 0.025 (2-sided). Formal testing was to stop at an endpoint for which a p-value exceeded 0.025 for one of two parallel tests.

Table 7. Statistical Testing Strategy for studies 309 and 310

F1: Primary endpoint (Family F1): superiority test of sotagliflozin (200mg or 400mg) versus placebo on HbA1c
F2: Secondary endpoint 1 (Family F2): superiority test of sotagliflozin (200mg or 400mg) versus placebo on proportion of patients with HbA1c <7.0% and no episode of SH and no episode of DKA
F3: Secondary endpoint 2 (Family F3): superiority test of sotagliflozin (200mg or 400mg) versus placebo on body weight (absolute change)
F4: Secondary endpoint 3 (Family F4): superiority test of sotagliflozin (200mg or 400mg) versus placebo on mean daily bolus insulin (as an average over the 3-5 days prior to the visit)
F5: Secondary endpoint 4 (Family F5): superiority test of sotagliflozin (200mg or 400mg) versus placebo on FPG
F6: Secondary endpoint 5 (Family F6): superiority test of sotagliflozin (200mg or 400mg) versus placebo on Diabetes Treatment Satisfaction as measured by DTSQs scores
F7: Secondary endpoint 6 (Family F7): superiority test of sotagliflozin (200mg or 400mg) versus placebo on Diabetes Distress as measured by the 2-item DDS2 scores

Study 312

For study 312 the applicant's pre-specified analysis of the primary endpoint, the proportion of subjects with HbA1c < 7.0% at week 24 and no episode of severe hypoglycemia and no episode of DKA from randomization to week 24 (the applicant defined net benefit), was performed using a Cochran-Mantel-Haenszel test stratified by the different levels of the randomization stratification factors of BMI at screening (<25 kg/m^2, ≥25 kg/m2), week -2 HbA1c (≤9.0%, >9.0%), and use of CSII at screening (yes, no). The treatment group comparisons were to be performed at week 24 only. Note this endpoint is a combination of efficacy (HbA1c) and safety (severe hypoglycemia and DKA). Only positively adjudicated severe hypoglycemia and DKA events were used in this analysis. Missing observations at week 24 were imputed as non-responders.

The secondary endpoints were change from baseline in sotagliflozin 400 mg compared with placebo for each of the following:

- HbA1c at week 24
- Body weight at week 24 (absolute and percent changes)
- SBP at week 16 in the subset of patients with baseline SBP ≥130 mm Hg
- Bolus insulin dose at week 24 (as an average over the 3-5 days prior to the visit)

A step-down testing approach was used to account for multiplicity across the secondary endpoints in study 312. Using this approach, the inference for the primary efficacy endpoint for the sotagliflozin 400 mg dose versus placebo was performed at the 2-sided 5% significance level. If statistical significance at the 5% level was achieved for the primary efficacy endpoint, then the secondary endpoints were tested in the hierarchical order specified above so that the overall type 1 error rate was controlled at a 2-sided 5% significance level across those endpoints.

The sponsor analyzed these endpoints using MMRM statistics based on the restricted maximum likelihood method for estimation. The model included treatment, randomization strata of BMI at screening (<25 kg/m^2, ≥25 kg/m^2), randomization strata of week -2 HbA1c (≤9.0%, >9.0%), randomization strata of use of CSII at screening (yes, no), time (study week), and a treatment-by-

time interaction as fixed categorical effects, and baseline-dependent variable-by-time interaction as a covariate.

We requested that the applicant provide a retrieve drop-out imputation, as well as a wash-out imputation to address missing values. The applicant conducted a washout analysis that assumed that after discontinuation, subjects discontinued from the experimental arm will exhibit a response similar to subjects in the placebo arm. For subjects on sotagliflozin with missing values at week 24, these missing values were imputed with observed baseline and week 24 data from the placebo group, no intermediate values from either placebo or sotagliflozin arms were used in the imputation for the sotagliflozin group. For subjects on placebo, intermediate observed values were used while imputing missing values at week 24. The results using the wash-out analysis will be shown, not the results using MMRM. Since the amount of retrieved drop-out data was low for studies 309 and 310, the applicant conducted a retrieve drop-out analysis for study 312 only at week 24. The applicant conducted these analyses for HbA1c, body weight, and FPG.

Efficacy Results

The pre-specified primary analysis for the primary endpoint, change from baseline in HbA1c (%) at week 24 in studies 309 and 310 and the first secondary endpoint in study 312 are shown in Table 8. The mean baseline HbA1c in study 309 was 7.6% for both sotagliflozin groups and 7.5% for the placebo group. In study 310, the mean baseline HbA1c was 7.7% for both sotagliflozin groups and 7.8% for the placebo group. In study 312, baseline HbA1c was higher compared to studies 309 and 310, with a mean baseline value of 8.2% in both the sotagliflozin 400 mg group and placebo group. The results shown in Table 8 include imputed data for missing HbA1c values using a wash-out imputation. In all three studies, the sotagliflozin groups achieved a statistically significant difference in mean change in HbA1c from baseline compared to placebo. The magnitude of difference ranged from -0.3% to -0.35% in the sotagliflozin 200 mg group and -0.35% to -0.45% in the sotagliflozin 400 mg group in the three studies. There were no meaningful differences in HbA1c reduction between the 200 mg and 400 mg doses.

Table 8. Change from Baseline in HbA1c (%) at Week 24 - mITT Population - Core Treatment Period

Study 309			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	268	263	262
Change from baseline at Week 24			
Mean Estimate	-0.03	-0.36	-0.42
Treatment difference		-0.33	-0.39
95% CI		-0.42, -0.24	-0.48, -0.30
p-value		<0.001	<0.001
Study 310			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	258	261	263
Change from baseline at Week 24			
Mean Estimate	0.04	-0.31	-0.31
Treatment difference		-0.35	-0.35
95% CI		-0.46, -0.23	-0.46, -0.23
p-value		<0.001	<0.001
Studies 309 and 310 Combined			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	526	524	525
Change from baseline at Week 24			
Mean Estimate	-0.01	-0.35	-0.38
Treatment difference		-0.34	-0.37
95% CI		-0.41, -0.27	-0.45, -0.30
Nominal p-value		<0.001	<0.001
Study 312			
Treatment	Placebo		Sota 400mg
FAS	703		699
Change from baseline at Week 24			
Mean Estimate	-0.29		-0.73
Treatment difference			-0.44
95% CI			-0.52, -0.36
p-value			<0.001

Source: Response to Information Request dated November 6, 2018 and November 28, 2018
Multiple imputation: Wash-out analysis
Note: Post-Baseline mean estimates and p-values were obtained from ANCOVA model with treatment, study specific randomization strata (insulin delivery (MDI, CSII) and Week -2 HbA1c *(≤8.5%, >8.5%) for studies 309 and 310; BMI at Screening (<25 kg/m2, ≥25 kg/m2), Week -2* HbA1c *(≤9.0%, >9.0%), and use of CSII at Screening (yes, no) for study 312), and study (studies 309 and 310 combined) as fixed categorical effects, and baseline* HbA1c *as a covariate.*

Table 9 shows the results for change from baseline in HbA1c (%) at week 52 in the mITT population for the long-term extension period for studies 309 and 310 that include imputed data for missing HbA1c values using a wash-out imputation. The results show numerically lower (vs. 24 weeks) but statistically significant difference in mean change in HbA1c in the sotagliflozin

groups compared to placebo in both studies. Study 312 was a 24-week study so was not included in the analyses of endpoints at Week 52.

Table 9. Change from Baseline in HbA1c (%) at Week 52 - mITT Population

Study 309			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	268	263	262
Change from baseline at Week 52			
Mean Estimate	0.06	-0.17	-0.24
Treatment difference		-0.22	-0.29
95% CI		-0.33, -0.11	-0.41, -0.17
Nominal p-value		<0.001	<0.001
Study 310			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	258	261	263
Change from baseline at Week 52			
Mean Estimate	0.09	-0.13	-0.23
Treatment difference		-0.23	-0.32
95% CI		-0.37, -0.09	-0.46, -0.18
Nominal p-value		0.001	<0.001
Studies 309 and 310 Combined			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	526	524	525
Change from baseline at Week 24			
Mean Estimate	0.06	-0.17	-0.25
Treatment difference		-0.22	-0.31
95% CI		-0.31, -0.13	-0.40, -0.22
Nominal p-value		<0.001	<0.001

Source: Response to Information Request dated November 6, 2018 and November 28, 2018
Multiple imputation: Wash-out analysis
Note: Post-Baseline mean estimates and p-values were obtained from ANCOVA model with treatment, study specific randomization strata (insulin delivery (MDI, CSII) and Week -2 HbA1c *(≤8.5%, >8.5%)), and study as fixed categorical effects (studies 309 and 310 combined), and baseline* HbA1c *as a covariate.*

Table 10 shows the results of a responder analysis at week 24, where a responder is defined as a subject whose HbA1c is less than 7% at week 24. If a subject had a missing week 24 value, then that subject was considered a non-responder. There were more subjects in the sotagliflozin groups that achieved HbA1c < 7% than in the placebo group.

Table 10. Proportion of Subjects with HbA1c < 7% at Week 24 – mITT Population - Core Treatment Period

Study 309			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	268	263	262
Responder	61 (22.8%)	97 (36.9%)	123 (46.9%)
Non-responder	207 (77.2%)	166 (63.1%)	139 (53.1%)
Difference in % of responders from Placebo		14.12	24.19
95% CI		6.43, 21.82	16.33, 32.04
Nominal p-value		0.0004	<0.0001
Study 310			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	258	261	263
Responder	39 (15.1%)	87 (33.3%)	89 (33.8%)
Non-responder	219 (84.9%)	174 (66.7%)	174 (66.2%)
Difference in % of responders from Placebo		18.22	18.72
95% CI		11.02, 25.42	11.53, 25.92
Nominal p-value		<0.0001	<0.0001
Studies 309 and 310 Combined			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	526	524	525
Responder	100 (19.0%)	184 (35.1%)	212 (40.4%)
Non-responder	426 (81.0%)	340 (64.9%)	313 (59.6%)
Difference in % of responders from Placebo		16.10	21.37
95% CI		10.82, 21.39	16.00, 26.74
Nominal p-value		<0.0001	<0.0001
Study 312			
Treatment	Placebo		Sota 400mg
FAS	703		699
Responder	111 (15.8%)		207 (29.6%)
Non-responder	592 (84.2%)		492 (70.4%)
Difference in % of responders from Placebo			13.82
95% CI			9.5, 18.15
Nominal p-value			<0.0001

Source: Statistical Reviewer's Analysis

Note: Model included treatment, randomization strata of insulin delivery (MDI, CSII) and week -2 A1C (≤8.5%, >8.5%)

Table 11 shows the results of a responder analysis for studies 309 and 310, where a responder is defined as a subject who's HbA1c is less than 7% at week 52. If a subject had a missing week 52

value, then that subject was considered a non-responder. There were more subjects in the sotagliflozin groups that achieved HbA1c < 7% than in the placebo group.

Table 11. Proportion of Subjects with HbA1c < 7% at Week 52 – mITT Population

Study 309			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	268	263	262
Responder	56 (20.9%)	79 (30.0%)	93 (35.5%)
Non-responder	212 (79.1%)	184 (70.0%)	169 (64.5%)
Difference in % of responders from Placebo		9.14	14.60
95% CI		1.77, 16.52	7.03, 22.17
Nominal p-value		0.0157	0.0002
Study 310			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	258	261	263
Responder	40 (15.5%)	71 (27.2%)	73 (27.8%)
Non-responder	218 (84.5%)	190 (72.8%)	190 (72.2%)
Difference in % of responders from Placebo		11.70	12.25
95% CI		4.72, 18.67	5.27, 19.24
Nominal p-value		0.0012	0.0007
Studies 309 and 310 Combined			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	526	524	525
Responder	96 (18.3%)	150 (28.6%)	166 (31.6%)
Non-responder	430 (81.7%)	374 (71.4%)	359 (68.4%)
Difference in % of responders from Placebo		10.38	13.37
95% CI		5.29, 15.46	8.20, 18.54
Nominal p-value		<0.0001	<0.0001

Source: Statistical Reviewer's Analysis
Note: Model included treatment, randomization strata of insulin delivery (MDI, CSII) and week -2 HbA1c *(≤8.5%, >8.5%)*

The proportion of subjects with HbA1c <7% at week 24 and no episode of severe hypoglycemia, and no episode of DKA (severe hypoglycemia and DKA occurrence over the cumulative randomized double-blind 24-week core treatment period) was the primary endpoint in study 312 and the first secondary endpoint in studies 309 and 310. Since the by-treatment group comparison for the first primary efficacy endpoint, change from baseline in HbA1c (%) at week 24, achieved superiority for both the sotagliflozin 200 mg and 400 mg doses in studies 309 and 310, according to the pre-specified multiplicity plan, inferential statistical analysis may proceed to the first key secondary efficacy endpoint, the applicant-defined net benefit. A responder was defined as a subject who achieved HbA1c <7% at week 24 and had no episode of severe hypoglycemia, and no episode of DKA from randomization to week 24. Table 12 shows the results for all three studies. The superiority of sotagliflozin over placebo in proportions of patients achieving HbA1c target <7% at week 24, no episode of severe hypoglycemia from randomization to week 24 and no episode of DKA from randomization to week 24 was achieved for both sotagliflozin doses compared to placebo in each of the studies. Since the composite

endpoint incorporates both 'benefits' and 'risks' the component results are located elsewhere in this document. The HbA1c responder analysis was shown above in Table 10 and analyses of severe hypoglycemia and DKA are shown in the Safety Summary in Table 41 and Table 29, respectively. As is discussed in the Safety Summary, the risk of DKA was notably higher with sotagliflozin vs. placebo while there was no significant difference with regard to severe hypoglycemia. The statistically significant result for the prespecified composite appears to be driven mostly by the HbA1c component.

Table 12. Proportion of Subjects with HbA1c < 7% at week 24, and No Episode of Severe Hypoglycemia from Randomization to Week 24, and No Episode of DKA from Randomization to Week 24 – mITT Population

Study 309			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	268	263	262
Responder	58 (21.6%)	88 (33.5%)	114 (43.5%)
Non-responder	210 (78.4%)	175 (66.5%)	148 (56.5%)
Difference in % of responders from Placebo		11.82	21.87
95% CI		4.28, 19.36	14.10, 29.64
p-value		0.0023	<0.0001
Study 310			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	258	261	263
Responder	39 (15.1%)	82 (31.4%)	85 (32.3%)
Non-responder	219 (84.9%)	179 (68.6%)	178 (67.7%)
Difference in % of responders from Placebo		16.30	17.20
95% CI		9.17, 23.43	10.06, 24.35
p-value		<0.0001	<0.0001
Studies 309 and 310 Combined			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	526	524	525
Responder	97 (18.4%)	170 (32.4%)	199 (37.9%)
Non-responder	429 (81.6%)	354 (67.6%)	326 (62.1%)
Difference in % of responders from Placebo		14.00	19.46
95% CI		8.80, 19.20	14.15, 24.77
Nominal p-value		<0.0001	<0.0001
Study 312			
Treatment	Placebo		Sota 400mg
FAS	703		699
Responder	107 (15.2%)		200 (28.6%)
Non-responder	596 (84.8%)		499 (71.4%)
Difference in % of responders from Placebo			13.39
95% CI			9.12, 17.67
p-value			<0.0001

Source: Statistical Reviewer's Analysis, Sotagliflozin Integrated Summary of Efficacy Table 2.3.1.2, page 157

Table 13 shows tabulations for all three studies that includes eight categories for HbA1c, severe hypoglycemia, and DKA. While numbers are small, more sotagliflozin randomized patients as

compared to placebo patients were in the category of HbA1c ≥ 7%, and 'yes' DKA (and either yes or no SH). Further, in the category of HbA1c ≥ 7% and 'yes' DKA and 'yes' SH, the numbers are very small suggesting that severe hypoglycemia may not contribute much information to the composite endpoint.

Table 13. Categories of HbA1c, DKA, and Severe Hypoglycemia – Core Treatment Period + Extension

			Placebo	Sota 200mg	Sota 400mg
Study 309					
HbA1c < 7%	**DKA No**	**SH No**	51	69	85
		SH Yes	4	6	6
	DKA Yes	**SH No**	0	3	2
		SH Yes	1	1	0
HbA1c≥ 7%	**DKA No**	**SH No**	191	169	149
		SH Yes	21	10	11
	DKA Yes	**SH No**	0	5	9
		SH Yes	0	0	0
Study 310					
HbA1c < 7%	**DKA No**	**SH No**	37	67	70
		SH Yes	3	4	2
	DKA Yes	**SH No**	0	0	0
		SH Yes	0	0	1
HbA1c ≥ 7%	**DKA No**	**SH No**	208	175	179
		SH Yes	10	9	3
	DKA Yes	**SH No**	0	6	8
		SH Yes	0	0	0
Studies 309 and 310 Combined					
HbA1c < 7%	**DKA No**	**SH No**	88	136	155
		SH Yes	7	10	8
	DKA Yes	**SH No**	0	3	2
		SH Yes	1	1	1
HbA1c ≥ 7%	**DKA No**	**SH No**	399	344	328
		SH Yes	31	19	14
	DKA Yes	**SH No**	0	11	17
		SH Yes	0	0	0
Study 312 *					
HbA1c < 7%	**DKA No**	**SH No**	107		200
		SH Yes	4		4
	DKA Yes	**SH No**	0		2
		SH Yes	0		1
HbA1c ≥ 7%	**DKA No**	**SH No**	575		459
		SH Yes	13		15
	DKA Yes	**SH No**	4		17
		SH Yes	0		1

Source: Statistical Reviewer's Analysis

SH: Severe hypoglycemia
* Study 312 only had core treatment period

Table 14 shows the contingency table for categorical HbA1c and DKA. This table emphasizes that more patients were in the category of HbA1c≥ 7% and 'yes' DKA on sotagliflozin than on placebo.

Table 14. HbA1c and DKA – Core Treatment Period + Extension

		Placebo	Sota 200mg	Sota 400mg
Study 309				
HbA1c < 7%	**DKA No**	55	75	91
	DKA Yes	1	4	2
HbA1c ≥ 7%	**DKA No**	212	179	160
	DKA Yes	0	5	9
Study 310				
HbA1c < 7%	**DKA No**	40	71	72
	DKA Yes	0	0	1
HbA1c≥ 7%	**DKA No**	218	184	182
	DKA Yes	0	6	8
Studies 309 and 310 Combined				
HbA1c < 7%	**DKA No**	95	146	163
	DKA Yes	1	4	3
HbA1c ≥ 7%	**DKA No**	430	363	342
	DKA Yes	0	11	17
Study 312 *				
HbA1c< 7%	**DKA No**	111		204
	DKA Yes	0		3
HbA1c ≥ 7%	**DKA No**	588		474
	DKA Yes	4		18

Source: Statistical Reviewer's Analysis
* Study 312 only had core treatment period

Continuing with the hierarchical testing procedure, since the by-treatment group comparisons for the primary and first secondary endpoint were statistically significant, inferential statistical analysis may continue to the next secondary endpoint, change from baseline to week 24 in body weight (kg) in all three studies. In study 309, the mean baseline body weight was 87 kg. In study 310, the mean baseline body weight was slightly lower at 81-82 kg. In study 312, the mean body weight was 82 kg. Table 15 shows the results for change in body weight using a wash-out analysis to account for missing data in all three studies. A statistically significant decrease in body weight at week 24 for the sotagliflozin group was seen compared to placebo in all three studies. The magnitude of difference in change in body weight varied between 2 – 3 kg.

Table 15. Change from Baseline in Body Weight (kg) at Week 24 – mITT Population - Core Treatment Period

Study 309			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	268	263	262

Change from baseline at Week 24			
Mean Estimate	0.82	-1.40	-2.35
Treatment difference		-2.22	-3.17
95% CI		-2.74, -1.70	-3.69, -2.65
p-value		<0.001	<0.001
Study 310			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	258	261	263
Change from baseline at Week 24			
Mean Estimate	0.23	-1.62	-2.10
Treatment difference		-1.85	-2.33
95% CI		-2.40, -1.31	-2.87, -1.78
p-value		<0.001	<0.001
Studies 309 and 310 Combined			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	526	524	525
Change from baseline at Week 24			
Mean Estimate	0.57	-1.47	-2.18
Treatment difference		-2.04	-2.75
95% CI		-2.42, -1.66	-3.13, -2.38
Nominal p-value		<0.001	<0.001
Study 312			
Treatment	Placebo		Sota 400mg
FAS	703		699
Change from baseline at Week 24			
Mean Estimate	0.89		-1.86
Treatment Difference			-2.75
95% CI			-3.08, -2.42
p-value			<0.001

Source: Response to Information Request dated November 6, 2018 and November 28, 2018
Multiple imputation: Wash-out analysis
Note: Post-Baseline mean estimates and p-values were obtained from ANCOVA model with treatment, study specific randomization strata (insulin delivery (MDI, CSII) and Week -2 HbA1c *(≤8.5%, >8.5%) for studies 309 and 310; BMI at Screening (<25 kg/m2, ≥25 kg/m2), Week -2* HbA1c *(≤9.0%, >9.0%), and use of CSII at Screening (yes, no) for study 312), and study (studies 309 and 310 combined) as fixed categorical effects, and baseline A1C as a covariate.*

Table 16 shows the results for change in absolute body weight using a wash-out analysis to account for missing data at week 52 in studies 309 and 310.

Table 16. Change from Baseline in Absolute Body Weight (kg) at Week 52 – mITT Population

Study 309			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	268	263	262

Change from baseline at Week 52			
Mean Estimate	1.31	-1.45	-2.54
Treatment difference		-2.76	-3.85
95% CI		-3.45, -2.06	-4.55, -3.14
Nominal p-value		<0.001	<0.001
Study 310			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	258	261	263
Change from baseline at Week 52			
Mean Estimate	0.49	-1.43	-2.09
Treatment difference		-1.93	-2.58
95% CI		-2.63, -1.22	-3.28, -1.88
Nominal p-value		<0.001	<0.001
Studies 309 and 310 Combined			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	526	524	525
Change from baseline at Week 24			
Mean Estimate	0.95	-1.41	-2.28
Treatment difference		-2.36	-3.23
95% CI		-2.86, -1.87	-3.72, -2.73
Nominal p-value		<0.001	<0.001

Source: Response to Information Request dated November 6, 2018 and November 28, 2018
Multiple imputation: Wash-out analysis
Post-Baseline mean estimates and p-values were obtained from ANCOVA model with treatment, study specific randomization strata (insulin delivery (MDI, CSII) and Week -2 HbA1c *(≤8.5%, >8.5%)), and study as fixed categorical effects (studies 309 and 310 combined), and baseline* HbA1c *as a covariate.*

Absolute change in body weight at week 24 was statistically significant, thus, the next secondary endpoint in the hierarchical testing procedure in studies 309 and 310, mean daily bolus insulin (as an average over the 3-5 days prior to the visit), was tested. Note, in study 312, daily bolus insulin is fourth (last) endpoint in the hierarchical testing procedure.

Analyses for change from baseline in mean daily insulin were performed using MMRM, and no missing values were imputed. Table 17 shows the results for mean daily bolus insulin at week 24. In study 309, the sotagliflozin 200 mg group did not achieve statistical significance in change in daily bolus insulin compared to placebo. Therefore, neither the superiority of sotagliflozin 400 mg versus placebo on mean daily bolus insulin or the rest of the endpoints in the hierarchal order were tested for statistical significance. To complete the review, the results for the remaining secondary endpoints will be shown. These results are for descriptive purposes only and the p-values reported are nominal p-values for study 309.

In both studies 310 and 312, the sotagliflozin groups had a statistically significant change in mean daily bolus insulin at week 24 in favor of sotagliflozin compared to placebo.

Table 17. Change from Baseline of Mean Daily Bolus Insulin at Week 24 - mITT Population

Study 309			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	268	263	262
Change from baseline at Week 24			
N	241	242	242
Mean Estimate	-0.84	-2.33	-4.13
Treatment difference		-1.50	-3.30
95% CI		-3.30, 0.30	-5.09, -1.50
p-value		0.1031	0.0003
Study 310			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	258	261	263
Change from baseline at Week 24			
N	238	237	240
Mean Estimate	-1.19	-4.38	-4.78
Treatment difference		-3.20	-3.60
95% CI		-4.86, -1.53	-5.26, -1.94
p-value		0.0002	<0.0001
Studies 309 and 310 Combined			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	526	524	525
Change from baseline at Week 24			
N	479	479	482
Mean Estimate	-1.08	-3.43	-4.53
Treatment difference		-2.35	-3.44
95% CI		-3.57, -1.12	-4.67, -2.22
Nominal p-value		0.0002	<0.0001
Study 312			
Treatment	Placebo		Sota 400mg
FAS	703		699
Change from baseline at Week 24			
N	626		619
Mean Estimate	-1.09		-3.93
Treatment Difference			-2.84
95% CI			-4.05, -1.64
p-value			<0.0001

Source: Clinical Study Report-Protocol Number LX4211.309 Table 11.4.1.2.3-1, page 186, Statistical Reviewer study 310, Clinical Study Report-Protocol Number LX4211.312 Table 11.4.1.2.4-1, page 152, Sotagliflozin Integrated Summary of Efficacy Table 2.7.1.2, page 212-213

Note: Post-Baseline mean estimates and p-values were obtained from MMRM model with treatment, randomization strata (insulin delivery (MDI, CSII) and week -2 HbA1c *(≤8.5%, >8.5%) for studies 309 and 310 and use of CSII at*

Screening (yes, no) for study 312), time (study week), and a treatment-by-time interaction as fixed categorical effects, and baseline HbA1c*-by-time interaction as a covariate.*

Table 18 shows the results of mean daily basal insulin at week 24.

Table 18. Change from Baseline of Mean Daily Basal Insulin at Week 24 - mITT Population

Study 309			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	268	263	262
Change from baseline at Week 24			
N	241	243	242
Mean Estimate	1.48	-0.26	-1.50
Treatment difference		-1.74	-2.98
95% CI		-2.83, -0.64	-4.08, -1.89
Nominal p-value		0.0019	<0.0001
Study 310			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	258	261	263
Change from baseline at Week 24			
N	238	239	241
Mean Estimate	0.24	-1.34	-1.14
Treatment difference		-1.59	-1.38
95% CI		-2.63, -0.54	-2.42, -0.34
Nominal p-value		0.0029	0.0091
Studies 309 and 310 combined			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	526	524	525
Change from baseline at Week 24			
N	479	482	483
Mean Estimate	-0.91	-0.73	-1.30
Treatment difference		-1.64	-2.21
95% CI		-2.41, -0.87	-2.97, -1.44
Nominal p-value		<0.0001	<0.0001
Study 312			
Treatment	Placebo		Sota 400mg
FAS	703		699
Change from baseline at Week 24			
N	630		626
Mean Estimate	0.89		-1.71
Treatment Difference			-2.60
95% CI			-3.39, -1.81
Nominal p-value			<0.0001

Source Statistical Reviewer's Analysis

Note: Post-Baseline mean estimates and p-values were obtained from MMRM model with treatment, randomization strata (insulin delivery (MDI, CSII) and week -2 HbA1c *(≤8.5%, >8.5%) for studies 309 and 310 and use of CSII at*

Screening (yes, no) for study 312), time (study week), and a treatment-by-time interaction as fixed categorical effects, and baseline HbA1c-*by-time interaction as a covariate.*

Table 19 shows the results of mean daily total insulin at week 24.

Table 19. Change from Baseline of Mean Daily Total Insulin at Week 24 - mITT Population

Study 309			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	268	263	262
Change from baseline at Week 24			
N	241	242	242
Mean Estimate	0.81	-2.17	-5.54
Treatment difference		-2.98	-6.36
95% CI		-5.20, -0.76	-8.58, -4.14
Nominal p-value		0.0086	<0.0001
Study 310			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	258	261	263
Change from baseline at Week 24			
N	238	237	240
Mean Estimate	-0.91	-5.72	-5.88
Treatment difference		-4.80	-4.96
95% CI		-6.85, -2.76	-7.00, -2.93
Nominal p-value		<0.0001	<0.0001
Studies 309 and 310 combined			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	526	524	525
Change from baseline at Week 24			
N	479	479	482
Mean Estimate	-0.12	-4.01	-5.81
Treatment difference		-3.89	-5.68
95% CI		-5.41, -2.36	-7.20, -4.17
Nominal p-value		<0.0001	<0.0001
Study 312			
Treatment	Placebo		Sota 400mg
FAS	703		699
Change from baseline at Week 24			
N	626		619
Mean Estimate	-0.07		-5.32
Treatment Difference			-5.25
95% CI			-6.67, -3.83
Nominal p-value			<0.0001

Source: Statistical Reviewer's Analysis

Note: Post-Baseline mean estimates and p-values were obtained from MMRM model with treatment, randomization strata of insulin delivery (MDI, CSII) and week -2 HbA1c *(≤8.5%, >8.5%), time (study week), and a treatment-by-time interaction as fixed categorical effects, and baseline* HbA1c*-by-time interaction as a covariate.*

Change in mean daily bolus insulin at week 24 was statistically significant in study 310, thus, the next secondary endpoint in the hierarchical testing procedure, fasting plasma glucose (FPG) was tested. Since change in mean daily bolus insulin at week 24 was not statistically significant in study 309, FPG is shown as a descriptive analysis for this study. Table 20 shows the results of FPG at week 24. The results are from the wash-out analysis to account for missing data. In Study 310, both sotagliflozin groups had a statistically significant reduction in mean FPG change from baseline at week 24 compared to placebo. The results for study 312 are also shown, however, FPG was not part of the hierarchical testing procedure.

Table 20. Change from Baseline in Fasting Plasma Glucose (FPG) at Week 24 - mITT Population

Study 309			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	268	263	262
Change from baseline at Week 24			
Mean Estimate	1.88	-7.98	-14.90
Treatment difference		-9.87	-16.78
95% CI		-19.35, -0.38	-16.78, -7.28
Nominal p-value		0.041	<0.001
Study 310			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	258	261	263
Change from baseline at Week 24			
Mean Estimate	10.01	-9.94	-13.80
Treatment difference		-19.95	-23.80
95% CI		-30.97, -8.93	-34.82, -12.79
p-value		<0.001	<0.001
Study 312			
Treatment	Placebo		Sota 400mg
FAS	703		699
Change from baseline at Week 24			
Mean Estimate	9.77		-11.61
Treatment difference			-21.38
95% CI			-28.75, -14.00
Nominal p-value			<0.001

Source: Response to Information Request dated November 6, 2018
Multiple imputation: Wash-out analysis
Note: Post-Baseline mean estimates and p-values were obtained from ANCOVA model with treatment, study specific randomization strata (insulin delivery (MDI, CSII) and Week -2 HbA1c *(≤8.5%, >8.5%) for studies 309 and 310; BMI at Screening (<25 kg/m2, ≥25 kg/m2), Week -2* HbA1c *(≤9.0%, >9.0%), and use of CSII at Screening (yes, no) for study 312), and study (studies 309 and 310 combined) as fixed categorical effects, and baseline* HbA1c *as a covariate.*

Table 21 shows the results of FPG at week 52 for studies 309 and 310. The results are from the wash-out analysis to account for missing data. At 52 weeks, the sotagliflozin 200 mg group in

both studies 309 and 310 are no longer more efficacious, measured by reduction in change in FPG, than the placebo group.

Table 21. Change from Baseline in Fasting Plasma Glucose at Week 52 - mITT Population

Study 309			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	268	263	262
Change from baseline at Week 52			
Mean Estimate	7.67	-3.77	-9.83
Treatment difference		-11.44	-17.49
95% CI		-22.75, -0.13	-28.92, -6.07
Nominal P-value		0.047	0.003
Study 310			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	258	261	263
Change from baseline at Week 52			
Mean Estimate	1.71	-3.92	-13.74
Treatment difference		-5.63	-15.45
95% CI		-17.69, 6.43	-27.55, -3.35
Nominal P-value		0.36	0.012

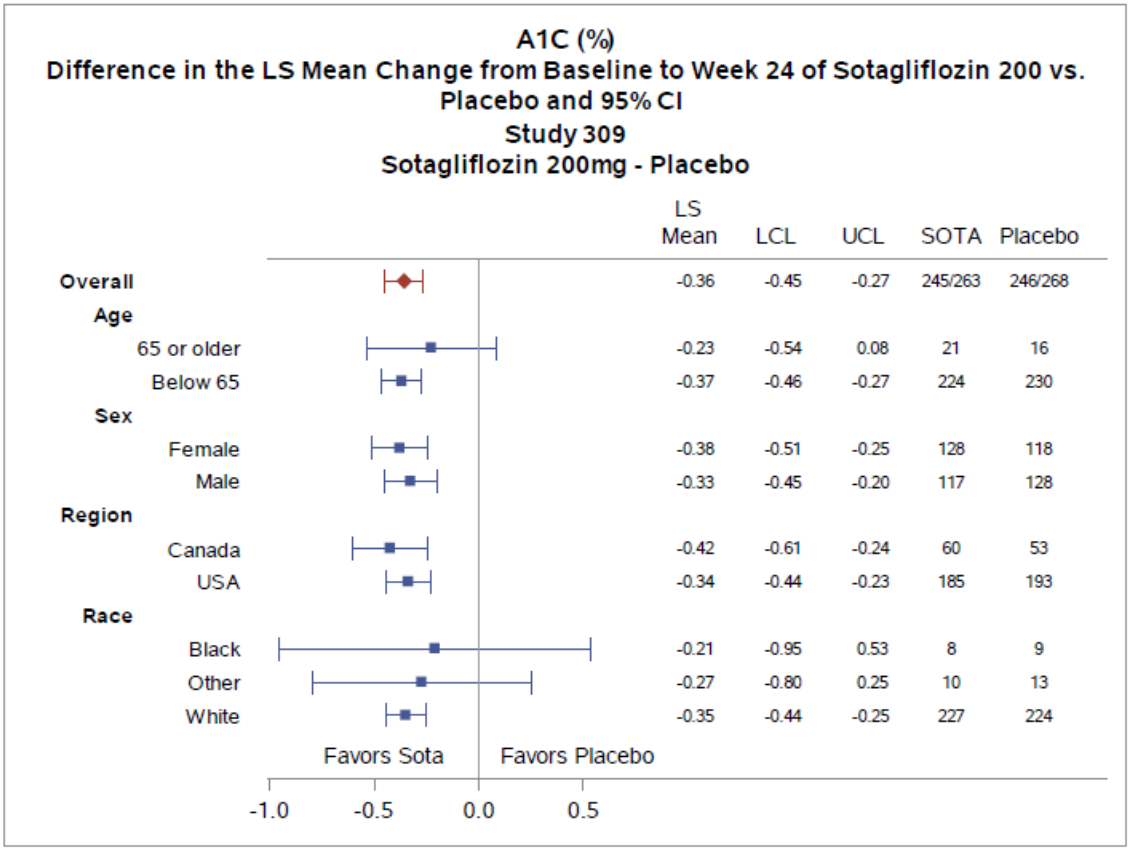
Source: Response to Information Request dated November 6, 2018
Multiple imputation: Wash-out analysis studies 309 and 310
Post-Baseline mean estimates and p-values were obtained from ANCOVA model with treatment, study specific randomization strata (insulin delivery (MDI, CSII) and Week -2 HbA1c *(≤8.5%, >8.5%)), and study as fixed categorical effects (studies 309 and 310 combined), and baseline* HbA1c *as a covariate.*

Subgroup efficacy analysis

Subgroup analyses were performed on the primary endpoint, HbA1c (%) by age (<65, ≥65), sex (Male, Female), region, and race. Study 310 was not conducted in the United States (USA). The subgroup analyses were performed using the mITT population. The forest plot combining all results are presented in the following figures. Note that Figure 15 and Figure 16 display the results of studies 309 and 310 combined.

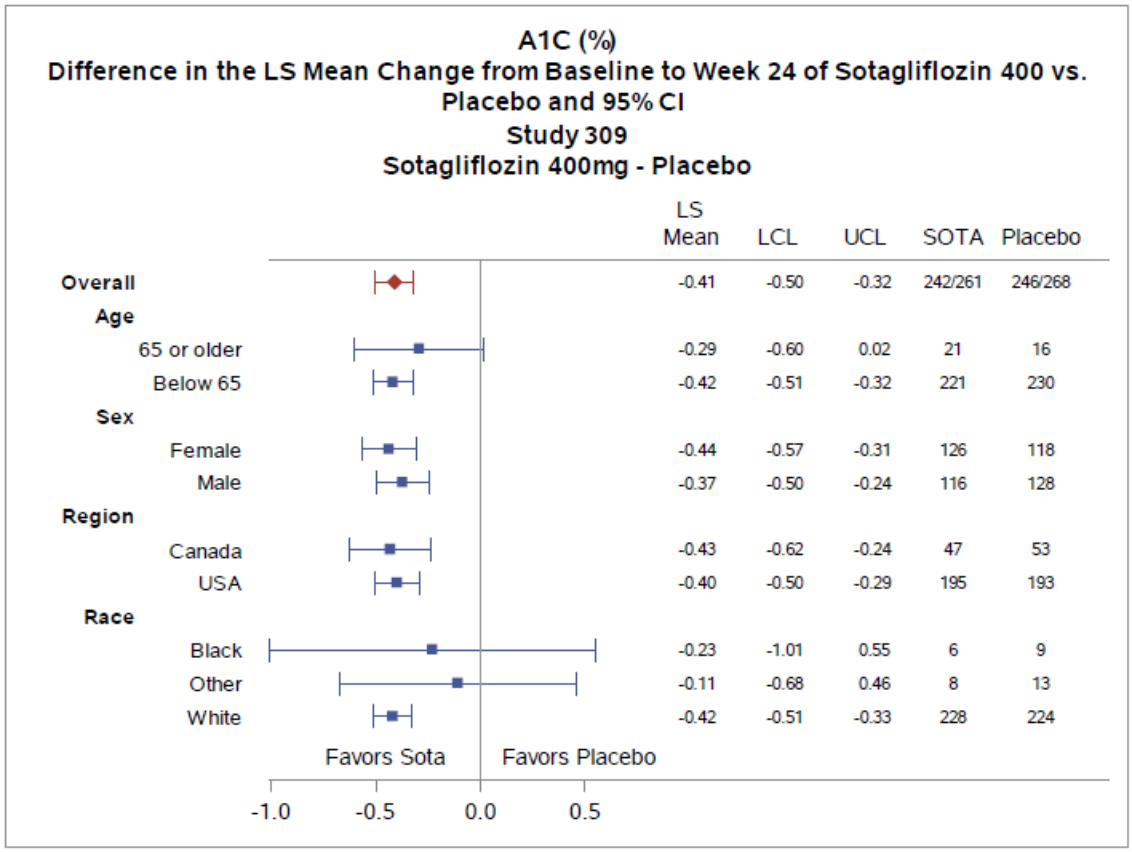
Overall, the treatment effects of the subgroups were consistent with the primary analysis.

Figure 11. Subgroup Analysis 200 mg vs. Placebo- Study 309



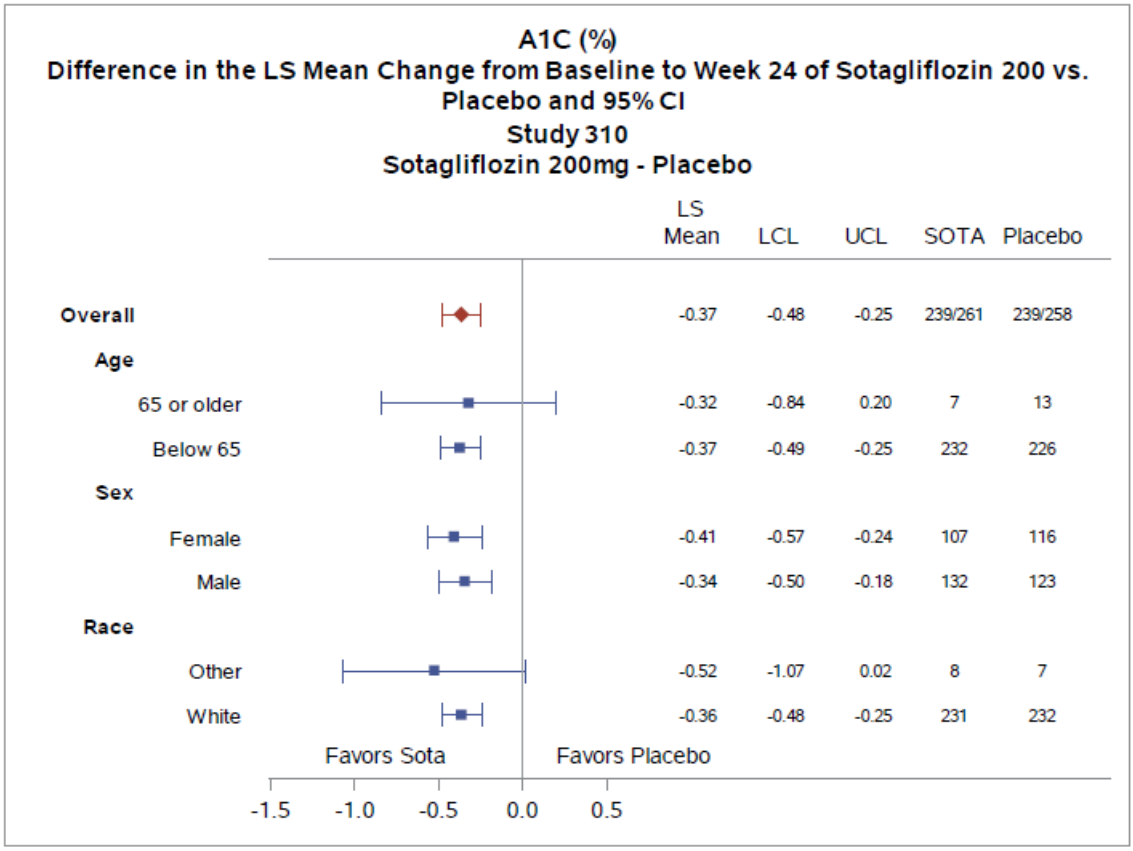
Source: Statistical Reviewer's Analysis

Figure 12. Subgroup Analysis 400 mg vs. Placebo- Study 309



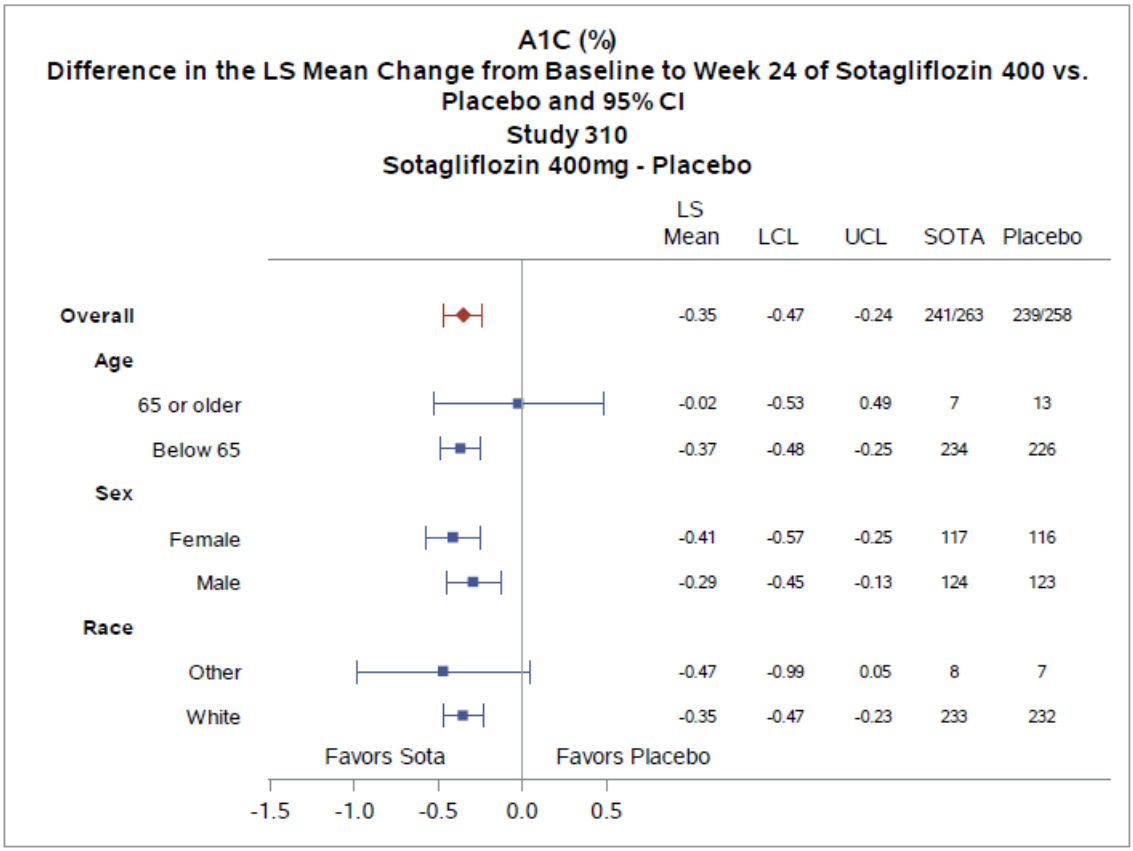
Source: Statistical Reviewer's Analysis

Figure 13. Subgroup Analysis 200 mg vs. Placebo- Study 310



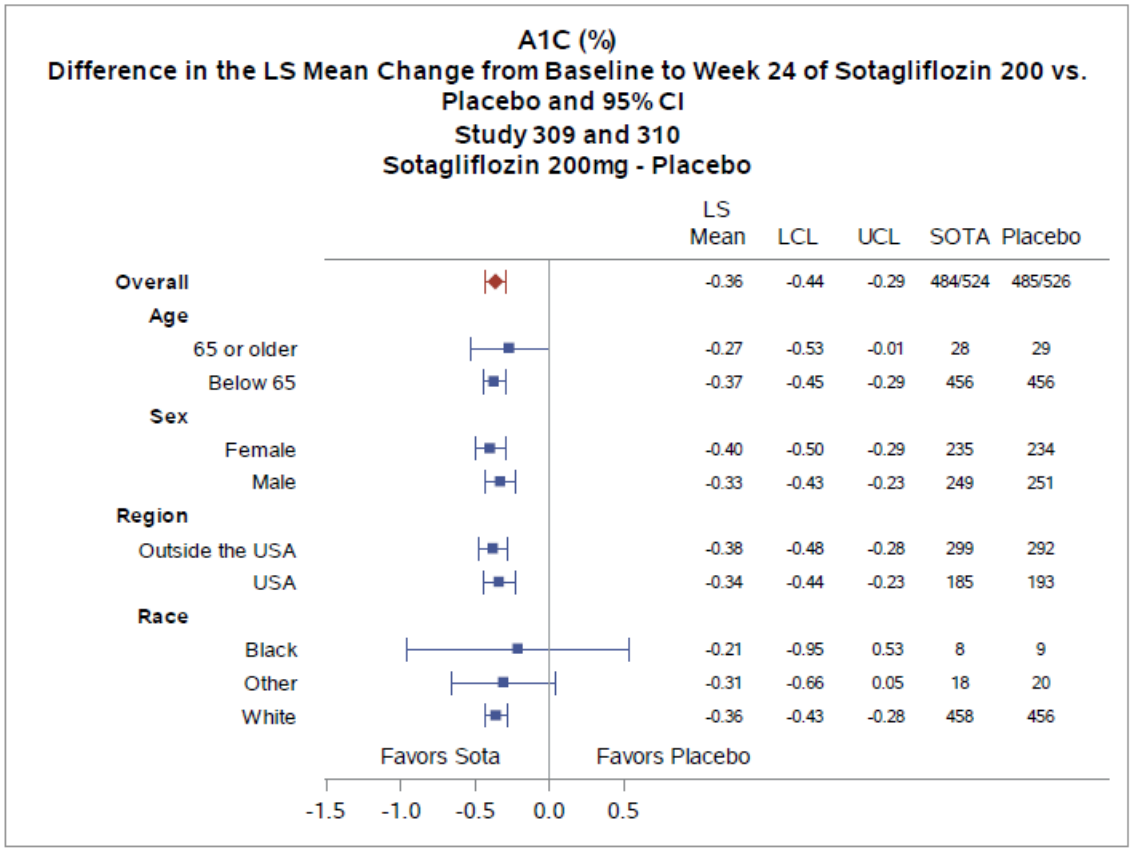
Source: Statistical Reviewer's Analysis

Figure 14. Subgroup Analysis 400 mg vs. Placebo- Study 310



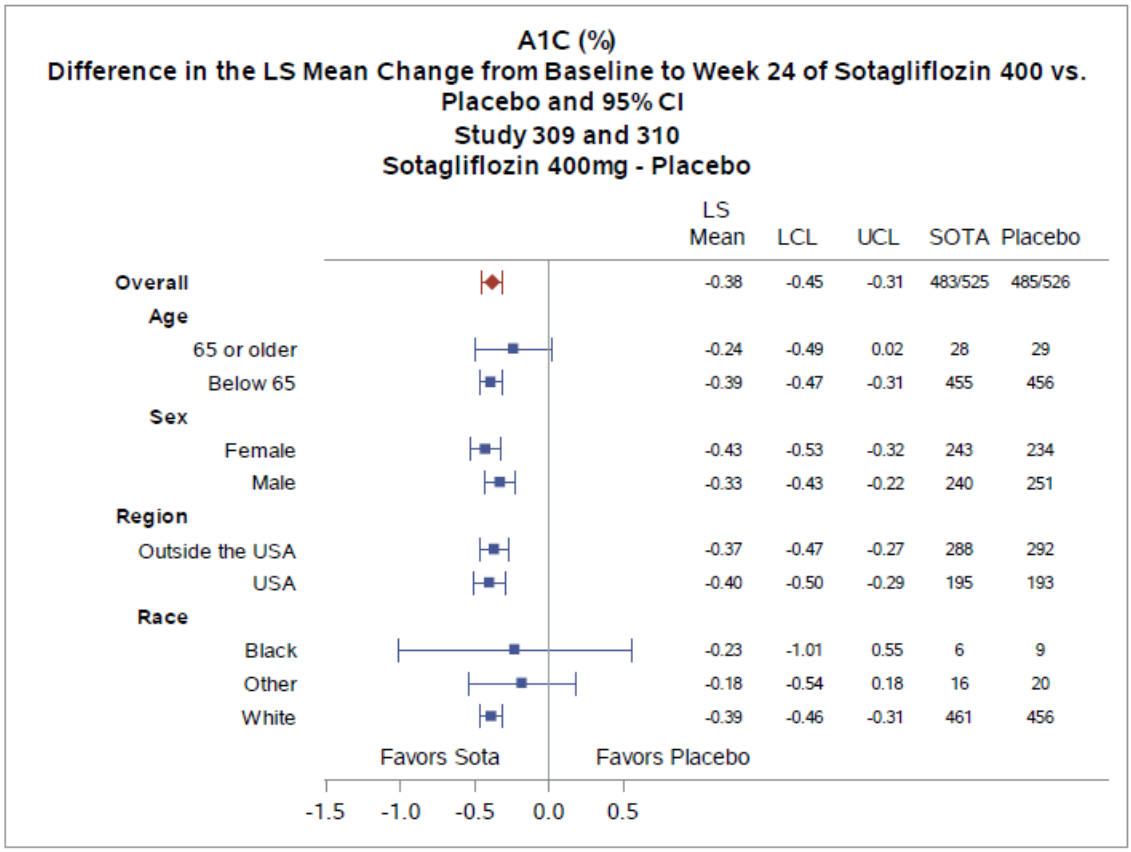
Source: Statistical Reviewer's Analysis

Figure 15. Subgroup Analysis 200 mg vs. Placebo- Studies 309 and 310



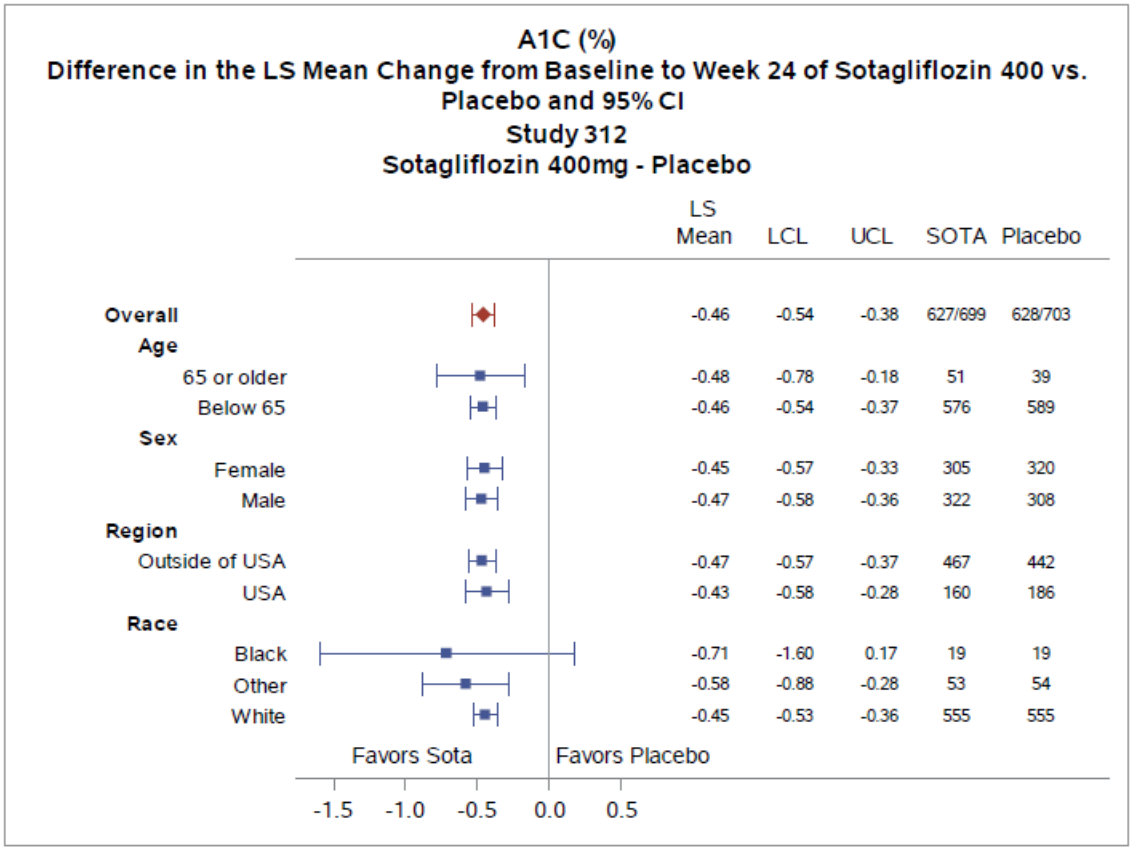
Source: Statistical Reviewer's Analysis

Figure 16. Subgroup Analysis 400mg vs. Placebo- Studies 309 and 310



Source: Statistical Reviewer's Analysis

Figure 17. Subgroup Analysis 400mg vs. Placebo- Study 312

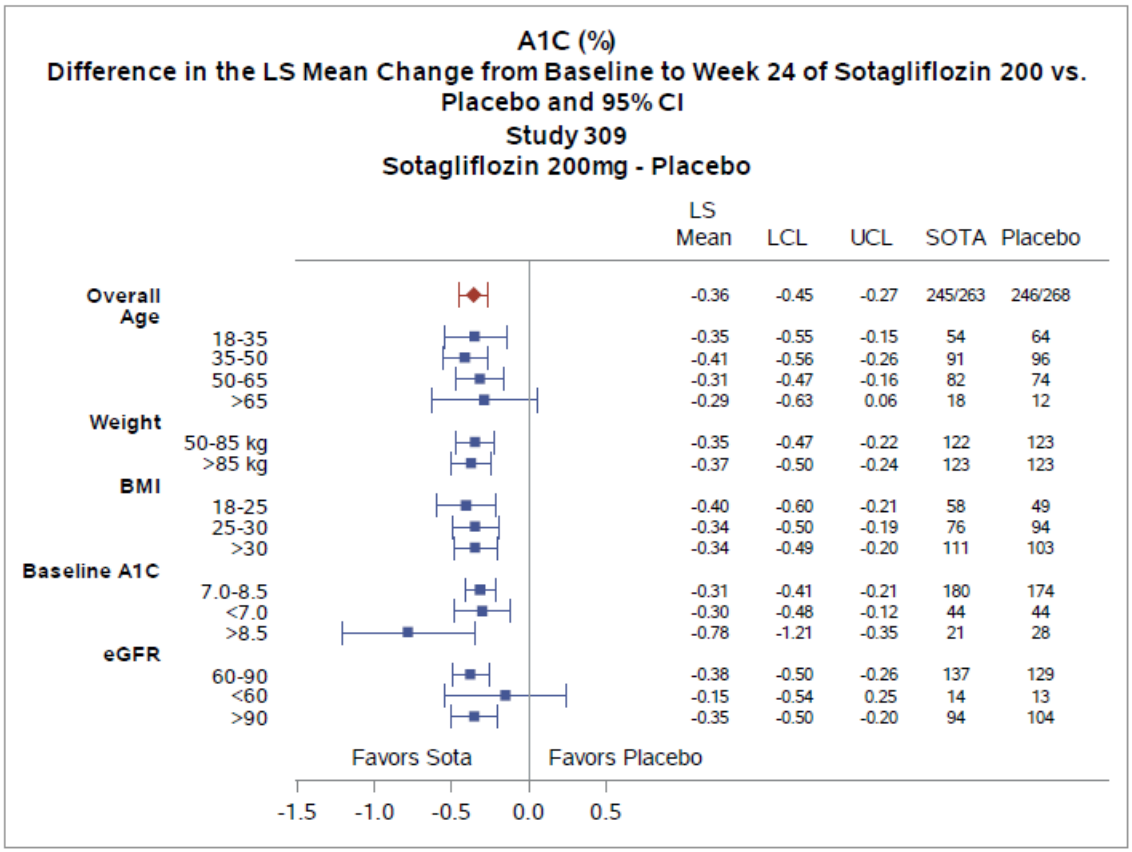


Source: Statistical Reviewer's Analysis

Additional subgroup analyses were performed on the primary endpoint, HbA1c (%), by age group (18-35, 35-50, 50-65, >65), weight (50-85 kg, >85 kg), baseline A1C (7.0-8.5, <7.0, >8.5), and eGFR (<60, 60-90, >90). The subgroup analyses were performed using the mITT population. The forest plot combining all results are presented in the following Figures. Note that Figure 22 and Figure 23 display the results of studies 309 and 310 combined.

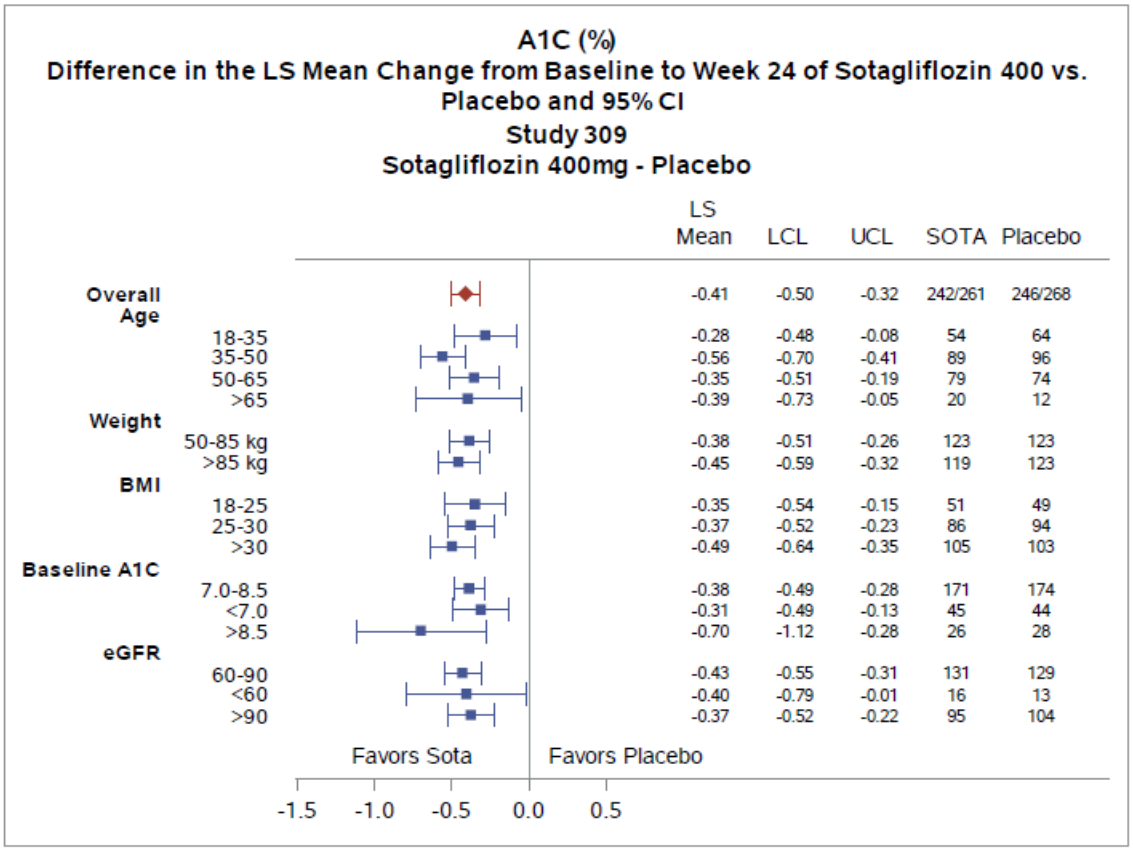
Overall, the treatment effects of the subgroups were consistent with the primary analysis, except in study 310 for the comparison of sotagliflozin 400mg vs. placebo. The age subgroup category 'greater than 65' was in favor of placebo, but there were few subjects in this subgroup to be able to draw meaningful conclusions.

Figure 18. Additional Subgroup Analysis 200 mg vs Placebo - Study 309



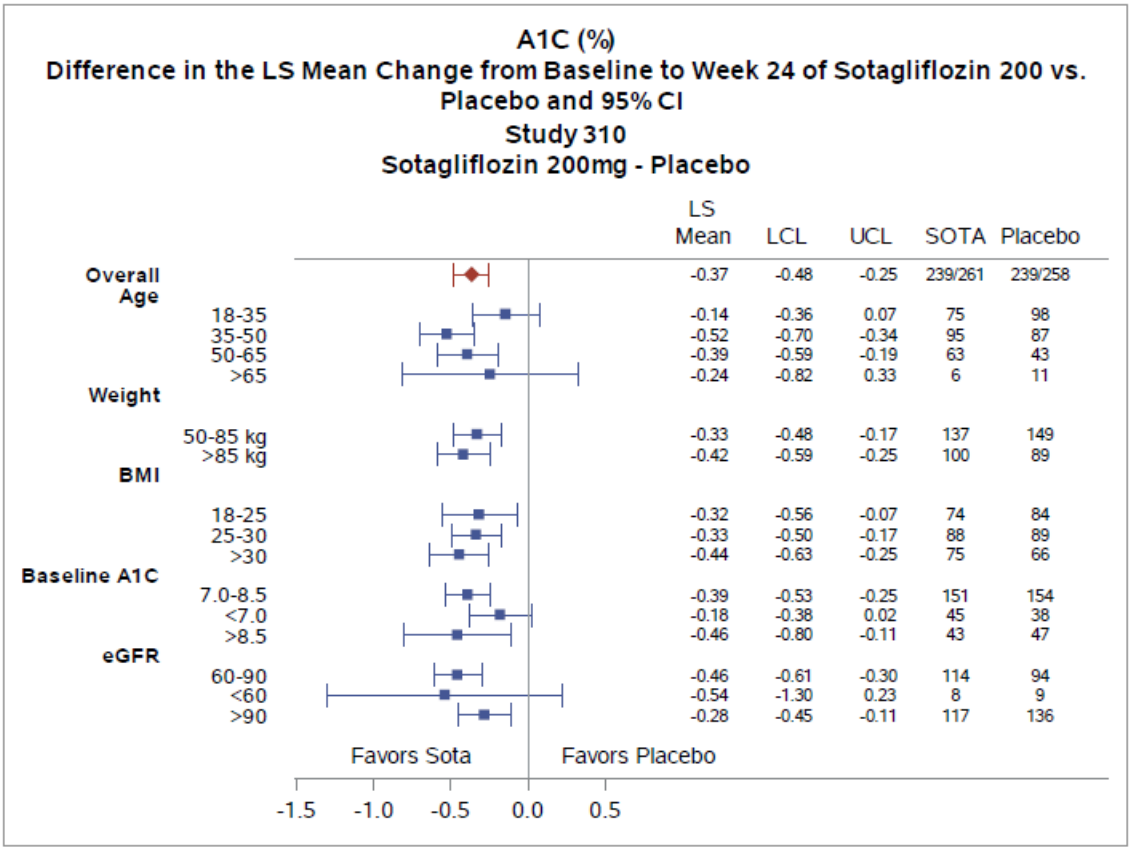
Source: Statistical Reviewer's Analysis

Figure 19. Additional Subgroup Analysis 400 mg vs Placebo - Study 309



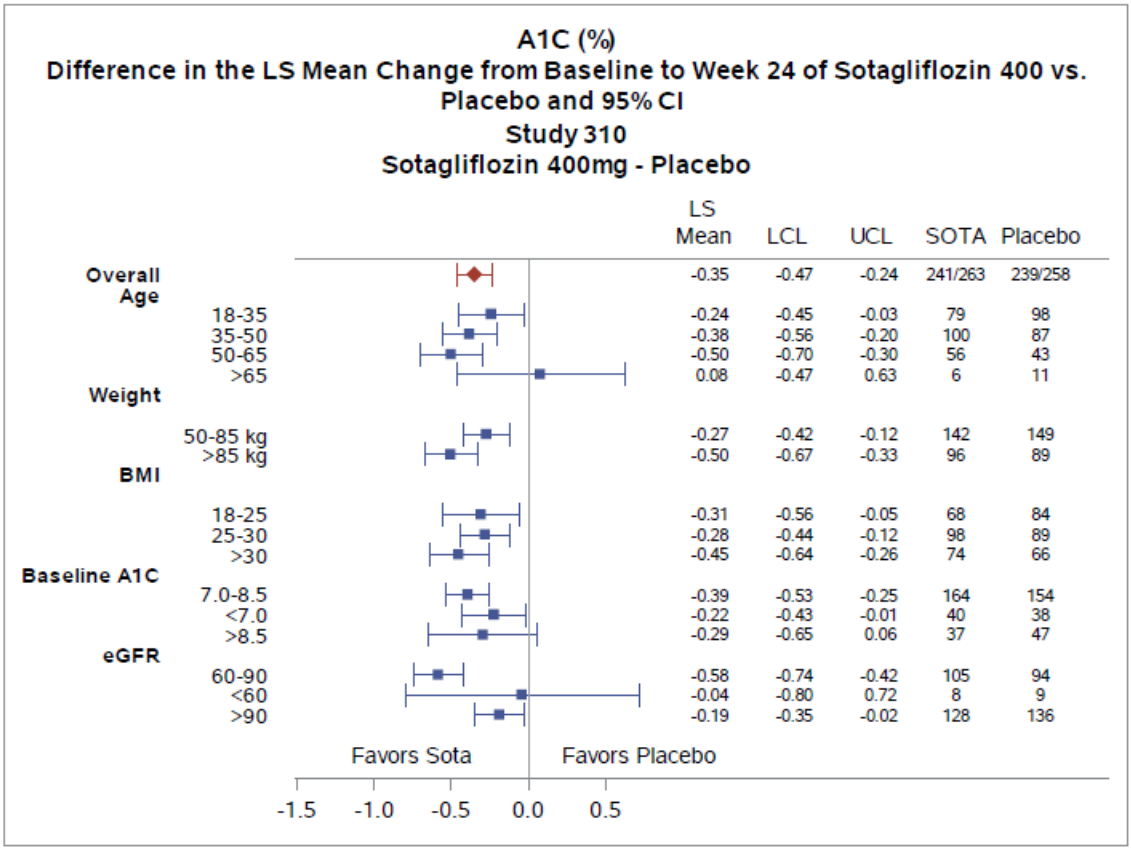
Source: Statistical Reviewer's Analysis

Figure 20. Additional Subgroup Analysis 200 mg vs Placebo - Study 310



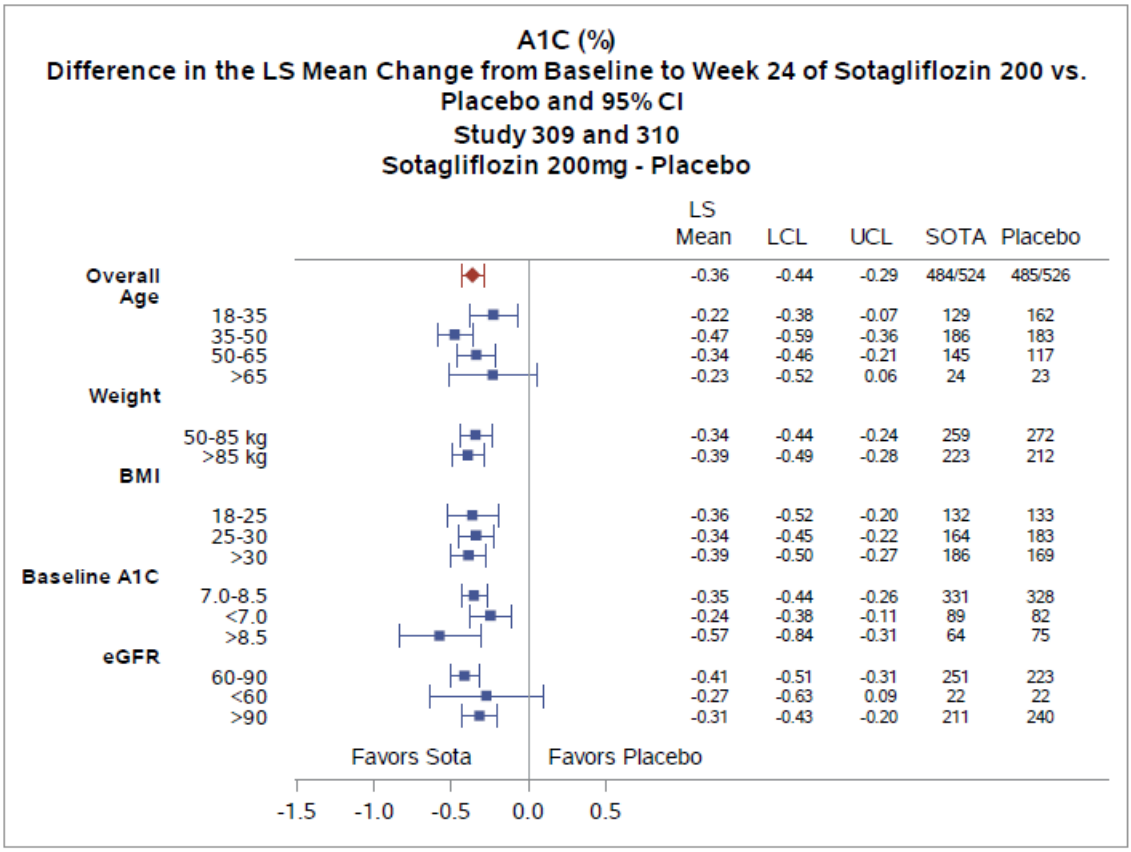
Source: Statistical Reviewer's Analysis

Figure 21. Additional Subgroup Analysis 400 mg vs Placebo - Study 310



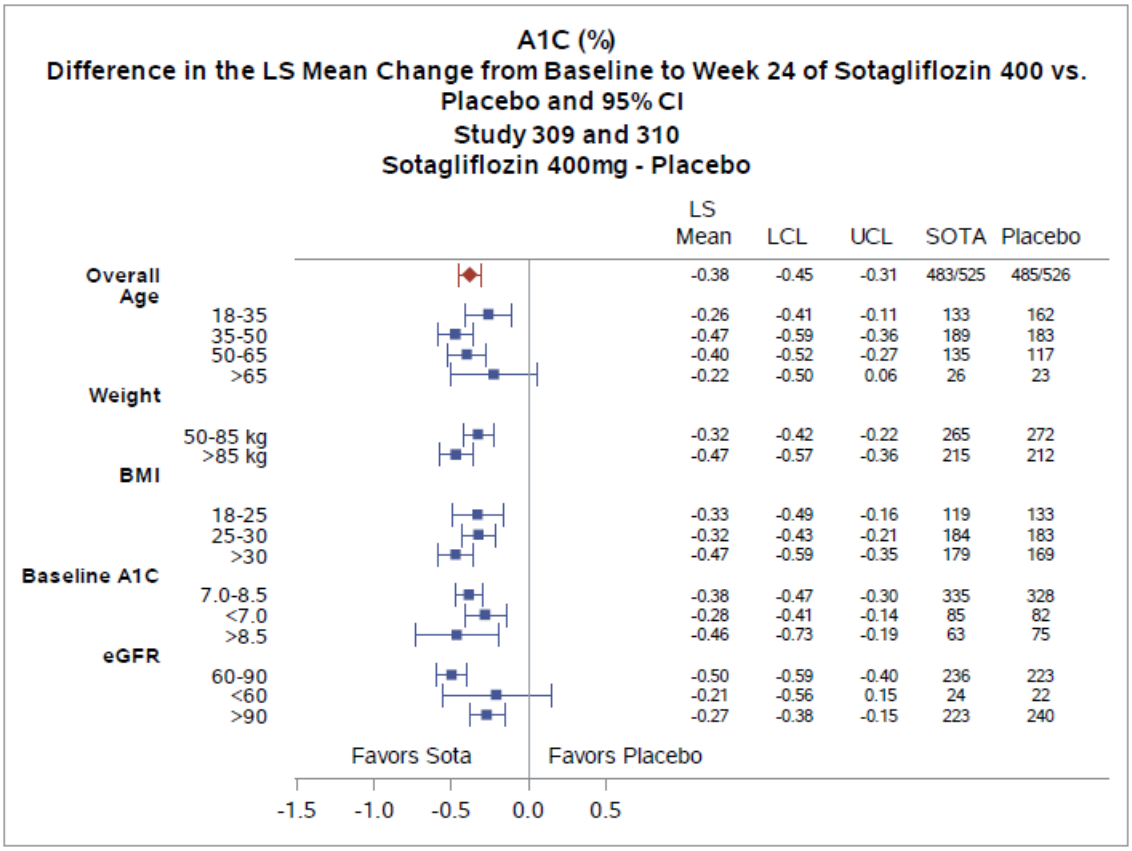
Source: Statistical Reviewer's Analysis

Figure 22. Additional Subgroup Analysis 200 mg vs Placebo – Studies 309 and 310



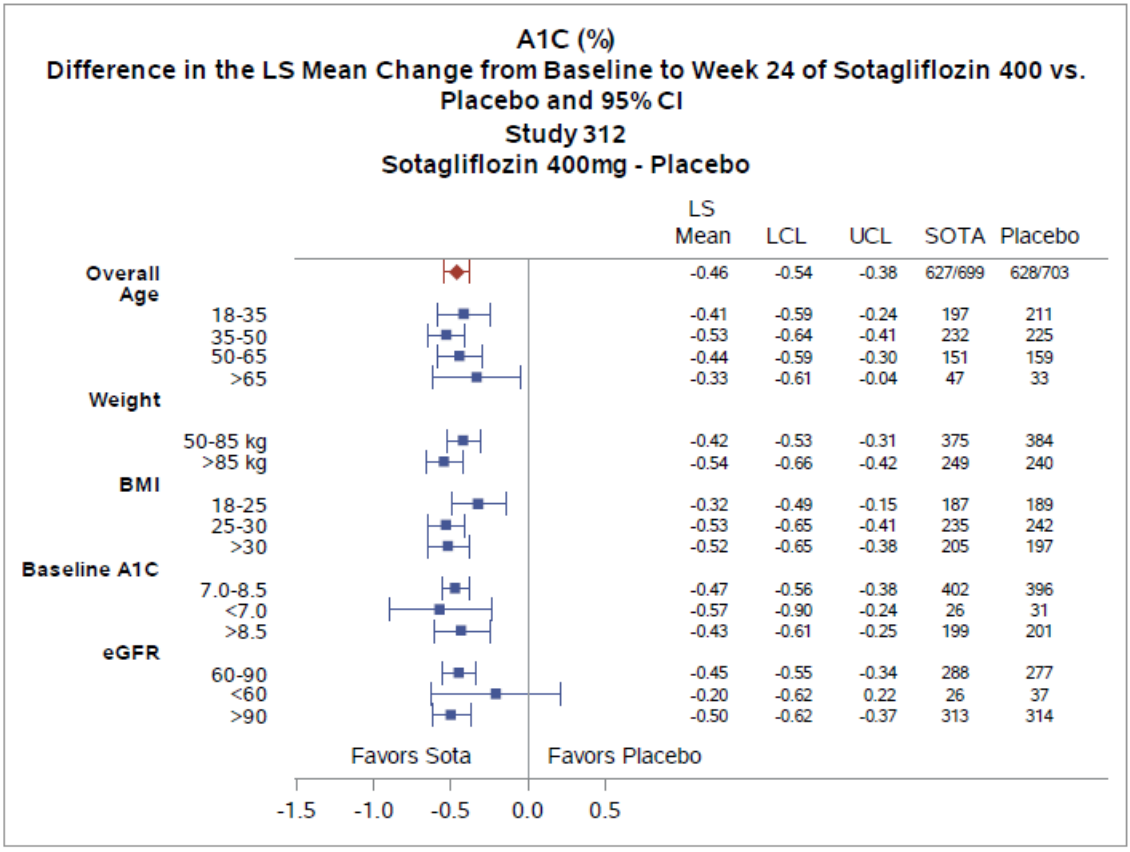
Source: Statistical Reviewer's Analysis

Figure 23. Additional Subgroup Analysis 400 mg vs Placebo – Studies 309 and 310



Source: Statistical Reviewer's Analysis

Figure 24. Additional Subgroup Analysis 400 mg vs Placebo - Study 312



Source: Statistical Reviewer's Analysis

Summary of Safety

This section will focus on the clinical and statistical safety findings from the phase 3 studies conducted by the applicant as part of the sotagliflozin development program.

Studies Reviewed for Safety

The Applicant conducted a total of 30 clinical trials, which included 22 Phase 1 studies. The Phase 1 clinical development program included 17 studies in healthy volunteers, 2 studies in patients with T2DM, 1 study in patients with T2DM and renal impairment, and 2 studies in patients with hepatic or renal impairment. There were 5 Phase 2 studies, which included 3 studies in patients with T1DM, and 2 studies in patients with T2DM. As noted previously, the 3 Phase 3 clinical studies were Study 309, Study 310, and Study 312 (Table 22).

Table 22. Phase 3 Studies to Support Safety

Study ID	***Trial Design***	**Treatment arms**	**Number of Patients**	**Treatment Duration/ Follow Up**	**Study Population**
LX4211.1-309-T1DM	DB sotagliflozin vs. placebo as adjunct to insulin in adults with T1DM	Sota 200mg OD Sota 400 mg OD Placebo OD	263; 262; 268	24 week core treatment period, 28 week long-term extension	Multinational, T1DM with HbA1c 7.0-11.0%, eGFR>45 ml/min/1.73 m^2
LX4211.1-310-T1DM	DB sotagliflozin vs. placebo as adjunct to insulin in adults with T1DM	Sota 200mg OD Sota 400 mg OD Placebo OD	261; 263; 258	24 week core treatment period, 28 week long-term extension	Multinational, T1DM with HbA1c 7.0-11.0%, eGFR>45 ml/min/1.73 m^2
LX4211.1-312-T1DM	DB sotagliflozin vs. placebo as adjunct to insulin in adults with T1DM	Sota 400 mg OD Placebo OD	699; 703;	24 week core treatment period	Multinational, T1DM with HbA1c 7.0-11.0%, eGFR>45 ml/min/1.73 m^2

DB=double blind, OD=once daily
Source: Reviewer generated table

Categorization of Adverse Events

Events of Special Interest (EOSI) were identified by the Applicant based on review of labelled safety concerns of approved SGLT2 inhibitors, data from the literature, as well as preclinical data from the sotagliflozin development program. The Applicant designated metabolic acidosis and DKA, hypoglycemia, major adverse cardiovascular events (MACE) and selected cardiovascular (CV) events, volume depletion, drug-induced liver injury, renal events, bone fractures, genital mycotic infections, urinary tract infections, diarrhea, malignancies of special interest, amputations, pancreatitis, and venous thromboembolisms (VTE). These events were included if they occurred after the first dose of study drug until 30 days after the last dose of study drug. However, given the long latency of some of the events, CV events (including death), fractures, VTEs, drug-induced liver injury (DILI), and malignancies were included even if the onset was more than 30 days from the last dose of study drug. Hypoglycemic events were only included until the date of the last dose of study drug.

A Clinical Events Committee (CEC) performed an additional blinded review to determine whether selected adverse events met the pre-defined criteria and to provide a formal judgement (adjudication). The following events were sent for adjudication by the CEC: death, hypoglycemic events (specifically severe hypoglycemia and hypoglycemia reported as an SAE), metabolic acidosis including DKA, MACE/select CV events, and DILI. The preferred terms (PTs) used to identify an EOSI were prespecified, with the exception of amputation, which was added after the initiation of the studies. The standard medical dictionary for regulatory activities (MedDRA) terms were used to perform searches for potential events.

Safety Findings

As with the presentation of efficacy findings, Studies 309 and 310 were pooled for the safety evaluation (SAF-1), given their identical study design, while Study 312 is presented separately.

Serious Adverse Events

Overall, there was a greater number of subjects in the sotagliflozin treatment group that reported treatment-emergent serious adverse events[5] (SAEs) in comparison to the placebo group, with a total of 103/1049 subjects (9.8%) in the pooled sotagliflozin group, and 37/526 subjects (7.0%) in the placebo group. The greatest number of SAEs occurred in the system organ class (SOC) “Metabolism and Nutrition SOC”, which occurred in 56/1049 subjects (5.3%) in the pooled sotagliflozin group, and in 9/526 subjects (1.7%) in the placebo group. The large majority of PTs within this SOC were “diabetic ketoacidosis”, which occurred in 45 subjects (4.3%) in the pooled sotagliflozin group, and 3 subjects (0.6%) in the placebo arm. There was no imbalance in events of hypoglycemia, represented by the PT “hypoglycemia” within the “Metabolism and Nutrition SOC, and “hypoglycemic unconsciousness” within the “Nervous System Disorders

[5] A Serious Adverse Event (SAE) is defined as any event that results in any of the following outcomes: death; life-threatening situation; persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; inpatient hospitalization or prolonging a hospitalization; congenital anomaly/birth defect in the offspring of a patient who received study drug or; medical or surgical intervention that is necessary to prevent 1 of the outcomes listed in this definition

SOC", with similar number of events in the three groups. Events of DKA and hypoglycemia are discussed in more detail below.

The next most common SOC was "Infections and Infestations", with a slightly greater number of events occurring in the pooled sotagliflozin group (1.6%) compared to the placebo group (1.0%). The PTs that occurred with greater frequency in the sotagliflozin group within this SOC were "pneumonia" and "gastroenteritis". There was no major imbalance in the incidence of SAEs in the remaining SOCs or PTs between treatment groups. The incidence of SAEs is presented in Table 23.

Table 23. Treatment-Emergent Serious Adverse Events (by MedDRA System Organ Class and Preferred Term), Occurring in ≥ 2 Patients in any treatment group in SAF-1

System Organ Class	LX4211 200 mg N=524		LX4211 400 mg N=525		LX4211 200/400 mg N=1,049		Placebo N=526	
	N	%	N	%	N	%	N	%
Cardiac disorders	5	1.0	2	0.4	7	0.7	4	0.8
-Acute myocardial infarction	2	0.4	2	0.4	4	0.4	2	0.4
Endocrine disorders	0	0.0	1	0.2	1	0.1	0	0.0
Eye disorders	1	0.2	1	0.2	2	0.2	2	0.4
Gastrointestinal disorders	2	0.4	2	0.4	4	0.4	3	0.6
General disorders and administration site conditions	2	0.4	2	0.4	4	0.4	0	0.0
Hepatobiliary disorders	2	0.4	0	0.0	2	0.2	0	0.0
Infections and infestations	11	2.1	6	1.1	17	1.6	5	1.0
-Pneumonia	2	0.4	1	0.2	3	0.3	1	0.2
-Gastroenteritis	2	0.4	1	0.2	3	0.3	0	0.0
-Appendicitis	1	0.2	1	0.2	2	0.2	0	0.0
-Gastroenteritis viral	2	0.4	0	0.0	2	0.2	0	0.0
Injury, poisoning and procedural complications	3	0.6	3	0.6	6	0.6	4	0.8
Investigations	0	0.0	1	0.2	1	0.1	0	0.0
Metabolism and nutrition disorders	25	4.8	31	5.9	56	5.3	9	1.7
-Diabetic ketoacidosis	19	3.6	26	5.0	45	4.3	3	0.6
-Hypoglycaemia	5	1.0	5	1.0	10	1.0	5	1.0
Musculoskeletal and connective tissue disorders	1	0.2	0	0.0	1	0.1	2	0.4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	0.8	3	0.6	7	0.7	3	0.6
Nervous system disorders	3	0.6	4	0.8	7	0.7	11	2.1
-Hypoglycaemic unconsciousness	2	0.4	2	0.4	4	0.4	4	0.8
Pregnancy, puerperium and perinatal conditions	0	0.0	0	0.0	0	0.0	1	0.2
Psychiatric disorders	1	0.2	0	0.0	1	0.1	0	0.0
Renal and urinary disorders	1	0.2	1	0.2	2	0.2	0	0.0
Reproductive system and breast disorders	1	0.2	1	0.2	2	0.2	0	0.0
Respiratory, thoracic and mediastinal disorders	0	0.0	1	0.2	1	0.1	0	0.0

Skin and subcutaneous tissue disorders	1	0.2	1	0.2	2	0.2	1	0.2
Surgical and medical procedures	0	0.0	1	0.2	1	0.1	0	0.0
Vascular disorders	0	0.0	0	0.0	0	0.0	1	0.2

Source: Reviewer generated table

The overall incidence of SAEs by SOC and PT were similar in trial 312 in comparison to trials 309 and 310. There was a greater number of subjects in the sotagliflozin treatment group that reported treatment-emergent serious adverse events in comparison to the placebo group, with 48 subjects (6.9%) in the sotagliflozin group, and 23 subjects (3.3%) in the placebo group. The most common SOC was "Metabolism and Nutrition", with a greater incidence in the sotagliflozin group. SAEs from this SOC occurred in 26 subjects (3.7%) in the sotagliflozin group, and in 7 subjects (1.0%) in the placebo group, which was primarily due to the PT "diabetic ketoacidosis", which occurred in 22 subjects (3.1%) in the pooled sotagliflozin group, and 5 subjects (0.7%) in the placebo arm.

There was no major imbalance in events of hypoglycemia, represented by the PT "hypoglycemia" within the "Metabolism and Nutrition SOC, and "hypoglycemic unconsciousness" within the "Nervous System Disorders SOC", with similar number of events between groups.

The second most common SOC was "Infections and Infestations"; there was a similar incidence of events in both treatment groups. There was a slight increase in the incidence of "Cardiac disorders" and "Gastrointestinal disorders" SOCs in the treatment group, but the increase was not due to any single PT in either SOC. There was no major imbalance in the incidence of SAEs in the remaining SOCs or PTs between treatment groups. The incidence of SAEs in trial 312 is presented below in Table 24.

Table 24. Treatment-Emergent Serious Adverse Events (by MedDRA System Organ Class and Preferred Term), Occurring in ≥ 2 Patients in any treatment group in Trial 312

System Organ Class	**LX4211 400 mg N=699**		**Placebo N=703**	
	Subject Count	**%**	**Subject Count**	**%**
Cardiac disorders	5	0.7	0	0.0
-Coronary artery disease	2	0.3	0	0.0
Ear and labyrinth disorders	1	0.1	0	0.0
Endocrine disorders	1	0.1	0	0.0
Eye disorders	0	0.0	1	0.1
Gastrointestinal disorders	4	0.6	1	0.1
General disorders and administration site conditions	0	0.0	1	0.1
Infections and infestations	5	0.7	4	0.6
Injury, poisoning and procedural complications	2	0.3	0	0.0
Investigations	1	0.1	1	0.1
Metabolism and nutrition disorders	26	3.7	7	1.0

-Diabetic ketoacidosis	22	3.1	5	0.7
-Hypoglycemia	3	0.4	1	0.1
Musculoskeletal and connective tissue disorders	1	0.1	0	0.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0.1	2	0.3
Nervous system disorders	4	0.6	5	0.7
Psychiatric disorders	2	0.3	2	0.3
Renal and urinary disorders	2	0.3	0	0.0
Respiratory, thoracic and mediastinal disorders	0	0.0	1	0.1
Vascular disorders	1	0.1	1	0.1

Source: Reviewer generated table

Diabetic Ketoacidosis

Events of metabolic acidosis and DKA were identified by investigator-reported AEs that included PTs suggestive of possible DKA (Table 25), laboratory values suggestive of DKA, and an additional review by the applicant/Clinical Research Organization (CRO) of AE and laboratory data.

Table 25. PTs suggestive of possible DKA

PTs associated with elevated BHB	PTs that may not be associated with elevated BHB
Acetonemia	Acidosis
Blood ketone body	Acidosis hyperchloremic
Blood ketone body increased	Diabetic coma
Blood ketone body present	Diabetic hyperglycemia coma
Diabetic ketoacidosis	Diabetic metabolic decompensation
Diabetic ketoacidotic hyperglycemic coma	Hyperglycemic coma
Ketoacidosis	Hyperglycemic seizure
Ketosis	Hyperglycemic unconsciousness
Urine ketone body	Lactic acidosis
Urine ketone body present	Metabolic acidosis
Renal tubular acidosis	
Uremic acidosis	

Source: Table 16 from Applicant's Summary of Clinical Safety

Definition of DKA

Metabolic acidosis events were defined by the presence of decreased serum bicarbonate and/or the presence of decreased arterial blood pH. These events of metabolic acidosis were further subdivided based on the presence or absence of an anion gap. The diagnosis of DKA was determined by evidence of an anion-gap acidosis, related to excessive ketone production in a clinical setting of insulin deficiency without an alternative etiology (e.g. lactic acidosis, alcoholic ketoacidosis). All cases of metabolic acidosis, as well as possible DKA were sent to the Clinical

Events Committee (CEC) for adjudication.

The clinical study protocols also contained a table of diagnostic criteria for DKA for patients not treated with investigational agents to aid the CEC in the identification of DKA events. See Table 26 below:

Table 26. Diagnostic Criteria for DKA for Patients Not Treated with Investigational Agents

	Mild	Moderate	Severe
Plasma glucose (mg/dL)	>250	>250	>250
Arterial pH	7.25 - 7.30	7.00 - 7.24	<7.0
Serum bicarbonate (mEq/L)	15 - 18	10 - <15	<10
Urine ketones[a]	Positive	Positive	Positive
Serum ketones[a]	Positive	Positive	Positive
Effective serum osmolality (mOsm/kg)[b]	Variable	Variable	Variable
Anion gap[c]	>10	>12	>12
Alteration in sensorial or mental obtundation	Alert	Alert/drowsy	Stupor/coma

Source: Table 9.5.2-1 from Clinical Study Protocol (p. 98)

The CEC Charter also emphasized that typical signs or symptoms of DKA, as well as associated hyperglycemia, were not required for the diagnosis of DKA, given that euglycemic DKA has been associated with the use of SGLT2 inhibitors. A specific emphasis was placed on the presence of elevated plasma betahydroxybutyrate (BHB) over serum or urine ketones. It is noted in the briefing document provided by the applicant, DKA was defined including criteria for BHB>3.0 mmol/L. However, we did not note any specific elevation in BHB defined in the study protocol or CEC Charter, although for BHB levels >0.6 mmol/L, subjects were advised to contact Investigators for possible further treatment.

Instructions for DKA given in study protocol

Patients were given instructions regarding the avoidance, recognition, and management of DKA. Patients were instructed to avoid dehydration, and to increase fluids if they had a fever, diarrhea, vomiting, polyuria, exercise, or when dizzy. If patients were scheduled for a procedure or surgery that required them to be fasting, the study drug was to be held the day prior and resumed the day after the procedure or surgery was complete and once the patient was tolerating oral intake. If patients developed symptoms consistent with DKA, including weakness, nausea, or vomiting, they were instructed to check ketones (either urine or blood). If ketones were present, which was defined as moderate or higher for urine ketones, or serum BHB level > 0.6 mmol/L, patients were instructed to contact the site immediately. The Investigator was instructed to consider having the patient take rapid acting insulin every 2 hours until ketones normalized, along with increased carbohydrates (15-30 grams of carbohydrates each hour by a glucose-containing drink). If the patient was unable to tolerate oral intake, they were to be evaluated in an Emergency Room. The site was to determine whether an additional assessment for metabolic acidosis was appropriate. A “Possible DKA” eCRF was to be completed if laboratory testing confirmed metabolic acidosis.

DKA Events

There was a total of 71 Investigator-Reported events in 69 subjects (6.6%) of metabolic acidosis/DKA in the pooled sotagliflozin group, in comparison to 7 Investigator-Reported events in 7 subjects (1.3%) in the placebo group (Table 27). Following adjudication by the CEC, there were a total of 36 positively-adjudicated events in 35 subjects (3.3%) of DKA in the pooled sotagliflozin group, in comparison to 1 positively-adjudicated event in 1 subject (0.2%) in the placebo group. Of the subjects with positively-adjudicated DKA events, there was a total of 12 out of 35 subjects in the sotagliflozin group who discontinued the study drug as a result of the DKA event, while there were no subjects in the placebo group. These positively-adjudicated events had a mean event duration of between 4.0-5.5 days for all treatment groups. Events that did not meet criteria for adjudication were reported by the Applicant to be lacking laboratory data to confirm the diagnosis (such as pH or bicarbonate levels) or had laboratory values which were marginal, while some patients lacked ketone levels.

Table 27. Metabolic Acidosis/DKA Events from Studies 309 and 310

Source of Metabolic Acidosis/ DKA Event	Sota 200 mg N=524			Sota 400 mg N=525			Sota ALL N=1049			Placebo N = 526		
	Subjects	%	Events	Subjects	%	Events	Subjects	%	Events	Subjects	%	Events
Investigator-Reported Metabolic Acidosis/DKA	30	5.7	32	39	7.4	39	69	6.6	71	7	1.3	7
Positively-Adjudicated DKA	15	2.9	16	20	3.8	20	35	3.3	36	1	0.2	1

Source: Reviewer generated table

Note: The Reviewer-adjudicated DKA column include positively-adjudicated events of DKA, in addition to additional events that were investigator-reported DKA that were determined by the CEC to not be DKA events, but which were determined during the course of review to be consistent with DKA events.

In Study 312, there was a total of 35 Investigator-Reported events in 31 subjects (4.4%) of metabolic acidosis/DKA in the pooled sotagliflozin group, in comparison to 8 Investigator-Reported events in 8 subjects (1.1%) in the placebo group (Table 28). Following adjudication by the CEC, there were a total of 21 positively-adjudicated events in 21 subjects (3.0%) of DKA in the sotagliflozin arm, in comparison to 4 positively-adjudicated events in 4 subjects (0.6%) in the placebo group. Of the subjects with positively-adjudicated DKA events, there was a total of 11 out of 21 subjects in the sotagliflozin group who discontinued the study drug as a result of the DKA event, while there was 1 subject out of 4 in the placebo group.

Table 28. Metabolic Acidosis/DKA Events from Study 312

Source of Metabolic Acidosis/ DKA Event	Sota 400 mg N=699			Placebo N=703		
	Subjects	%	Events	Subjects	%	Events
Investigator-Reported Metabolic Acidosis/DKA	31	4.4	35	8	1.1	8
Positively-Adjudicated DKA	21	3.0	21	4	0.6	4

Source: Reviewer generated table

Table 29 shows the results of DKA events that occurred in the core treatment period and extension period (study 312 only had core treatment period). There were more subjects with at least one DKA event in the sotagliflozin groups compared to placebo in all three studies. The percentage of patients who had a DKA event in the with sotagliflozin group was statistically significantly greater than in the with placebo group.

Table 29. Number of Subjects with DKA Event – Core Treatment Period + Extension

Study 309			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	268	263	262
Yes DKA	1 (0.4%)	9 (3.4%)	11 (4.2%)
No DKA	267 (99.6%)	254 (96.6%)	251 (95.8%)
Difference in % of subjects with DKA from Placebo			
		3.05	3.83
95% CI		0.73, 5.36	1.29, 6.36
Nominal p-value		0.0098	0.0031
Study 310			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	258	261	263
Yes DKA	0	6 (2.3%)	9 (3.4%)
No DKA	258 (100%)	255 (97.7%)	254 (96.6%)
Difference in % of subjects with DKA from Placebo			
		2.30	3.42
95% CI		0.48, 4.12	1.22, 5.62
Nominal p-value		0.0144	0.0027
Studies 309 and 310 Combined			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	526	524	525
Yes DKA	1 (0.2%)	15 (2.9%)	20 (3.8%)
No DKA	525 (99.8%)	509 (97.1%)	505 (96.2%)
Difference in % of subjects with DKA from Placebo			
		2.67	3.62
95% CI		1.20, 4.15	1.94, 5.30
Nominal p-value		0.0004	<0.0001
Study 312 *			
Treatment	Placebo		Sota 400mg
FAS	703		699
Yes DKA	4 (0.6%)		21 (3.0%)
No DKA	699 (99.4%)		678 (97.00%)
Difference in % of subjects with DKA from Placebo			
			2.44
95% CI			1.05, 3.82
Nominal p-value			0.0006

Source: Statistical Reviewer's Analysis
* Study 312 only had core treatment period.

Characteristics of DKA events

Several characteristics were noted to be common amongst the DKA events (Table 30). Specifically, it was noted that up to 43% of cases were associated with a prior illness immediately preceding the DKA event, such as a viral upper respiratory illness, or gastroenteritis. This may have been due to a decrease in oral intake, which may have led to a reduction in insulin dosing (which may not have been captured in the narrative or eCRF), or which may have predisposed patients to dehydration. Approximately one-third of DKA events were associated with a blood glucose < 250 mg/dL, which has been termed by some as "euglycemic DKA", and differs from more typical DKA events, which are associated with elevated blood glucose values. These characteristics did not appear to be dependent on treatment group, i.e. sotagliflozin vs. placebo.

Table 30. Factors associated with DKA events in Studies 309 and 310 (SAF-1)

Characteristics	**Positively Adjudicated N=37**
Insulin Dose Reduction	12 (32.4%)
Insulin Pump Malfunction	9 (24.3%)
Prior Illness	16 (43.2%)
Blood Glucose < 250 mg/dL	12 (32.4%)

Source: Reviewer generated table
Note: The total number of events includes DKA events in both the sotagliflozin arm and the placebo arm

In contrast to studies 309 and 310, in Study 312 there was a lower percentage (24%) of DKA events that were precipitated by a prior illness. There was also a lower rate of DKA events associated with glucose < 250 mg/dL (Table 31).

Table 31. Factors associated with DKA events for Study 312

Characteristics	**Positively Adjudicated N=25**
Insulin Dose Reduction	8 (32.0%)
Insulin Pump Malfunction	3 (12.0%)
Prior Illness	6 (24.0%)
Blood Glucose < 250 mg/dL	7 (28.0%)

Source: Reviewer generated table
Note: The total number of events includes DKA events in both the sotagliflozin arm and the placebo arm

Characteristics of Subjects with DKA Events

The baseline demographic characteristics of subjects with DKA events were compared with subjects who did not have DKA events. There was a greater percentage of female subjects who had DKA events, in comparison to subjects who did not (63.9% vs. 49.6%). The mean age of subjects with DKA events was younger (40.1 vs. 43.8 yrs), and more often were insulin pump users (61.1% vs. 42.4%) in comparison to subjects without DKA events. The bolus insulin dosing (in u/kg) was lower in subjects with DKA events in comparison to subjects without DKA events (25.6 vs. 31.4), although basal and total insulin dosing was similar between the two groups. For further details, see *Appendix E: Baseline Demographics of Subjects with DKA versus no DKA in SAF-1*. These characteristics did not appear to be dependent on treatment group, i.e. sotagliflozin vs. placebo.

Pre-DKA events

Per the study protocol, reporting of AE terms suggestive of possible DKA was to trigger completion of the "Possible DKA" eCRF, which was to be sent to the CEC for adjudication. In addition, the Applicant performed additional review of AE terms to ensure the "Possible DKA" eCRF was completed when deemed appropriate by the Investigator. A search for preferred terms suggestive of DKA events using a standardized medical dictionary (MedDRA query) was performed to identify additional potential DKA events. There was a total of 177 events in 133 subjects in the pooled sotagliflozin group, and 14 events in 14 subjects in the placebo group, of reported AE terms suggestive of DKA (Table 32). The Applicant has reported these events as "Investigator-reported treatment-emergent acidosis-related events" (See ISS Table 1.10.3.1). Out of these events, 72 events in 69 subjects in the pooled sotagliflozin group, and 7 events in 7 subjects in the placebo group, were sent for adjudication as "Investigator-Reported Metabolic Acidosis/DKA events". See Table 32 for the list of PTs. This list includes all events that were sent for adjudication as "Investigator-Reported Metabolic Acidosis/DKA events", as well as additional events that were not sent for adjudication.

Table 32. MedDRA query for DKA PTs- SAF-1

	Sota 200 mg N=524			Sota 400 mg N=525			Sota ALL N=1049			Placebo N = 526		
PT	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**
Acetonemia	5	0.95	6	6	1.14	6	11	1.04	12	2	0.38	2
Acidosis	1	0.19	1	0	0	0	1	0.10	1	0	0	0
Blood ketone body increased	21	4.01	43	27	5.14	37	48	4.58	80	3	0.57	3
Diabetic ketoacidosis	21	4.01	22	30	5.71	30	51	4.86	52	5	0.95	5
Ketoacidosis	1	0.19	1	0	0	0	1	0.10	1	1	0.19	1
Ketosis	4	0.76	6	17	3.24	25	21	2.00	31	3	0.57	3
Total	53	10.12	79	80	15.24	98	133	12.68	177	14	2.66	14
Investigator-Reported Metabolic Acidosis/DKA	30	5.7	32	39	7.4	40	69	6.6	72	7	1.3	7

Source: table generated by Reviewer based on custom MedDRA query

A MedDRA query was also performed for Study 312 to identify additional potential DKA events. There was a total of 76 events in 63 subjects in the sotagliflozin arm, and 22 events in 20 subjects in the placebo group, of reported AE terms suggestive of DKA (Table 33). Out of these events, 35 events in 31 subjects in the sotagliflozin arm, and 8 events in 8 subjects in the placebo group, were sent for adjudication as "Investigator-Reported Metabolic Acidosis/DKA events". See Table 33 for the list of PTs.

Table 33. MedDRA query for DKA- Study 312

	Sota 400 mg N=699			Placebo N=703		
PT	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**
Acetonaemia	5	0.72	6	1	0.14	3
Acidosis	1	0.14	1	0	0	0
Blood ketone body	1	0.14	1	0	0	0
Blood ketone body increased	25	3.58	32	8	1.14	8
Diabetic ketoacidosis	25	3.58	29	7	1.00	7
Ketoacidosis	2	0.29	2	0	0	0
Ketosis	3	0.43	4	1	0.14	1
Metabolic acidosis	1	0.14	1	0	0	0
Urine ketone body	0	0	0	1	0.14	1
Urine ketone body present	0	0	0	2	0.28	2
Total	63	9.01	76	20	2.85	22
Investigator-Reported Metabolic Acidosis/DKA	31	4.4	35	8	1.1	8

Source: table generated by Reviewer based on custom MedDRA query

Per the study protocol, serum beta-hydroxybutyrate (BHB) levels were monitored at every study visit by both central laboratory and point of care testing. Subjects were also given a home BHB monitor, along with urine ketone strips. The number of subjects that had elevations in serum BHB levels that were not sent for adjudication were also reviewed. In order to evaluate only clinically significant events, a cutoff of 1.2 mmol/L, which represents double the upper limit of normal, was determined as the cutoff for BHB. There were 13.1% of subjects in the pooled sotagliflozin group and 5.5% of subjects in the placebo had elevations in BHB that were not sent for adjudication. There were also subjects with reported MedDRA PTs suggestive of DKA events that were not sent for adjudication (5.4% for the pooled sotagliflozin group and 1.3% for the placebo group). The number of subjects that had both an elevation in BHB, and a MedDRA DKA event which were not sent for adjudication was 26 subjects (2.5%) in the pooled sotagliflozin group versus 2 subjects (0.4%) in the placebo group. Additional details regarding potential treatment interventions are not available for these subjects. See Table 34 for details.

Table 34. Subjects with Abnormal BHB or MedDRA DKA Events Not Sent for Adjudication-SAF-1

	Sota 200 mg N=524	Sota 400 mg N=525	Sota All N=1049	Placebo N=526
BHB > 1.2	76 (14.50%)	61 (11.62%)	137 (13.10%)	29 (5.51%)
MedDRA DKA event	22 (4.20%)	35 (6.67%)	57 (5.43%)	7 (1.33%)
BHB > 1.2 AND MedDRA DKA event	8 (1.53%)	18 (3.43%)	26 (2.48%)	2 (0.38%)

Source: Reviewer generated table

The number of subjects that had elevations in BHB that were not sent for adjudication were also reviewed for Study 312. See Table 35 for details.

Table 35. Subjects with Abnormal BHB or MedDRA DKA Events Not Sent for Adjudication- 312

	Sota400 mg N=699	Placebo N=703
BHB > 1.2	73 (10.4%)	21 (3.0%)
MedDRA DKA event	29 (4.2%)	9 (1.3%)
BHB > 1.2 AND MedDRA DKA event	12 (1.7%)	1 (0.1%)

Source: Reviewer generated table

Statistical Analysis of DKA (CEC-adjudicated Events)

DKA Primary Analysis Method and Results

The primary endpoint in this section is treatment-emergent diabetic ketoacidosis (DKA) events adjudicated by the CEC. All analyses were conducted in an on-treatment population, with data truncated at **30 days** after the end of treatment, or at the end of trial, whichever occurred earlier. The primary analysis was carried out separately for Trials 309/310 and Trial 312 due to trial design differences. A time-to-event Cox proportional hazards model stratified by trial was used for the Trial 309/310 analysis, with actual treatment as the only covariate. A non-stratified Cox model was used for the Trial 312 analysis, with actual treatment as the only covariate. These models estimated the hazard ratio (HR) for the time to first DKA event associated with sotagliflozin (200mg and 400mg doses combined) relative to placebo.

The estimated hazard ratio of DKA in Trials 309/310 was 17.57 with corresponding 95% CI [2.41, 128.20]. The estimated hazard ratio in Trial 312 was 5.37 [1.84, 15.64] (Table 36). Kaplan-Meier curves for individual sotagliflozin doses vs. placebo are presented for Trials

309/310 and Trial 312 separately to show the observed cumulative probability of DKA events over time (Figure 25 and Figure 26).

Table 36. Primary Analysis Results of CEC-Adjudicated DKA

Trials	**Sotagliflozin** Events/N (IR per 100 PY)	**Placebo** Events/N (IR per 100PY)	**HR*** [95% CI]	**EA MH RD^** per 100 PY [95% CI]	**NNH†** [95% CI]
309/310	35/1049 (3.40)	1/526 (0.19)	17.57 [2.41,128.20]	3.21 [2.04,4.38]	31.1 [22.8,49.0]
312	21/699 (6.00)	4/703 (1.11)	5.37 [1.84,15.64]	4.89 [2.17,7.60]	20.5 [13.2,46.1]

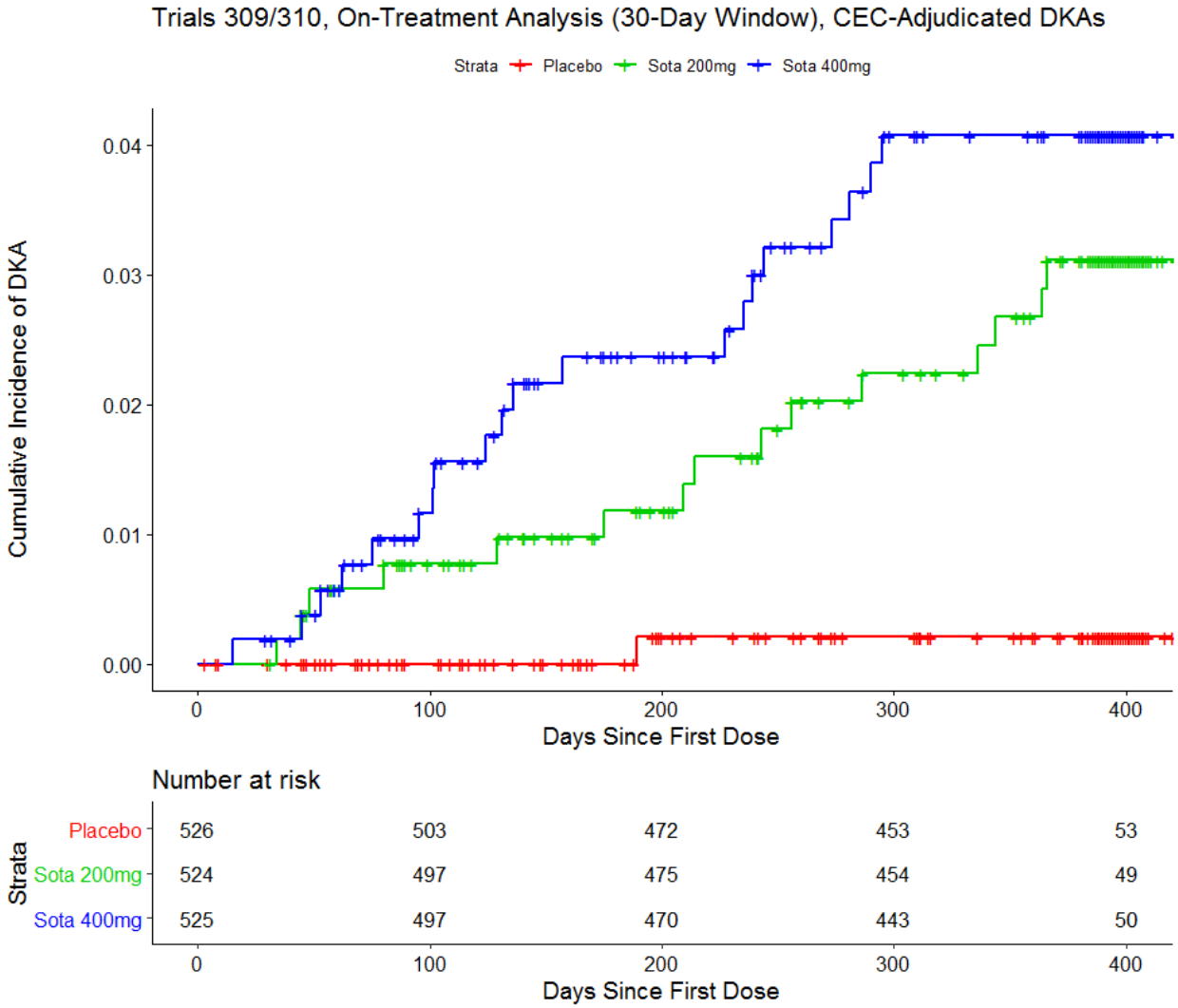
* A Cox proportional hazards model stratified by trial was used for the 309/310 analysis, and a non-stratified Cox model was used for the 312 analysis, with actual treatment as the only covariate, with the two doses of sotagliflozin combined. Data were truncated 30 days after treatment end date.

^ Exposure-adjusted Mantel-Haenszel Risk Difference, stratified by trial; the 95% CI was calculated using Sato's Method.

† Number Need to Harm: Number of PY of exposure to sotagliflozin to observe 1 additional DKA event.

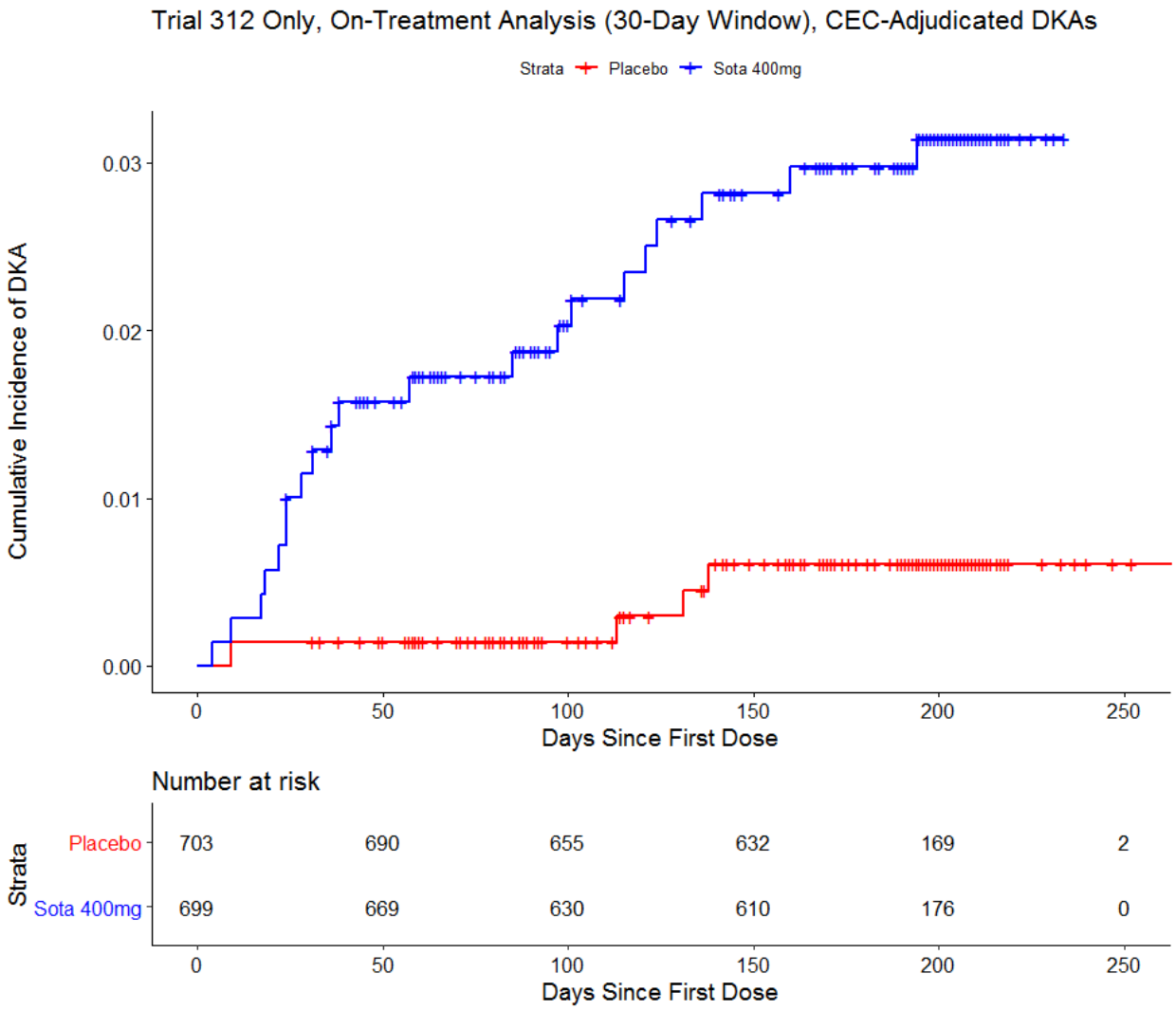
Source: Generated by FDA reviewer

Figure 25. Cumulative Incidence for DKA Events- Studies 309/310



Source: Generated by FDA reviewer

Figure 26. Cumulative Incidence for DKA Events- Study 312



Source: Generated by FDA reviewer

Analysis by Individual Treatment Dose in Trials 309 and 310

The table below shows estimated hazard ratios, risk differences and number-needed to harm for the risk of DKA associated with sotagliflozin 200 mg and sotagliflozin 400 mg relative to placebo in trials 309 and 310 (Table 37). The estimated hazard ratio of DKA associated with sotagliflozin 200 mg in Trials 309/310 was 14.97 [1.98, 113.30]. The estimated hazard ratio for sotagliflozin 400 mg was 20.20 [2.71, 150.50]. Because trial 312 had a single sotagliflozin treatment arm (400mg) no additional analyses by dose were conducted in this trial.

Table 37. Analysis of CEC-Adjudicated DKA by Individual Doses of Sotagliflozin in Trials 309/310

Trials 309/310	**Sotagliflozin** Event/N (IR/100 PY)	**Placebo** Event/N (IR/100PY)	**HR*** [95% CI]	**EA MH RD^** per 100 PY [95% CI]	**NNH†** [95% CI]
200mg	15/524 (2.91)	1/526 (0.19)	14.97 [1.98,113.30]	2.71 [1.21,4.21]	36.9 [23.8,83.4]
400mg	20/525 (3.91)	1/526 (0.19)	20.20 [2.71,150.50]	3.72 [2.00,5.45]	26.8 [18.4,50.0]

* Cox proportional hazards models stratified by trial, with actual treatment as the only covariate. The two doses of sotagliflozin were fitted simultaneously using only the data from Trials 309/310. Data were truncated 30 days after treatment end date.

^ Exposure-adjusted Mantel-Haenszel Risk Difference, stratified by trial; the 95% CI was calculated using Sato's Method.

† Number Need to Harm: Number of PY of exposure to sotagliflozin to observe 1 additional DKA event.

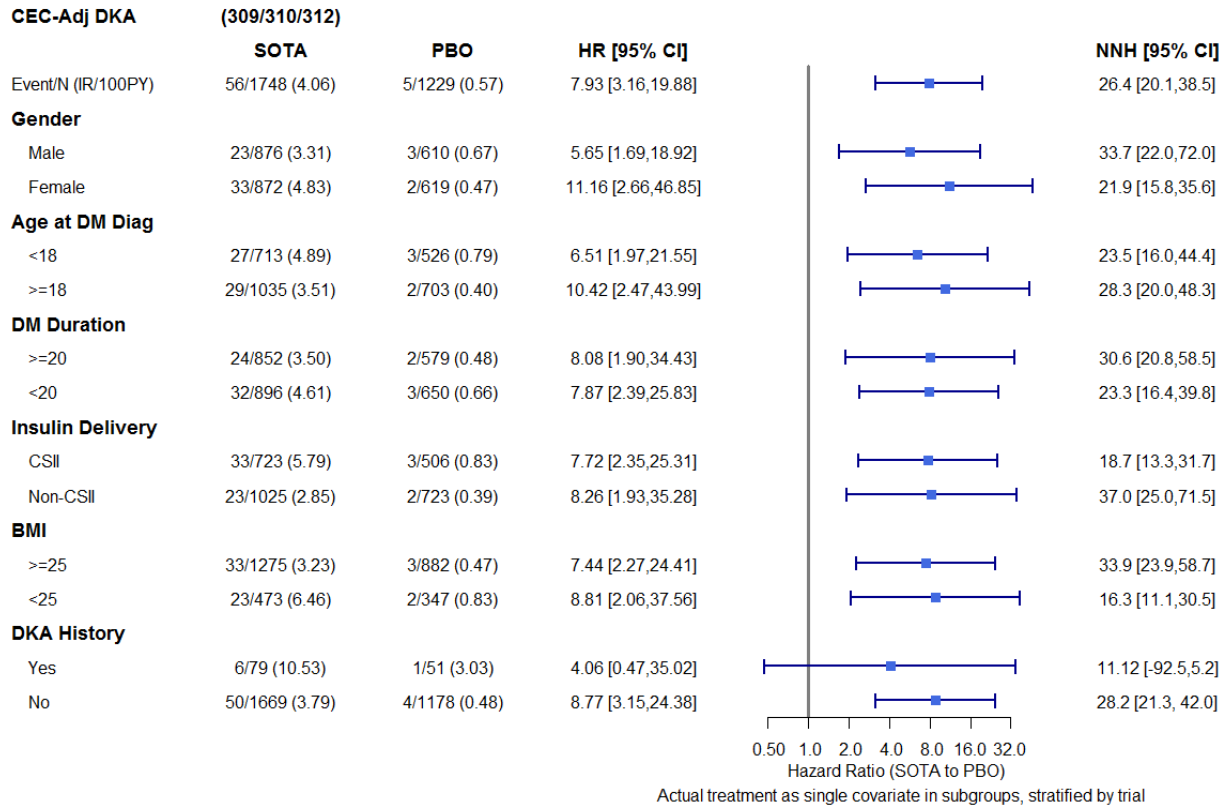
Source: Generated by FDA reviewer

Subgroup Analyses of CEC-Adjudicated DKA (Trials 309/310/312 Combined)

This section discusses subgroup analyses of DKA associated with sotagliflozin (200mg and 400mg doses combined) relative to placebo by subjects' baseline characteristics. Analyses in this section combine data from Trials 309, 310 and 312 to achieve larger sample sizes in subgroups. The Cox proportional hazards models used for subgroup analyses were stratified by trial to account for trial differences and potentially different baseline hazards. These subgroup analyses were conducted post-hoc and are considered exploratory.

The following forest plot shows analyses of DKA by subgroups defined by gender, age at T1/T2DM Diagnosis, T1/T2DM duration, insulin delivery method, BMI, and DKA history. No statistically significant interaction was observed between any of these subgroups and sotagliflozin on the risk of DKA. An increased risk of DKA associated with sotagliflozin was consistently observed across all subgroups.

Figure 27. Subgroup Analyses of CEC-Adjudicated DKA (Trials 309/310/312 Combined)



Note: The calculation in this forest plot was based on a Cox proportional hazards model with treatment as the only covariate for each subgroup. The Cox model was stratified by trial, with both sotagliflozin doses combined, using pooled data from Trials 309/310/312 to achieve larger sample size in subgroups.
Source: Generated by FDA reviewer

Variables Correlated with Higher Risk of DKA Independently of Treatment
A Cox proportional hazards model stratified by trial was fit to explore the association between variables other than treatment and increased risk of DKA. The model included treatment and the individual variables discussed in this section but did not include an interaction term. This analysis incorporates data from Trials 309, 310, and 312 and combined the two doses of sotagliflozin.

The variables discussed in this section were observed to have a nominally significant effect on the risk of DKA in both treatment arms. None of these variables showed statistically significant interaction with treatment. Note that this is a post-hoc analysis and some of these observed association may be attributable to chance. The following characteristics were associated with an increased risk of DKA, regardless of treatment: prior history of DKA, younger age, CSII insulin delivery (insulin pump) and higher baseline HbA1c (Table 38).

Table 38. Variables Associated with an Observed Higher Risk of DKA in Trials 309, 310 and 312

Variable	**Range**	**Main Effect P-value, Point Estimate and 95% CI***
DKA History	Y (130) vs. N (2847)	0.012 (Est: 2.770 [1.256, 6.112])
Age	18 to 79	0.007 (Est: 0.974 [0.955, 0.993])
Insulin Delivery Method	CSII (1229) vs. Non-CSII (1748)	0.009 (Est: 2.025 [1.193, 3.440])
Baseline A1c (%) (2 missing)	5.6 to 15.4	0.019 (Est: 1.367 [1.054, 1.773])

* The p-value, point estimate and 95% CI were calculated from a Cox proportional hazards model with treatment and corresponding variable as covariates, with no term for interaction. The Cox model was stratified by trial with both doses of sotagliflozin combined, using pooled data from Trials 309/310/312.
Source: Generated by FDA reviewer

Hypoglycemia

Hypoglycemic events were defined by the following criteria:

- Documented Hypoglycemia:
  - Symptomatic: an event during which typical symptoms of hypoglycemia were accompanied by a concurrent fingerstick (from SMBG) or venous glucose result of ≤70 mg/dL
  - 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
- 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?

In cases in which criteria were met for both documented and severe hypoglycemia, both eCRFs were completed. Documented hypoglycemia with a BG ≤ 55 mg/dL was also collected by the Applicant.

There was a similar incidence of subjects with both documented hypoglycemia with BG ≤ 70 mg/dL, and documented hypoglycemia with BG ≤ 55. There was a greater number of hypoglycemic events with BG ≤ 55 mg/dL in the placebo group in comparison to the sotagliflozin groups. With respect to severe hypoglycemia, there was a greater number of subjects with both Investigator-reported (5.2% for the pooled sotagliflozin group versus 8.0% in the placebo group) and Positively-Adjudicated (5.1% for the pooled sotagliflozin group versus 7.4% in the placebo group) severe hypoglycemia in the placebo group vs. sotagliflozin groups (Table 39).

Table 39. Hypoglycemia in SAF-1

Hypoglycemia Events	Sota 200 mg (N=524)	Sota 400 mg (N=525)	Sota All N=1049	Placebo (N=526)
Subjects with Documented Hypoglycemia (BG ≤ 70)	515 (98.3%)	518 (98.7%)	1033 (98.5%)	518 (98.5%)
Documented Hypoglycemic Events (BG ≤ 70)	39015	39937	78952	45327
Subjects with Symptomatic Hypoglycemia (BG ≤ 70)	485 (92.6%)	488 (93.0%)	973 (92.8%)	491 (93.3%)
Symptomatic Hypoglycemic Events (BG ≤ 70)	26751	27248	53999	30629
Subjects with Documented Hypoglycemia (BG ≤ 55)	481 (91.8%)	482 (91.8%)	963 (91.8%)	478 (90.9%)
Hypoglycemic Events (BG ≤ 55)	7129	7133	14262	8995
Subjects with Investigator-Reported Severe Hypoglycemia	30 (5.7%)	25 (4.8%)	55 (5.2%)	42 (8.0%)
Investigator-Reported Severe Hypoglycemic Events	68	35	103	54
Subjects with Positively Adjudicated Severe Hypoglycemia	30 (5.7%)	23 (4.4%)	53 (5.1%)	39 (7.4%)
Positively-Adjudicated Severe Hypoglycemic Events	68	33	101	50

Source: table generated by Reviewer based on custom MedDRA query

The number of subjects with positively-adjudicated events of severe hypoglycemia, along with the number of positively-adjudicated events of severe hypoglycemia are also presented by individual trial (Table 40), along with event rates per 100 patient years (which was used due to the small number of events). With respect to the number of events per subject, most subjects had a single event of severe hypoglycemia. Overall, there were 96 subjects that had 1 event, 16

subjects that had 2 events, 15 subjects that had 3 events, and 2 subjects that had 4 events of severe hypoglycemia. However, there was one subject that had 17 events of severe hypoglycemia in the sotagliflozin 200 mg arm, which resulted in an increase in events of severe hypoglycemia in Study 309 due to this outlier.

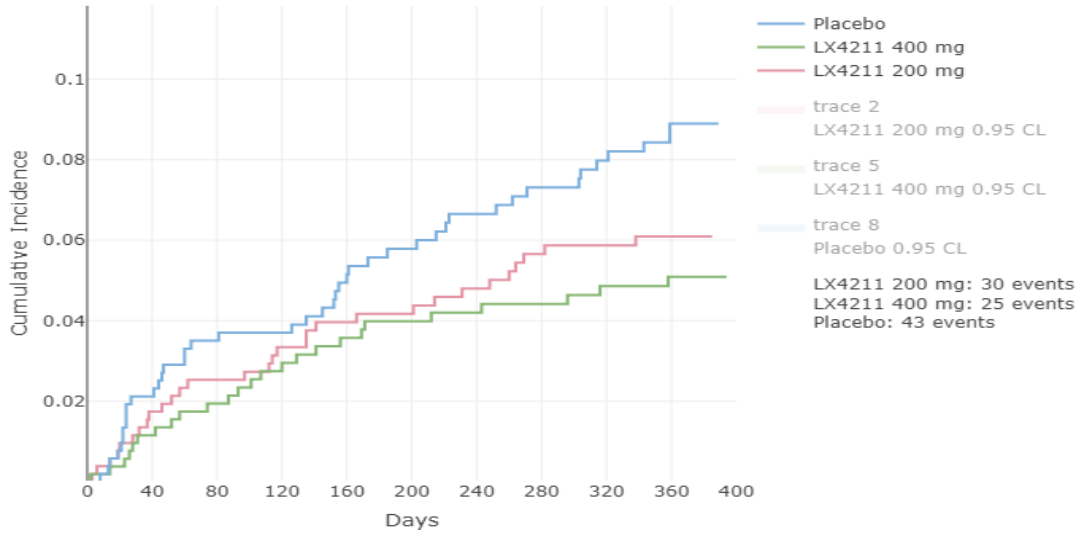
Table 40. Adjudicated Severe Hypoglycemia- All Phase 3 Studies

	Sota 200 mg	Sota 400 mg	Placebo
Study 309			
Subjects with Events/ Total Subjects	17/263 (6.5%)	17/262 (6.5%)	26/268 (9.7%)
Total # Events/Exposure	49/241.0	19/236.2	34/236.9
Event rate/100 pt. years	20.3/100PY	8.0/100PY	14.4/PY
Study 310			
Subjects with Events/ Total Subjects	13/261 (5.0%)	6/263 (2.3%)	13/258 (5.0%)
Total # Events/Exposure	19/239.0	14/241.0	16/237.3
Event rate/100 pt. years	7.9/100PY	5.8/100PY	6.7/100PY
Study 312			
Subjects with Events/ Total Subjects		21/699 (3.0%)	17/703 (2.4%)
Total # Events/Exposure		25/298.2	22/303.9
Event rate/100 pt. years		8.4/100PY	7.2/100PY
Total			
Subjects with Events/ Total Subjects	30/524 (5.7%)	44/1224 (3.6%)	56/1229 (4.6%)
Total # Events/Exposure	68/480.0	58/775.3	72/778.1
Event rate/100 pt. years	14.2/100PY	7.5/100PY	9.3/100PY

Source: courtesy of Safety Statistics Reviewer

The time to first event of Investigator-Reported severe hypoglycemia is presented below (Figure 28). The 95% CI overlap for all three groups.

Figure 28. Time to First Event for Severe Hypoglycemia Investigator-Reported SAF-1



Source: generated by the Reviewer

Statistical Analysis of Hypoglycemia Results

Severe Hypoglycemia

Table 41 shows the results for positively adjudicated severe hypoglycemia for the core treatment phase in all three studies. There were 41 subjects in study 309, 23 subjects in study 310, and 38 subjects in study 312, that had at least one event. There was no statistical significance between any of the sotagliflozin groups and placebo.

Table 41. Positively Adjudicated Severe Hypoglycemic Episodes – Core Treatment Period

Study 309			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	268	263	262
Yes SH	18 (6.7%)	11 (4.2%)	12 (4.6%)
No SH	250 (93.3%)	252 (95.8%)	183 (76.6%)
Number of Events	23	31	13
Rate ratio (95% CI)		1.31 (0.52, 3.29)	0.50 (0.18, 1.37)
Nominal P-value		0.5587	0.1762
Study 310			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	258	261	263
Yes SH	7 (2.7%)	10 (3.8%)	6 (2.3%)
No SH	251 (97.3%)	251 (96.2%)	257 (97.7%)
Number of Events	8	14	9
Rate ratio (95% CI)		1.71 (0.56, 5.22)	1.03 (0.32, 3.38)
Nominal P-value		0.3448	0.9594
Studies 309 and 310 Combined			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	526	524	525
Yes SH	25 (4.7%)	21 (4.0%)	18 (3.4%)
No SH	501 (95.3%)	503 (96.0%)	507 (96.6%)
Number of Events	31	45	22
Rate ratio (95% CI)		1.41 (0.68, 2.94)	0.61 (0.27, 1.35)
Nominal P-value		0.3607	0.2183
Study 312			
Treatment	Placebo		Sota 400mg
FAS	703		699
Yes SH	17 (2.4%)		21 (3.0%)
No SH	686 (97.6%)		678 (97.0%)
Number of Events	22		25
Rate ratio (95% CI)			1.18 (0.59, 2.39)
Nominal P-value			0.6404

Source: Statistical Reviewer's Analysis
SH: Severe Hypoglycemia, Yes SH: number of patients with at least one event
Rate Ratio with 95% CL and p-values were obtained from a GLM, which included fixed, categorical effects of treatment, insulin delivery method (MDI, CSII), week -2 A1C (≤8.5%, >8.5%), and an offset term for log of study duration. The event rates were modeled as a negative binomial process.

Table 42 shows the results for this reviewer's analysis of positively adjudicated severe hypoglycemic episodes in the core treatment period and the extension period (studies 309 and 310). There were 60 subjects that experienced at least one positively adjudicated severe hypoglycemic episode in study 309, 32 subjects in study 310. No significant difference was seen between the sotagliflozin groups doses and placebo in any of the studies.

Table 42. Positively Adjudicated Severe Hypoglycemic – Core Treatment Period + Extension (Studies 309 and 310 only)

Study 309			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	268	263	262
Yes SH	26 (9.7%)	17 (6.5%)	17 (6.5%)
No SH	242 (90.3%)	246 (93.5%)	245 (93.5%)
Difference in % of responders from Placebo		-3.24	-3.21
95% CI		-7.86, 1.39	-7.84, 1.42
Nominal P-value		0.1719	0.1760
Study 310			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	258	261	263
Yes SH	13 (5.0%)	13 (5.0%)	6 (2.3%)
No SH	245 (95.0%)	248 (95.0%)	257 (97.7%)
Difference in % of responders from Placebo		-0.06	-2.76
95% CI		-3.81, 3.70	-5.98, 0.46
Nominal P-value		0.9759	0.0935
Studies 309 and 310 Combined			
Treatment	Placebo	Sota 200mg	Sota 400mg
FAS	526	524	525
Yes SH	39 (7.4%)	30 (5.7%)	23 (4.4%)
No SH	487 (92.6%)	494 (94.3%)	502 (95.6%)
Difference in % of responders from Placebo		-1.69	-3.03
95% CI		-4.68, 1.31	-5.88, -0.19
Nominal P-value		0.2696	0.0370

Source: Statistical Reviewer's Analysis
SH: Severe hypoglycemia, Yes SH: number of patients with at least one event

Table 43 shows the results for the number of positively adjudicated severe hypoglycemic episodes in the core treatment period and extension period (studies 309 and 310). Numerically, in studies 309 and 310 it is seen that more events occurred in the sotagliflozin 200 mg group compared to the placebo.

Table 43. Number of Positively Adjudicated Severe Hypoglycemic Episodes – Core Treatment Period + Extension (Studies 309 and 310 only)

	Placebo	Sota 200mg	Sota 400mg
Study 309			
Number of Events	34	49	19
Rate Ratio (95% CI)		1.54 (0.70, 3.39)	0.51 (0.22, 1.21)
Nominal P-value		0.2800	0.1286
Study 310			
Number of Events	16	19	14
Rate Ratio (95% CI)		1.11 (0.41, 2.98)	0.82 (0.29, 2.30)
Nominal P-value		0.8392	0.7032
Study 309 and 310			
Number of Events	50	68	33
Rate Ratio (95% CI)		1.29 (0.70, 2.38)	0.58 (0.30, 1.12)
Nominal P-value		0.4229	0.1030

Source: Statistical Reviewer's Analysis
Rate Ratio with 95% CL and p-values were obtained from a GLM, which included fixed, categorical effects of treatment, insulin delivery method (MDI, CSII), week -2 A1C (≤8.5%, >8.5%), and an offset term for log of study duration. The event rates were modeled as a negative binomial process.

Table 44 shows the results for the number of positively adjudicated severe hypoglycemic episodes with sotagliflozin 200 mg and 400 mg doses combined in the core treatment period and extension period (studies 309 and 310 only). Numerically fewer events occurred in the placebo group in all three studies.

Table 44. Number of Positively Adjudicated Severe Hypoglycemia: Sota 200mg+400mg versus Placebo - Core + Extension

	Placebo	Sota 200mg + 400mg
Study 309		
Number of Events	34	68
Rate ratio (95% CI)	1.01 (0.49, 2.07)	
Nominal p-value	0.9856	
Study 310		
Number of Events	16	33
Rate ratio (95% CI)	0.96 (0.40, 2.32)	
Nominal p-value	0.9339	
Study 309 and 310		
Number of Events	50	101
Rate ratio (95% CI)	0.92 (0.53, 1.60)	
Nominal p-value	0.7661	

Source: Statistical Reviewer's Analysis
Rate Ratio with 95% CL and p-values were obtained from a GLM, which included fixed, categorical effects of treatment, insulin delivery method (MDI, CSII), week -2 A1C (≤8.5%, >8.5%), and an offset term for log of study duration. The event rates were modeled as a negative binomial process.

Table 45 displays the results from the analysis of documented symptomatic hypoglycemic episodes where subjects had blood glucose ≤55 mg/dL in the core treatment period and the extension period (study 312 only had core treatment period). Numerically, more documented symptomatic hypoglycemic events (≤55 mg/dL) occurred in the placebo group in all three studies.

Table 45. Number of Documented Symptomatic Hypoglycemic Events (≤55 mg/dL) – Core Treatment Period + Extension

	Placebo	Sota 200mg	Sota 400mg
Study 309			
Number of Events	3178	2632	2581
Rate ratio (95% CI)		0.81 (0.66, 0.99)	0.83 (0.67, 1.01)
Nominal p-value		0.0437	0.0642
Study 310			
Number of Events	3373	2558	2534
Rate ratio (95% CI)		0.72 (0.57, 0.90)	0.78 (0.62, 0.98)
Nominal p-value		0.0046	0.0352
Studies 309 and 310 Combined			
Number of Events	6551	5190	5115
Rate ratio (95% CI)		0.76 (0.66, 0.89)	0.80 (0.69, 0.93)
Nominal p-value		0.0005	0.0047
Study 312 *			
Number of Events	3310		2479
Rate ratio (95% CI)			0.76 (0.65, 0.89)
Nominal p-value			0.0006

Source: Statistical Reviewer's Analysis

** Study 312 only had core treatment period.*

Rate Ratio with 95% CL and p-values were obtained from a GLM, which included fixed, categorical effects of treatment, insulin delivery method (MDI, CSII), week -2 A1C (≤8.5%, >8.5%), and an offset term for log of study duration. The event rates were modeled as a negative binomial process.

Additional Safety Findings

Genital Mycotic Infections

An increased risk for genital mycotic infections has previously been reported as a safety concern with approved SGLT2 inhibitors, and subjects in the sotagliflozin clinical development program were given instructions on basic genitourinary hygiene to decrease the number of events. A MedDRA search for PTs related to genital mycotic infections was performed, and the results are listed below in Table 46. There was a higher incidence of genital mycotic infections in patients treated with sotagliflozin compared to placebo patients (12.5% in the pooled sotagliflozin group versus 2.9% in the placebo group).

Due to the re-categorization of some events by Investigators, the Applicant's analysis differed from the results of custom MedDRA queries. The Applicant reported a total of 159 events in 111 subjects in the pooled sotagliflozin arm (10.6%) versus 27 events in 15 subjects in the placebo arm (2.9%). The Applicant also reported the incidence by gender, as well as events resulting in study discontinuation and the use of antimycotic therapy. For the Applicant's analysis, the incidence was increased in both male and female patients treated with sotagliflozin, and the risk appeared to be dose related. The majority of subjects with genital mycotic infections were female (75-83% in the pooled sotagliflozin group versus 80% in the placebo group), and most of the male subjects in the sotagliflozin group who developed infections were uncircumcised (75-87%). None of the events were reported as serious, and only a few events (0.6-0.8%) resulted in study drug discontinuation. However, the vast majority of events (95-97%) required treatment with antimycotic therapy.

Table 46. Genital Mycotic Infections in SAF-1

	Sota 200 mg N=524			Sota 400 mg N=525			Sota ALL N=1049			Placebo N = 526		
PT	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**
Balanitis Candida	2	0.38	2	1	0.19	1	3	0.29	3	0	0	0
Balanoposthitis	3	0.57	3	4	0.76	4	7	0.67	7	0	0	0
Candida infection	0	0	0	2	0.38	2	2	0.19	2	0	0	0
Genital Burning Sensation	0	0	0	1	0.19	1	1	0.1	1	0	0	0
Genital candidiasis	0	0	0	3	0.57	3	3	0.29	3	0	0	0
Genital discomfort	0	0	0	1	0.19	1	1	0.1	1	0	0	0
Genital Infection	1	0.19	1	2	0.38	5	3	0.29	6	0	0	0
Genital Infection Fungal	18	3.44	25	21	4	34	39	3.72	59	1	0.19	3
Pruritis Genital	0	0	0	2	0.38	2	2	0.19	2	1	0.19	1
Vaginal discharge	1	0.19	1	0	0	0	1	0.1	1	0	0	0
Vaginal Infection	1	0.19	1	2	0.38	3	3	0.29	4	0	0	0
Vulvitis	1	0.19	1	0	0	0	1	0.1	1	0	0	0
Vulvovaginal Candidiasis	3	0.57	3	6	1.14	13	9	0.86	16	1	0.19	6
Vulvovaginal discomfort	1	0.19	1	0	0	0	1	0.1	1	0	0	0
Vulvovaginal Dryness	1	0.19	1	2	0.38	2	3	0.29	3	0	0	0
Vulvovaginal Mycotic Infection	15	2.86	20	27	5.14	32	42	4	52	10	1.9	13

Vulvovaginal Pruritis	4	0.76	4	2	0.38	2	6	0.57	6	3	0.57	3
Vulvovaginitis	2	0.38	2	2	0.38	6	4	0.38	8	0	0	0
Total	52	9.92	65	68	12.95	111	120	12.49	176	15	2.85	26

Source: table generated by Reviewer based on custom MedDRA query

As with SAF-1, there was a higher incidence of genital mycotic infections in patients treated with sotagliflozin compared to placebo patients (7.2% in the sotagliflozin arm versus 2.6% in the placebo arm) in Study 312. The Applicant reported 71 events in 45 subjects (6.4%) in the sotagliflozin arm, versus 18 events in 15 subjects (2.1%) in the placebo group. The majority of subjects with genital mycotic infections were female (84.4 in the sotagliflozin group versus 86.7% in the placebo group), and none of the male subjects in the sotagliflozin group who developed infections were circumcised.

None of the events were reported as serious, and only a few events (0.6%) in the sotagliflozin group resulted in study drug discontinuation. However, 92.1% of events overall required treatment with antimycotic therapy.

Table 47. Genital Mycotic Infections in Study 312

	Sota 400 mg N=699			Placebo N=703		
PT	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**
Balanitis candida	0	0	0	1	0.14	1
Balanoposthitis	5	0.72	5	0	0	0
Candida infection	1	0.14	2	1	0.14	1
Fungal infection	2	0.29	2	0	0	0
Genital burning sensation	0	0	0	1	0.14	1
Genital candidiasis	1	0.14	1	2	0.28	2
Genital discomfort	2	0.29	2	0	0	0
Genital infection	1	0.14	1	0	0	0
Genital infection fungal	10	1.43	15	5	0.71	5
Genital rash	1	0.14	1	0	0	0
Penile discharge	1	0.14	1	0	0	0
Penile infection	1	0.14	1	0	0	0
Vaginal infection	4	0.57	5	1	0.14	1
Vulvovaginal burning sensation	1	0.14	1	0	0	0
Vulvovaginal candidiasis	10	1.43	10	3	0.43	4
Vulvovaginal mycotic infection	14	2.00	32	6	0.85	6
Vulvovaginitis	1	0.14	1	0	0	0
Total	50	7.15	77	18	2.56	21

Source: table generated by Reviewer based on custom MedDRA query

Renal Events

An increased incidence of acute kidney injury and renal impairment events was noted with the use of SGLT2 inhibitors, and this risk is included in the Warnings and Precautions section of labeling for approved SGLT2 inhibitors for the treatment of patients with T2DM. For this reason, the Applicant included renal events as an AEOSI during the development program for sotagliflozin. In SAF-1, the Applicant reported a total of 18 events in 15 subjects (1.4%) in the pooled sotagliflozin group, and 11 events in 8 subjects (1.5%) in the placebo group. It was noted that the Applicant's analysis included several terms such as "nephrolithiasis", "ureterolithiasis" and "urine ketone body present" which were not considered to be specific to events of renal injury. In addition, Investigators did not classify all events with PTs suggestive of renal events as an AEOSI so the Applicant's analysis differs somewhat from the analysis presented in Table 48.

Based on the results of the custom MedDRA query, there were a total of 22 events in 21 subjects (2.0%) in the pooled sotagliflozin group, and 7 events in 5 subjects (1.0%) in the placebo group. One event of "acute kidney injury" in the sotagliflozin 200 mg group, was classified as an SAE. This event occurred in association with, and immediately prior to a hospitalization and surgery for an acute appendicitis with a post-operative wound infection, with a creatinine of 0.7 mg/dL

prior to the event, which increased to a creatinine of 1.25 mg/dL, and resolved following aggressive IV hydration.

Table 48. Renal Events in SAF-1

	Sota 200 mg N=524			Sota 400 mg N=525			Sota ALL N=1049			Placebo N = 526		
PT	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**
Acute kidney injury	1	0.19	1	0	0	0	1	0.10	1	2	0.38	2
Blood creatinine increased	6	1.15	6	3	0.57	3	9	0.86	9	3	0.57	4
Blood urea increased	0	0	0	1	0.19	1	1	0.1	1	0	0	0
Blood urea nitrogen/creatinine ratio increased	2	0.38	2	0	0	0	2	0.19	2	0	0	0
Glomerular filtration rate decreased	3	0.57	3	2	0.38	2	5	0.48	5	2	0.38	2
Renal impairment	0	0	0	1	0.19	1	1	0.1	1	1	0.19	1
Urine output increased	2	0.38	2	1	0.19	1	3	0.29	3	0	0	0
Total	14	2.67	14	7	1.33	8	21	2.00	22	5	0.95	7

Source: table generated by Reviewer based on custom MedDRA query

In Study 312, the Applicant reported a total of 5 events in 5 subjects (0.7%) in the sotagliflozin arm, and 4 events in 3 subjects (0.4%) in the placebo arm. Based on the results of the custom MedDRA query, there were a total of 10 events in 21 subjects (2.0%) in the pooled sotagliflozin group, and 7 events in 5 subjects (1.0%) in the placebo group. One event of "acute kidney injury", which occurred in a subject in the sotagliflozin 400 mg group, was classified as an SAE. This event occurred in association with an event of DKA, and resolved following aggressive IV hydration. One additional event of "urine ketone body present" from the Applicant's analysis, which occurred in a subject in the placebo group, was also classified as an SAE.

Table 49. Renal Events in Study 312

	Sota 400 mg N=699			Placebo N=703		
PT	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**
Acute kidney injury	2	0.29	2	2	0.29	2
Blood creatinine increased	2	0.29	2	0	0	0
Blood urea increased	2	0.29	3	0	0	0
Blood urea nitrogen/creatinine ratio increased	1	0.14	1	0	0	0
Glomerular filtration rate decreased	1	0.14	1	0	0	0
Renal impairment	1	0.14	1	0	0	0
Renal failure	0	0	0	1	0.14	1
Total	7	1.00	10	3	0.43	3

Source: table generated by Reviewer based on custom MedDRA query

Laboratory Assessments of Renal Function:
In addition to MedDRA custom queries of renal events, the laboratory assessments of renal function were evaluated for subjects in all three Phase 3 studies. Since not all datasets for individual studies were included in the ISS, the analyses of renal function laboratory assessments are presented by individual study (see *Appendix F: Kidney Function Tables*). There were no subjects that developed marked changes in serum creatinine (defined as an increase > 2.5 mg/dl) during the study in either treatment group. However, with respect to eGFR, there was an increased incidence in the number of subjects with downward shifts in eGFR from baseline to Week 52/end of treatment (EOT) in the sotagliflozin group versus placebo in Studies 310 and 312 (2.5% in the pooled sotagliflozin group vs. 1.3% in the placebo, and 3.5% in the sotagliflozin arm vs. 1.9% in the placebo group, respectively), although the rates were similar in Study 309. Changes in albumin/creatinine ratios (ACR), as well as downward shifts in ACRs, were similar between treatment groups in Studies 309 and 312, although there was a higher incidence of subjects with downward shifts in ACRs in the sotagliflozin group in Study 310.

Volume Depletion Events

There was a greater incidence of subjects with volume depletion events in the sotagliflozin group compared to placebo (3.2% in the pooled sotagliflozin group versus 1.3% in the placebo group) based on MedDRA query of PTs associated with volume depletion. There were two volume depletion events that were reported as SAEs, one event of "syncope" and one event of "orthostatic hypotension", both of which occurred in the placebo group.

The Applicant reported a total of 20 events in 20 subjects in the pooled sotagliflozin group (1.9%) versus 5 events in 5 subjects in the placebo group (1.0%). However, the list of PTs reported in the Applicant's Integrated Summary of Safety differs slightly from the list of PTs included in the SAP and included additional PTs as "diarrhea" and "vomiting".

Table 50. Volume Depletion Events in SAF-1

	Sota 200 mg N=524			Sota 400 mg N=525			Sota ALL N=1049			Placebo N = 526		
PT	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**
Blood urea nitrogen/creatinine ratio increased	2	0.38	2	0	0	0	2	0.19	2	0	0	0
Dehydration	4	0.76	4	3	0.57	3	7	0.67	7	2	0.38	2
Heart rate increased	0	0	0	1	0.19	1	1	0.1	1	0	0	0
Hypotension	6	1.15	6	3	0.57	4	9	0.86	10	0	0	0
Hypovolemia	2	0.38	2	1	0.19	1	3	0.29	3	0	0	0
Orthostatic hypotension	0	0	0	0	0	0	0	0	0	1	0.19	1
Presyncope	1	0.19	1	0	0	0	1	0.1	1	2	0.38	3
Syncope	1	0.19	1	3	0.57	3	4	0.38	4	2	0.38	2
Thirst	3	0.57	3	4	0.76	5	7	0.67	8	0	0	0
Total	19	3.63	19	15	2.86	17	34	3.24	36	7	1.33	8

Source: table generated by Reviewer based on custom MedDRA query

In Study 312, as in SAF-1, there was an increased incidence of subjects with volume depletion events in the sotagliflozin group versus the placebo group (2.2% vs. 0.6%). Two of the events, "syncope" and "hypotension", both of which occurred in the sotagliflozin 400 mg group, were reported as SAEs. The Applicant reported a total of 13 events in 13 subjects in the sotagliflozin group (1.9%) versus 4 events in 2 subjects in the placebo group (0.3%).

Table 51. Volume Depletion Events in Study 312

	Sota 400 mg N=699			Placebo N=703		
PT	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**
Blood pressure decreased	2	0.29	2	0	0	0
Blood urea nitrogen/creatinine ratio increased	1	0.14	1	0	0	0
Dehydration	3	0.43	3	1	0.14	1
Hypotension	3	0.43	3	0	0	0
Hypovolemia	0	0	0	1	0.14	1
Orthostatic hypotension	1	0.14	1	1	0.14	1
Syncope	1	0.14	1	1	0.14	1
Thirst	4	0.57	4	1	0.14	1
Total	15	2.15	15	4	0.57	5

Source: table generated by Reviewer based on custom MedDRA query

Urinary Tract Infections

The overall incidence of UTIs was similar between treatment groups; based on a MedDRA custom query, the incidence was 6.5% for the pooled sotagliflozin group and 6.5% for the placebo group. One of the events of "cystitis", which occurred in the sotagliflozin 400 mg group was an SAE.

The Applicant reported a total of 90 events in 66 subjects (6.3%) in the pooled sotagliflozin group, and 40 events in 32 subjects (6.1%) in the placebo group. There were fewer events in the Applicant's analysis as several events of "dysuria" were determined by the Investigator to not be events of UTI, and the event of "bacterial infection fungal" was determined to be an AEOSI of a genital mycotic infection, rather than UTI. Of these events, the Applicant also included an event of "cystitis noninfective" which was an SAE, and occurred in a subject in the sotagliflozin 400 mg group.

Table 52. Urinary Tract Infections in SAF-1

	Sota 200 mg N=524			Sota 400 mg N=525			Sota ALL N=1049			Placebo N = 526		
PT	Subjects	%	Events	Subjects	%	Events	Subjects	%	Events	Subjects	%	Events
Bacterial prostatitis	1	0.19	1	0	0	0	1	0.1	1	0	0	0
Cystitis	1	0.19	1	1	0.19	2	2	0.19	3	3	0.57	3
Cystitis glandularis	0	0	0	0	0	0	0	0	0	1	0.19	1
Dysuria	4	0.76	4	6	1.14	6	10	0.95	10	5	0.95	5
Genitourinary tract infection	0	0	0	1	0.19	1	1	0.1	1	0	0	0
Prostatitis	0	0	0	1	0.19	1	1	0.1	1	0	0	0
Pyuria	0	0	0	1	0.19	1	1	0.1	1	0	0	0
Urethritis	0	0	0	0	0	0	0	0	0	2	0.38	2
Urinary tract infection	32	6.11	47	20	3.81	27	52	4.96	74	26	4.94	31
Urinary tract infection fungal	0	0	0	1	0.19	1	1	0.1	1	0	0	0
White blood cells urine positive	0	0	0	1	0.19	1	1	0.1	1	0	0	0
Bacterial prostatitis	1	0.19	1	0	0	0	1	0.1	1	0	0	0
Total	38	7.25	53	31	5.71	39	68	6.48	92	34	6.46	42

Source: table generated by Reviewer based on custom MedDRA query

As in SAF-1, the incidence of subjects with UTIs in Study 312 was similar across treatment groups, there were a total of 35 events in 29 subjects (4.2%) in the sotagliflozin 400 mg group,

and 37 events in 30 subjects (4.3%) in the placebo group based on a custom MedDRA query. None of the UTI events were reported as SAEs.

The Applicant reported 30 events in in 25 subjects (3.6%) in the sotagliflozin 400 mg group and 34 events in 27 subjects (3.8%) in the placebo group.

Table 53. Urinary Tract Infections in Study 312

	Sota 400 mg N=699			Placebo N=703		
PT	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**
Cystitis	4	0.57	4	3	0.43	3
Cystitis bacterial	1	0.14	1	0	0	0
Dysuria	3	0.43	3	3	0.43	3
Kidney infection	0	0	0	1	0.14	1
Pyuria	1	0.14	1	0	0	0
Urinary tract infection	22	3.15	25	24	3.41	29
Urinary tract infection fungal	1	0.14	1	1	0.14	1
Total	29	4.15	35	30	4.27	37

Source: table generated by Reviewer based on custom MedDRA query

Amputations

Due to findings of an increased risk for amputations associated with the use of some SGLT2 inhibitors approved for the treatment of T2DM, amputations were included by the Applicant as an AEOSI for the sotagliflozin development program. The Applicant reported two subjects that had events of amputations during Studies 309 and 310. Both subjects were in the sotagliflozin group. The narratives are included below:

> (b) (6) (sotagliflozin 400 mg): A 59 year old male with a prior history of left foot amputation, along with multiple toe amputations, DVT, and diabetic neuropathy, developed an SAE of skin ulcer over his second, third, and fifth toes on Study Day 287, which did not improve over the next 2 months despite debridement and antibiotic treatment. The patient underwent a transmetatarsal amputation on Study Day 351. The patient was discharged the same day.
>
> (b) (6) (sotagliflozin 200 mg): A 62 year-old male with a prior history of multiple toe amputations, diabetic retinopathy, and chronic heart failure presented with a wound of his fifth toe on Study Day 216, which did not improve despite antibiotic treatment. The patient was hospitalized on Study Day 252 for impaired wound healing, and underwent amputation of fifth toe, along with a dilation of his posterior tibial artery and stenting of

the superficial femoral artery. The patient was diagnosed with osteitis after a wound sample revealed the presence of *Pseudomonas aeruginosa*. The patient was discharged 10 days later on Study Day 267.

A MedDRA query was performed for additional potential events related to amputations. The results are displayed below in Table 54. Overall, there was a greater number of subjects with MedDRA events related to amputations in the sotagliflozin group in comparison to placebo (3.2% versus 2.5%). However, at baseline, there was also a greater number of subjects in the pooled sotagliflozin group (7 subjects, 0.7%) compared to the placebo group (1 subject, 0.2%) with a baseline medical history of toe amputations. Additionally, both subjects that had events of amputations had prior histories of amputations at baseline, and were at increased risk for impaired wound healing leading to amputations.

For Study 312, the Applicant did not report any events of amputations.

Table 54. MedDRA query for amputations in SAF-1

	Sota 200 mg N=524			Sota 400 mg N=525			Sota ALL N=1049			Placebo N = 526		
PT	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**
Abscess limb	2	0.38	2	0	0	0	2	0.19	2	0	0	0
Cellulitis	2	0.38	2	2	0.38	2	4	0.38	4	3	0.57	3
Diabetic ulcer	0	0	0	1	0.19	1	1	0.1	1	0	0	0
Foot amputation	0	0	0	1	0.19	1	1	0.1	1	0	0	0
Foot deformity	2	0.38	3	1	0.19	1	3	0.29	4	0	0	0
Joint swelling	2	0.38	2	4	0.76	4	6	0.57	6	3	0.57	3
Limb injury	4	0.76	4	1	0.19	1	5	0.48	5	1	0.19	1
Localized infection	2	0.38	2	0	0	0	2	0.19	2	1	0.19	1
Osteitis	1	1	0.19	0	0	0	1	1	0.1	0	0	0
Skin infection	0	0	0	1	0.19	1	1	0.1	1	1	0.19	1
Skin ulcer	3	0.57	5	2	0.38	2	5	0.48	7	2	0.38	2
Wound	3	0.57	4	1	0.19	1	4	0.38	5	3	0.57	4
Total	21	4.01	27	13	2.48	14	34	3.24	41	13	2.47	18

Source: table generated by Reviewer based on custom MedDRA query

Gastrointestinal Events

Diarrhea

As a result of the mechanism of action of sotagliflozin, which causes delayed absorption of glucose in the proximal intestine which can result in diarrhea, the Applicant included diarrhea as an AEOSI. There was an increased incidence in the number of subjects with events of diarrhea in the sotagliflozin group, although none of the events were categorized as SAEs. In SAF-1, the Applicant reported a total of 110 events of "diarrhea" in 80 subjects (7.6%) in the pooled sotagliflozin group, and 32 events in 27 subjects (5.1%) in the placebo group. Most of the events did not lead to study drug discontinuation, 5 subjects (0.5%) in the pooled sotagliflozin group and 2 subjects (0.4%) in the placebo group discontinued study drug as a result of diarrhea.

The results of a custom MedDRA query for "diarrhea", as well as terms suggestive of diarrhea, including "frequent bowel movements" and "mucous stools" are presented below in Table 55. There was a total of 123 events in 89 subjects (8.5%) in the pooled sotagliflozin group, and 35 events in 30 subjects (5.7%) in the placebo group.

Table 55. Diarrhea Events in SAF-1

	Sota 200 mg N=524			Sota 400 mg N=525			Sota ALL N=1049			Placebo N = 526		
PT	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**
Diarrhea	34	6.49	44	49	9.33	70	83	7.91	114	29	5.51	34
Diarrhea infectious	0	0	0	1	0.19	1	1	0.1	1	0	0	0
Frequent bowel movements	2	0.38	2	4	0.76	4	6	0.57	6	1	0.19	1
Mucous stools	1	0.19	1	0	0	0	1	0.1	1	0	0	0
Viral diarrhea	1	0.19	1	0	0	0	1	0.1	1	0	0	0
Total	37	7.06	48	52	9.90	75	89	8.48	123	30	5.70	35

Source: table generated by Reviewer based on custom MedDRA query

In Study 312, the Applicant reported a total of 35 events for 29 subjects (4.1%) in the sotagliflozin 400 mg group, and 21 events in 16 subjects (2.3%) in the placebo group. None of the events were categorized as SAEs. Only 3 subjects (0.4%), all in the sotagliflozin group, discontinued study drug as a result of diarrhea.

A custom MedDRA query for "diarrhea", as well as terms suggestive of diarrhea, including "frequent bowel movements" and "mucous stools" was also performed for Study 312, although unlike in SAF-1, only events of "diarrhea" were reported. The results are presented below in Table 56. There was a total of 41 events in 35 subjects (5.0%) in the sotagliflozin arm, and 22 events in 17 subjects (2.4%) in the placebo group.

Table 56. Diarrhea Events in Study 312

	Sota 400 mg N=699			Placebo N=703		
PT	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**
Diarrhea	35	5.01	41	17	2.42	22

Source: table generated by Reviewer based on custom MedDRA query

Pancreatitis

There was a single subject with an event of "edematous pancreatitis" in the sotagliflozin 400 mg group in SAF-1. The narrative is provided below:

> [redacted] (b) (6) (sotagliflozin 400 mg): 43-year old man with prior history of DKA presented with vomiting, intolerance to oral intake, and abdominal pain of 3 days duration on Study Day 295. His BG was 273 mg/dL, serum bicarbonate 7.2 mmol/L (reference range: 22.0 mmol/L to 26.0 mmol/L), pH 7.09, anion gap 36.8 mmol/L, lactic acid 3.39 mmol/L (reference range: 0.50 mmol/L to 2.00 mmol/L), amylase 3.6 x ULN, lipase 858 U/L, creatinine 1.97 mg/dL, urine ketones positive; and serum ketones 7.2 mEq/L. The patient's BHB was not measured. Computed tomography and ultrasound were normal. The patient received a diagnosis of acute edematous pancreatitis, DKA, and acute kidney failure secondary to dehydration and peptic esophagitis. The patient improved after admission, and DKA resolved after 2 days, and pancreatitis resolved after 7 days, and the patient was discharged.

There were no events of pancreatitis in Study 312.

MACE (Major Adverse Cardiovascular Events)

In order to evaluate the cardiovascular (CV) safety of sotagliflozin, the Applicant performed a meta-analysis of the ITT population in SAF-4, which included a pool of 7 trials (202, 203, 204, 206, 309, 310, and 312), and was limited to the 200 mg and 400 mg dose of sotagliflozin. All MACE events (CV death, non-fatal MI including silent MI, and non-fatal stroke) were referred to the CEC for adjudication (Study 201 was excluded as events were not adjudicated). The primary endpoint was time from randomization to the first occurrence of positively adjudicated MACE. Secondary endpoints included time from randomization to the first occurrence of positively adjudicated MACE+ (with the addition of hospitalization for unstable angina), as well as CV-related events, which included the addition of heart failure, cerebrovascular event, and coronary revascularization. The on-study analysis set was the primary dataset for analysis, and included all positively adjudicated MACE or MACE+ regardless of last dose of study drug.

The meta-analysis included a total of 3386 patients, which included 1998 subjects in the pooled sotagliflozin (200 mg and 400 mg) arm and 1388 in the placebo arm. There was also an additional 94 patients who received sotagliflozin 75 mg and 60 patients who received sotagliflozin 200 mg twice daily.

The overall incidence of both Investigator-reported and positively-adjudicated MACE and MACE+ events was similar between both treatment groups. There were a total of 14 subjects (0.7%) in the pooled sotagliflozin group and 8 subjects (0.6%) in the placebo group with Investigator-reported CV-related events. There were 9 subjects (0.5%) in the pooled sotagliflozin group and 7 subjects (0.5%) in the placebo group with positively-adjudicated MACE events. With respect to MACE+ events, there was one subject in the placebo group that had an event of MI (MACE event) that preceded an event of hospitalization for unstable angina (MACE+ event). There were also two events of CV death, both in the placebo group. For further details, see Table 57. By study, one subject in the placebo group from study 202 had a MACE event, all other subjects were from studies 309, 310, and 312.

Table 57. Meta-Analysis of Positively-adjudicated MACE and MACE+ Events

	Placebo **(N = 1388)** **Patients** **n (%)**	**SOTA 200** **(N = 619)** **Patients** **n (%)**	**SOTA 200 bid** **(N = 60)** **Patients** **n (%)** **r**	**SOTA 400** **(N = 1379)** **Patients** **n (%)**	**All SOTA** **(N = 1998)** **Patients** **n (%)**
All positively adjudicated MACE	7 (0.5) 8	5 (0.8) 5	0	4 (0.3) 4	9 (0.5) 9
EAIR per 1000 patient-years	8.65	9.97	0	4.95	6.88
Cardiovascular death	2 (0.1)	0	0	0	0
Non-fatal MI (including silent MI)	4 (0.3) 4	5 (0.8) 5	0	3 (0.2) 3	8 (0.4) 8
Non-fatal stroke	2 (0.1)	0	0	1 (0.1)	1 (0.1)
All positively adjudicated MACE+	7 (0.5) 9	5 (0.8) 5	0	4 (0.3) 4	9 (0.5) 9
EAIR per 1000 patient-years	8.65	9.97	0	4.95	6.88
Cardiovascular death	2 (0.1)	0	0	0	0
Non-fatal MI (including silent MI)	4 (0.3) 4	5 (0.8) 5	0	3 (0.2) 3	8 (0.4) 8
Non-fatal stroke	2 (0.1)	0	0	1 (0.1)	1 (0.1)
Hospitalization for unstable angina	1 (0.1)	0	0	0	0

Source: Table 7 from Applicant's Cardiovascular Safety Meta-analysis

Malignancies

The overall incidence of malignancies was similar between treatment groups. Using both the broad and narrow Standardized MedDRA Query (SMQ) for malignancies, the following events were obtained for SAF-1. There were a total of 8 events in 8 subjects (0.8%) in the pooled sotagliflozin group, and 3 events in 3 subjects (0.6%) in the placebo group. See Table 58 for further details. Six of the events occurred within 6 months of starting treatment, three of these events were within 3 months of treatment. Several other events of clear cell renal carcinoma and bladder transitional cell carcinoma were in subjects with known risk factors for malignancy, including histories of heavy smoking and use of alkylating agents. However, no risk factors were identified for one subject, a 43 year old male randomized to the sotagliflozin 200 mg group, who developed chronic myeloid leukemia which was diagnosed at the Week 52 visit, when leukocytosis was noted on routine laboratory examination.

An increased risk of bladder cancer is included in the Warnings and Precautions section of labeling for another member of the SGLT2 inhibitors, and the Applicant reported events of bladder, thyroid, breast, renal, pancreas, and prostate malignancies as malignancies of special interest. The Applicant reported events of malignancies of special interest in 6 subjects (0.3%) in the pooled sotagliflozin group and 2 subjects (0.1%) in the placebo group for the SAF-4 pooled group, which included the Phase 2 studies (201, 202, 203, 204, 206) as well as the 3 Phase 3 studies, and included subjects with T1DM as well as T2DM. The reported types of malignancies included 2 subjects with breast malignancies in the sotagliflozin 200 mg group; 2 subjects with bladder cancer, 1 subject with papillary thyroid cancer, and 1 subject with clear cell renal cell carcinoma in the sotagliflozin 400 mg group, and 2 subjects with breast malignancies in the placebo group.

Table 58. SMQ Malignancies in SAF-1

	Sota 200 mg N=524			Sota 400 mg N=525			Sota ALL N=1049			Placebo N = 526		
PT	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**
Basal cell carcinoma	0	0	0	1	0.19	1	1	0.1	1	1	0.19	1
Breast cancer metastatic	0	0	0	0	0	0	0	0	0	1	0.19	1
Clear cell renal cell carcinoma	0	0	0	1	0.19	1	1	0.1	1	0	0	0
Invasive breast carcinoma	1	0.19	1	0	0	0	1	0.1	1	0	0	0
Invasive ductal breast carcinoma	1	0.19	1	0	0	0	1	0.1	1	0	0	0
Intraductal proliferative breast lesion	0	0	0	1	0.19	1	1	0.1	1	0	0	0
Lung neoplasm malignant	0	0	0	0	0	0	0	0	0	1	0.19	1
Malignant melanoma in situ	1	0.19	1	0	0	0	1	0.1	1	0	0	0
Papillary thyroid cancer	0	0	0	1	0.19	1	1	0.1	1	0	0	0
Chronic Myeloid Leukemia	1	0.19	1	0	0	0	1	0.1	1	0	0	0
Total	4	0.76	4	4	0.76	4	8	0.76	8	3	0.57	3

Source: table generated by Reviewer based on custom MedDRA query

In Study 312, there was 1 event of bladder cancer in 1 subject (0.1%) in the sotagliflozin arm, in comparison to 3 events of malignancy in 3 subjects (0.4%) in the placebo group. The event of bladder cancer occurred in a 74 year-old woman on Study Day 86.

Table 59. Malignancies in Study 312

	Sota 400 mg N=699			Placebo N=703		
PT	**Subjects**	**%**	**Events**	**Subjects**	**%**	**Events**
Bladder cancer	1	0.14	1	0	0	0
Granular Cell Tumor	0	0	0	1	0.14	1
Invasive ductal breast carcinoma	0	0	0	1	0.14	1
Lung neoplasm malignant	0	0	0	1	0.14	1
Total	1	0.14	1	3	0.43	3

Source: table generated by Reviewer based on custom MedDRA query

Fractures

Bone Fractures and Bone Density (DEXA sub-study)

The overall incidence of bone fractures was low, with 26 events in 25 subjects (2.4%) in the pooled sotagliflozin group, and 18 events in 18 subjects (3.4%) in the placebo group. The mean time to onset for fracture events was 171.0 days for the pooled sotagliflozin group, and 192.7 days for the placebo group. Fractures occurred throughout the body and were not limited to any specific bone or location. For Study 312, there were 4 subjects (0.6%) in the sotagliflozin 400 mg group, and 5 subjects (0.7%) in the placebo group with fractures. The distribution of fractures included 5 events of foot fracture, followed by a single event each of lower limb, wrist, rib, and humerus fracture. As with SAF-1, fractures were not limited to a specific location.

Studies 309 and 310 also included a sub-study to assess changes in bone mineral density (BMD) based on DEXA measurements performed at baseline and at Week 52. Markers for bone and calcium metabolism were also obtained. Subjects included in the DEXA sub-study had baseline BMD T-scores greater than -2.5 at total hip, femoral neck, and lumbar spine. A total of 243 subjects were randomized to the DEXA sub-study, and 215 subjects completed the study.

Baseline characteristics for subjects in the sub-study included a mean age between 46.5-48.3 years, 50.0-52.0 % of patients were female, and greater than 90% were white. The mean BMI was 29.5-29.9 kg/m^2.

At Week 52, there were reductions in the percent change from baseline for BMD at the femoral neck, total hip, and lumbar spine in the sotagliflozin groups in comparison to placebo, although the BMDs were all within the normal range. There was a statistically significant reduction in comparison to placebo in BMD at the total hip and lumbar spine for the sotagliflozin 400 mg group.

Biomarkers of bone turnover, along with measurements of 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D, intact parathyroid hormone, serum calcium, urine calcium and phosphate excretion, and serum phosphate were obtained. There were statistically significant reductions in

percent change from baseline in 1,25-dihydroxyvitamin D levels in the sotagliflozin groups in comparison to placebo. The mean percent change from baseline (±SD) at Week 52 was -11.15 ± 33.456 for sotagliflozin 200 mg and -14.34 ± 31.351 for sotagliflozin 400 mg group, and -2.67 ± 59.928 for placebo. There were small but non-significant increases in markers of bone turnover (type 1 collagen c-telopeptides, procollagen 1 n-terminal propeptide), and the levels for both remained within the normal ranges for all groups. There were no other changes from baseline evident in other biomarkers obtained as part of the DEXA sub-study.

Postmarketing Experience: SGLT2 inhibitors and DKA in patients with T1DM, Office of Surveillance and Epidemiology

Analysis of FAERS Cases of Diabetic Ketoacidosis in Type 1 Diabetes Mellitus Patients Using a Sodium-Glucose Co-Transporter 2 Inhibitor

The Office of Surveillance and Epidemiology evaluated case reports of diabetic ketoacidosis (DKA) or ketoacidosis (KA) occurring in Type 1 diabetes mellitus (T1DM) patients using a sodium-glucose co-transporter 2 (SGLT2) inhibitor reported to the FDA Adverse Event Reporting System (FAERS) database.[6] The goal of this evaluation was to characterize cases of DKA in patients with T1DM using an FDA-approved SGLT2 inhibitor in the postmarket setting.

A search of the FAERS database on September 12, 2018 for all FDA-approved SGLT2 inhibitor products coded with the MedDRA Preferred Terms *Euglycaemic diabetic ketoacidosis*; *Diabetic ketoacidosis*; or *Ketoacidosis* retrieved 6,714 reports through September 11, 2018, of which 601 were identified as possibly of a patient with T1DM. After excluding duplicate reports, cases from clinical studies, and cases that did not describe ketoacidosis coincident with SGLT2 inhibitor exposure in a patient with T1DM, 444 cases were included in the case series of ketoacidosis reported in patients with T1DM on an SGLT2 inhibitor. Table 60 summarizes the characteristics reported in the 444 FAERS cases.

Table 60. Descriptive Characteristics of Cases Reporting Ketoacidosis with Sodium-Glucose Co-Transporter 2 Inhibitors in Patients with Type 1 Diabetes Mellitus, in FAERS Received by FDA through September 11, 2018

FAERS Reported Cases of Ketoacidosis in T1DM (n=444)		
Case Characteristics		**No. of Cases/Result**
Age (years) n=312	**Mean** **Median** **Range**	**41.1** **41.5** **14-76**
Sex n=403	**Male** **Female**	**133** **270**
Country of Case	**USA** **Foreign***	**313** **131**
Report Type	**Direct** **Expedited (15-day)** **Non-expedited**	**48** **365** **31**

[6] See *Appendix G. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)* for description of the FAERS database.

FAERS Reported Cases of Ketoacidosis in T1DM (n=444)			
Case Characteristics		**No. of Cases/Result**	
Report Year (n=444) and Event Year (n=272)	**Year**	**Report Year**	**Event Year**
	</=2013	**2**	**4**
	2014	**11**	**31**
	2015	**163**	**140**
	2016	**130**	**65**
	2017	**85**	**22**
	2018	**53**	**10**
Serious Regulatory Outcome[†] n=443	**Death**		**2**
	Hospitalizations		**336**
	Life-Threatening		**50**
	Disability (foot drop)		**1**
	Other serious important medical events		**166**
SGLT2 inhibitor active ingredient	**Canagliflozin**		**281**
	Dapagliflozin		**100**
	Empagliflozin		**63**
SGLT2 inhibitor Dose n=220	**Lower Daily Dose[‡]**		**100**
	Higher Daily Dose[‡]		**120**
Insulin Pump Use	**Yes**		**98**
	No		**47**
	Not Reported		**299**
Type of insulin[§]	**Short acting**		**134**
	Long acting		**99**
	Not Reported		**284**
Time to onset from SGLT2 inhibitor initiation to first DKA event (days) n=205	**Mean**		**181.2**
	Median		**96**
	Range		**1-1095**
Time from precipitating factor to DKA event (days) n=82	**Mean**		**6.4**
	Median		**2**
	Range		**0.5-6**
SGLT2 inhibitor discontinued n=261	**Yes**		**232**
	No		**29**
Recurrence of DKA after SGLT2 inhibitor restarted n=31	**Yes**		**15**
	Not Reported		**16**
Anion gap[‖] (mmol/L or mEq/L) n=120	**Mean**		**26.42**
	Median		**25.85**
	Range		**10.9-50**
pH[¶] n=92	**Mean**		**7.07**
	Median		**7.07**
	Range		**6.7-7.51**

FAERS Reported Cases of Ketoacidosis in T1DM (n=444)		
Case Characteristics		**No. of Cases/Result**
Bicarbonate mEq/L** n=110	**Mean**	**9.39**
	Median	**9.0**
	Range	**1-27**
Blood glucose†† level at time of DKA (mg/dL) n=198	**< 100 mg/dL**	**4**
	100-149 mg/dL	**18**
	150-199 mg/dL	**33**
	200-249 mg/dL	**36**
	250-299 mg/dL	**30**
	300-349 mg/dL	**21**
	≥ 350 mg/dL	**56**
	Range	**60 to >600**
Beta-hydroxybutyrate (mmol/L) n=20	**Mean**	**19.46**
	Median	**9.0**
	Range	**3.5-100.3**
Potential Precipitating Factors (a case may have more than one) n=218	**Insulin dose reduced and/or discontinued (see insulin status below)**	**94**
	Infection	**70**
	Alcohol use	**39**
	Reduced diet or inability to eat	**36**
	Insulin pump or pen malfunction, expired insulin	**15**
	Weight loss	**12**
	Lactic acidosis	**10**
	Exercise	**8**
	Recent increase in SGLT2 inhibitor dose	**7**
	Surgery	**7**
	Diarrhea	**6**
	Pancreatitis	**5**
	Uncontrolled diabetes	**2**
	Discontinued diabetes medication (NOS)	**1**
	Acute hepatitis	**1**
	Trauma	**1**
Insulin status (a case may report more than one change) n=94	**Insulin reduced**	**48**
	Insulin discontinued	**49**
	Insulin reduced prior to SGLT2 inhibitor initiation	**1**
	Insulin reduced after SGLT2 inhibitor initiation	**40**
	Insulin discontinued prior to SGLT2 inhibitor initiation	**10**
	Insulin discontinued after SGLT2 inhibitor initiation	**30**

FAERS Reported Cases of Ketoacidosis in T1DM (n=444)		
Case Characteristics		**No. of Cases/Result**
Precipitating factor excluded or not reported	**Excluded** **Not reported**	**10** **216**
Time to resolution of DKA (1st episode) (days) n=123	**Mean** **Median** **Range** **Death**	**4** **3** **1-24** **1**
Dehydration or Hypovolemia	**Yes**	**37**
Complications (a case may report more than one) n=82	**Acute kidney injury** **Central nervous system change**‡‡ **Recurrent DKA** **Hyponatremia** **Respiratory failure** **Hypoglycemia** **Atrial fibrillation** **Pancreatitis** **Reporter noted no complications**	**46** **18** **7** **7** **5** **3** **2** **2** **1**
Interventions (a case may report more than one) n=131	**Intensive care unit admission** **Emergency department management** **Respirator/intubation** **Bicarbonate infusion** **Dialysis** **Vasopressors** **ECMO**	**96** **53** **7** **7** **5** **3** **1**
Duration of hospitalization, days n=145	**Mean** **Median** **Range**	**4.4** **3** **0.5-21**
Acidosis Severity, CTCAE Criteria[14,§§]	**Grade 1** **Grade 2** **Grade 3** **Grade 4** **Grade 5**	**4** **N/A** **87** **17**^ **1**^
DKA Severity Classification¶¶	**Mild** **Moderate** **Severe** **↓pH, ↓bicarbonate, and ↑anion gap**	**15** **48** **76**^ **9**^

FAERS Reported Cases of Ketoacidosis in T1DM (n=444)	
Case Characteristics	**No. of Cases/Result**
* Foreign reports were from: Australia, Austria Belgium, Brazil, Canada, Chile, Columbia, Cyprus, Germany, Egypt, Finland, Spain, Great Britain, Greece, Hungary, India, Ireland, Israel, Italy, Japan, Mexico, Netherlands, Norway, Philippines, Poland, Portugal, Romania, Russia, Saudi Arabia, Sweden, Turkey, Taiwan, South Africa	
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A case may have more than one serious outcome.	
‡ Lower doses (canagliflozin 100 and 150 mg, dapagliflozin 5 mg, empagliflozin 10 mg and 12.5 mg). Upper doses (canagliflozin 300 mg, dapagliflozin 10 mg, empagliflozin 25 mg)	
§ A patient may use more than one type of insulin; short acting insulin include insulin aspart, insulin lispro and insulin glulisine; long acting insulins include insulin detemir, insulin glargine, insulin degludec and NPH insulin	
|| Anion gap units that were not specified were assumed to be mEq/L or mmol/L which are equivalent	
¶ pH: one case reported a pH of 5 was not included, this was most likely urine pH	
** Bicarbonate laboratory values reported as less than x mEq/L, x was used in calculating mean and median. Some values reported as mmol/L which is equivalent to mEq/L.	
†† Glucose values converted to mg/dL, values without units assigned mg/dL or mmol/L based on the value. Two values were not included because it was unclear if the units were mg/dL or mmol/L. If glucose range was reported, the highest glucose value was used in the calculation. Endomed was used for mmol/L to mg/dL conversion at http://www.endmemo.com/medical/unitconvert/Glucose.php	
‡‡ A case may have more than one complication, central nervous system changes include altered mental status (8), coma (5), encephalopathy (3), stroke/cerebrovascular accident (2)	
§§ Grade 1: pH < normal, but ≥ 7.3; Grade 2: not applicable; Grade 3: pH < 7.3; Grade 4: pH < 7.3 + life-threatening consequence; Grade 5: pH < 7.3 + life-threatening consequence + death	
¶¶ Modified from Kitabchi et al.[15] Severity of a DKA event in our case series was defined using the following parameters: mild if pH 7.25 to ≤ 7.3 or bicarbonate 15-18 mEq/L; moderate if pH was 7.00 to < 7.25 or bicarbonate 10 to < 15 mEq/L; severe if pH < 7.00, bicarbonate < 10 mEq/L, or the presence of stupor or coma. Of the severe DKA cases, cases with pH < 7.00 + bicarbonate < 10 mEq/L + anion gap > 12 mEq/L were also identified.	
^ Not mutually exclusive	
NOS=not otherwise specified, ECMO= Extracorporeal membrane oxygenation	

Use of SGLT2 inhibitors in T1DM

We identified 444 FAERS cases of DKA in patients with T1DM using an SGLT2 inhibitor. Use of SGLT2 inhibitors to treat T1DM is not an FDA-approved indication. FDA continues to receive reports of DKA in T1DM patients exposed to SGLT2 inhibitors; however, there has been a decline in reporting following the Drug Safety Communication issued on December 4, 2015.[7]

Notable characteristics of T1DM patients who had DKA with SGLT2 inhibitor use

Notable patient characteristics in this T1DM case series are an average age of 41 years and female predominance. The average age observed is not unexpected because T1DM is more common in a younger patient population and is the predominant diabetes type in children and adolescents.[8] There are possible explanations for the female predominance observed. The first is a possible preferential prescribing to females for the potential favorable body image effect of SGLT2 inhibitors and desire to lose weight. The second is infection, which is known to

[7] FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. December 4, 2015. Accessed on October 18, 2018 at https://www.fda.gov/Drugs/DrugSafety/ucm475463.htm

[8] Dabelea D, Bell RA, D'Agostino JR, Imperatore G, Johansen JM, Linder B et al., 2007, Incidence of diabetes in youth in the United States, JAMA, 297(24):2716-2724.

precipitate DKA and SGLT2 inhibitors are associated with increased genitourinary tract infections in females.[9,10,11,12] Alternatively, females with T1DM, in general, may be at higher risk for DKA due to other unidentified characteristics. Females were found to be associated with a higher frequency of DKA (5.5% vs. 4.0% in males; males odds ratio 0.73, CI 0.57-0.93, P value = 0.008) in a 12-month registry study of adults with T1DM.[13]

Severity of DKA cases in T1DM patients using SGLT2 inhibitors

To assess the severity of the DKA event in our case series, cases that reported laboratory data and complications were analyzed using: 1) the Common Terminology Criteria for Adverse Events (CTCAE) grading system for acidosis,[14] and 2) a modified classification system for DKA severity from Kitabchi et al.[15] Based on the CTCAE grading system for acidosis, 87 cases in our case series were assessed as grade 3 (pH < 7.3), of which, 17 were also assessed as grade 4 (pH < 7.3 + life-threatening consequences, e.g., AKI, respiratory failure, coma) and one as Grade 5. Because pH, bicarbonate, and anion gap were not all consistently reported, we defined a DKA event in our case series as severe if one of the following was present: pH < 7.0, bicarbonate <10 mEq/L, or the presence of stupor or coma. Based on these parameters, there were 76 severe cases of DKA in patients with T1DM while using an SGLT2 inhibitor. We note that there were nine cases with a pH of < 7.0 + bicarbonate < 10 mEq/L+ an anion gap > 12 mEq/L, which would meet the Kitabachi et al. blood laboratory criteria for severe DKA. Overall, the average pH was 7.07 with the lowest reported reading as pH 6.7, the mean bicarbonate level was 9.39 mEq/L and mean anion gap was 26.42 mEq/L in our case series.

Many patients in our case series required management in the intensive care units (ICUs) and treatment of serious complications. Notable complications experienced by the patients during their episode of DKA included coma, encephalopathy, respiratory failure, acute kidney injury (AKI), and hypotension/shock. Dehydration was reported in 37 cases, which is not unexpected considering the diuretic effect of SGLT2 inhibitors and the presence of hyperglycemia; however, 46 patients experienced AKI, of which 17 also reported dehydration, and five required dialysis treatments. To further support the magnitude of the severity of DKA in our case series, some patients required intubation and respiratory ventilation because of a coma or respiratory failure. In one case, a young patient who experienced DKA required extracorporeal membrane oxygenation (ECMO) for treatment of severe respiratory failure. There were two deaths; in the first fatal case, there was a potential delay in diagnosis of DKA as the patient presented with no identifiable precipitating factor for DKA, experienced worsening symptoms, shock and

[9] Bonora BM, Avogaro A, Fadini GP, 2018, Sodium‐glucose co‐transporter‐2 inhibitors and diabetic ketoacidosis: An updated review of the literature. Diabetes, Obesity and Metabolism. Jan;20(1):25-33.
[10] Invokana® (canagliflozin) [product label]. Titusville, NJ: Janssen Pharmaceuticals; revised July 2017.
[11] Farxiga (dapagliflozin) [product label]. Princeton, NJ: Bristol-Myers Squibb; revised October 2017.
[12] Jardiance® (empagliflozin) [product label]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; revised December 2017.
[13] Farsani, S. F., Brodovicz, K., Soleymanlou, N., Marquard, J., Wissinger, E., & Maiese, B. A. (2017). Incidence and prevalence of diabetic ketoacidosis (DKA) among adults with type 1 diabetes mellitus (T1D): a systematic literature review. BMJ open, 7(7), e016587.
[14] US Department of Health and Human Services. (2009). Common terminology criteria for adverse events (CTCAE) version 4.0. National Institutes of Health, National Cancer Institute, 4(03).
[15] Kitabchi AE, Umpierrez GE, Miles JM, and Fisher JE. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. July 2009; 32(7): 1335-1343.

subsequently died of renal failure. In the second fatal case, death occurred 10 months after the DKA event and therefore, it is difficult to assess because of limited clinical details leading up to the death and the cause of death was not reported.

In the 123 cases reporting time to resolution of the DKA, the average time was 4 days. Of 198 cases providing laboratory values, blood glucose levels varied at presentation with 91 cases (46%) reporting a blood glucose level < 250 mg/dL. Because of this lower blood glucose level compared to the blood glucose level of approximately 350 to 500 mg/dL typically seen in cases of DKA,[15] a delay in recognizing the symptoms of DKA and not seeking medical care immediately could have occurred. It is possible that some cases of DKA in our case series were more severe at presentation because of a delay in recognition of the event. For example, the patient in the first fatal DKA case noted above had symptoms for almost two weeks and only sought care when she developed dyspnea. Blood glucose levels that are not profoundly elevated and similarity of symptoms of metabolic acidosis (headache, malaise, lethargy, nausea, vomiting) with migraines or acute viral infections may also lead to delay in recognition of the development of DKA.

Potential precipitating factors for DKA in T1DM patients using SGLT2 inhibitors

We identified several potential precipitating factors for DKA. Potential precipitating factors newly identified from this review that were not seen in previous evaluations of DKA with the SGLT2 inhibitors[7] include weight loss, recent SGLT2 inhibitor dosage increase, and insulin pen or pump malfunction, although DKA can occur with insulin pen or pump malfunction in T1DM patients not taking an SGLT2 inhibitor. Potential precipitating factors noted in our case series that can possibly be anticipated are alcohol use, changes in diet (low carbohydrate diet, oral intake restricted), planned surgery, decreased or stopped insulin and exercise. Factors that cannot be anticipated are infections, acute illness, trauma, emergency surgery or dental procedures, and insulin pump or pen malfunction. Commonly reported infections were respiratory (e.g., pneumonia), gastrointestinal, and urinary tract. The average onset of DKA following a precipitating factor was 6.4 days.

Changes with insulin management is a precipitating factor that was identified in previous analyses of this safety issue[7] and is a significant concern in T1DM patients who have no endogenous insulin to prevent ketogenesis.[16] In our case series, insulin doses were reduced or insulin was discontinued – some at the time of initiation of the SGLT2 inhibitor and some when a precipitating factor (e.g., illness) presented. This is a concern in situations where counter-regulatory hormones are increased (secondary to illness, trauma or surgery) and increased insulin requirements may not be recognized due to lower than expected blood glucose levels. Additionally, there were 44 cases where there was no other reported precipitating factor and the changes to insulin dosing was the only identified factor preceding the DKA event.

Cases without precipitating factors were reviewed to determine if the reporter did not identify a precipitating factor or if the information was not reported in the case. Though infrequent, 10 cases reported that a precipitating factor for the DKA was not identified during the patient

[16] Kitabchi AE, Umpierrez GE, Miles JM, and Fisher JE. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. July 2009; 32(7): 1335-1343.

evaluation. We, however, acknowledge there were 216 cases that did not report whether a predisposing factor for DKA was identified. It is possible that this information was not reported in the cases (limited clinical details and limitation of FAERS data), or there really was no identifiable precipitating factor.

DKA usually presents at initial diagnosis of T1DM and patients who are adherent to diabetes self-management and obtain good glycemic control often do not experience another DKA episode unless a significant precipitating factor or interruption in insulin delivery occurs.[17,18] In review of the 31 FAERS cases reporting the SGLT2 inhibitor was reinitiated after temporary discontinuation during the initial DKA event, another episode of DKA occurred in half of these cases. Five cases reported that the patient had not experienced DKA prior to use of an SGLT2 inhibitor, except perhaps at initial diagnosis of T1DM.

Limitations of analysis of cases of DKA in T1DM patients using SGLT2 inhibitors

Findings from the analysis of DKA in T1DM patients using an SGLT2 inhibitor should be interpreted in the context of known limitations of the FAERS database and background risk for DKA in patients with T1DM. FAERS limitations that may influence the findings of this analysis include underreporting and reporting bias. Because FAERS is a spontaneous adverse event reporting system, not all reports of DKA with an SGLT2 inhibitor use are reported to the FDA. Furthermore, FAERS reports often lack detail. For this analysis, lack of information about diabetes type and laboratory information was a significant limitation. Reporting bias may influence HCPs or consumers to report the most severe cases of DKA. As noted earlier, having diabetes is a risk for DKA. Patients with T1DM are at particular risk because of the lack of endogenous insulin.[13] In consideration of this background risk and lack of details to exclude all possible alternative explanations, we acknowledge that development of DKA in patients with T1DM can occur during the natural history of the disease and may occurred in the absence of an SGLT2 inhibitor following a precipitating event. Lastly, our analysis was conducted on cases of DKA in patients using an FDA-approved SGLT2 inhibitor, not for sotagliflozin specifically.

Summary

In conclusion, T1DM patients using an SGLT2 inhibitor have experienced DKA in the postmarketing setting. Based on the data from this case series, the DKA in T1DM patients using an SGLT2 inhibitor can be severe with a considerably low pH, low bicarbonate level, and high anion gap and poor outcomes including death. Furthermore, many patients required management in the ICU and treatment of serious complications such as AKI and respiratory failure. Analysis of this case series identified potential precipitating factors that can be anticipated such as alcohol use and planned surgery, and some that cannot be anticipated such as infections and acute illness. In some cases, there were no precipitating factors identified. Approximately half of the patients did not have elevated blood glucose levels at initial evaluation for DKA. Lower than expected blood glucose levels typically seen with DKA may delay diagnosis and treatment.

[17] Mays, J. A., Jackson, K. L., Derby, T. A., Behrens, J. J., Goel, S., Molitch, M. E., ... & Wallia, A. (2016). An Evaluation of Recurrent Diabetic Ketoacidosis, Fragmentation of Care, and Mortality Across Chicago. Diabetes care, dc160668.

[18] Lohiya, S., Kreisberg, R., & Lohiya, V. (2013). Recurrent diabetic ketoacidosis in two community teaching hospitals. Endocrine Practice, 19(5), 829-833.

Sentinel analysis of SGLT-2 inhibitor use in patients with type-1 diabetes mellitus and rates of diabetic ketoacidosis

Objectives:

These analyses were conducted to help place in context the increased risk of diabetic ketoacidosis (DKA) that was observed in the clinical development program of sotagliflozin in type-1 diabetes mellitus (T1DM), in patients randomized to sotagliflozin compared with patients randomized to placebo. The current analyses query the Sentinel database to evaluate the rate of DKA among patients with T1DM exposed to SGLT-2 inhibitors in real world data sources. Specifically, the goals of the current analyses include:

1. Estimate the extent of real-life off-label utilization of approved SGLT-2 inhibitors (only indicated for the treatment of T2DM) in patients with T1DM
2. Estimate real-life rates of DKA following exposure to SGLT-2 inhibitors among patients with T1DM
3. Using data from sotagliflozin clinical trials as the reference, compare the observed and expected rates of DKA during off-label use of approved SGLT-2 inhibitor in patients with T1DM

Methods:

This analysis was conducted in 17 data partners of FDA's Sentinel system, including CMS-Medicare, with data from March 1, 2013 (approval of canagliflozin), until June 30, 2018 (varied by data partner). In addition to the SGLT-2 inhibitors canagliflozin, dapagliflozin, and empagliflozin, we included the dipeptidyl-peptidase-4 (DPP-4) inhibitor sitagliptin as a control exposure, for which off-label use among T1DM patients was not expected to be substantive. The primary intent of its inclusion was to track the performance of our algorithms used to categorize diabetes type. We included new users of SGLT-2 inhibitors or sitagliptin, defined as those with an available 365-days baseline period, with continuous medical and pharmacy benefits, without prior dispensing of a member of the same drug class. As such, initiators of an SGLT-2 inhibitor did not have baseline exposure to an SGLT-2 inhibitor and initiators of sitagliptin did not have baseline exposure to a DPP-4 inhibitor. For each study drug, we created exposure episodes using days of supply, allowing for a gap between dispensings of up to 10 days, with a 10-day extension at the end of an episode. Exposure episodes were censored at the end of SGLT-2 inhibitor or sitagliptin supply, disenrollment, or end of available data.

The study was descriptive. The control group of sitagliptin users served to provide context for findings of SGLT-2 inhibitors, without testing a prespecified hypothesis. To quantify off-label use among initiators of each study drug, we calculated the proportion and number of patients who met criteria for T1DM or for T2DM. Using an adaptation of a published and validated

algorithm(1, 2)[19], we defined T1DM using both a broad definition, requiring that a plurality (>50%) of diabetes diagnosis codes during the baseline period[20] were specific to T1DM, and a narrow definition that additionally required at least one prescription for a short- or rapid-acting insulin and no oral antidiabetic drug dispensing (other than metformin) during the baseline period. For T2DM, we used a definition that required the presence of at least one diagnosis code specific for T2DM, no diagnosis for T1DM, and that patients had at least one baseline dispensing of an oral antidiabetic drug.

Diabetic ketoacidosis was defined using an inpatient or emergency department diagnosis with an ICD-9-CM code 250.1x or an ICD-10 code E1x.1x in any diagnosis position.(3)[21] Incidence rates of DKA were calculated using counts of the first DKA events observed during exposure episodes in the numerator and cumulative person-years of exposure in the denominator. All analyses were stratified by age (<12, 12-18, 19-24, 25-44, 45-64, >=65) and sex (male or female). In addition, we extracted cohort-specific baseline characteristics of study patients, including age, sex, history of antidiabetic drug use, the use of insulin pumps, and diagnosis for DKA during the baseline period.

Lastly, we calculated age- and sex-adjusted standardized incidence ratios (SIRs) for DKA, comparing the Sentinel population of T1DM patients who were exposed to an SGLT-2 inhibitor with subjects randomized to sotagliflozin in Trials 309, 310, and 312. Using the distribution of age- and sex-specific follow-up time in Sentinel and age- and sex-specific DKA rates from the clinical trials, we calculated expected DKA event counts in Sentinel.[22] The SIR was then calculated as the number of observed events (in Sentinel) divided by the number of expected events that would be observed if the Sentinel population experienced DKA at the rate found in the clinical trials.[23]

Results:

The study sample consisted of 297,633 new users of canagliflozin, 79,311 new users of dapagliflozin, 98,583 new users of empagliflozin and 667,468 new users of sitagliptin. The average episode duration ranged from 4 to 5 months, with little difference by drug or diabetes type. On average, patients received approximately 4 dispensings during an episode.

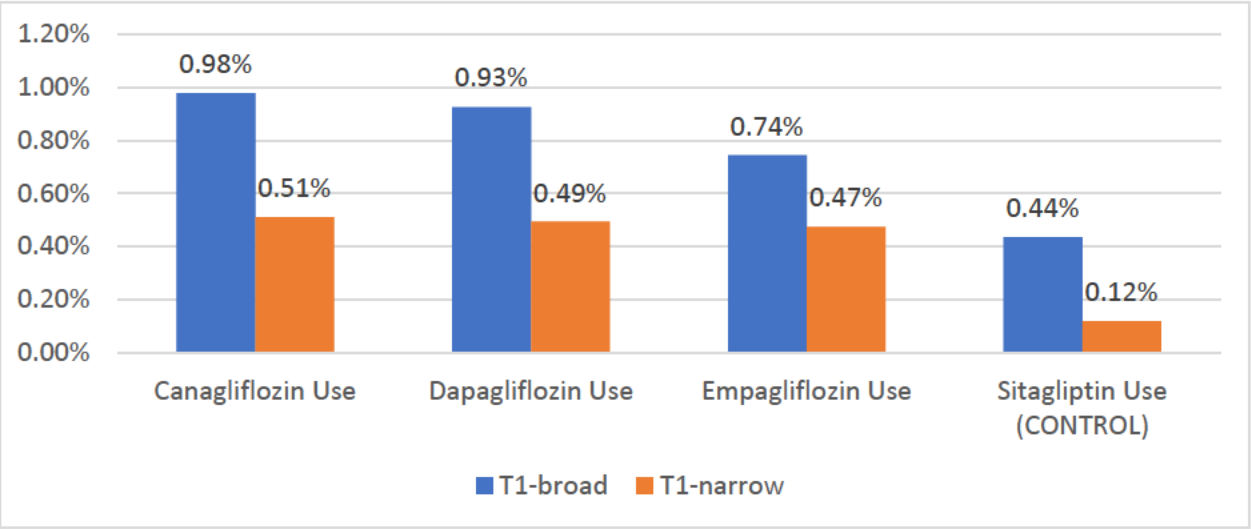
Use of SGLT-2 inhibitors among patients with T1DM

Among new users of SGLT-2 inhibitors, between 0.74% (empagliflozin) and 0.98% (canagliflozin) met criteria for T1DM-broad (Figure 29). Between 0.47% (empagliflozin) and

[19] For the T1DM-broad algorithm, Klompas et al. (1) measured sensitivity of 63% and positive predictive value of 94%. For the same algorithm, Schroeder et al. (2) measured sensitivity of a PPV of 96.4%.
[20] Diagnosis codes for diabetes were ascertained between 365 days and 5 days before cohort entry, to account for potential miscoding associated with the off-label prescription of an SGLT-2 inhibitor. The baseline period ranged from 365 before to 1 day before cohort entry for all other purposes.
[21] This algorithm had a PPV of 88.9% among children and youth (3)
[22] For these analyses, the Sentinel and clinical trial populations were limited to patients age 25 or older.
[23] SIR and 95% CI were calculated using OpenEpi. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. www.OpenEpi.com, updated 2013/04/06, accessed 2018/12/17.

0.51% (canagliflozin) of patients met criteria for T1DM-narrow. These rates were lower for initiators of sitagliptin.

Figure 29. Proportion of study drug users who meet criteria for T1DM-broad and T1DM-narrow, among all users of each study drug



Especially for SGLT-2 inhibitors, the proportion of new users who met criteria for T1DM-broad (Figure 30[24]) or T1DM-narrow (Figure 31[24]) were highly age-dependent. For instance, among patients who initiated canagliflozin between age 12 and 18, 14.0% met criteria for T1DM-broad and 10.8% met criteria for T1DM-narrow. In contrast, among canagliflozin initiators age 65 or older, 0.72% of patients met criteria for T1DM-broad and 0.24% met criteria for T1DM-narrow. Rates for T1DM were lower in users of sitagliptin across all age categories. Across all SGLT-2 inhibitors, the study sample included 4,375 patients who met criteria for T1DM-broad and 2,379 patients who met criteria for T1DM-narrow. The largest subgroup comprised the age category of 45-64 years (T1DM-broad: n=2,087; T1DM-narrow: n=1,163). Few exposed patients with T1DM were under the age of 25 (T1DM-broad: n=87; T1DM-narrow: n=75). Females comprised 50% of intiators of SGLT-2 inhibitors (pooled across class) who met criteria for T1DM-broad, and 53% of those who met criteria for T1DM-narrow.

[24] Figure 30 and Figure 31 do not include patients age <12 due to small cell counts.

Figure 30. Proportion of study drug users who meet criteria for T1DM-broad, by age

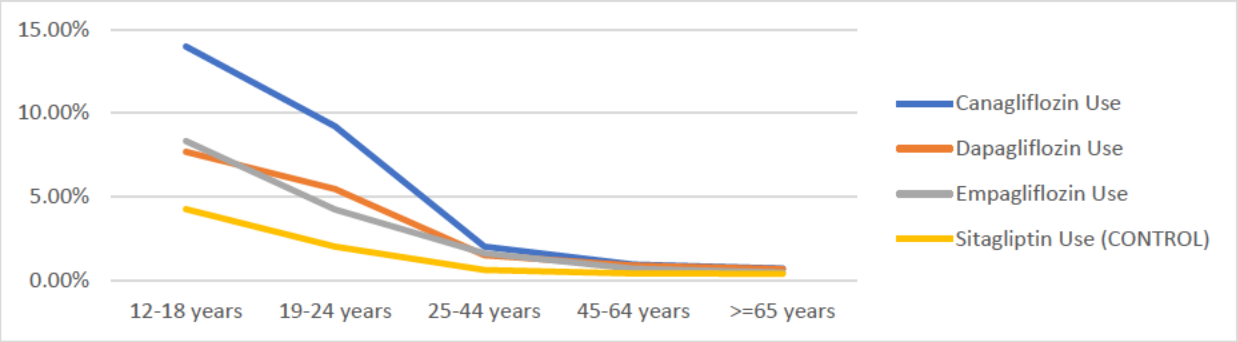
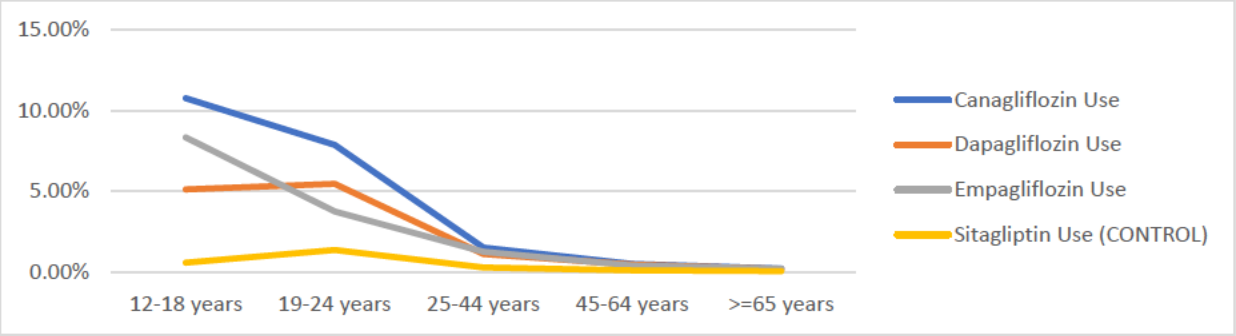


Figure 31. Proportion of study drug users who meet criteria for T1DM-narrow, by age



Baseline patient characteristics

Table 62 and Table 63, respectively, list baseline non-insulin antidiabetic drug use and insulin use for initiators or SGLT-2 inhibitors or sitagliptin with T1DM-narrow and T1DM-broad. Consistent with our criteria for T1DM-narrow, these patients did not use oral antidiabetic drugs other than metformin during the baseline period. Similarly, initiators of SGLT-2 inhibitors or sitagliptin did not use a drug of the same class during the baseline period. The use of metformin was more prevalent among patients who met the broad T1DM defintion compared with the narrow definition (46.6% vs. 29.0%), while the use of injectable GLP-1 analogs was largely comparable between the broad and narrow definition. Comparing initiators of SGLT-2 inhibitors with sitagliptin initiators, the latter were more likely to have used metformin and sulfonylureas during the baseline period but were less likely to have used GLP-1 analogs, especially liraglutide.

Consistent with our criteria for T1DM-narrow, the use of short- and rapid-acting insulin (i.e., lispro, regular, glulisine, aspart, lispro protamine) was more common among patients who met criteria for T1DM-narrow than T1DM-broad (Table 63). Among initiators of SGLT-2 inhibitors, the use of long- or intermediate acting insulin tended to be comparable between patients who met criteria for T1DM-narrow and T1DM-broad. Among initiators of sitagliptin, differences in the

use of long- or intermediate acting insulin were noticeable between between patients who met criteria for T1DM-narrow and T1DM-broad. In contrast to SGLT-2 inhibitors, among sitaglitpin users, the baseline use of long- or intermediate acting insulin tended to be more common among patients who met criteria for T1DM-narrow compared with T1DM-broad. Among initiators of SGLT-2 inhibitors, insulin pump use was present during the baseline period in 33.7% of those who met criteria for T1DM-narrow and 19.7 of those who met criteria for T1DM-broad. In contrast, only 1.6% of sitagliptin users who met crieria for T1DM-broad and 3.8% of sitagliptin users who met crieria for T1DM-narrow had prior use of insulin pumps.

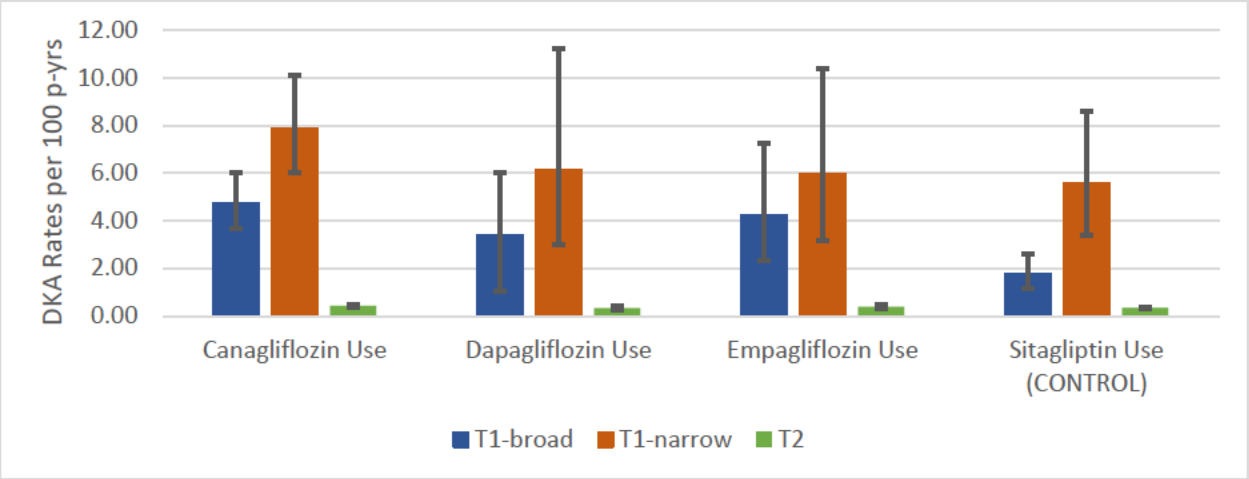
Diabetic Ketoacidosis

Across the combined SGLT-2 inhibitors, 3.4% and 5.3% of patients who met criteria for T1DM-broad and T1DM-narrow, respectively, had a DKA event during the baseline period. The prevalence of DKA ranged from 2.9% (empagliflozin) to 3.6% (canagliflozin) among those who met criteria for T1DM-broad and from 4.1% (empagliflozin) to 5.6% (canagliflozin) among those who met criteria for T1DM-narrow. Prior DKA occurred in 2.6% (T1DM-broad) and 6.7% (T1DM-narrow) of sitagliptin initiators.

Rates of DKA during exposure to SGLT-2 inhibitors ranged from 3.4 (95% CI, 1.0-6.0) for dapagliflozin to 4.7 (95% CI, 3.7-6.0) per 100 person-years for canagliflozin among patients with T1DM-broad (Figure 32).[25] Among patients with T1DM-narrow, DKA rates ranged from 6.0 (95% CI, 3.1-10.4) for empagliflozin to 7.9 (95% CI, 6.0-10.1) per 100 person-years for canagliflozin. Widely overlapping 95% confidence intervals suggest that these rates were not statistically significantly different between the different SGLT-2 inhibitors. Among sitagliptin users, DKA rates were 1.8 (95% CI, 1.2-2.6) in patients with T1DM-broad and 5.6 (95% CI, 3.4-8.6) per 100 patient-years in patients with T1DM-narrow. In contrast, among patients who met criteria for T2DM, DKA rates ranged from 0.32 (95% CI, 0.26-0.40) for dapagliflozin to 0.44 (95% CI, 0.40-0.48) per 100 person-years for canagliflozin.

[25] These rates were not adjusted for patient characteristics.

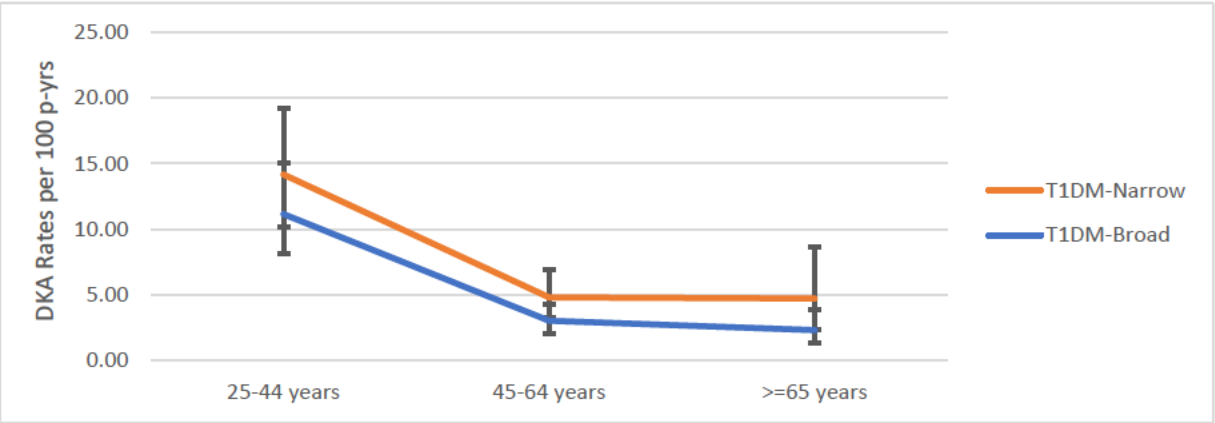
Figure 32. Rates of diabetic ketoacidosis per 100 person-years, by diabetes type; error bars indicate 95% confidence intervals



- Rates of DKA among initiators of SGLT-2 inhibitors (pooled across class) decreased with increasing age (

Figure 33[26]). Rates for DKA were 14.2 per 100 person-years (95% CI, 10.2-19.2) among patients age 25-44 who met criteria for T1DM-narrow. These rates decreased to 4.8 (95% CI, 3.2-6.9) among patients age 45-64, and 4.7 (95% CI, 2.3-8.7) among patients age 65 or older. Even though this trend was similar for females and males (Figure 34 and Figure 35), females had overall higher rates of DKA: females age 25-44 had a DKA rate of 19.7 (95% CI, 13.3-28.3) per 100 person-years.

Figure 33. Rates of diabetic ketoacidosis per 100 person-years among SGLT-2 inhibitor users, by age; error bars indicate 95% confidence intervals



[26] Figures 7, 8a, and 8b do not include patients age <25 due to small cell counts.

Figure 34. Rates of diabetic ketoacidosis per 100 person-years among SGLT-2 inhibitor users, by age and sex, T1DM-broad

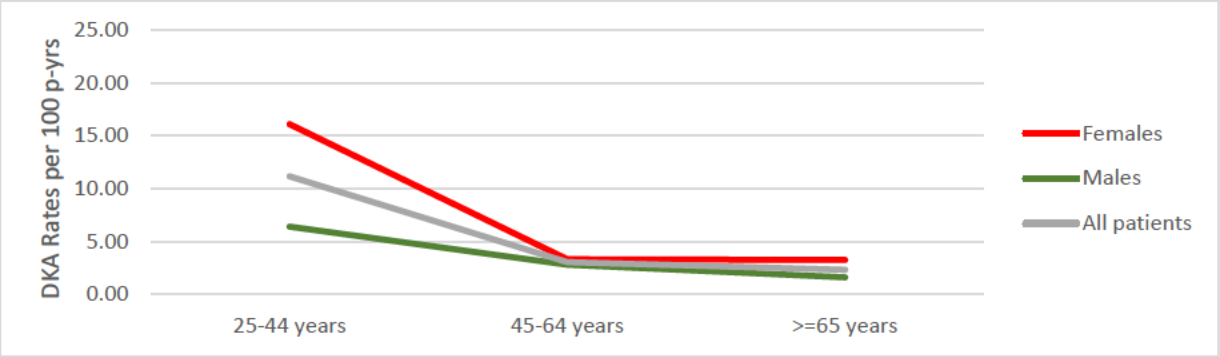
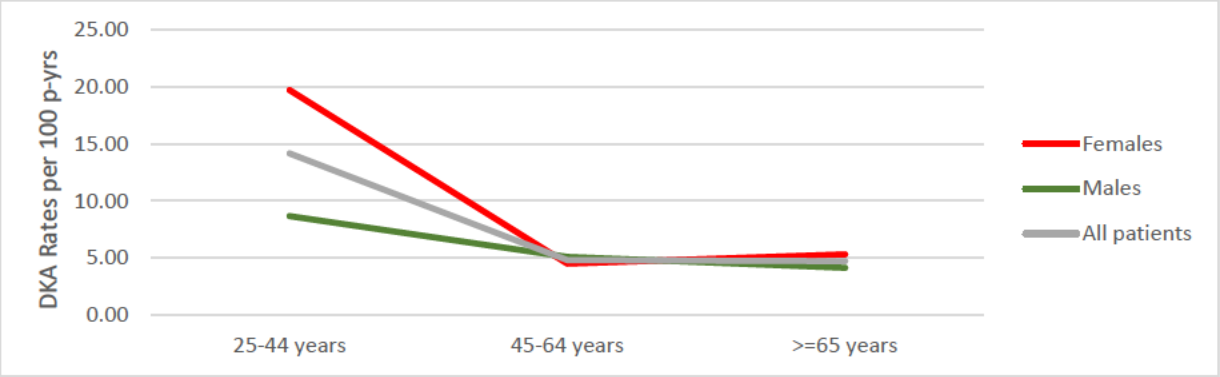


Figure 35. Rates of diabetic ketoacidosis per 100 person-years among SGLT-2 inhibitor users, by age and sex, T1DM-narrow



SIR analysis of DKA rates observed in Sentinel compared with expected rates based on the sotagliflozin clinical trial program

We calculated age- and sex-adjusted SIRs for DKA, by calculating expected event counts in the Sentinel population of T1DM patients who were exposed to an SGLT-2 inhibitor based on incidence rates observed in subjects randomized to sotagliflozin in Trials 309, 310, and 312. Of note, Trials 309 and 310 had a duration of 52 weeks and Trial 312 had a duration of 24 weeks. In comparison, average exposure duration to SGLT-2 inhibitors in Sentinel was between 18 and 23 weeks.

Patients who met criteria for T1DM-narrow experienced 75 DKA events during a total of 1,025.5 person-years at risk, resulting in a rate of 7.3 per 100 person-years. Based on age- and sex-specific incidence rates from the sotagliflozin clinical trial program, only 41 DKA events were expected in the Sentinel population, resulting in an SIR of 1.83 (95% CI, 1.45-2.28). Among patients who met criteria for T1DM-broad, 84 events were observed and 78 were expected, resulting in an SIR of 1.07 (95% CI, 0.86-1.32). Across both T1DM-broad and T1DM-narrow categories, age-specific SIRs decreased with increasing age. Patients with T1DM-narrow who were between 25 and 44 years old at the time of drug initiation had a 2.6-fold higher rate of DKA

compared to what would be expected based on clinical trial data (SIR=2.57; 95% CI, 1.85-3.45); see Table 61.

Table 61. Rates of diabetic ketoacidosis in Sentinel and standardized incidence ratios based on comparison with sotagliflozin clinical trials 309, 310, and 312

	Age category	DKA events in Sentinel	Expected events	SIR (95% CI)
T1DM-narrow	>25 years	75	41	1.83 (1.45-2.28)
	25-44	39	15	2.57 (1.85-3.45)
	45-64	27	16	1.65 (1.11-2.36)
	>65	9	10	0.95(0.46-1.75)
T1DM-broad	>25 years	84	78	1.07 (0.86-1.32)
	25-44	41	20	2.03 (1.47-2.72)
	45-64	30	29	1.03 (0.71-1.46)
	>65	13	29	0.45 (0.25-0.74)

Discussion:

This analysis of almost 500,000 users of SGLT-2 inhibitors found that the off-label use of SGLT-2 inhibitors in patients who met study criteria for T1DM was detectable but not widespread. Overall, approximately 0.5% of patients met criteria for T1DM-narrow and between 0.74% and 0.98% met criteria for T1DM-broad. However, these rates differed by age, with younger SGLT-2 inhibitor users being more likely to use them off-label for T1DM. Among patients who used SGLT-2 inhibitors off-label, the risk for DKA ranged from 3.4 to 4.7 per 100 person-years among patients with T1DM-broad and from 6.0 to 7.9 per 100 person-years for patients with T1DM-narrow. Rates of DKA among all SGLT-2 inhibitors were highest for younger patients: 14.2 per 100 person-years among patients age 25-44 who met criteria for T1DM-narrow. Rates were higher for females than males: females age 25-44 had a rate of 19.7 per 100 person-years. Finally, for patients who met the narrow T1DM criteria, DKA rates observed in Sentinel were 83% higher than expected based on the sotagliflozin clinical trials (SIR, 1.83), but were close to expected rates in patients who met criteria for T1DM-broad. Patients with T1DM-narrow who were between 25 and 44 years old at the time of drug initiation had a 2.6-fold higher rate of DKA compared to what would be expected based on clinical trial data.

We observed that the proportion of off-label use of sitagliptin for T1DM was, as expected, lower than that of SGLT-2 inhibitors. Also, rates of DKA among sitagliptin users who met criteria for

T1DM-broad tended to be lower than those for SGLT-2 inhibitors (Figure 32). However, DKA rates were comparable between initiators of sitagliptin, dapagliflozin, and empagliflozin in patients who met criteria for T1DM-narrow. It is unclear whether the DKA rates observed among sitagliptin users who met criteria for T1DM-narrow reflect pharmacologic properties, different patient characteristics (compared with SGLT-2 inhibitor users, sitagliptin users with T1DM-narrow tended to be older, were more likely to have used metformin or insulin glargine, and were substantially less likely to have used an insulin pump during the baseline period), or random error.

Strengths of this analysis include the large size and diverse nature of the database. However, even though it includes large commercial data partners and CMS-Medicare, it underrepresents patients covered by Medicaid and patients who are uninsured. Thus, the present analysis is not nationally representative. Indeed, overall rates of off-label use of SGLT-2 inhibitors in T1DM patients and rates of DKA may differ in databases with different patient characteristics, including different prevalence of T1DM due to age. Thus, our age- specific analyses are of particular interest.

Possible limitations arise from the use of diagnostic codes to categorize patients into those with T1DM and to ascertain events of DKA. Even though our criteria were derived from algorithms that have performed well in validation studies, it is possible that both the T1DM-narrow and to a lesser degree the T1DM-broad cohorts missed some patients with type-1 diabetes, thus underestimating off-label use. However, especially the T1DM-broad cohort may inadvertently include some type 2 diabetes patients. Similarly, even though we used a validated algorithm for DKA, in the absence of adjudication, we may have missed some events while possibly including others that were false-positives.

Finally, the calculation of SIRs should be interpreted with caution. Some factors can lead to **higher rates** of DKA in Sentinel compared with clinical trials. These include:

- Event definition and adjudication procedures in the clinical trials
- Education of trial patients on how to prevent DKA

Some factors may affect rates of DKA in Sentinel compared with clinical trials; however, in an **unknown direction**:

- Differences in DKA risk between the approved SGLT-2 inhibitors and sotagliflozin
- Different samples based on inclusion/exclusion criteria, international vs. U.S., etc.
- Shorter average duration of follow-up in Sentinel

In summary, the off-label use of SGLT-2 inhibitors in patients who met study criteria for T1DM was not widespread in the overall study population, but rates of off-label use were higher in younger patients. Among patients who used SGLT-2 inhibitors off-label, the risk for DKA was notable, especially among patients under the age of 45. For patients who met the narrow T1DM criteria, DKA rates observed in Sentinel were higher than expected based on the sotagliflozin clinical trials, especially among younger patients.

References

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2. Schroeder EB, Donahoo WT, Goodrich GK, Raebel MA. Validation of an algorithm for identifying type 1 diabetes in adults based on electronic health record data. Pharmacoepidemiol Drug Saf. 2018;27(10):1053-9.

3. Bobo WV, Cooper WO, Epstein RA, Jr., Arbogast PG, Mounsey J, Ray WA. Positive predictive value of automated database records for diabetic ketoacidosis (DKA) in children and youth exposed to antipsychotic drugs or control medications: a Tennessee Medicaid Study. BMC Med Res Methodol. 2011;11:157.

Additional tables:

Table 62. Baseline use of non-insulin antidiabetic drugs

	SGLT-2 inhibitors, pooled		Sitagliptin	
	T1DM-narrow[27]	T1DM-broad	T1DM-narrow[27]	T1DM-broad
Acarbose	-	0.5%	-	0.5%
Albiglutide	0.3%	0.4%	0.1%	0.1%
Alogliptin	-	0.3%	-	-
Canagliflozin	-	-	-	2.2%
Dapagliflozin	-	-	-	0.4%
Dulaglutide	1.1%	1.1%	0.3%	0.1%
Empagliflozin	-	-	-	0.2%
Exenatide	2.4%	3.9%	2.0%	1.7%
Glimiperide	-	8.0%	-	11.8%
Glipizide	-	7.2%	-	16.2%
Glyburide	-	3.3%	-	7.8%
Linagliptin	-	2.1%	-	-
Liraglutide	10.6%	11.8%	3.4%	2.6%
Metformin	29.0%	46.6%	40.6%	55.1%

[27] The narrow T1DM definition excluded patients with baseline oral AD drug use other than metformin

Nateglinide	-	0.8%	-	1.0%
Pioglitazone	-	5.8%	-	6.8%
Repaglinide	-	0.9%	-	1.2%
Saxagliptin	-	3.1%	-	-
Sitagliptin	-	11.2%	-	-

Table 63. Baseline use of insulin products

		SGLT-2 inhibitors, pooled		Sitagliptin	
		T1DM-narrow	T1DM-broad	T1DM-narrow	T1DM-broad
short- and rapid-acting	Insulin lispro	54.4%	35.9%	44.5%	16.3%
	Insulin regular, human	7.7%	7.7%	16.8%	10.2%
	Insulin glulisine	7.4%	4.5%	3.2%	1.2%
	Insulin aspart	43.4%	31.6%	51.3%	21.6%
	Insulin lispro protamine	2.6%	2.8%	9.1%	3.6%
long- or intermediate acting	Insulin glargine,human recombinant analog	38.4%	38.9%	54.7%	36.8%
	Insulin NPH human isophane	3.7%	5.3%	9.5%	8.8%
	Insulin detemir	16.5%	18.3%	22.1%	14.8%
	Insulin aspart protamine human	1.6%	3.8%	5.4%	5.0%
	Insulin degludec	1.6%	1.1%	1.0%	0.4%
	Insulin pump	33.7%	19.7%	3.8%	1.6%

Appendices

Appendix A: Supplemental Clinical Pharmacology Information

Pharmacokinetics

Absorption: Following a single dose sotagliflozin in healthy subjects in a fasted state, the median time to maximum concentration (Tmax) of sotagliflozin ranged from 1.25 to 4.5 hours. When a single dose sotagliflozin (2×200 mg tablets) was administered with a high-fat and high-caloric meal, sotagliflozin was absorbed with the median Tmax (range) of 1.50 (1.50-5.00) hours, and maximum concentration (Cmax) and area under the concentration time curve (AUC_{0-inf}) increased by 149% and 50%, respectively. Following once daily dosing, steady state was generally achieved by 5 days and the accumulation ratios for Cmax and AUC_{0-24h} on Day 10 were approximately 1.5- to 2.0-fold, respectively.

Distribution: Both sotagliflozin and its major human metabolite, sotagliflozin-3-O-glucuronide (M19), exhibited high binding to human plasma proteins in vitro (>93% bound) which was not dependent on the concentration of sotagliflozin and M19. Following a single 400 mg oral dose of [^{14}C]-sotagliflozin in healthy subjects, the mean apparent volume of distribution of sotagliflozin was 9392 L. The mean whole blood to plasma concentration ratio of sotagliflozin ranged from 0.481 to 0.596, indicating a low level of distribution to red blood cells.

Metabolism: In vitro metabolism studies indicated that the key enzymes responsible for the metabolism of sotagliflozin were UGT1A9 and, to a lesser extent, CYP3A4. Following the administration of single dose of 400 mg [^{14}C]-sotagliflozin in healthy subjects, the unchanged sotagliflozin exposure in plasma were <2% of the total radioactivity exposure in plasma. The predominant metabolite in the plasma was M19 and represented a mean of 94.3% of the radioactivity in plasma. M19 had significantly diminished (>275 fold) activity toward SGLT1 and SGLT2 compared with sotagliflozin. Therefore, sotagliflozin parent drug is the primary pharmacologically active circulating moiety.

Elimination: Following the administration of single dose of 400 mg [^{14}C]-sotagliflozin in healthy subjects, the mean recovery of the total administered radioactivity is 94.2% over 216 hours. The mean cumulative radioactive dose recovered in the urine and feces through 144 hours post-dose were 51.3% and 32.7%, respectively, suggesting that the renal elimination of radioactivity associated sotagliflozin and metabolites contributes more than the fecal route.

In urine, unchanged [^{14}C]-sotagliflozin was present in trace amounts (0.21%) and the predominant metabolite detected in urine was M19, representing a mean of 33.2% of the administered radioactive dose through 144 hours post-dose. Other minor metabolites detected in urine were M10/M11, M14, and M22, representing a mean of 5.05%, 5.19%, and 2.13% of the administered radioactive dose through 144 hours post-dose, respectively.

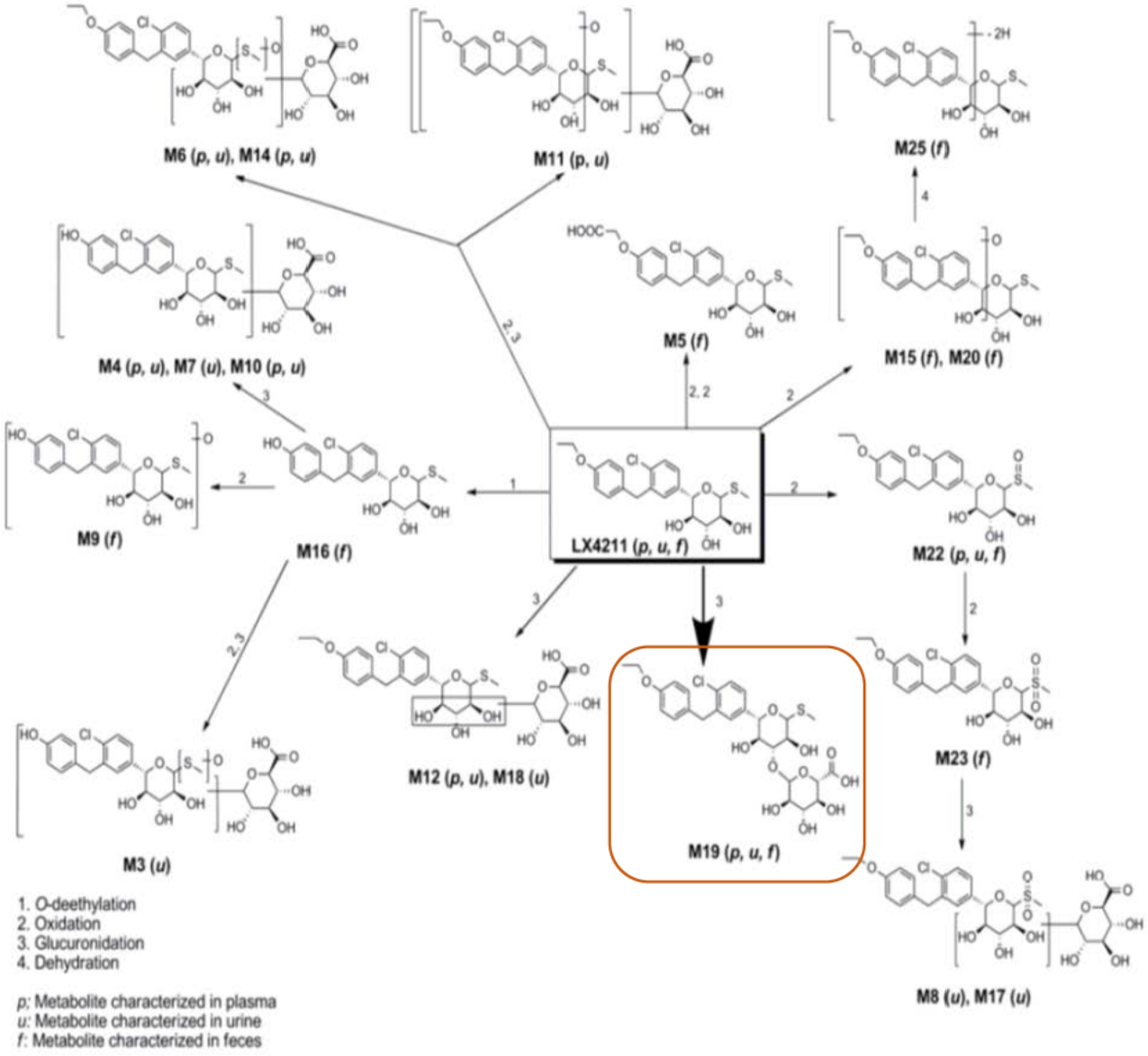
In fecal extracts, unchanged [^{14}C]-sotagliflozin was the predominant radioactive peak detected, representing a mean of 23.4% of the total administered radioactive dose. Minor metabolites detected in fecal extracts were M5 (oxidation to a carboxylic acid), M15 (mono-oxidation)/M16

(O-deethylation) co-eluting, and M22 representing a mean of 2.98%, 3.41%, and 1.31% of the administered radioactive dose through 144 hours post-dose, respectively.

Following the administration of 200 and 400 mg sotagliflozin in healthy volunteers, mean apparent clearance (CL/F) of sotagliflozin ranged from 261 to 374 L/hr. The estimated average CL/F in T1DM patients using population PK analysis was 239 L/hr. The mean terminal $t_{1/2}$ ranged from 21 to 35.0 hours for sotagliflozin and from 19.2 to 26.0 hours for M19.

The proposed metabolic pathway of sotagliflozin is shown in the Figure 36 below:

Figure 36. Proposed biotransformation pathway of sotagliflozin in human



Source: LX4211.108 CSR Figure 11.4.3.4-1

Pharmacodynamics

Drug-Drug Interactions

In vitro studies showed that the key enzymes responsible for the metabolism of sotagliflozin were UGT1A9 and, to a lesser extent, CYP3A4. Sotagliflozin was also shown to be a weak inhibitor of P-glycoprotein (P-gp) and an inhibitor of breast cancer resistance protein (BCRP). The major human metabolite of sotagliflozin, M19, was shown to inhibit CYP3A4 and CYP2D6, and induce CYP3A4.

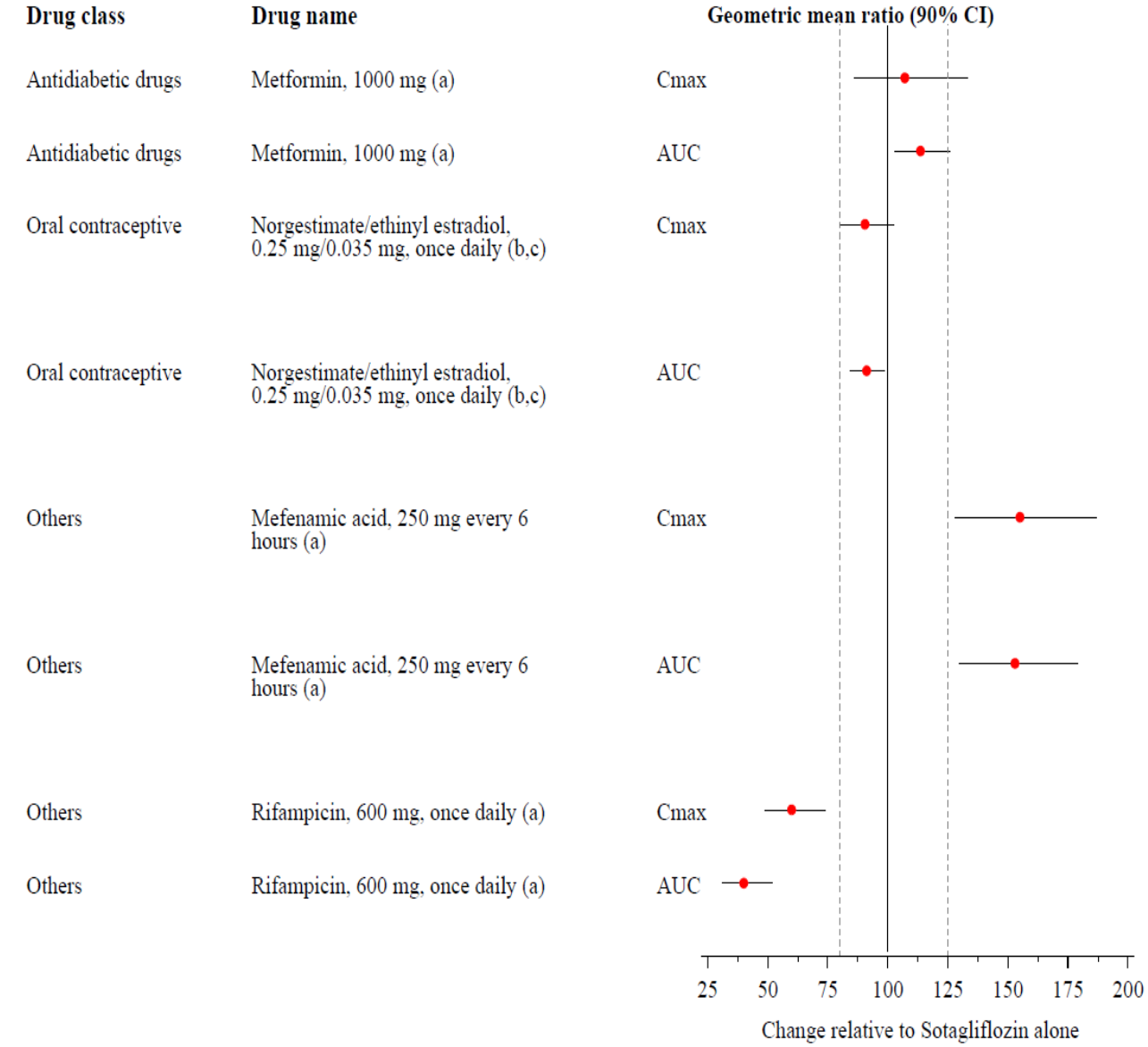
Effects of concomitant medications on pharmacokinetics of sotagliflozin

When sotagliflozin was co-administered with rifampicin (a UGTs and CYP3A4 inducer), sotagliflozin exposure decreased by 60% for AUC0-inf and by 40% for Cmax, which may consequently decrease the efficacy. Therefore, frequent monitoring of glucose levels should be considered if a UGT inducer is co-administered. When sotagliflozin was co-administered with mefenamic acid (a UGT inhibitor), or potential concomitant medications such as metformin or an oral contraceptive, there was no clinically meaningful difference in sotagliflozin PK.

Effects of sotagliflozin on pharmacokinetics of concomitant medications

When sotagliflozin was co-administered with digoxin (a P-gp substrate), the mean Cmax, AUC0-last, and AUC0-inf values for digoxin increased by 51.9%, 31.1%, and 26.9%, respectively, in the presence of sotagliflozin compared to digoxin alone. Since digoxin is a narrow therapeutic index drug, digoxin concentration should be monitored when sotagliflozin is co-administered with digoxin. When sotagliflozin was co-administered with rosuvastatin (a BCRP substrate), metoprolol (a CYP2D6 substrate), or midazolam (a CYP3A4 substrate), or potential concomitant medications such as metformin or an oral contraceptive, there was no clinically meaningful effect of sotagliflozin on the PK of these concomitant medications.

Figure 37. Effect of concomitant medications on the pharmacokinetics of sotagliflozin

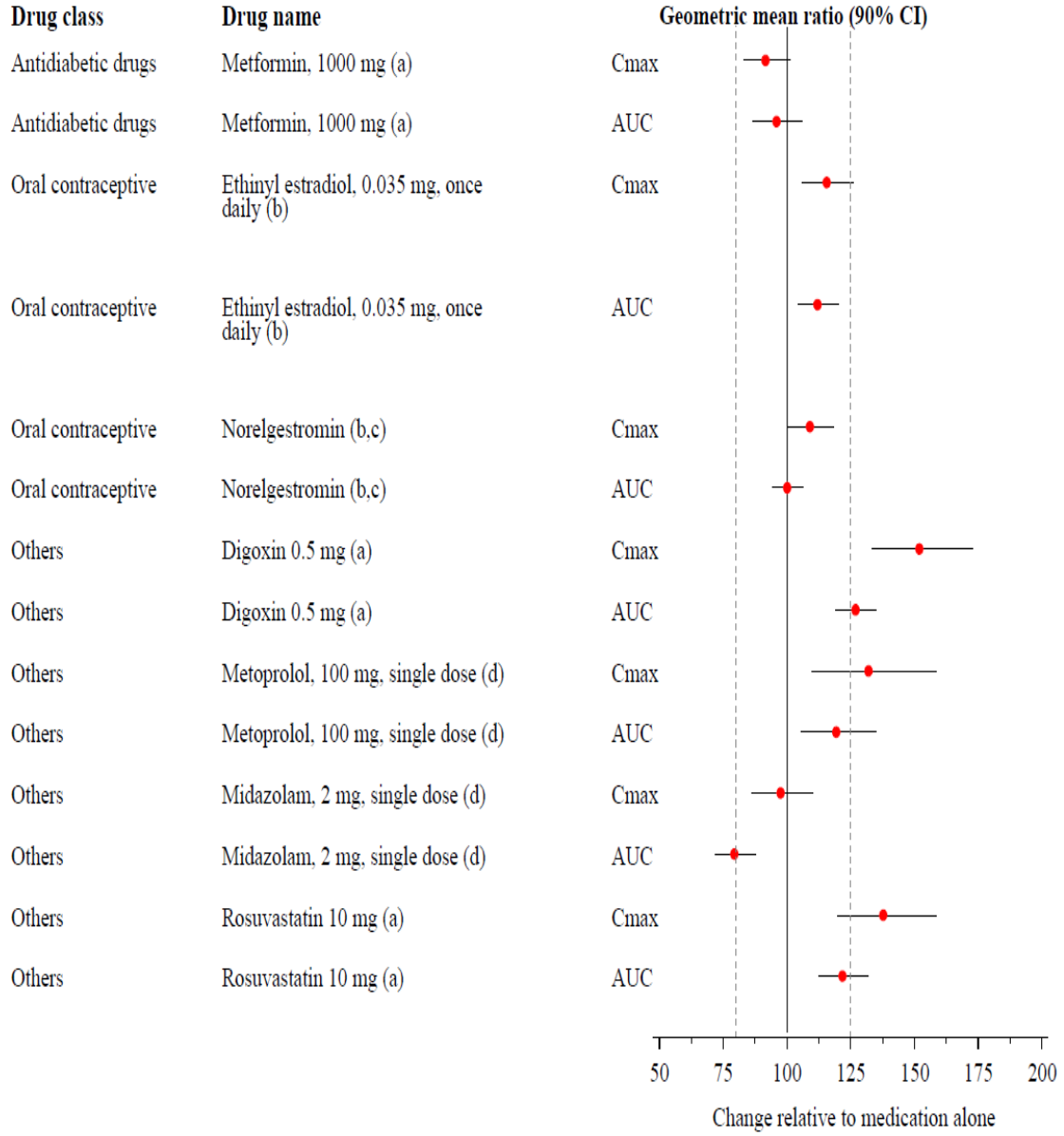


Note: (a) 400 mg sotagliflozin; (b) 400 mg sotagliflozin once daily for 7 days; (c) Administered as Ortho-cyclen
*AUC refers to $AUC_{0\text{-inf}}$ except for metformin and Ortho-cyclen ($AUC_{0\text{-last}}$)

Displayed as 90% CI of Geometric Mean AUC and Cmax Ratios [Reference Lines Indicate 100% (80%–125%)]

Source: Figure 11 of Summary of Clinical Pharmacology

Figure 38. Effect of sotagliflozin on the pharmacokinetics of concomitant medications



Note: (a) 400 mg sotagliflozin; (b) 400 mg sotagliflozin once daily for 7 days; (c) Norelgestromin is the primary active metabolite of norgestimate (0.25 mg, once daily); (d) 400 mg sotagliflozin once daily for 12 days

*AUC refers to $AUC_{0\text{-}inf}$ except for ethinyl estradiol/norelgestromin ($AUC_{0\text{-}tau}$) and metformin ($AUC_{0\text{-}last}$)

Displayed as 90% CI of Geometric Mean AUC and Cmax Ratios [Reference Lines Indicate 100% (80%–125%)]

Source: Figure 12 of Summary of Clinical Pharmacology

Specific Populations

Hepatic impairment

Sotagliflozin is proposed as not to be given for patients with moderate or severe hepatic impairment. The impact of various degrees of hepatic impairment (as defined using Child-Pugh criteria) on sotagliflozin PK was assessed in an open-label, parallel group, single dose study (Study 116). All subjects received a single dose of 400 mg sotagliflozin on Day 1 under fasted condition.

For subjects with mild hepatic impairment, sotagliflozin Cmax, AUC0-t and AUC0-inf remained comparable or was ~45% lower as compared to matched subjects with normal hepatic function. Therefore, no dose adjustment is needed for patients with mild hepatic impairment. It is prudent to not recommend the use of sotagliflozin for patients with moderate or severe hepatic impairment since the available dose strengths do not permit adequate dose adjustments. In addition, if gut effects of sotagliflozin are of any importance from efficacy perspective, the efficacy and safety of 6-fold or 3-fold lower doses have not been established in these patients.

Table 64. Summary of sotagliflozin PK comparison in subjects with normal or impaired hepatic function

Parameters	Group comparison (Test *vs* Reference)	N	GMR	90% CI of GMR
Cmax (ng/mL)	Mild *vs* Normal	7/7	1.06	(0.67, 1.68)
	Moderate *vs* Normal	7/7	2.91	(0.82, 10.4)
	Severe *vs* Normal	6/6	13.57	(7.12, 25.9)
AUC0-t (h*ng/mL)	Mild *vs* Normal	7/7	0.55	(0.27, 1.13)
	Moderate *vs* Normal	7/7	1.68	(0.42, 6.64)
	Severe *vs* Normal	6/6	6.55	(4.68, 9.16)
AUC0-inf (h*ng/mL)	Mild *vs* Normal	5/5	0.73	(0.38, 1.40)
	Moderate *vs* Normal	5/5	3.04	(0.65, 14.2)
	Severe *vs* Normal	5/5	5.57	(3.78, 8.21)

GMR: geometric mean ratio.
Source: Tables 11.4.1.1-1 of Study 116 CSR

Renal impairment

Sotagliflozin is proposed not to be given for patients with eGFR<45 mL/min/1.73m^2. The impact of various degrees of renal impairment (based on creatinine clearance (CLcr) as estimated by Cockcroft-Gault) on sotagliflozin PK was assessed in a dedicated, open-label, parallel group, single dose (400 mg sotagliflozin) study (Study 121). Sotagliflozin PK was compared between subjects with normal renal function and impaired renal function based on estimated glomerular filtration rate (eGFR), which was converted from CLcr.

For subjects with mild renal impairment [eGFR (mL/min/1.73m^2): 60-89], sotagliflozin Cmax, AUC0-t and AUC0-inf increased 74%, 75%, and 72%, respectively, as compared to those in matched subjects with normal renal function.

For subjects with moderate renal impairment [eGFR (mL/min/1.73m^2): 30-59], sotagliflozin Cmax, AUC0-t and AUC0-inf increased 26%, 97%, and 121%, respectively, as compared to those in matched subjects with normal renal function. Only two subjects had eGFR≥45 and <60 mL/min/1.73m^2.

Population PK modeling showed that for subjects with chronic kidney disease (CKD) stage IIIa (eGFR ≥45 and <60 mL/min/1.73m^2), sotagliflozin systemic exposure (AUC) was predicted to be 54% higher than subjects with normal renal function, and those with CKD stage II (eGFR > 60 and < 90 mL/min/1.73m2) was predicted to be 52% higher than subjects with normal renal function.

Table 65. Summary of sotagliflozin PK comparison in subjects with normal or impaired renal function based on eGFR

Parameters	**Group comparison* (Test *vs* Reference)**	**N**	**GMR**	**90% CI of GMR**
Cmax (ng/mL)	Mild *vs* Normal	7/10	1.74	(1.05, 2.90)
	Moderate *vs* Normal	7/10	1.26	(0.76, 2.10)
AUC0-t (h*ng/mL)	Mild *vs* Normal	7/10	1.75	(1.08, 2.84)
	Moderate *vs* Normal	7/10	1.97	(1.22, 3.18)
AUC0-inf (h*ng/mL)	Mild *vs* Normal	7/10	1.72	(1.07, 2.78)
	Moderate *vs* Normal	6/10	2.21	(1.34, 3.65)

**Normal renal function: eGFR≥90 mL/min/1.73m^2; mild renal impairment: eGFR 60-89 mL/min/1.73m^2; moderate renal impairment: eGFR 30-59 mL/min/1.73m^2.*
(Reviewer's analysis)

The efficacy of SGLT1/SGLT2 inhibitors including sotagliflozin is dependent on the degree of renal impairment with renal SGLT2 inhibition as one of the primary mechanism to eliminate filtered glucose through urine. While sotagliflozin efficacy and safety have not been established in patients with eGFR<45 mL/min/1.73m^2, the data in subjects with eGFR between 45 to 60 may be limited to inform about appropriate benefit-risk.

In Phase 3 efficacy and safety studies with sotagliflozin, only T1DM patients with eGFR baseline ≥45 mL/min/1.73m^2 were enrolled, of which the number of patients in the subgroup with eGFR baseline ≥45 to <60 mL/min/1.73m^2 is limited: 14 of 263 (5.3%) patients were with 200 mg and 16 of 262 (6.1%) patients were with 400 mg sotagliflozin in Study 309; 8 of 261 (3.1%) patients were with 200 mg and 9 of 263 (3.4%) patients were with 400 mg sotagliflozin in Study 310; 32 of 699 (4.6%) patients were with 400 mg sotagliflozin in Study 312.

The placebo adjusted mean change (95% CI) in HbA1c (%) from baseline at Week 24 was -0.28 (-0.64, 0.09) for 200 mg (n=22, pooled data from Studies 309 and 310), and -0.21 (-0.57, 0.14) (n=24, pooled data from Studies 309 and 310) or -0.21 (-0.48, 0.06) (n=50, pooled data from Studies 309, 310, and 312) for 400 mg QD dose levels in the subgroup with eGFR≥45 and <60 mL/min/1.73m^2.

For safety, the overall incidences of adverse events and discontinuations were generally similar between placebo and sotagliflozin-treated patients with eGFR ≥60 to <90 mL/min/1.73 m^2 and eGFR ≥90 mL/min/1.73 m^2. However, the incidence rates appeared to be higher in patients with eGFR <60 mL/min/1.73 m^2. Additionally, among patients with eGFR <60 mL/min/1.73 m^2, 2

patients had TEAEs leading to study drug discontinuation and both were on sotagliflozin 400 mg (Table 66).

Table 66. Overall summary of treatment-emergent adverse events through 52 weeks of treatment by Baseline eGFR

	Placebo			Sotagliflozin 200 mg			Sotagliflozin 400 mg		
	(N = 24) n (%)	(N = 245) n (%)	(N = 257) n (%)	(N = 22) n (%)	(N = 270) n (%)	(N = 232) n (%)	(N = 25) n (%)	(N = 259) n (%)	(N = 241) n (%)
eGFR category	**<60**	**≥60 to <90**	**≥90**	**<60**	**≥60 to <90**	**≥90**	**<60**	**≥60 to <90**	**≥90**
Patients with any TEAEs	19 (79.2)	178 (72.7)	177 (68.9)	19 (86.4)	207 (76.7)	167 (72.0)	21 (84.0)	188 (72.6)	181 (75.1)
Patients with treatment-related TEAEs	4 (16.7)	51 (20.8)	51 (19.8)	10 (45.5)	88 (32.6)	69 (29.7)	13 (52.0)	90 (34.7)	90 (37.3)
Patients with severe TEAEs	4 (16.7)	22 (9.0)	11 (4.3)	6 (27.3)	27 (10.0)	17 (7.3)	4 (16.0)	26 (10.0)	18 (7.5)
Patients with severe treatment-related TEAEs	0	7 (2.9)	4 (1.6)	3 (13.6)	10 (3.7)	6 (2.6)	3 (12.0)	9 (3.5)	10 (4.1)
Patients with treatment-emergent SAEs	3 (12.5)	22 (9.0)	12 (4.7)	3 (13.6)	27 (10.0)	23 (9.9)	5 (20.0)	25 (9.7)	20 (8.3)
Patients with treatment-emergent treatment-related SAEs	0	6 (2.4)	4 (1.6)	1 (4.5)	10 (3.7)	7 (3.0)	3 (12.0)	8 (3.1)	12 (5.0)
Patients with TEAEs Leading to study drug discontinuation	0	12 (4.9)	8 (3.1)	0	12 (4.4)	11 (4.7)	2 (8.0)	21 (8.1)	12 (5.0)
Patients with treatment-related TEAEs leading to study drug discontinuation	0	6 (2.4)	6 (2.3)	0	11 (4.1)	8 (3.4)	2 (8.0)	17 (6.6)	12 (5.0)
Patients with TEAEs leading to death	0	3 (1.2)	0	0	0	0	0	0	0

Source: Modified Table using the Table 46 of Summary of Clinical Safety

QT Prolongation:

No significant QTc prolongation effect of sotagliflozin (800 mg and 2000 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between sotagliflozin (800 mg and 2000 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated, indicating that assay sensitivity was established.

UGT1A9 polymorphism

A total of 70 samples from Studies INT14972, INT14936, INT14937 and PKM15047 were analyzed for polymorphism UGT1A9*3 (rs72551330, T→C) and only one subject was identified to be heterozygous UGT1A9*3 carrier. Due to the limited data, the impact of UGT1A9*3 polymorphism on sotagliflozin PK has not been assessed.

Appendix B: Insulin Dose Adjustment Guidelines

I. For Pump Therapy

Before making changes to insulin per gram of carbohydrate (I/C ratio), it is recommended that the amount of high blood glucose correction bolus (sliding scale) regular insulin (Regular) or rapid-acting insulin analogue (RAI) coverage is evaluated for appropriateness.

Glucose pattern (2-3 days)	Suggested changes
BG pre-breakfast	**HIGH** • If bedtime BG is out of range, consider correcting that prior to changing the overnight basal insulin. • Consider increasing the basal rate by ~10% from midnight to 1 hour prior to pre-breakfast BG check • Consider increasing bedtime snack I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) • Consider stopping bedtime snack • After increasing overnight basal insulin or I/C ratio of bedtime snack, consider checking some blood sugars overnight to make sure they are not low
	LOW • If bedtime BG is out of range, consider correcting that prior to changing the overnight basal insulin. • Consider decreasing the basal insulin rate by ~10 to 20% starting ~3-4 hours before morning BG is checked • Consider decreasing bedtime snack I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20) • Consider adding protein or fat to bedtime snack
BG post-breakfast	**HIGH** • Consider increasing breakfast I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10)
	LOW • Consider decreasing breakfast I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20)

3G pre-lunch	**HIGH** • Consider increasing morning snack I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) • Consider stopping morning snack • Consider increasing the basal rate by ~ 10% for the period after breakfast to before lunch
	LOW • Consider decreasing morning snack ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20) • Consider adding morning snack if no current morning snack • Consider decreasing the basal rate by ~10 to 20% for the period after breakfast to before lunch
3G post-lunch	**HIGH** • Consider increasing lunch I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10)
	LOW • Consider decreasing the Lunch I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20)
3G pre-dinner	**HIGH** • Consider eliminating afternoon snack or increasing snack I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) • Consider increasing the basal rate by ~ 10% for the period after lunch to before dinner
	LOW • Consider decreasing the afternoon snack I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20) • Consider decreasing the basal rate by ~10 to 20% for the period after lunch to before dinner
3G post-dinner or Bedtime	**HIGH** • Consider increasing dinner I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) • If BG post-dinner not high, but BG at bedtime is high, then consider increasing the basal rate by ~10% between dinner and Bedtime • After increasing dinner I/C ratio or basal insulin, consider checking some blood sugars overnight to make sure they are not low
	LOW • Consider decreasing dinner I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20) • If BG post-dinner not low, but BG at bedtime is low, then consider decreasing the basal rate by ~10 to 20% between dinner and Bedtime

II. For MDI Therapy

Before making changes to insulin per gram of carbohydrate (I/C ratio), it is recommended that the amount of high blood glucose correction bolus (sliding scale) regular insulin (Regular) or rapid-acting insulin analogue (RAI) coverage is evaluated for appropriateness.

Glucose pattern (2-3 days)	Suggested changes
BG pre-breakfast	**HIGH** • If bedtime BG is out of range, consider correcting that prior to changing the overnight basal insulin • If taking 1 daily dose of basal insulin, then consider increasing dose by ~10% • If taking 2 daily doses of basal insulin, then consider increasing EVENING dose by ~10% • Consider increasing bedtime snack I/C ratio, by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) • Consider stopping bedtime snack • After increasing basal insulin or I/C ratio of bedtime snack, consider checking some blood sugars overnight to make sure they are not low
	LOW • If bedtime BG is out of range, consider correcting that prior to changing the overnight insulin. • If taking 1 daily dose of basal insulin, then consider decreasing dose by ~10 to 20% • If taking 2 daily doses of basal insulin, then consider decreasing EVENING dose by ~10 to 20% • Consider decreasing bedtime snack I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20) • Consider adding protein or fat to bedtime snack
BG post-breakfast	**HIGH** • Consider increasing Breakfast I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10)
	LOW • Consider Decreasing Breakfast I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20)

BG pre-lunch	**HIGH** • Consider increasing morning snack I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) • Consider stopping morning snack
	LOW • Consider decreasing morning snack ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20) • Consider adding morning snack if no current morning snack
BG post-lunch	**HIGH** • Consider increasing lunch I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10)
	LOW • Consider decreasing the Lunch I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20)
BG pre-dinner	**HIGH** • Consider eliminating afternoon snack or increase snack I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) • If BG post lunch in range, and taking 1 daily dose of basal insulin, then consider increasing dose by ~10% • If BG post lunch in range, and taking 2 daily doses of basal insulin, then consider increasing MORNING dose by ~10% • After increasing basal insulin, consider checking some blood sugars overnight to make sure they are not low
	LOW • Consider decreasing the afternoon snack I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20) • If BG post lunch in range, and taking 1 daily dose of basal insulin, then consider decreasing dose by ~10 to20% • If BG post lunch in range, and taking 2 daily doses of basal insulin, then consider decreasing MORNING dose by ~10 to 20%
BG post-dinner or Bedtime	**HIGH** • Consider increasing dinner I/C ratio by 3-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:12 or 1:10) • After increasing dinner I/C ratio, consider checking some blood sugars overnight to make sure they are not low
	LOW • Consider decreasing dinner I/C ratio by 2-5 grams of carb per unit of insulin (Example: If 1 unit:15 g carb, change to 1:17 or 1:20)

Appendix C: Demographics Table for EFF-1

Subgroup	SOTA 200 mg (N=524) n (%)	SOTA 400 mg (N=525) n (%)	SOTA ALL (N=1049) n (%)	Placebo (N=526) n (%)
Sex				

Subgroup	SOTA 200 mg (N=524) n (%)	SOTA 400 mg (N=525) n (%)	SOTA ALL (N=1049) n (%)	Placebo (N=526) n (%)
F	259 (49.4)	272 (51.8)	531 (50.6)	255 (48.5)
M	265 (50.6)	253 (48.2)	518 (49.4)	271 (51.5)
Age				
Mean	44.4	44.0	44.2	42.5
Standard Deviation	13.7	13.4	13.5	13.3
Minimum	18	19	18	18
Median	45	44	45	42
Maximum	79	78	79	77
Age Group				
Under 65 (AGE < 65)	492 (93.9)	493 (93.9)	985 (93.9)	493 (93.7)
Over 65 (65 <= AGE)	32 (6.1)	32 (6.1)	64 (6.1)	33 (6.3)
Race				
Asian	7 (1.3)	5 (1.0)	12 (1.1)	4 (0.8)
Black	11 (2.1)	8 (1.5)	19 (1.8)	10 (1.9)
Native American	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)
Other	10 (1.9)	16 (3.0)	26 (2.5)	16 (3.0)
Pacific Islander	2 (0.4)	0 (0.0)	2 (0.2)	2 (0.4)
White	493 (94.1)	496 (94.5)	989 (94.3)	494 (93.9)
Ethnicity				
Hispanic	15 (2.9)	22 (4.2)	37 (3.5)	11 (2.1)
Missing	2 (0.4)	1 (0.2)	3 (0.3)	1 (0.2)
Non-Hispanic	507 (96.8)	502 (95.6)	1009 (96.2)	514 (97.7)
Region				
Asia	16 (3.1)	16 (3.0)	32 (3.1)	17 (3.2)
Canada	63 (12.0)	50 (9.5)	113 (10.8)	57 (10.8)
Europe	245 (46.8)	247 (47.0)	492 (46.9)	241 (45.8)
United States	200 (38.2)	212 (40.4)	412 (39.3)	211 (40.1)
Insulin Delivery				
CSII	224 (42.7)	224 (42.7)	448 (42.7)	226 (43.0)
MDI	300 (57.3)	301 (57.3)	601 (57.3)	300 (57.0)
HbA1c at Baseline				
Mean	7.68	7.64	7.66	7.66
Standard Deviation	0.773	0.776	0.774	0.808
Minimum	6.0	5.9	5.9	5.8
Median	7.6	7.5	7.6	7.6
Maximum	10.3	10.7	10.7	10.8
HbA1c Category				
<= 8.5%	423 (80.7)	425 (81.0)	848 (80.8)	422 (80.2)

Subgroup	SOTA 200 mg (N=524) n (%)	SOTA 400 mg (N=525) n (%)	SOTA ALL (N=1049) n (%)	Placebo (N=526) n (%)
> 8.5%	101 (19.3)	100 (19.0)	201 (19.2)	104 (19.8)
Fasting Plasma Glucose at Baseline (mg/dL)				
Mean	159.3	159.9	158.1	157.0
Standard Deviation	71.7	67.62	69.67	64.97
Minimum	44	46	44	41
Median	149.0	146.0	148.0	152.0
Maximum	511	380	511	391
Duration of T1DM (yrs)				
Mean	21.6	21.5	21.5	21.2
Standard Deviation	12.5	12.3	12.4	12.0
Minimum	1	1	1	1
Median	20	19	20	19
Maximum	61	64	64	57
BHB at Baseline				
Mean	0.2	0.2	0.2	0.2
Standard Deviation	0.2	0.2	0.2	0.2
Minimum	0.1	0.1	0.1	0.1
Median	0.13	0.14	0.13	0.13
Maximum	1.46	1.75	1.75	3.33
BMI Category				
< 18.5	3 (0.6)	2 (0.4)	5 (0.5)	0 (0.0)
>= 30	205 (39.1)	192 (36.6)	397 (37.8)	186 (35.4)
>=18.5 to <25	139 (26.5)	125 (23.8)	264 (25.2)	141 (26.8)
>=25 to <30	177 (33.8)	206 (39.2)	383 (36.5)	199 (37.8)
Basal Insulin Dose				
Mean	32.0	31.4	31.7	32.5
Standard Deviation	20.5	16.9	18.8	17.5
Minimum	6	3.9	3.9	7.3
Median	26.75	28	27.3	28
Maximum	200	160	200	155
Basal Insulin Dose (U/kg)				
Mean	0.4	0.4	0.4	0.4
Standard Deviation	0.2	0.2	0.2	0.2
Minimum	0.09	0.05	0.05	0.11
Median	0.33	0.334	0.33	0.354

Subgroup	SOTA 200 mg (N=524) n (%)	SOTA 400 mg (N=525) n (%)	SOTA ALL (N=1049) n (%)	Placebo (N=526) n (%)
Maximum	2.58	1.43	2.58	1.153
Bolus Insulin Dose				
Mean	30.7	31.3	31.0	31.9
Standard Deviation	20.8	21.1	20.9	23.4
Minimum	0	2.3	0	1
Median	26	27	26	26.2
Maximum	165	178	178	181.2
Bolus Insulin Dose (U/kg)				
Mean	0.4	0.4	0.4	0.4
Standard Deviation	0.2	0.2	0.2	0.2
Minimum	0	0.03	0	0.02
Median	0.31	0.32	0.32	0.32
Maximum	1.54	1.56	1.56	1.94
Total Insulin Dose				
Mean	62.7	62.8	62.7	64.4
Standard Deviation	36.6	33.5	35.0	36.6
Minimum	12	11.9	11.9	13
Median	54	55.5	55	55.7
Maximum	290	278	290	290
Total Insulin Dose (U/kg)				
Mean	0.7	0.7	0.7	0.7
Standard Deviation	0.3	0.3	0.3	0.3
Minimum	0.2	0.14	0.14	0.19
Median	0.65	0.68	0.67	0.68
Maximum	3.74	2.42	3.74	3.04
eGFR at Baseline				
Mean	89.3	89.1	89.2	90.2
Standard Deviation	19.6	18.3	19.0	18.5
Minimum	46.2	40.3	40.3	43.4
Median	87.5	88	87.8	89.7
Maximum	170.7	167.1	170.7	153.7
eGFR by Category				
< 60	22 (4.2)	25 (4.8)	47 (4.5)	24 (4.6)
>= 90	232 (44.3)	241 (45.9)	473 (45.1)	257 (48.9)
>=60 to <90	270 (51.5)	259 (49.3)	529 (50.4)	245 (46.6)

Source: table generated by Reviewer

Appendix D: Demographics for Study 312

Subgroup	SOTA 400 mg (N=699) n (%)	Placebo (N=703) n (%)	Total (N=1402) n (%)
Sex			
F	341 (48.8)	364 (51.8)	705 (50.3)
M	358 (51.2)	339 (48.2)	697 (49.7)
Age			
Mean	43.3 (14.2)	42.4	42.8
Standard Deviation	14.2	14.0	14.1
Minimum	18	18	18
Median	43	42	42
Maximum	79	78	79
Age Group			
Under 65 (AGE < 65)	644 (92.1)	657 (93.5)	1301 (92.8)
Over 65 (65 <= AGE)	55 (7.9)	46 (6.5)	101 (7.2)
Race			
Asian	7 (1.0)	5 (0.7)	12 (0.9)
Black	24 (3.4)	22 (3.1)	46 (3.3)
Native American	1 (0.1)	5 (0.7)	6 (0.4)
Other	47 (6.7)	50 (7.1)	97 (6.9)
Pacific Islander	1 (0.1)	0 (0.0)	1 (0.1)
White	619 (88.6)	621 (88.3)	1240 (88.4)
Ethnicity			
Hispanic	49 (7.0)	47 (6.7)	96 (6.8)
Missing	1 (0.1)	10 (1.4)	11 (0.8)
Non-Hispanic	649 (92.8)	646 (91.9)	1295 (92.4)
Region			
Africa	49 (7.0)	49 (7.0)	98 (7.0)
Asia	22 (3.1)	17 (2.4)	39 (2.8)
Canada	84 (12.0)	88 (12.5)	172 (12.3)
Europe	261 (37.3)	237 (33.7)	498 (35.5)
Other	63 (9.0)	69 (9.8)	132 (9.4)
South America	27 (3.9)	29 (4.1)	56 (4.0)
United States	193 (27.6)	214 (30.4)	407 (29.0)

Subgroup	SOTA 400 mg (N=699) n (%)	Placebo (N=703) n (%)	Total (N=1402) n (%)
HbA1c at Baseline			
Mean	8.26	8.21	8.23
Standard Deviation	0.965	0.921	0.943
Minimum	6.1	5.6	5.6
Median	8.10	8.10	8.10
Maximum	15.4	11.4	15.4
FPG at Baseline (mg/dL)			
Mean	165.1	163.4	164.3
Standard Deviation	71.60	69.08	70.33
Minimum	41	39	39
Median	154.0	153.0	153.0
Maximum	424	412	424
Insulin Delivery Method			
MDI	424 (60.7)	423 (60.2)	847 (60.4)
CSII	275 (39.3)	280 (39.8)	555 (39.6)
A1C Category			
<=8.5%	423 (60.5)	417 (59.3)	840 (59.9)
>8.5%	276 (39.5)	284 (40.4)	560 (39.9)
Missing	0 (0.0)	2 (0.3)	2 (0.1)
Duration of T1DM (yrs)			
Mean	20.5	19.6	20.0
Standard Deviation	12.4	12.1	12.2
Minimum	1	1	1
Median	18	18	18
Maximum	64	64	64
eGFR at Baseline			
Mean	91.5	92.5	92.0
Standard Deviation	19.8	21.9	20.9
Minimum	43.6	41.9	41.9
Median	90.4	90.8	90.6
Maximum	186.2	199.6	199.6
Basal Insulin			

Subgroup	SOTA 400 mg (N=699) n (%)	Placebo (N=703) n (%)	Total (N=1402) n (%)
Mean	29.5	29.6	29.6
Standard Deviation	16.3	15.5	15.9
Minimum	0	2	0
Median	26	26.4	26
Maximum	160	130	160
Bolus Insulin			
Mean	27.3	28.7	28.0
Standard Deviation	17.0	19.0	18.0
Minimum	0	0	0
Median	24	24	24
Maximum	154	153	154
Total Insulin			
Mean	56.9	58.3	57.6
Standard Deviation	27.6	29.1	28.4
Minimum	8	6.5	6.5
Median	50.6	51.4	51
Maximum	246	253	253
Total Insulin U/KG			
Mean	0.7	0.7	0.7
Standard Deviation	0.3	0.3	0.3
Minimum	0.07	0.12	0.07
Median	0.64	0.66	0.65
Maximum	2.52	2.38	2.52
BMI			
Mean	28.3	28.1	28.2
Standard Deviation	5.1	5.2	5.2
Minimum	18	18.3	18
Median	27.5	27.4	27.5
Maximum	48.2	58.1	58.1
A1C Category			
<=8.5%	423 (60.5)	417 (59.3)	840 (59.9)
>8.5%	276 (39.5)	284 (40.4)	560 (39.9)

Subgroup	SOTA 400 mg (N=699) n (%)	Placebo (N=703) n (%)	Total (N=1402) n (%)
Missing	0 (0.0)	2 (0.3)	2 (0.1)

Source: table generated by Reviewer

Appendix E: Baseline Demographics of Subjects with DKA versus no DKA in SAF-1

Subgroup	DKA (N = 36) n (%)	No DKA (N = 1539) n (%)	Total (N = 1575) n (%)
Sex			
F	23 (63.9)	763 (49.6)	786 (49.9)
M	13 (36.1)	776 (50.4)	789 (50.1)
Age			
Mean	40.14	43.75	43.66
Standard Deviation	14.18	13.46	13.49
Minimum	20	18	18
Median	37.5	44	43
Maximum	71	79	79
Age Group			
Under 65	33 (91.7)	1445 (93.9)	1478 (93.8)
Over 65	3 (8.3)	94 (6.1)	97 (6.2)
Race			
American Indian or Alaska Native	0 (0.0)	1 (0.1)	1 (0.1)
Asian	1 (2.8)	15 (1.0)	16 (1.0)
Black or African American	0 (0.0)	29 (1.9)	29 (1.8)
Native Hawaiian or Other Pacific Islander	0 (0.0)	4 (0.3)	4 (0.3)
Other	1 (2.8)	41 (2.7)	42 (2.7)
White	34 (94.4)	1449 (94.2)	1483 (94.2)
Ethnicity			
Hispanic or Latino	0 (0.0)	48 (3.1)	48 (3.0)
Missing	0 (0.0)	10 (0.6)	10 (0.6)
Not Hispanic or Latino	36 (100.0)	1481 (96.2)	1517 (96.3)
Region			

Subgroup	DKA (N = 36) n (%)	No DKA (N = 1539) n (%)	Total (N = 1575) n (%)
Asia	3 (8.3)	46 (3.0)	49 (3.1)
Canada	4 (11.1)	166 (10.8)	170 (10.8)
Europe	12 (33.3)	721 (46.8)	733 (46.5)
United States	17 (47.2)	606 (39.4)	623 (39.6)
Insulin Delivery Method			
Insulin Pump	22 (61.1)	652 (42.4)	674 (42.8)
MDI	14 (38.9)	887 (57.6)	901 (57.2)
Baseline A1c			
<= 8.5%	28 (77.8)	1242 (80.7)	1270 (80.6)
> 8.5%	8 (22.2)	297 (19.3)	305 (19.4)
Duration of T1DM			
Mean	20.36	21.45	21.42
Standard Deviation	11.19	12.29	12.26
Minimum	5	1	1
Median	17	20	19
Maximum	47	64	64
Baseline BHB (mmol/L)			
Mean	0.22	0.2	0.2
Standard Deviation	0.17	0.18	0.18
Minimum	0.1	0.1	0.1
Median	0.15	0.13	0.13
Maximum	0.8	3.33	3.33
BMI Category			
< 18.5	0 (0.0)	5 (0.3)	5 (0.3)
≥ 30	13 (36.1)	570 (37.0)	583 (37.0)
≥ 18.5 to <25	13 (36.1)	392 (25.5)	405 (25.7)
≥ 25 to <30	10 (27.8)	572 (37.2)	582 (37.0)
Basal Insulin at Baseline			
Mean	32.67	31.96	31.98
Standard Deviation	18.46	18.35	18.35
Minimum	15.9	3.9	3.9
Median	25.9	28	28

Subgroup	DKA (N = 36) n (%)	No DKA (N = 1539) n (%)	Total (N = 1575) n (%)
Maximum	96	200	200
Basal Insulin (U/kg)			
Mean	0.38	0.37	0.37
Standard Deviation	0.16	0.18	0.18
Minimum	0.17	0.05	0.05
Median	0.35	0.34	0.34
Maximum	0.81	2.58	2.58
Bolus Insulin at Baseline			
Mean	25.61	31.44	31.3
Standard Deviation	12.18	21.93	21.77
Minimum	6.6	0	0
Median	22.9	26	26
Maximum	52.8	181.2	181.2
Bolus Insulin (U/kg)			
Mean	0.31	0.36	0.36
Standard Deviation	0.13	0.21	0.21
Minimum	0.1	0	0
Median	0.29	0.32	0.32
Maximum	0.59	1.94	1.94
Total Insulin at Baseline			
Mean	58.27	63.4	63.28
Standard Deviation	24.85	35.76	35.55
Minimum	22.5	11.9	11.9
Median	53.25	55	55
Maximum	143.7	290	290
Total Insulin (U/kg)			
Mean	0.7	0.74	0.73
Standard Deviation	0.21	0.32	0.32
Minimum	0.35	0.14	0.14
Median	0.66	0.67	0.67
Maximum	1.17	3.74	3.74
EGFR at Baseline			

Subgroup	DKA (N = 36) n (%)	No DKA (N = 1539) n (%)	Total (N = 1575) n (%)
Mean	92.33	89.47	89.53
Standard Deviation	20.24	18.8	18.83
Minimum	48	40.3	40.3
Median	92.4	88.4	88.6
Maximum	167.1	170.7	170.7
EGFR Category			
< 60	3 (8.3)	68 (4.4)	71 (4.5)
>= 90	20 (55.6)	710 (46.1)	730 (46.3)
>=60 to <90	13 (36.1)	761 (49.4)	774 (49.1)

Source: table generated by Reviewer

Appendix F: Kidney Function Tables

Study 309

Laboratory Changes and Downward Shifts	Sota 200 mg (N = 263)	Sota 400 mg (N = 262)	Placebo (N = 268)
Serum creatinine, mg/dL (Baseline): Mean, median ± SD	0.87, 0.85 ± 0.18	0.86, 0.86 ± 0.16	0.87, 0.86 ± 0.17
Change in serum creatinine, mg/dL (Baseline to Week 52 or EOT/EW): Mean, median ± SD	0.02, 0.01 ± 0.11	0.02, 0.02 ± 0.1	0.01, 0.01 ± 0.1
Marked abnormality in SrCr (developed change from Baseline >2.5 mg/dL)	0/252 (0)	0/251 (0)	0/254 (0)
eGFR, mL/min/1.73 m^2 (Baseline): Mean, median ± SD	86.67, 85.6 ± 19.73	86.75, 84.7 ± 18.85	87.16, 87.4 ± 18.59
Change in eGFR, mL/min/1.73 m^2 (Baseline to Week 52 or EOT/EW): Mean, median ± SD	-2.3, -2 ± 11.87	-1.88, -2.5 ± 10.62	-1.23, -1.1 ± 10.15
Downward shifts in eGFR (Baseline to Week 52 or EOT/EW)			
Mild to moderate renal impairment (>60 mL/min/1.73 m^2 to <60 mL/min/1.73m^2)	11/237 (4.64)	5/236 (2.12)	9/239 (3.77)
Moderate to severe renal impairment (≥30 - <60 mL/min/1.73 m^2 to <30 mL/min/1.73 m^2)	0/14 (0)	1/15 (6.67)	0/15 (0)
ACR, mg/g (Baseline): Mean, median ± SD	38.71, 6.98 ± 176.34	17.02, 5.46 ± 50.25	29.74, 5.86 ± 124.48
ACR, mg/g (Baseline to Week 52 or EOT/EW): Mean, median ± SD	14.02, 1.01 ± 247.8	-1.24, 0.56 ± 27.71	-2.87, 0.55 ± 111.28

Laboratory Changes and Downward Shifts	Sota 200 mg (N = 263)	Sota 400 mg (N = 262)	Placebo (N = 268)
Downward shifts in ACR (Baseline to Week 52 or EOT/EW)			
Normo- to microalbuminuria (<30 mg/g to >=30 mg/g)	10/211 (4.74)	6/221 (2.71)	9/214 (4.21)
Normo- to macroalbuminuria (<30 mg/g to >300 mg/g)	0/211 (0)	0/221 (0)	0/214 (0)
Micro- to macroalbuminuria (>=30 - <=300 mg/g to >300 mg/g)	0/28 (0)	0/17 (0)	2/24 (8.33)

Source: table generated by Reviewer

Kidney Function Study 310

Laboratory Changes and Downward Shifts	Sota 200 mg (N = 261)	Sota 400 mg (N = 263)	Placebo (N = 258)
Serum creatinine, mg/dL (Baseline): Mean, median ± SD	0.85, 0.84 ± 0.15	0.84, 0.83 ± 0.17	0.84, 0.82 ± 0.16
Serum creatinine, mg/dL (Baseline to Week 52 or EOT/EW): Mean, median ± SD	0.01, 0.02 ± 0.1	0, 0 ± 0.1	0, -0.01 ± 0.09
Marked abnormality in SrCr (developed change from Baseline >2.5 mg/dL)	0/251 (0)	0/252 (0)	0/246 (0)
eGFR, mL/min/1.73 m^2 (Baseline): Mean, median ± SD	90.91, 89.4 ± 18.51	91.87, 91.65 ± 17.28	93.13, 92.75 ± 18.33
eGFR, mL/min/1.73 m^2 (Baseline to Week 52 or EOT/EW): Mean, median ± SD	-1.5, -2.2 ± 12.07	-0.19, -0.4 ± 12.77	0.5, 0.15 ± 10.9
Downward shifts in eGFR (Baseline to Week 52 or EOT/EW)			
Mild to moderate renal impairment (>60 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2)	8/243 (3.29)	4/244 (1.64)	3/237 (1.27)
Moderate to severe renal impairment (>=30 - <60 mL/min/1.73 m^2 to <30 mL/min/1.73 m^2)	0/8 (0)	0/8 (0)	0/9 (0)
ACR, mg/g (Baseline): Mean, median ± SD	36.67, 6.94 ± 146.04	59.31, 6.93 ± 253.9	50.99, 6.67 ± 350.64
ACR, mg/g (Baseline to Week 52 or EOT/EW): Mean, median ± SD	-5.88, 0.36 ± 71.02	-9.06, 0.58 ± 190.18	8.32, 0.17 ± 94.79
Downward shifts in ACR (Baseline to Week 52 or EOT/EW)			
Normo- to microalbuminuria (<30 mg/g to >=30 mg/g)	14/212 (6.6)	11/215 (5.12)	7/214 (3.27)
Normo- to macroalbuminuria (<30 mg/g to >300 mg/g)	0/212 (0)	1/215 (0.47)	0/214 (0)
Micro- to macroalbuminuria (>=30 - <=300 mg/g to >300 mg/g)	1/28 (3.57)	2/27 (7.41)	2/27 (7.41)

Source: table generated by Reviewer

Kidney Function Study 312

Laboratory Changes and Downward Shifts	Sota 400 mg (N = 699)	Placebo (N = 703)
Serum creatinine, mg/dL (Baseline): Mean, median ± SD	0.84, 0.84 ± 0.16	0.84, 0.82 ± 0.19
Serum creatinine, mg/dL (Baseline to Week 24 or EOT/EW): Mean, median ± SD	0.02, 0.01 ± 0.1	0.01, 0.01 ± 0.1
Marked abnormality in SrCr (developed change from Baseline >2.5 mg/dL)	0/662 (0)	0/667 (0)
eGFR, mL/min/1.73 m^2 (Baseline): Mean, median ± SD	91.24, 90.15 ± 19.74	92.07, 90.1 ± 21.94
eGFR, mL/min/1.73 m^2 (Baseline to Week 24 or EOT/EW): Mean, median ± SD	-1.74, -1.8 ± 11.58	-1.72, -1.1 ± 11.78
Downward shifts in eGFR (Baseline to Week 24 or EOT/EW)		
Mild to moderate renal impairment (>60 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2)	22/630 (3.49)	12/626 (1.92)
Moderate to severe renal impairment (>=30 - <60 mL/min/1.73 m^2 to <30 mL/min/1.73 m^2)	0/31 (0)	1/41 (2.44)
ACR, mg/g (Baseline): Mean, median ± SD	55.82, 7.36 ± 296.91	48.01, 7.27 ± 266.61
ACR, mg/g (Baseline to Week 24 or EOT/EW): Mean, median ± SD	-12.04, 0.16 ± 287	11.24, 0 ± 151.6
Downward shifts in ACR (Baseline to Week 24 or EOT/EW)		
Normo- to microalbuminuria (<30 mg/g to >=30 mg/g)	19/546 (3.48)	30/558 (5.38)
Normo- to macroalbuminuria (<30 mg/g to >300 mg/g)	1/546 (0.18)	0/558 (0)
Micro- to macroalbuminuria (>=30 - <=300 mg/g to >300 mg/g)	1/69 (1.45)	6/66 (9.09)

Source: table generated by Reviewer

Appendix G. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.