CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216203Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	216203
Priority or standard	Standard
Submit date(s)	5/27/2022
Received date(s)	5/27/2022
PDUFA goal date	5/27/2023
Division/office	Division of Cardiology and Nephrology (DCN)
Review completion date	3/7/2023
Established name	Sotagliflozin
(Proposed) trade name	(b) (4) or INPEFA
Pharmacologic class	SGLT2 inhibitor
Code name	LX4211/SAR439954
Applicant	Lexicon Pharmaceuticals, Inc
Dose form/formulation(s)	Tablets
Dosing regimen	200 mg orally once daily increased to 400 mg orally once daily, as tolerated
Applicant proposed indication(s)/population(s)	• Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure. • Reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.
Proposed SNOMED indication	Heart failure Diabetes mellitus type 2, chronic kidney disease and at increased risk of cardiovascular disease
Regulatory action	Approval
Approved indication(s)/population(s) (if applicable)	Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with: • heart failure • type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors
Approved SNOMED indication	Heart failure Diabetes mellitus type 2, chronic kidney disease and at increased risk of cardiovascular disease

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Glossary

AC	advisory committee
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	adverse reaction
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor and neprilysin inhibitor
BB	beta blocker
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CMQ	customized MedDRA query
eCRF	electronic case report form
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy - defibrillator
CV	cardiovascular
CVA	cerebrovascular accident
CVOT	cardiovascular outcomes trial
DILI	drug-induced liver injury
DKA	diabetic ketoacidosis
ECG	electrocardiogram
ED	emergency department
FDA	Food and Drug Administration
FMQ	FDA medical query
GCP	good clinical practice
GLP-1	glucagon-like peptide-1
GMI	genital mycotic infections
HbA1c	hemoglobin A1c
HF	heart failure
HHF	hospitalization for heart failure
ICD	implantable cardioverter defibrillator
ICH	International Conference on Harmonization
IMP	investigational medical product
IND	investigational new drug
ITT	intention-to-treat

KCCQ-12	Kansas City cardiomyopathy questionnaire
IV	intravenous
LDL-C	low density lipoprotein cholesterol
LLN	lower limit of normal
LOCF	last observation carried forward
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
MRA	mineralocorticoid receptor antagonist
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PT	preferred term
PVC	premature ventricular complex
RAAS	renin-angiotensin-aldosterone system
RD	risk difference
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SGLT1	sodium glucose co-transporter 1
SGLT2	sodium glucose co-transporter 2
SMQ	standard MedDRA query
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
UHFV	urgent heart failure visit
ULN	upper limit of normal
UTI	urinary tract infection

I. Executive Summary

1. Summary of Regulatory Action

Regulatory Assessment and Recommendation
The data submitted in support of NDA 216203 meets the statutory requirement for substantial evidence of effectiveness and supports a favorable benefit-risk assessment of sotagliflozin "to reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visits in adults with heart failure or type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors." The review team recommends approval of sotagliflozin for this indication statement.

Background
On 27 May 2022, the Applicant submitted NDA 216203 for sotagliflozin, a New Molecular Entity (NME), purported to be a dual sodium-glucose cotransporter (SGLT) 1 and 2 inhibitor for the following proposed indications:

- *To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure.*

- *To reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.*

To support the proposed indications, the Applicant submitted two pivotal randomized controlled trials – SOLOIST and SCORED – with the same primary composite endpoint of cardiovascular (CV) death, total (first and recurrent) hospitalization for heart failure (HHF) and urgent heart failure visit (UHFV).

Past regulatory history of sotagliflozin includes issuance of a Complete Response letter dated 22 March 2019, under NDA 210934, due to increased severity and eight-fold the risk of diabetic ketoacidosis (DKA) associated with sotagliflozin (200 mg and 400 mg) as compared to placebo leading to an unfavorable benefit-risk assessment of sotagliflozin for glycemic control indication in patients with type 1 diabetes mellitus (TIDM).

Efficacy
SOLOIST was a phase 3, placebo-controlled, double-blind trial designed to evaluate the efficacy and safety of sotagliflozin to reduce the risk of CV death, HHF and UHV in patients with heart failure (HF) and type 2 diabetes mellitus (T2DM). SOLOIST randomized 1222 patients in 1:1 ratio to sotagliflozin versus placebo and demonstrated decreased incidence of the primary composite endpoint with sotagliflozin with a hazard ratio (HR) 0.67 (95% CI 0.53, 0.85); P-value <0.001.

SCORED was a phase 3, placebo-controlled, double-blind trial designed to evaluate the efficacy and safety of sotagliflozin to reduce the risk of CV death, HHF, and UHV in patients with T2DM, chronic kidney disease with estimated glomerular filtration rate (eGFR) ≥25 to ≤60 mL/min/1.73 m^2, and either a major CV risk factor or age ≥55 years with at least 2 minor CV risk factors. SCORED randomized 10,584 patients in 1:1 ratio to sotagliflozin versus placebo and demonstrated decreased incidence of the primary composite endpoint with a HR 0.75 (95%CI 0.63, 0.88); p-value <0.0004.

In both trials, all components of the primary composite endpoint contributed to the overall results, with largest treatment effect on HHF (HR for HHF [95% CI]: 0.65 [0.49, 0.87], SOLOIST; 0.66 [0.53, 0.82], SCORED). For the planned secondary endpoints, only the first endpoint of HHF and UVHF was formally tested. Prespecified subgroup analyses for SOLOIST and SCORED demonstrated consistent treatment benefit with sotagliflozin on the primary composite endpoint across key subgroups, including left ventricular ejection fraction (LVEF) at screening, presence of HF, and main etiology of HF. Background therapies used for the treatment of HF were consistent with standard of care at the time of trial conduct. Treatment effect was observed across the range of baseline HbA1c values, with no statistically significant treatment effect interaction between primary endpoint results and HbA1c.

Safety
The mean duration of exposure to sotagliflozin was 252 (± 161) and 441 (± 182) days in SOLOIST and SCORED, respectively and was similar to placebo. Safety analyses of SOLOIST and SCORED did not demonstrate any important imbalance in the incidence of deaths, serious treatment emergent adverse events (TEAEs), or TEAEs leading to treatment discontinuation between treatment groups. In these trials, the most commonly reported TEAE by preferred term was diarrhea. In both studies, TEAEs related to volume depletion were more likely to occur in elderly patients and in patients with lower baseline eGFR (<30 mL/min/1.73m^2 in SCORED and <60 mL/min/1.73m^2 in SOLOIST). Genital mycotic infections occurred more frequently in female patients, with a relative risk (95% CI) of 3.2 (0.3, 30.6) and 2.9 (1.9, 4.4) in SOLOIST and SCORED, respectively. The incidence rate of diabetic ketoacidosis (DKA) and amputations was low in both trials, with no clinically relevant imbalance between the treatment groups. The TEAEs observed with sotagliflozin, except diarrhea, are consistent with the known safety profile of other approved SGLT2 inhibitors.

2. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Heart Failure (HF) is a clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress. HF is a chronic condition associated with premature mortality and significant morbidity, largely due to high rates of hospitalization for heart failure (HHF). It afflicts 1 to 3% of the population worldwide, with annual incidence of ~1,000,000 and prevalence of ~6,000,000 in the United States (US). Although HF survival has modestly improved, 1-year mortality is estimated at 29.6% and 5-year mortality is estimated at 52.6% with uneven outcomes across U.S. states.[1]	HF remains a highly prevalent condition with significant morbidity and mortality.
Current Treatment Options	Pharmacologic agents and drug classes currently approved for treatment of major morbidity and mortality in patients with HF with reduced left ventricular ejection fraction (LVEF) include angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin-receptor neprilysin inhibitors (ARNI), beta blockers (BB), digoxin, ivabradine, mineralocorticoid receptor antagonists (MRAs), sodium-glucose co-transporter 2 inhibitors (SGLT2i), and vericiguat. Among these pharmacologic agents and drug classes, only SGLT2i have been approved for treatment of major morbidity and mortality in patients with HF and normal LVEF. Approved device therapies to treat patients with HF with reduced LVEF are implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy defibrillator (CRT-D).	For patients with HF and reduced LVEF, there are several pharmacologic treatment options. For patients with HF and normal LVEF, there are limited tretament options. HF, regardless of LVEF, continues to be associated with significant morbidity and mortality, and represents an unmet medical need.

[1] Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association [published online ahead of print, 2023 Jan 25]. Circulation. 2023;10.1161/CIR.0000000000001123. doi:10.1161/CIR.0000000000001123

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	SOLOIST was a randomized, placebo-controlled, parallel-group, multi-center, double-blind trial comparing sotagliflozin to placebo in patients with HF and type 2 diabetes mellitus (T2DM). SOLOIST randomized n=1222 subjects (~1:1 sotagliflozin vs. placebo) with a history of HF who were hemodynamically stable after hospital admission, urgent heart failure visit (UHFV) or emergency department (ED)/infusion center visit for worsening HF and requiring intravenous (IV) diuresis. The primary composite endpoint was total (first and recurrent) cardiovascular (CV) death, hospitalization for heart failure (HHF) and UHFV. SOLOIST demonstrated a reduction in the primary composite endpoint with sotagliflozin compared to placebo with a respective incidence rate of 51.3 versus 76.4 per 100 patient years; hazard ratio 0.67 (95%CI 0.53, 0.85); p-value <0.001. Although SOLOIST enrolled patients with HF and T2DM, T2DM is considered an enrichment factor for risk of adverse outcomes in a HF population, and not to be a requisite to derive treatment benefit with sotagliflozin. SCORED was a randomized, placebo-controlled, parallel-group, multi-center, double-blind trial comparing sotagliflozin to placebo in patients with T2DM, chronic kidney disease (eGFR ≥25 to ≤60 mL/min/1.73 m^2) and either a major CV risk factor or age ≥55 years or with at least 2 minor CV risk factors. SCORED randomized n=10,584 subjects in 1:1 ratio to sotagliflozin vs. placebo. The primary composite endpoint was total (first and recurrent) CV death, HHF and UHFV. SCORED demonstrated a reduction in the primary composite endpoint with sotagliflozin compared to placebo with a respective incidence rate of 5.6 versus 7.5 per 100 patient years; hazard ratio 0.75 (95% CI 0.63, 0.88); p-value <0.0004.	SOLOIST and SCORED provided substantial evidence of effectiveness of sotagliflozin to reduce the risk of CV death, HHF and UHFV in adults with 1) heart failure, and 2) T2DM, CKD and other CV risk factors, respectively.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	In SOLOIST and SCORED, there was no important imbalance in the incidence of deaths, serious treatment emergent adverse events (TEAEs), or TEAEs leading to treatment discontinuation between the treatment groups. In SOLOIST, there were more TEAEs, mild in severity, for sotagliflozin versus placebo treated patients. Volume depletion, urinary tract infection (UTI), genital mycotic infection (GMI), and diarrhea occurred at an increased frequency in patients treated with sotagliflozin versus placebo in both studies. Incidence rates of diabetes ketoacidosis (DKA) events were low in SCORED (0.7 and 0.5 per 100 patient-years in sotagliflozin and placebo groups, respectively) and SOLOIST (1.0 and 1.7 per 100 patient-years in sotagliflozin and placebo groups, respectively).	The safety profile of sotagliflozin is generally consistent with other approved SGLT2i, except for diarrhea.

Conclusions Regarding Benefit-Risk

Sotagliflozin is a new molecular entity (NME) purported to be a dual sodium glucose co-transporter 1 (SGLT1) and SGLT2 inhibitor. On 27 May 2022, Lexicon Pharmaceuticals, Inc. (the Applicant) submitted a new drug application (NDA) for the following proposed indications: 1) to *reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure* and 2) to *reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.* Despite currently available therapeutic options, heart failure is a highly prevalent condition with significant morbidity and mortality, thus representing unmet need.

To support the proposed indications, the Applicant submitted the results of two pivotal phase 3 trials, SOLOIST and SCORED. SOLOIST and SCORED were randomized, placebo-controlled, multi-center, double-blind, trials of sotagliflozin in patients with T2DM. SOLOIST randomized 1222 patients with a history of HF in 1:1 ratio to sotagliflozin versus placebo. SCORED randomized 10584 patients with eGFR ≥25 to ≤60 mL/min/1.73 m^2 with either a major CV risk factor or age ≥55 years with at least 2 minor CV risk factors in 1:1 ratio to sotagliflozin versus placebo. The primary composite endpoint for SOLOIST and SCORED was total (first and recurrent) CV death, HHF and UHFV.

SOLOIST demonstrated a reduction in risk of the primary composite endpoint compared to placebo with a respective incidence rate of 51.3 versus 76.4 per 100 patient years; hazard ratio 0.67 (95% CI 0.53, 0.85); p-value <0.001. Although SOLOIST enrolled patients

with HF and T2DM, T2DM is considered an enrichment factor for risk of adverse outcomes in a HF population, and not to be a requisite to derive treatment benefit with sotagliflozin. SCORED demonstrated a reduction in risk of the primary composite endpoint compared to placebo with a respective incidence rate of 5.6 versus 7.5 per 100 patient years; hazard ratio 0.75 (95%CI 0.63, 0.88); p-value <0.0004. In both SOLOIST and SCORED, early divergence of the hazard function curves occurred with 95% CI crossing below 1 at 4 and 8 months, respectively. The data from SOLOIST and SCORED demonstrated substantial evidence of effectiveness of sotagliflozin to reduce the risk of CV death, HHF and UHFV in patients with HF or with T2DM, CKD and other CV risk factors.

In SOLOIST and SCORED, sotagliflozin was administered to a total of 5896 patients, with approximately 3600 patients exposed to sotagliflozin for ≥52 weeks.

There were no important imbalances in the incidence of deaths, serious TEAEs, and TEAEs leading to discontinuation between treatment groups in both studies. In SOLOIST, there were more non-serious TEAEs overall for sotagliflozin treated patients, but the imbalance was only observed for mild adverse events. There was no imbalance in non-serious TEAEs in SCORED. Volume depletion, UTI, GMI, and diarrhea occurred at an increased frequency in patients treated with sotagliflozin versus placebo in both studies. Incidence rates of DKA events were low in SCORED (0.7 and 0.5 per 100 patient-years in sotagliflozin and placebo groups, respectively) and SOLOIST (1.0 and 1.7 per 100 patient-years in sotagliflozin and placebo groups, respectively); however, the risk of DKA was slightly higher for sotagliflozin treated patients in SCORED. These AEs, except diarrhea, are consistent with the known safety profile of other SGLT2 inhibitors.

In conclusion, overall benefit-risk assessment supports the approval of sotagliflozin to *reduce the risk of CV death, HHF, and UHFV in adults with 1) heart failure, or 2) T2DM, CKD and other CV risk factors*.

II. Interdisciplinary Assessment

3. Introduction

Sotagliflozin is an NME purported to be a dual SGLT1 and SGLT2 inhibitor. SGLT1 inhibition in the intestine results in delayed intestinal glucose absorption and stimulates gastrointestinal peptides. SGLT2 inhibition results in decreased glucose reabsorption in the renal proximal tubules and increased urinary glucose excretion and osmotic diuresis.

The Applicant submitted two phase 3 pivotal trials (EFC15156, SOLOIST and EFC14875, SCORED) in support of NDA for sotagliflozin for the following indications:

- *Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure.*
- *Reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease and other cardiovascular risk factors, including a history of heart failure.*

Disease Background
The 2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure defines heart failure (HF) as a "complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood."[2] HF causes significant morbidity and mortality in the U.S. affecting 6 million adults. In 2020, HF was the underlying cause of death for 85,855 patients, and in 2019, HF accounted for 1.3 million hospital discharges.[3] The readmission rate for patients with HF is high, with a 1-month readmission rate of 25%.[4] Known risk factors with high relative risk and population attributable risk for development of HF include hypertension, obesity, prediabetes, diabetes and atherosclerotic coronary vascular disease. Age is also a significant risk factor with data showing the incidence

[2] Heidenreich, P.A., et al., 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation, 2022. 145(18): p. e895-e1032.

[3] Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association [published online ahead of print, 2023 Jan 25]. Circulation. 2023;10.1161/CIR.0000000000001123. doi:10.1161/CIR.0000000000001123

[4] Krumholz, H.M., et al., Patterns of hospital performance in acute myocardial infarction and heart failure 30-day mortality and readmission. Circ Cardiovasc Qual Outcomes, 2009. 2(5): p. 407-13.

for individuals aged 65 to 69 years is approximately 20 per 1,000 whereas the incidence increases to >80 per 1,000 individuals for subjects ≥85 years of age.[5]

To guide clinical management, HF is typically characterized by the level of functional impairment, as graded by LVEF, and the presence of symptoms. In patients with reduced LVEF, treatment goals are aimed at reducing HF morbidity and mortality through a combination of medical therapeutics and cardiac device therapies (e.g., implantable cardioverter-defibrillator [ICD], cardiac resynchronization therapy with biventricular pacing [CRT] or a CRT device with defibrillation capability [CRT-D]). [6] FDA approved drugs and drug classes that have been shown to decrease hospitalizations and or prolong survival for HF patients with reduced LVEF include BB, ARB, ACEi, ARNI, MRA, hydralazine/isosorbide dinitrate, digoxin, ivabradine, vericiguat and the SGLT2i agents dapagliflozin and empagliflozin. FDA approved drugs shown to decrease hospitalizations due to HF and or prolong survival for HF patients with normal LVEF include SGLT2i agents. There are currently no FDA approved cardiac device therapies HF patients with normal LVEF. Management also considers treatment of the underlying etiology of the HF diagnosis to limit progression of disease. Despite advances in HF medical management, there remains an unmet need to reduce morbidity and mortality in patients with HF.

Brief Regulatory History

NDA 216203 was initially filed on 30 December 2021, but the filing was subsequently withdrawn on 28 February 2022 after the Applicant notified the Agency of significant discrepancies with manual protocol deviation reporting in the clinical trial database. The Agency later agreed with the Applicant's proposed data quality mitigation plan which facilitated the resubmission of NDA 216203 on 27 May 2022.

NDA 216203 is the first market approval filing for sotagliflozin, indicated for the treatment of HF morbidity and mortality. However, sotagliflozin has previously undergone regulatory review for a glycemic control indication. On 22 March 2018, the Applicant submitted NDA 210934 seeking an indication to improve glycemic control when used with insulin in adult patients with type 1 diabetes mellitus (T1DM). On 22 March 2019, FDA issued a Complete Response letter due to an unfavorable benefit-risk assessment. Data from three phase 3 trials submitted under NDA 210934 demonstrated eightfold increased risk of diabetic ketoacidosis (DKA) associated with sotagliflozin (200 mg and 400 mg) as compared to placebo. The Applicant, contemporaneous to NDA 216203, is pursuing a dispute resolution with the FDA to find a path forward for a glycemic control indication in patients with T1DM.

[5] Curtis L.H., Whellan D.J., Hammill B.G.et al. : "Incidence and prevalence of heart failure in elderly persons, 1994–2003". Arch Intern Med 2008; 168: 418.

[6] Yancy C.W., Jessup M., Bozkurt B., et al. "2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines". J Am Coll Cardiol 2013;62:e147-e239

Under IND 102191, the Applicant has a clinical development program in T2DM; safety data from the T2DM program were submitted in support of NDA 216203. (b) (4)
(b) (4)
(per review of last submitted Annual Report dated 04 February 2022).

3.1. Approach to the Review

This is a joint clinical and statistical review. Jordan Pomeroy and Ququan (Cherry) Liu focused on the data supporting efficacy reported from the SOLOIST and SCORED trials. Tejas Patel and Yanyan (Claire) Ji focused on the data supporting safety. Table 3Table 3 provides a list of the pivotal clinical trials submitted in support of efficacy and safety of sotagliflozin in the intended population.

Additionally, sotagliflozin has been evaluated in 30 clinical trials (22 Phase 1 trials, 5 Phase 2 trials, and 3 Phase 3 trials) in healthy volunteers and patients with T1DM or T2DM submitted under NDA 210934. Summary of FDA's review of NDA 210934 is included in the section above under brief regulatory history. Overall, sotagliflozin had been administered to over 12,011 subjects in clinical trials.

Table 3. Pivotal Clinical Trials Submitted in Support of Efficacy and Safety Determinations[1] for Sotagliflozin

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
EFC15156 SOLOIST (phase 3)	Hemodynamically stable adults (age ≥ 18 years) with T2DM with a history of heart failure (≥ 3 months prior to screening) treated with loop diuretics (≥30 days prior to index event). Index event is defined as an admission to the hospital or seen for an urgent HF visit in the ED or infusion center, for worsening HF and treated for intravascular volume overload with IV diuretics	Control Type: Placebo Randomization: Randomized 1:1 to sotagliflozin: placebo Blinding: Double-blind	Drug: Sotagliflozin/Placebo Dose: 200 mg titrated to 400 mg Number treated: 608/614 sotagliflozin/placebo Duration (quantity and units): median follow- up 235 days	Primary: Number of total occurrences of CV death, HHF and UVHF Secondary: 1. Total occurrence of HHF and UVHF 2. Time CV death 3. Total occurrence of CV death, HHF, non-fatal MI, and Non-fatal stroke 4. Total occurrence of HHF, UVHF, CV death and HF while hospitalized 5. Time to all-cause mortality 6. Change in KCCQ-12 scores from baseline to month 4 7. Change in eGFR after week 4 to end of study	Planned: 4000 Randomized: 1,222	322 investigational sites 32 countries
EFC14875 SCORED (Phase 3)	Adults with T2DM (HbA1c ≥ 7%), eGFR ≥ 25 to ≤ 60 mL/min/1.73m2 (MDRD) and either: 1. Age ≥ 18 years and at least one major CV risk factor^ or 2. Age ≥ 55 years with at least 2 minor CV risk factors*	Control Type: Placebo Randomization: Randomized 1:1 to Sotagliflozin: placebo Blinding: Double-blind	Drug: Sotagliflozin/Placebo Dose: 200 mg titrated to 400 mg Number treated: 5292/5292 sotagliflozin/placebo Duration (quantity and units): median follow- up 433 days	Primary: Number of total occurrences of CV death, HHF and UVHF Secondary: 1. Total occurrence of HHF and UVHF 2. Time CV death 3. Total occurrence of CV death, HHF, non-fatal MI, and Non-fatal stroke 4. Total occurrence of HHF, UVHF, CV death and HF while hospitalized 5. First occurrence of sustained ≥50% decrease in eGFR from baseline (for ≥30 days), chronic	Planned: 10,500 Randomized: 10,584	750 investigational sites 44 countries

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
				dialysis, renal transplant, or sustained eGFR<15 mL/min/1.73m2 (for ≥30 days) in the total patient population 6. All-cause mortality 7. Total occurrence of CV death, non-fatal MI, and non-fatal stroke.		

Source: Reviewer
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled"
Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HF, heart failure; HHF, hospitalization for heart failure; KCCQ-12, Kansas City cardiomyopathy questionnaire; MI, myocardial infarction; MDRD, Modification of Diet in Renal Disease; Type 2 Diabetes Mellitus, T2DM,
^The following were the major risk factor criteria: HHF during previous 2 years, EF ≤ 40%, Diagnosis LVH (electrocardiogram [ECG] or Echo), CAC score ≥ 300 Agaston Units, NT-proBNP ≥ 400 pg/mL (47 pmol/L), HsTnT >15.0 pg/mL (0.015 µg/L) for men and >10.0 pg/mL (0.010 µg/L) for women, hsCRP > 3 mg/L (28.6 nmol/L), UACR ≥300 mg/g (34 mg/mmol)
* The following are the minor risk factor criteria: BMI ≥35 kg/m2, dyslipidemia despite maximally-tolerated statin therapy (LDL cholesterol >130 mg/dL (>3.36 mmol/L) or HDL cholesterol <40 mg/dL (<1.03 mmol/L) for men or <50 mg/dL (<1.29 mmol/L) for women), currently smoking tobacco, CAC score >100 and <300 Agaston Units, UACR ≥30 mg/g and <300 mg/g (3 and 34 mg/mmol), SBP >140 mmHg and DBP >90 mmHg despite antihypertensive therapy at the Screening Visit, family history of premature coronary heart disease (defined as MI or coronary revascularization procedure) in a first degree relative - *In a male relative <55 years or in a female relative <65 years*

4. Patient Experience Data

The SOLOIST trial collected data on patient's perception of their HF symptoms at baseline and at various timepoints during the trial by using the Kansas City Cardiomyopathy Questionnaire (KCCQ-12) patient-reported outcome tool.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	Section 5.4.6
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	Not Applicable
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (but Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	Not Applicable
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Evidence of Benefit (Assessment of Efficacy)

5.1. Assessment of Dose and Potential Effectiveness

A full assessment of the data examining sotagliflozin dose and treatment effect is provided by the Clinical Pharmacology review discipline in a separate review document. In general, assessment of treatment effect as a function of dose is constrained by lack of independent treatment arms for sotagliflozin doses studied (200 mg and 400 mg), dose-titration design and that no exposure data were collected in the two phase 3 pivotal trials. Majority (74.4% sotagliflozin, 75.4% placebo) and greater than half (55.5% sotagliflozin, 53.3% placebo) of study subjects were successfully up titrated per protocol in SCORED and SOLOIST, respectively. Only a small minority of subjects in both trials (~5%) required down titration for investigational medical product intolerability. Given that we do not have sufficient data to stratify treatment effect by dose, we have provided guidance in Section 2 of the approved sotagliflozin USPI that recommends starting patients at sotagliflozin 200 mg with subsequent dose increase to sotagliflozin 400 mg in patients tolerating the 200 mg dosage. This recommendation follows the conduct of the SOLOIST and SCORED phase 3 pivotal trials. Furthermore, based on the conduct of SOLOIST, we will describe in Section 2 of the label that hemodynamically stable patients may start sotagliflozin while hospitalized.

5.2. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

5.2.1. Trial Design

The Applicant conducted two phase 3 trials in support of the proposed indications:

- SOLOIST (EFC15156) titled, “A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Effects of Sotagliflozin on Clinical Outcomes in Hemodynamically Stable Patients Post Worsening Heart Failure.” The first Global Clinical Study Protocol Version 1 dated 05 January 2018 was amended twice (Amended Protocol No 01, v1 dated 17 December 2018 and Amended Protocol No 02, v1 dated 10 December 2019). The protocol overview presented here is based on the Amended Protocol No 01, v1 and statistical analysis plan (SAP) version 1 dated 09 August 2020 (no subjects were enrolled under Amended Protocol No 02, v1). The study enrolled its first subject on 15 June 2018 and was terminated on 24 March 2020 for Applicant-reported business reasons.
- SCORED (EFC14875) titled, “A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Demonstrate the Effects of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes, Cardiovascular Risk Factors and Moderately Impaired Renal Function.” The first Global Clinical Study

Protocol Version 2 (after the first patient enrolled) dated 07 September 2017 was not globally amended. The protocol overview presented here is based on the protocol amendment Version 2 and SAP version 1, dated 21 August 2020. The study enrolled its first subject on 15 December 2017 and was terminated on 24 March 2020 for Applicant-reported business reasons.

SOLOIST and SCORED were randomized, placebo-controlled, parallel-group, multi-center, double-blind, trials comparing sotagliflozin to placebo in T2DM subjects. SOLOIST enrolled subjects with a history of HF who were hemodynamically stable after an admission to the hospital, urgent heart failure visit or emergency department/infusion center visit for worsening HF and requiring intravenous (IV) diuresis. SCORED enrolled subjects with eGFR≥25 to ≤60 mL/min/1.73 m^2 with either a major CV risk factor or age ≥55 years with at least 2 minor CV risk factors (as detailed in section 5.2.2).

Based on the original study plans, goal enrollment for SOLOIST was n=4000 (sotagliflozin n=2000, placebo n=2000) with study treatment intended to continue until achieving n=1341 positively adjudicated primary composite events in the total population and n=947 positively adjudicated events in trial subjects with LVEF <50%. Goal enrollment for SCORED was n= 10,500 (sotagliflozin n=5250, placebo n=5250) with study treatment intended to continue until achieving n=844 positively adjudicated CV death or HHF events and n=1189 positively adjudicated 3-point MACE events. However, given early termination of the studies for financial reasons and inability to capture the planned number of fully adjudicated clinical endpoints, the Applicant revised the final SAPs to a primary composite of total (first and recurrent) CV death, HHF and UHFV. With early termination, the SOLOIST study did not meet target randomized enrollment (sotagliflozin n=608, placebo n=614) or target primary composite events (n=355). Despite early termination, SCORED did achieve target randomized enrollment (sotagliflozin n=5292, placebo n=5292), but was shy of target primary composite events (n=530). Notably, the final SAPs shifted to investigator-reported events from a plan for positively adjudicated events for final statistical analysis.

Refer to Figure 11 and Figure 12 (Appendix 11) for study design schematics for SOLOIST and SCORED, respectively.

Randomization: In both trials, subjects were randomized to sotagliflozin or matching placebo in a 1:1 ratio. Randomization was stratified by region (North America, Latin America, Western Europe, Eastern Europe and rest of world). SOLOIST also stratified by screening LVEF (<50% and ≥ 50%). SCORED also stratified by HF-related criteria (when the patient met at least one of the following: left ventricular ejection fraction ≤40% in the past year, or HHF during the previous 2 years).

Study Drug Dosage: Sotagliflozin or matching placebo was to be taken in addition to regional standard of care HF therapies. Sotagliflozin was supplied as 200 mg tablets. Subjects took 1 tablet (200 mg) daily starting at randomization. After 2 weeks in SOLOIST and after 4 weeks in SCORED, the approved protocols instructed study site investigators to increase the dose to

400 mg of sotagliflozin or matching placebo should the investigator's opinion deem the study subject is in satisfactory clinical condition and tolerating the IMP.

Study Objectives: The primary objective was to demonstrate the effect of sotagliflozin comparing to placebo on the total occurrences (first and subsequent) of CV death, HHF, and UHFV in hemodynamically stable patients after admission for WHF in SOLOIST and in patients with T2DM, moderate-to-severe renal impairment, and other CV risk factors (≥1 major or ≥ 2 minor) in SCORED.

Study Endpoints:

Primary Efficacy Endpoint: The primary endpoint for both SOLOIST and SCORED was time to total occurrences (first and subsequent) of CV death, HHF, and UHFV after randomization of investigator reported.

Reviewer's Comment*: During a Type C Meeting (meeting minutes; 06 January 2021), the Division agreed in principle to the finalized SAPs which shifted from a time-to-event driven analysis of adjudicated events to a total of investigator-reported events for the primary composite endpoint of CV Death, HHF and UHFV. The SAPs (SOLOIST: 09 August 2020; SCORED: 21 August 2020) were finalized prior to data lock and unblinding (SOLOIST: 10 August 2020; SCORED: 26 August 2020). The individual components of the primary composite are widely accepted to represent clinically relevant indicators of major CV morbidity and mortality. Additionally, there is Agency and Division precedent for utilization of investigator-reported events in large cardiovascular outcomes trials (CVOTs) in which principal investigators are practicing cardiology specialists. I have provided analysis for concordance of positively adjudicated and investigator-reported events as a review issue in Section 5.4.4.*

The overall trial design and final enrollment characteristics of these two large, phase 3 CVOTs is adequate to generate data to support substantial evidence of effectiveness for the final labeled indications. Early termination of the trials for business decisions did not impact successful randomization, stratification or blinding and allowed for sufficient follow-up time to characterize the effect of sotagliflozin on the pre-specified primary composite endpoint.

Secondary Efficacy Endpoints:

SOLOIST trial:

- Time to total occurrences (first and subsequent) of HHF and UHFV
- Time to occurrence of CV death
- Time to total occurrences (first and subsequent) of CV death, HHF, non-fatal MI, and non-fatal stroke
- Time to total occurrences (first and subsequent) of HHF, UHFV, CV death, and HF while hospitalized
- Time to all-cause mortality
- Change in KCCQ-12 scores from baseline to Month 4

- Change in eGFR after Week 4 to the end of the study

SCORED trial:

- Time to total occurrences (first and subsequent) of HHF and UVHF
- Time to CV death
- Time to total occurrences (first and subsequent) of CV death, HHF, non-fatal MI, and non-fatal stroke
- Time to total occurrences (first and subsequent) of CV death, HHF, UHFV, and HF while hospitalized
- 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 m2 (for ≥30 days)
- Time to all-cause mortality
- Time to total occurrences (first and subsequent) of CV death, non-fatal MI, and non-fatal stroke (3-point MACE)

Safety Endpoints:

SOLOIST and SCORED trials:

- Adverse events (AEs): Include occurrence of AEs (including serious adverse events [SAEs], and AEs of special interest [AESIs])
- Laboratory safety: Include measures of hematology, clinical chemistry, renal function, liver function, and lipids
- Vital signs: Include weight, heart rate, and systolic and diastolic blood pressure in sitting position

Exploratory Endpoints:

SOLOIST trial:

- Occurrences of CV death, non-fatal MI, or non-fatal stroke (3-point MACE)
    - Total occurrences of composite 3-point MACE and contribution of individual components
    - Time-to-first occurrence of composite 3-point MACE and contribution of individual components
    - Occurrence of fatal and non-fatal MI
    - Occurrence of fatal and non-fatal stroke
- First occurrence of the composite renal endpoint 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)
- Days alive and out of the hospital

- Atrial fibrillation and flutter

SCORED trial:

- First occurrence of CV death, HHF, or UHFV
- First occurrence of CV death, HHF, UHFV, or hospitalization with HF
- Total occurrences of HHF
- First occurrence of CV death, HHF, non-fatal MI, or non-fatal stroke
- First occurrence of CV death, non-fatal MI, or non-fatal stroke
- First occurrence of MI (fatal and non-fatal)
- First occurrence of stroke (fatal and non-fatal)
- First occurrence of atrial fibrillation or flutter (AEs with preferred terms [PTs] of atrial fibrillation or atrial flutter)
- First occurrence of severe hypoglycemia (defined as symptomatic events requiring assistance by another person)
- Total occurrences of the following hypoglycemia categories:
    - Severe hypoglycemia
    - Hypoglycemia with documented glucose value <54 mg/dL
    - Hypoglycemia with documented glucose value <70 mg/dL
- First occurrence of the composite of sustained ≥40% decrease in eGFR from baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73m2 (for ≥30 days)
- First occurrence of the composite of sustained ≥30% decrease in eGFR from baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73m2 (for ≥30 days)
- Change in eGFR after Week 4 (mL/min/1.73m2) to the end of the study
- Days alive and out of hospital (DAOH) and percent DAOH (PDAOH)
- Changes from baseline in:
    - NT-proBNP in the overall population
    - NT-proBNP among those with baseline NT-proBNP ≥400 pg/ml
    - Hematocrit
    - HbA1c defined by baseline eGFR (<30, ≥30 to <45, ≥45 mL/min/1.73m2) in the overall population, and subgroups.
    - Body weight
    - Urinary albumin-to-creatinine ratio (UACR):
        - defined by baseline UACR (<30 [normal], ≥30 to 300 [microalbuminuria], ≥300 mg/g [macroalbuminuria]) in the overall population, and subgroups
        - defined by baseline eGFR (<30, ≥30 to <45, ≥45 mL/min/1.73m2) in subgroups
    - Systolic blood pressure (SBP) defined by baseline SBP (<130, ≥130; <140, ≥140 mm Hg) in the overall population, and subgroups.

Eligibility Criteria:

Key Inclusion Criteria for SOLOIST (EFC15156):

- Hemodynamically stable adults (age ≥18years) with an index HF event (index event is defined as an admission to the hospital or seen for an urgent HF visit in the emergency department (ED), HF unit or infusion center for worsening HF and treated for intravascular volume overload with IV diuretics)
- Diagnosis of T2DM (HbA1c ≥6.5% or fasting plasma glucose ≥126 mg/dL or random plasma glucose ≥200 mg/dL or documentation supportive of diagnosis at screening)
- History of HF (≥3 months prior to screening)
- Prior chronic treatment with loop diuretics ≥30 days prior to index HF event
- Patients with LVEF <40% should be on BB or renin-angiotensin-aldosterone system (RAAS) inhibitors per local guidelines unless contraindicated

Key Exclusion Criteria for SOLOIST (EFC15156):

- Age <18 years (or legal age for the country of participation) or >85 years at the screening visit
- Index HF event primarily triggered by pulmonary embolism, cerebrovascular accident or acute MI
- Index HF event not caused primarily by intravascular volume overload, but rather arrhythmia, infection, severe anemia or chronic obstructive pulmonary disease
- Hospitalization for Index HF Event >2 weeks
- Acute coronary syndrome within 3 months prior to Randomization
- End-stage HF defined as requiring left ventricular assist device (LVAD), intra-aortic balloon pump or any type of mechanical circulatory support at the time of Randomization
- History of dialysis within 1 year prior to Randomization
- Any SGLT2i <1 month prior to Screening Visit or between Screening and Randomization
- History of DKA or nonketotic hyperosmolar coma within 3 months prior to the Screening Visit
- Severe renal disease as defined by eGFR <30 mL/min/1.73m^2

Key Inclusion Criteria for SCORED (EFC14875):

- Adults with T2DM (HbA1c ≥7% at screening) and CKD (eGFR ≥25 to ≤60 mL/min/1.73m2 (MDRD) at screening) and either:

    1. Age ≥18 years old and at least one *major CV risk factor*
    -or-
    2. Age ≥55 years old with at least two *minor CV risk factors*

Major CV risk factors: HHF during previous 2 years, EF ≤ 40%, left ventricular hypertrophy (diagnosed by ECG or Echo), CAC score ≥ 300 Agaston Units, NT-proBNP ≥ 400 pg/mL (47 pmol/L), HsTnT >15.0 pg/mL (0.015 μg/L) for men and >10.0 pg/mL (0.010 μg/L) for women, hsCRP > 3 mg/L (28.6 nmol/L), UACR ≥300 mg/g (34 mg/mmol)

Minor CV risk factors: Body mass index (BMI) ≥35 kg/m^2, dyslipidemia despite maximally-tolerated statin therapy (LDL cholesterol >130 mg/dL (>3.36 mmol/L) or HDL cholesterol <40 mg/dL (<1.03 mmol/L) for men or <50 mg/dL (<1.29 mmol/L) for women), currently smoking tobacco, CAC score >100 and <300 Agaston Units, UACR ≥30 mg/g and <300 mg/g (3 and 34 mg/mmol), SBP >140 mmHg and DBP >90 mmHg despite antihypertensive therapy at the Screening Visit, family history of premature coronary heart disease (defined as MI or coronary revascularization procedure) in a first degree relative - *In a male relative <55 years or in a female relative <65 years*

Key Exclusion Criteria for SCORED (EFC14875):

- History of DKA or nonketotic hyperosmolar coma within 3 months prior to the Screening Visit
- Any SGLT2i <1 month prior to Screening Visit or between Screening and Randomization
- End-stage HF defined as requiring left ventricular assist device (LVAD), intra-aortic balloon pump or any type of mechanical circulatory support at the time of Randomization
- History of dialysis within 1 year prior to Randomization

Protocol and Statistical Analysis Plan Amendments: Described in Appendix (III.10.1)

Recommended Source Documents for Primary Composite Endpoint: Described in Appendix (III.10.2)

Primary Composite Endpoint Adjudication Criteria: Described in Appendix (III.10.3)

5.2.2. Statistical Analysis Plan

Analysis Data Set

All efficacy analyses were performed based on the intention-to-treat (ITT) population that included events occurring, for a given patient, from the date of randomization to their date last known alive, including events that occurred after the patient had discontinued treatment.

Statistical Analysis

Statistical analysis method (SOLOIST and SCORED):

- Primary efficacy analysis: A marginal Cox proportional hazard model using Fine and Gray method was used to derive the estimates of the hazard ratio (HR) and corresponding 2-sided 95% confidence interval (CI), stratified by region and LVEF, with non-cardiovascular (non-CV) death treated as a competing event. By using a robust sandwich covariance matrix estimate, the model allowed for the possibility of multiple events within a given patient. If a given patient had more than one event on a given day, the event times were varied by 0.1 day so that every event time was unique.

  A Wald test was used to compare the number of total occurrences (first and potentially subsequent) of events of CV death, HHF, and urgent HF between the two treatment groups stratified by region (North America, Latin America, Western Europe, Eastern Europe, and rest of world) and LVEF (<50%, ≥50%) in SOLOIST trial; and stratified by region (North America, Latin America, Western Europe, Eastern Europe, and rest of world) and HF-related criteria (yes/no) in SCORED trial. The primary comparison was conducted at 2-sided 0.05 significance level.

  Deaths not included among the events in the endpoint were treated as competing events. Patients alive at the end of the study were right censored on the date they were last known to be alive.

- Secondary efficacy analysis:

SOLOIST trial

- Time-to-event secondary efficacy endpoints were analyzed using the same statistical methodology as for the primary endpoint. Deaths that were not part of a given endpoint were treated as competing events.
- Change in KCCQ-12 scores from baseline to Month 4 was analyzed by analysis of covariance (ANCOVA) with treatment group as factor and baseline KCCQ-12 score and randomization stratification factors as covariates.
- The rate of decline in eGFR was analyzed by repeated measures mixed effects models with absolute change in eGFR from baseline as the outcome, a random effect for intercept, and fixed effects for treatment, baseline value, and time.

SCORED trial

- Time-to-event secondary efficacy endpoints were analyzed using the same statistical methodology as for the primary endpoint. Deaths that are not part of a given endpoint will be treated as competing events for and.

Sensitivity and supportive analysis: The following sensitivity analyses of primary efficacy were performed in both trials:

- An on-treatment analysis was performed for the primary endpoint including events through 30 days or through 7 days after last dose.

- The primary analysis of the primary endpoints was repeated by including only events from randomization to last IMP administration date + 30 days or patient's last study visit date/planned study close-out visit, whichever was earlier. For patient not having a primary endpoint during this period, the patient was right censored at the earlier date of last IMP administration date + 30 days.
- The primary analysis of the primary endpoints was repeated using the ITT analysis set, by excluding deaths adjudicated as undetermined cause of death by the CEC.
- The primary analysis was repeated using the actual stratification of HF related criteria based on the electronic Case Report Form (eCRF) if discrepancy in stratum assignment between Interactive Response Technology (IRT) and eCRF occurred in more than 5% of patients.
- The primary endpoint was analyzed censoring patients at the earlier date of start of SGLT-2 inhibitor if a treatment imbalance in patients starting an SGLT-2 inhibitor occurred in more than 5% of patients.

Subgroup analysis: The analysis of primary endpoint was conducted in the following subgroups:

SOLOIST trial:

- LVEF in two categories (<50%, ≥50%)
- LVEF in three categories (<40%, ≥40% <50%, ≥50%)
- Region in three categories (The Americas, Europe, Rest of the world)
- Age (<65, ≥65 years)
- Gender (male, female)
- Race/ethnicity (white, black, Hispanic, Asian, other)
- Baseline eGFR (<60 mL/min/1.73m2, ≥60 mL/min/1.73m^2)
- Baseline BMI (<30, ≥30 kg/m^2)
- New York Heart Association (NYHA) Class (II, III, IV)
- NT-proBNP (≤Median, >Median)
- MRA at Baseline
- Glucagon-like peptide-1 (GLP-1) receptor agonist at Baseline
- Sacubitril-valsartan at Baseline
- ICD/CRT at Baseline
- Insulin at Baseline
- Atrial fibrillation or flutter at Baseline
- LVH at Baseline
- Main cause of HF (ischemic vs. non-ischemic or unknown)
- Start of first IMP dose prior to vs. after hospital discharge (or urgent care facility where appropriate)

SCORED trial:

- Presence/absence of HF-related criteria: HF-related criteria are present when a patient meets at least 1 of: EF ≤40% documented within the past year, or hospitalization for HF during the previous 2 years
- LVEF in two categories (<50%, ≥50%)
- LVEF in three categories (<40%, ≥40% <50%, ≥50%)
- LVEF in two categories (<50%, ≥50%) among those with HF-related criteria
- LVEF in three categories (<40%, ≥40% <50%, ≥50%) among those with HF-related criteria
- Presence/absence of major CV risk factor
- History of CVD (defined as MI, stroke, coronary revascularization, or peripheral vascular disease)
- Region (North America, Latin America, Europe, Rest of the world)
- Age (<65, ≥65 years)
- Gender (male, female)
- Race/ethnicity (Asian, Black or African American, White, Hispanic, other)
- Baseline eGFR (<30, ≥30 to <45, ≥45 to <60 mL/min/1.73m^2)
- Baseline category of UACR (<30, ≥30 mg/g)
- Baseline BMI group (<30, ≥30 kg/m^2)
- NT-proBNP (≤Median, >Median)
- MRA at Baseline (among those with HF-related criteria)
- GLP-1 receptor agonist at Baseline
- Sacubitril-valsartan at Baseline (among those with HF-related criteria)
- ICD/CRT at Baseline
- Insulin at Baseline
- Atrial fibrillation or flutter at Baseline
- LVH at Baseline
- Main cause of HF (ischemic vs. non-ischemic or unknown)

Handling of missing data:

- In the original SAP (08 July 2019), the following censoring rules were specified: Patients were right-censored if they had not experienced any positively adjudicated component of the primary composite CV events on or before the patient's last study visit date/planned study close-out visit. The censoring date was defined as follows:
  - Patients who completed the study were censored at their last visit date (study close-out or final follow-up visit). Patients who died without discontinuing the study before death (i.e., death reported on the Completion of End of Study form) were censored at their date of non-CV death.
  - Patients who discontinued the study were censored at their later of study discontinuation date or latest date with potential CV efficacy endpoint information (MI/UA, HF, cerebrovascular event, admission to hospital/emergency room, coronary

procedure or cardiac markers) collected.

- Missing or incomplete dates: In both trials, if the onset dates of time-to-event endpoints was missing (complete or partial), the partial missing onset date was imputed by using the following algorithm:
  - If only month of the event was known, then the 15th day of this month was imputed for a missing day and year of the start date was imputed as the year
  - If only the year of the event was known, then 1st of July was imputed for the missing day and month
  - If the resulting imputed dates were prior to the randomization date, imputed date was reset to the randomization date.
  - For non-death event, no imputation was made for completely missing date.
  - For death, the impute date was the latest of all imputed event dates and patient's last trial contact date.
- Change in KCCQ-12 scores: In SOLOIST trial, the last available post-baseline score was carried forward to Month 4 if the patient was alive at Month 4, but the Month 4 value was missing; and a worst score (0) was imputed for the clinical summary score at all subsequent scheduled visits after the date of death.

Multiplicity:

In both trials, a sequential inferential approach was used to control the overall type I error rate of 0.05. If a success of primary endpoint was achieved at the 0.05 2-sided alpha level, the secondary endpoints were tested hierarchically in the following order at the 2-sided 0.05 alpha level:

SOLOIST trial:

- Time to total occurrences (first and subsequent) of HHF and urgent HF visits
- Time from randomization to occurrence of CV death
- Time to total occurrences (first and subsequent) of CV death, HHF, non-fatal MI, and non-fatal stroke
- Time to total occurrences (first and subsequent) of HHF, urgent HF visit, CV death, and HF while hospitalized
- Time from randomization to all-cause mortality
- Change in KCCQ-12 scores from baseline to Month 4
- Rate of decline in eGFR after Week 4 (mL/min/1.73m2/year) to the end of the study

SCORED trial:

- Time to total occurrences of HHF and urgent HF visits after randomization
- Time to occurrence of CV death after randomization
- Time to total occurrences of CV death, HHF, non-fatal stroke, and non-fatal MI
- Time to total occurrences of CV death, HHF, urgent HF visit, and HF while hospitalized

- 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/1.73m^2 (for ≥30 days) in the total patient population
- Time to occurrence of all-cause mortality after randomization
- Time to total occurrences of CV death, non-fatal stroke, and non-fatal MI

5.3. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients

Patient Screening and Randomization
In SOLOIST, 1549 subjects were screened and 1222 were randomized. In SCORED, 19191 subjects were screened and 10584 were randomized (Table 5).

Table 5. Patient Screening and Randomization

Disposition	SOLOIST	SCORED
No. patients screened	1549	19191
No. of screening failures (%)	327 (21.1)	8604 (44.8)
No. of patients randomized	1222	10584

Source: Table 14.1.1.2 CSR, SOLOIST & SCORED

Disposition of patients
In SOLOIST trial, 1549 subjects were screened and 327 (21.1%) failed at screening. In SCORED trial, 19191 subjects were screened and 8604 (44.8%) failed at screening. The most common reasons for screening failures included:
SOLOIST

1) Unmet lab criteria as defined by:
   - BNP >=150 pg/mL or N-terminal B-type natriuretic peptide >=600 pg/mL between admission for the index event and randomization (5.5%)
   - ALT or AST >3 times the upper limit of normal (ULN), total bilirubin >1.7 times the ULN (except in case of Gilbert's syndrome), serum potassium >5.5 mEq/L) before randomization (1.2%)
2) Diagnosis of severe kidney disease as defined by eGFR <30 mL/min/1.73 m^2 at the screening (1.1%)

SCORED

1) Unmet lab criteria as defined by:
   - eGFR greater than or equal to 25 mL/min/1.73 m^2 and less than or equal to 60 mL/min/1.73 m^2 (27.7%)
   - HbA1c greater than or equal to 7% (53 mmol/mol) at screening (12.9%)
2) Presence of any other conditions (e.g., geographic, social) actual or anticipated, that the Investigator feels would restrict or limit the patient's participation for the duration of the study (2.1%)

The enrolled subjects were randomized 1:1 to receive sotagliflozin or placebo. In SOLOIST trial, 608 subjects were randomized to the sotagliflozin group and 614 to the placebo group (Table 6). In SCORED trial, 5292 subjects were randomized to the sotagliflozin group and 5292 to the placebo group (Table 7). Of the total subjects randomized, 6 patients (0.5%, 3 in each treatment group) in SOLOIST, and 7 patients (<0.1%, 6 in the placebo group and 1 in the sotagliflozin group) in SCORED were not treated. The major reasons for treatment discontinuation included:

- Early study termination by Applicant: 78.3% in SOLOIST (76.9% and 79.8% for the sotagliflozin and placebo groups, respectively); and 86.6% in SCORED (87.0% and 86.1% for the sotagliflozin and placebo groups, respectively).
- Death: 7.0% in SOLOIST (6.7% and 7.3% for the sotagliflozin and placebo groups, respectively); and 2.4% in SCORED (2.2% and 2.6% for the sotagliflozin and placebo groups, respectively).
- AE: 5.5% in SOLOIST (5.6% and 5.4% for the sotagliflozin and placebo groups, respectively); and 4.7% in SCORED (5.0% and 4.5% for the sotagliflozin and placebo groups, respectively).
- Withdrawal by patient: 6.3% in SOLOIST (5.4% and 7.2% for the sotagliflozin and placebo groups, respectively); and 4.6% in SCORED (4.4% and 4.8% for the sotagliflozin and placebo groups, respectively).

Table 6. Patient Disposition – ITT Population, SOLOIST

	Sotagliflozin N (%)	**Placebo N (%)**	**Total N (%)**
Randomized	608	614	1222
Randomized but not treated	3 (0.5)	3 (0.5)	6 (0.5)
Study treatment discontinued	605 (99.5)	611 (99.5)	1216 (99.5)
Reason for treatment discontinuation			
Study prematurely terminated by Sponsor (Including site terminated by sponsor)	485 (79.8)	472 (76.9)	957 (78.3)
Death	41 (6.6)	45 (7.3)	86 (7.0)
Withdrawal by patient	33 (5.4)	44 (7.2)	77 (6.3)
Adverse event	34 (5.6)	33 (5.4)	67 (5.5)
Physician decision	7 (1.2)	13 (2.1)	20 (1.6)
Progressive disease	2 (0.3)	3 (0.5)	5 (0.4)
Lost to follow-up	3 (0.5)	1 (0.2)	4 (0.3)
Study follow-up discontinued	608 (100)	614 (100)	1222 (100)

	Sotagliflozin N (%)	Placebo N (%)	Total N (%)
Reason for study discontinuation			
Study terminated by Sponsor (Including site terminated by sponsor)	522 (85.9)	509 (82.9)	1031 (84.4))
Death	65 (10.7)	76 (12.4)	141 (11.5)
Withdrawal by patient	18 (3.0)	22 (3.6)	40 (3.3)
Lost to follow-up	3 (1.0)	6 (1.0)	9 (0.7)
Physician decision	0	1 (0.2)	1 (0.1)

Source: Statistical reviewer analysis and Table 2, CSR-Addendum 1

Table 7. Patient Disposition – ITT Population, SCORED

	Sotagliflozin N (%)	Placebo N (%)	Total N (%)
Randomized	5292	5292	10584
Randomized but not treated	1 (<0.1)	6 (0.1)	7 (<0.1)
Study treatment discontinued	5291 (>99.9)	5286 (99.9)	10577 (>99.9)
Reason for treatment discontinuation			
Study prematurely terminated by Sponsor (Including site terminated by Sponsor)	4604 (87.0)	4557 (86.1)	9161 (86.6)
Adverse event	264 (5.0)	238 (4.5)	502 (4.7)
Withdrawal by patient	233 (4.4)	255 (4.8)	488 (4.6)
Death	114 (2.2)	139 (2.6)	253 (2.4)
Physician decision	52 (1.0)	45 (0.9)	97 (0.9)
Progressive disease	16 (0.3)	29 (0.5)	45 (0.4)
Lost to follow-up	5 (<0.1)	18 (0.3)	23 (0.2)
Other	3 (<0.1)	5 (<0.1)	8 (<0.1)
Study follow-up discontinued	5292	5292	10584
Reason for study discontinuation			
Study terminated by Sponsor (Including site terminated by	4968 (93.9)	4938 (93.3)	9906 (93.6)

	Sotagliflozin N (%)	Placebo N (%)	Total N (%)
Sponsor)			
Death	246 (4.6)	246 (4.6)	492 (4.6)
Withdrawal by patient	56 (1.1)	70 (1.3)	126 (1.2)
Lost to follow-up	19 (0.4)	30 (0.6)	49 (0.5)
Adverse event	1 (<0.1)	5 (<0.1)	6 (<0.1)
Other	1 (<0.1)	1 (<0.1)	2 (<0.1)
Physician decision	1 (<0.1)	1 (<0.1)	2 (<0.1)
Missing	0	1 (<0.1	1 (<0.1)

Source: Statistical reviewer analysis and Table 2, CSR-Addendum-1

Reviewer's Comment: *In the resubmission (NDA 216203/SN0021, dated 27 May,2022), the Applicant provided the following clarifications/information to address the issue of the discrepancy on patient disposition in the original submission (NDA 216203/SN0001, dated 15 December 2021):*

- *Reevaluation of patient disposition: For treatment discontinuation and study termination disposition, the category of "other" that was used in the original CSR was updated with more specific reasons as the followings:*

  In SOLOIST trial, there were 14 subjects listed in "other' category in the original submission and updated with specific reasons in the re-submission:

  - *Withdrawal by patient: n=2*
  - *Physician decision: n=3*
  - *Adverse event: n=4*
  - *Progressive disease: n=1*
  - *Lost to follow-up: n=4*

  In SCORED, there were 100 subjects listed in "other' category in the original submission and updated with specific reasons in the re-submission:

  - *Study/Site terminated by sponsor: n=9*
  - *Death: n=3*
  - *Withdrawal by patient: n=45*
  - *Physician decision: n=6*
  - *Adverse event: n=14*
  - *Lost to follow-up: n=23*

- *Death disposition: All deaths were captured correctly for the original CSR; however, the study disposition reasons should have had "death" listed as the' reason for study discontinuation. It resulted in 3 more deaths added in SOLOIST and 7 more deaths added in SCORED in the re-submission.*
- *Vital status follow-up: Details were provided to clarify the procedures used to determine the vital status of patients after the study was terminated early:*
  1) *In the informed consent form, clear statement was provided to allow for follow-up even if treatment was stopped.*
  2) *Study sites were contacted and asked to check with internal sources to see if the patients who were listed as lost to follow-up were seen by their practice or their institution since study close-out or if they have been in further contact with the patient or patient's relatives.*

The clarifications appear reasonable.

Patient baseline demographic and characteristics

In both trials, majority of patient baseline demographic and characteristics were generally balanced between treatment groups. The patient populations in both trials were similar in age (median of 69 years old), baseline BMI (median of 31 kg/m^2), baseline SBP (median of 124 mmHg) and baseline DBP (median of 73 mmHg). There were more male (>50%) and white (>82%) patients. The patient population in SOLOIST trial appeared sicker than in SCORED trial, including majority patients with baseline LVEF <50% (79% in SOLOIST and 20% in SCORED) and HF (100% in SOLOIST and 31% in SCORED) (Table 8 & Table 9).

Table 8. Baseline Demographic and Clinical Characteristics, ITT Population, SOLOIST

	Placebo (N=614)	**Sotagliflozin (N=608)**	**Overall (N=1222)**
Age (years)			
Mean [standard deviation (SD)]	69.3 (8.8)	68.6 (9.5)	68.9 (9.2)
Median	70.0	69.0	70.0
Age group (years) [n (%)]			
<55	39 (6.4)	48 (7.9)	87 (7.1)
≥55 to <65	132 (21.5)	145 (23.8)	277 (22.7)
≥65 to <75	251 (40.9)	241 (39.6)	492 (40.3)
≥75	192 (31.3)	174 (28.6)	366 (30.0)
Gender [n (%)]			
Sex [n (%)]			
Male	400 (65.1)	410 (67.4)	810 (66.3)

	Placebo (N=614)	Sotagliflozin (N=608)	Overall (N=1222)
Female	214 (34.9)	198 (32.6)	412 (33.7)
Race [n (%)]			
White	572 (93.2)	567 (93.3)	1139 (93.2)
Black or African American	25 (4.1)	25 (4.1)	50 (4.1)
Asian	7 (1.1)	8 (1.3)	15 (1.2)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	3 (0.5)	1 (0.2)	4 (0.3)
Multiple	1 (0.2)	1 (0.2)	2 (0.2)
Not Reported	5 (0.8)	6 (1.0)	11 (0.9)
Unknown	1 (0.2)	0	1 (<0.1)
Randomization strata of Baseline LVEF [n (%)]			
<50%	485 (79.0)	481 (79.1)	966 (79.1)
≥50%	129 (21.0)	127 (20.9)	256 (20.9)
Randomization strata of region [n (%)]			
North America	41 (6.7)	39 (6.4)	80 (6.5)
Latin America	134 (21.8)	132 (21.7)	266 (21.8)
Western Europe	155 (25.2)	155 (25.5)	310 (25.4)
Eastern Europe	246 (40.1)	244 (40.1)	490 (40.1)
Rest of World	38 (6.2)	38 (6.3)	76 (6.2)
Baseline BMI (kg/m^2)			
Mean (SD)	31.5 (6.3)	30.9 (6.1)	31.2 (6.2)
Median	31.1	30.4	30.8
Baseline SBP (mmHg)			
Mean (SD)	123.9 (15.4)	124.6 (16.1)	124.2 (15.7)
Median	122.0	122.0	122.0
Baseline DBP (mmHg)			
Mean (SD)	73.3 (10.1)	73.0 (10.2)	73.1 (10.1)

	Placebo (N=614)	Sotagliflozin (N=608)	Overall (N=1222)
Median	72.8	72.0	72.5
Duration of diabetes (years)			
Mean (SD)	11.9 (8.9)	11.7 (8.0)	11.8 (8.9)
Baseline HbA1c (%)			
Mean (SD)	7.6 (1.7)	7.6 (1.6)	7.6 (1.6)
Baseline HbA1c (%) categories [n (%)]			
<7.0	265 (43.2)	251 (41.3)	516 (42.2)
≥7.0 to <8.0	152 (24.8)	138 (22.7)	290 (23.7)
≥8.0	175 (28.5)	182 (29.9)	357 (29.2)
Baseline eGFR (mL/min/1.73 m^2)			
Mean (SD)	53.9 (18.6)	52.46 (18.6)	53.2 (18.6)
Median	50.7	49.1	49.7
Baseline eGFR categories (mL/min/1.73m^2) [n (%)]			
<60	403 (65.6)	426 (70.1)	829 (67.8)
≥60	194 (31.6)	160 (26.3)	354 (29.0)
LVEF at Screening (%)			
Mean (SD)	37.1 (13.21)	37.8 (13.50)	37.4 (13.35)
Median	35.0	35.5	35.0
LVEF at Screening (%) [n (%)]			
Overall	612 (99.7)	608 (100))	1220 (99.8)
<50	479 (78.0)	476 (78.3)	955 (78.2)
≥50	133 (21.7)	132 (21.7)	265 (21.7)
Baseline NT-proBNP (pg/mL)			
Mean (SD)	3259.8 (5063.0)	3059.1 (3680.6)	3160.6 (4433.4)
Median	1756.0	1830.1	1805.7
Duration of heart failure (years)			
Mean (SD)	6.4 (6.4)	5.9 (5.6)	6.2 (6.0)

	Placebo (N=614)	Sotagliflozin (N=608)	Overall (N=1222)
Median	4.6	4.2	4.4
Main cause of heart failure [(n, (%)]			
Ischemic	359 (58.5)	353 (58.1)	712 (58.3)
Non-ischemic	250 (40.7)	253 (41.6)	503 (41.2)

Source: Tables 6 & 8 in CSR, verified by statistical reviewer

Table 9. Baseline Demographic and Clinical Characteristics, ITT Population, SCORED

	Placebo (N=5292)	Sotagliflozin (N=5292)	Overall (N=10584)
Age (years)			
Mean (SD)	68.2 (8.4)	68.4 (8.4)	68.3 (8.4)
Median	69.0	69.0	69.0
Age group (years) [n (%)]			
<55	312 (5.9)	309 (5.8)	621 (5.9)
≥55 to <65	1330 (25.1)	1273 (24.1)	2603 (24.6)
≥65 to <75	2440 (46.1)	2470 (46.7)	4910 (46.4)
≥75	1210 (22.9)	1240 (23.4)	2450 (23.1)
Sex [n (%)]			
Male	2885 (54.5)	2945 (55.7)	5830 (55.1)
Female	2407 (45.5)	2347 (44.3)	4754 (44.9)
Race [n (%)]			
Number	5285	5289	10574
White	4329 (81.8)	4383 (82.8)	8712 (82.3)
Black or African American	187 (3.5)	176 (3.3)	363 (3.4)
Asian	365 (6.9)	317 (6.0)	682 (6.4)
American Indian or Alaska Native	216 (4.1)	205 (3.9)	421 (4.0)
Native Hawaiian or Other Pacific Islander	15 (0.3)	25 (0.5)	40 (0.4)
Multiple	114 (2.2)	129 (2.4)	243 (2.3)
Not Reported	27 (0.5)	29 (0.5)	56 (0.5)

	Placebo (N=5292)	Sotagliflozin (N=5292)	Overall (N=10584)
Unknown	32 (0.6)	25 (0.5)	57 (0.5)
Randomization strata of HF criteria [n (%)]			
Yes	1054 (19.9)	1054 (19.9)	2108 (19.9)
No	4238 (80.1)	4238 (80.1)	8476 (80.1)
Randomization strata of region [n (%)]			
North America	747 (14.1)	746 (14.1)	1493 (14.1)
Latin America	1586 (30.0)	1586 (30.0)	3172 (30.0)
Western Europe	709 (13.4)	711 (13.4)	1420 (13.4)
Eastern Europe	1613 (30.5)	1613 (30.5)	3226 (30.5)
Rest of World	637 (12.0)	636 (12.0)	1273 (12.0)
Baseline BMI (kg/m^2)			
Mean (SD)	32.44 (6.3)	32.58 (6.3)	32.51 (6.3)
Median	31.7	31.9	31.8
Baseline SBP (mm Hg)			
Mean (SD)	137.7 (16.7)	137.85 (16.7)	137.8 (16.7)
Median	139.0	138.0	138.0
Baseline DBP (mm Hg)			
Mean (SD)	77.35 (10.8)	77.16 (10.9)	77.25 (10.9)
Median	78.0	78.0	78.0
Duration of diabetes (years)			
Mean (SD)	17.0 (9.0)	17.2 (9.0)	17.1 (9.0)
Median	16.2	16.6	16.4
Baseline HbA1c (%)			
Mean (SD)	8.7 (1.4)	8.7 (1.5)	8.7 (1.5)
Median	8.3	8.3	8.3
Baseline eGFR (mL/min/1.73 m^2)			

	Placebo (N=5292)	Sotagliflozin (N=5292)	Overall (N=10584)
Mean (SD)	44.3 (9.5)	44.1 (9.6)	44.2 (9.5)
Median	44.7	44.4	44.5
Baseline eGFR categories (mL/min/1.73m^2) [n (%)]			
<30	393 (7.4)	418 (7.9)	811 (7.7)
≥30 to <45	2308 (43.6)	2347 (44.3)	4655 (44.0)
≥45	2590 (48.9)	2526 (47.7)	5116 (48.3)
Baseline UACR (mg/g)			
Mean (SD)	650.0 (1466.8)	610.6 (1319.4)	630.3 (1395.2)
Median	84.1	79.5	81.8
LVEF at Screening (%)			
Mean (SD)	56.8 (11.7)	56.8 (11.4)	56.8 (11.6)
Median	60.0	60.0	60.0
LVEF at Screening (%) [n (%)]			
Overall	5279 (99.8)	5286 (99.9)	10565 (99.8)
<40	528 (10.0)	505 (9.5)	1033 (9.8)
≥40 to <50	555 (10.5)	572 (10.8)	1127 (10.6)
≥50	4203 (79.4)	4202 (79.4)	8405 (79.4)
Baseline NT-proBNP (pg/mL)			
Mean (SD)	715.0 (1683.1)	694.0 (1529.8)	704.5 (1608.2)
Median	242.0	238.0	239.5

Source: Tables 6 & 8 in CSR, verified by statistical reviewer

Efficacy

Primary endpoint analysis: In both trials, the results showed that sotagliflozin was superior to placebo in reducing the risk of the primary composite endpoint (HR [95% CI]: 0.67 [0.53, 0.85], p=0.001 SOLOIST; 0.75 [0.63, 0.88], p = 0.0004 SCORED). The primary endpoint event rate was statistically significantly lower in the sotagliflozin group compared with the placebo group (51.3 and 76.4 events per 100 patient-years for the sotagliflozin and placebo groups, respectively

SOLOIST; 5.6 and 7.5 events per 100 patient-years for the sotagliflozin and placebo groups, respectively SCORED (Table 10 & Table 11).
Although all components positively contributed to the overall results in favor of sotagliflozin, the primary efficacy appeared to be driven by a large effect on HHF (HR [95% CI]: 0.65 [0.49, 0.87], SOLOIST; 0.66 [0.53, 0.82], SCORED).

Table 10. Primary Composite Efficacy Endpoint and Individual Components (Investigator-Reported) – ITT Population, SOLOIST

Investigator-reported Endpoints	Placebo N=614			Sotagliflozin N=608			Hazard Ratio (95% CI)	p-value
	Total No. of Events	No. Patients with Events	Events per 100 PY	Total No. of Events	No. Patients with Events	Events per 100 PY		
Total Occurrences of CV Death, HHF or UVHF	355	194	76.4	245	142	51.3	0.67(0.53,0.85)	0.001
HHF	241	137	51.9	161	99	33.7	0.65 (0.49, 0.87)	
UVHF	56	41	12.1	33	24	6.9	0.60 (0.34, 1.06)	
CV Death [a]	58	58	9.4	51	51	8.4	0.84 (0.58, 1.23)	

CI = confidence interval; CV = cardiovascular; HHF = hospitalization for heart failure; No. = number; PY = patient-years; UVHF = urgent visit for heart failure.

[a] Time-to-Event Analysis; results are number of patients with an event (percentage of patients with an event).

Source: Table 14 CSR, verified by statistical reviewer.

Table 11. Primary Composite Efficacy Endpoint and Individual Components (Investigator-Reported) – ITT Population, SCORED

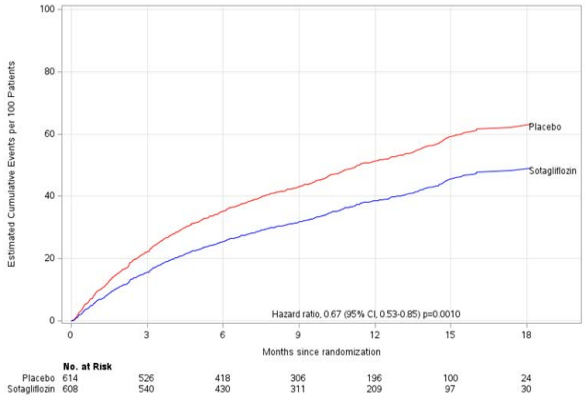
Investigator-Reported Endpoints	Placebo N=5292			Sotagliflozin N=5292			Hazard Ratio (95% CI)	p-value
	Total No. of Events	No. Patients with Events	Events per 100 PY	Total No. of Events	No. Patients with Events	Events per 100 PY		
Total Occurrences of CV Death, HHF or UVHF	530	391	7.5	400	310	5.6	0.75 (0.63, 0.88)	0.0004
HHF	296	225	4.2	198	158	2.8	0.66 (0.53, 0.82)	
UVHF	64	54	0.9	47	43	0.7	0.73 (0.48, 1.11)	
CV Death [a]	170	170	3.2[a]	155	155	2.9[a]	0.903 (0.727, 1.122)	

CI = confidence interval; CV = cardiovascular; HHF = hospitalization for heart failure; ITT = intent-to-treat; No = number; PY = patient-years; UVHF = urgent visit for heart failure.
[a] Time-to-event analysis; results are number of patients with an event (percentage of patients with an event)
Source: Table 16 CSR, verified by statistical reviewer

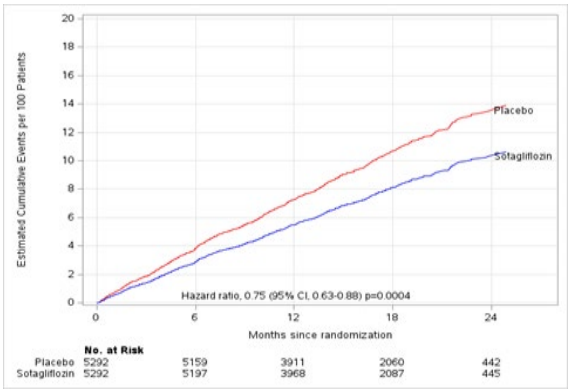
The cumulative event plot of the primary endpoint showed that the sotagliflozin and placebo event curves separated early. (Figure 1).

Figure 1. Total Number of Occurrences of Primary Composite Outcomes Versus Time (Investigator-Reported) – ITT Population, SOLOIST and SCORED

SOLOIST



SCORED

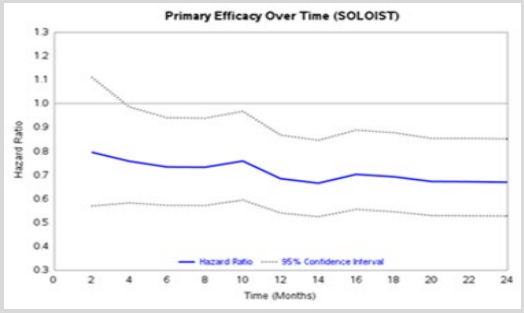


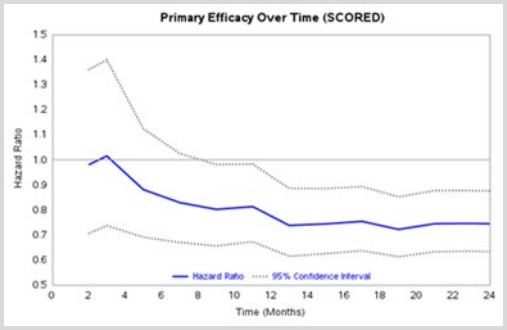
Source: Statistical reviewer analysis

Reviewer's Comment:

1. *History: The first randomized patient enrolled was on 15 June 2018 in SOLOIST and 19 December 2017 in SCORED. Both trials were terminated on 24 March 2020 for applicant-reported business reasons (a decision based principally on the financial burden of the study). The End-of-Trial (EOT) visits were performed by 15 June 2020, with Safety Follow-up visits to be conducted 2 weeks later (no later than 30 June 2020). The last Safety Follow-up visit was performed on 08 July 2020. The data lock was completed on 10 August 2020 for SOLOIST and 26 Aug 2020 for SCORED. At the time of SOLOIST study termination, patients had achieved a median follow-up duration of approximately 9.0 months (interquartile range approximately 4.9 to 13.4 months); and a median follow-up duration of approximately 16.0 months (interquartile range approximately 12.0 to 20.3 months) for SCORED.*
2. *This reviewer conducted additional analyses:*
   a. *To check the proportional hazard assumption for the Fine–Gray model: An analysis was conducted by including the interaction of time by treatment. The results of a non-significant interaction (p=0.9583, p=0.6003 for SOLOIST and SCORED, respectively) suggested that the proportional hazard assumption was held.*
   b. *To assess the trend of treatment effect: The treatment benefit seemed to start early, approximately at 4 months in SOLOIST and 8 months in SCORED, and was maintained through the study periods in both trials (Figure 2)*

Figure 2. Hazard Ratio for Primary Composite Outcome Versus Time (Investigator-Reported), SOLOIST and SCORED



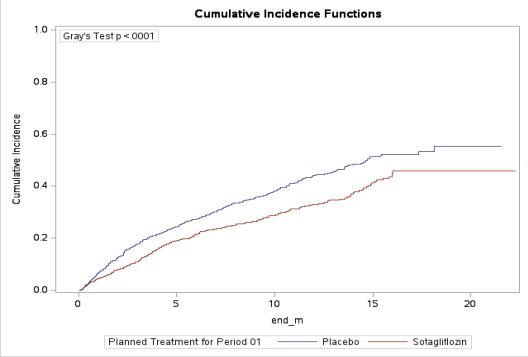


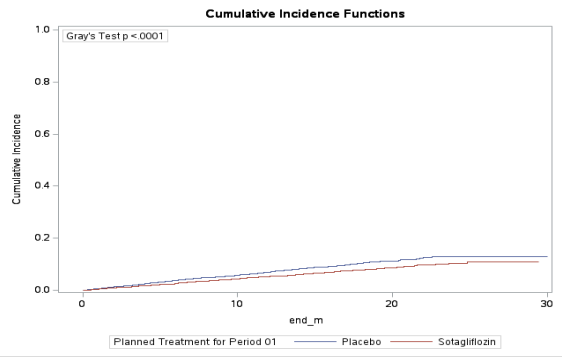
Source: Statistical reviewer analysis

*c. To generate and compare cumulative incidence function (CIF). CIFs suggested that the subjects in the placebo group had a higher risk of outcome events compared with those in the sotagliflozin group (Gray's test p<0.0001) in both trials (*Figure 3*).*

Figure 3. Cumulative Incidence Function of Primary Composite Outcomes Versus Time (Investigator-Reported) – ITT Population, SOLOIST and SCORED

SOLOIST SCORED





Source: Statistical reviewer analysis

d. To conduct sensitivity analysis to verify robustness of the primary efficacy result using a worse-scenario strategy, i.e., treated the censoring (in the treatment arm) due to discontinuation of treatment/study as an event. The result was consistent with the primary endpoint analysis (HR [95%CI]:0.71(0.56, 0.90) SOLOIST; 0.83 (0.71, 0.96) SCORED).

Secondary efficacy analyses: For the secondary endpoints, a sequential inferential approach was employed to control for overall type I error. In both trials, only the first listed secondary endpoint of HHF and UVHF was formally tested. Total occurrences of Investigator-reported

HHF and UVHF events were statistically significantly lower in the sotagliflozin group compared with placebo (HR [95% CI] = 0.64 [0.50, 0.84], p=0.0009, SOLOIST; 0.67 [0.55,0.82], p=0.0001, SCORED). The remaining secondary endpoints were not formally tested, and the results were reported at their nominal values (Table 12 & Table 13).

Table 12. Secondary Endpoint Results (Investigator-Reported) – ITT Population, SOLOIST

Endpoints	Placebo (N=614)	Sotagliflozin (N=608)	Hazard Ratio (95% CI)	p-value
HHF and UVHF[b] [n (event rate per 100 PY)]	**297 (63.9)**	**194 (40.6)**	**0.64 (0.50, 0.84)**	**0.0009**
CV death[c] [n (%)]	58 (9.4)	51 (8.4)	0.84 (0.58, 1.23)	0.3711
CV death, HHF, non-fatal MI, and non-fatal stroke[b] [n (event rate per 100 PY)]	321 (69.1)	244 (51.1)	0.73 (0.57, 0.94)	0.0130[e]
CV death, HHF, UVHF, and HF while hospitalized[b] [n (event rate per 100 PY)]	375 (80.7)	263 (55.0)	0.68 (0.54, 0.86)	0.0012[e]
All-cause mortality[c] [n (%)]	76 (12.4)	65 (10.7)	0.82 (0.59, 1.14)	0.2324[e]
Change in KCCQ-12 score from Baseline to Month 4[d] [Mean (SD)]	14.0	17.7	3.75 (0.94, 6.56)[d]	0.0089[e]
Change in eGFR (mL/min/1.73 m^2) from Week 4 to end-of-study[d] [Mean (SD)]	-2.22	-0.20	2.02 (0.51, 3.53)[d]	0.0087[e]

CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; HHF = hospitalization for HF; KCCQ = Kansas City Cardiomyopathy Questionnaire; MI = myocardial infarction; UVHF = urgent visit for HF.

[a] Endpoints are presented in order of hierarchical testing.

[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] Time-to-event analysis; results are number of patients with an event (percentage of patients with an event)

[d] Change from Baseline analysis; results are LS mean change and between-group difference (95% CI) in LS mean change

[e] Nominal p-value.

Source: Table 20 CSR, verified by statistical reviewer

Table 13. Secondary Endpoint Results (Investigator-Reported) – ITT Population, SCORED

Endpoints[a]	Placebo (N=5292)	Sotagliflozin (N=5292)	Hazard Ratio (95% CI)	p-value
Total occurrences of HHF and UVHF[b] [n (event rate per 100 PY)]	**360 (5.1)**	**245 (3.5)**	**0.67 (0.55, 0.82)**	**0.0001**

Time to CV death[c] [n (%)]	170 (3.2)	155 (2.9)	0.90 (0.73, 1.12)	0.3566
Total occurrences of CV death, HHF, non-fatal MI, or non-fatal stroke[b] [n (event rate per 100 PY)]	680 (9.6)	504 (7.1)	0.73 (0.64, 0.84)	<0.0001[d]
Total occurrences of CV death, HHF, UVHF, or HF while hospitalized[b] [n (event rate per 100 PY)]	589 (8.3)	453 (6.4)	0.76 (0.65, 0.89)	0.0005[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)[c] [n (%)]	65 (1.2)	43 (0.8)	0.65 (0.45, 0.96)	0.0303[d]
Time to all-cause mortality[c] [n (%)]	246 (4.6)	246 (4.6)	0.99 (0.83, 1.18)	0.9256[d]
Total occurrences of CV death, non-fatal MI, or non-fatal stroke[b] [n (event rate per 100 PY)]	384 (5.4)	306 (4.3)	0.79 (0.67, 0.93)	0.0047[d]

CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; HHF = hospitalization for heart failure; ITT = intent-to-treat; MI = myocardial infarction; UVHF = urgent visit for heart failure.

[a] Endpoints are presented in order of hierarchical testing.

[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] Time-to-event analysis; results are number of patients with an event (percentage of patients with an event)

[d] Nominal p-value.

Source: Table 22 CSR, verified by statistical reviewer

***Reviewer's Comment**: In both trials, a list of pre-specified secondary endpoints was planned to be tested hierarchically in the pre-specified order at the 2-sided 0.05 alpha level, conditioning on a success of primary endpoint tested at the 2-sided 0.05 alpha level. For the listed secondary endpoints, only the first endpoint of HHF and UVHF was formally tested, and it might be claimed in the label.*

Sensitivity and Supportive Analyses

Adjudicated outcome: In both trials, a sensitivity analysis of primary composite endpoint was performed based on adjudicated events. The results were consistent with the primary endpoint analysis based on investigator-reported events (HR [95%CI]: 0.70 [0.52, 0.94], and 0.72 [0.59, 0.88] for SOLOIST and SCORED, respectively) (Table 19 CSR SOLOIST, Table 21 CSR SCORED).

Investigator-reported events with non-CV death censored as Non-informative: An analysis was performed on the primary endpoint censoring non-CV deaths as non-informative. The

results were consistent with the primary endpoint analysis in favor of sotagliflozin (HR [95% CI]: 0.67 [0.53, 0.85], SOLOIST; 0.75 [0.64, 0.88], SCORED) (Table 14.2.1.1.2 CSRs, SOLOIST & SCORED). The result was verified.

Time-to-first event – investigator-reported and adjudicated outcomes: An analysis was performed on the primary endpoint using time to first event analysis based on both investigator-reported and adjudicated events. The results were also consistent with the primary analysis (HR [95% CI]:0.69 [0.56, 0.85] and 0.74 [0.57, 0.95] for investigator-reported and adjudicated events, respectively SOLOIST; 0.78 [0.67, 0.90] and 0.72 [0.59, 0.86] for investigator-reported and adjudicated events, respectively SCORED) (Tables 14.2.1.8.1&14.2.1.8.2 CSRs, SOLOIST & SCORED). The results were verified.

On-treatment analysis: An analysis was conducted using only investigator-reported clinical events during treatment plus 7/ 30 days post treatment. The results were consistent with the primary endpoint analysis (HR [95% CI] = 0.61 [0.47, 0.78] and 0.63 [0.49, 0.80] for plus 7 days and plus 30 days, respectively SOLOIST; 0.64 [0.54, 0.77] and 0.69 [0.58, 0.82] for plus 7 days and plus 30 days, respectively SCORED) (Tables 14.1.7.1 &14.1.7.2 CSRs, SOLOIST & SCORED).

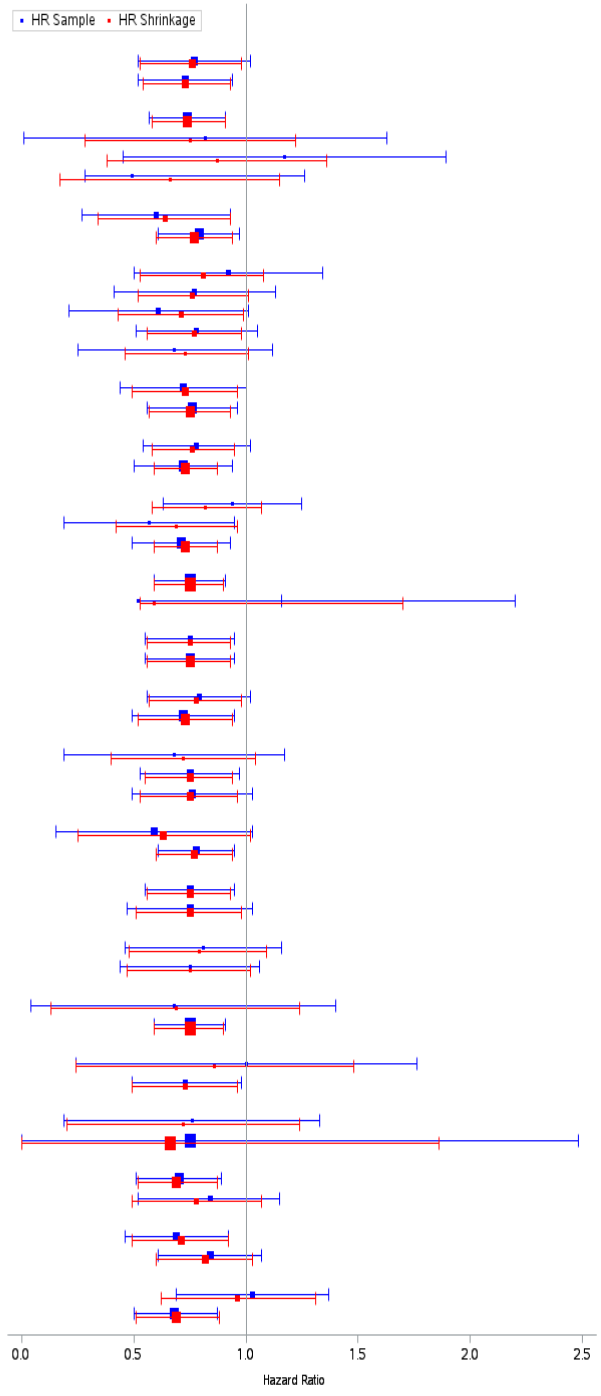
Sensitivity analyses based on incorrect stratification at randomization: To determine whether the incorrect stratification at randomization (found in the original submission) may have affected efficacy results, sensitivity analyses were conducted for primary endpoint with a statistical model that included stratification factors based on the actual data and a statistical model with no stratification factors. The result indicated that the randomization inaccuracies did not seem to have any impact on efficacy results (Table 7 CSR Addendum-1 SCORED, Table 8 CSR Addendum-1 SOLOIST).

Subgroup Analysis

Analyses of the primary endpoint were conducted by subgroups identified based on important baseline demographic and clinical characteristics using both frequentist (i.e., sample estimate was based on stratified Cox proportional hazard model) and Bayesian approach (i.e., shrinkage estimate was derived based on the Bayesian hierarchical model using a set of fairly noninfluential priors (μ~normal (0, 100), τ~ inverse_gamma (0.001, 0.001)) (Figure 4 & Figure 5). The treatment benefit of sotagliflozin on reduction of the risk of total occurrences of investigator-reported primary endpoint events was generally consistent across all subgroups**.** The estimates of shrinkage analysis were consistent with the sample estimates and the shrinkage analysis generally provided narrower CIs for the subgroups with small sample sizes. Some of the extreme results from smaller subgroups should be interpreted with caution, as these smaller subgroups were more sensitive to outliers.

Figure 4. Subgroup Analysis of Primary Composite Endpoint, SCORED

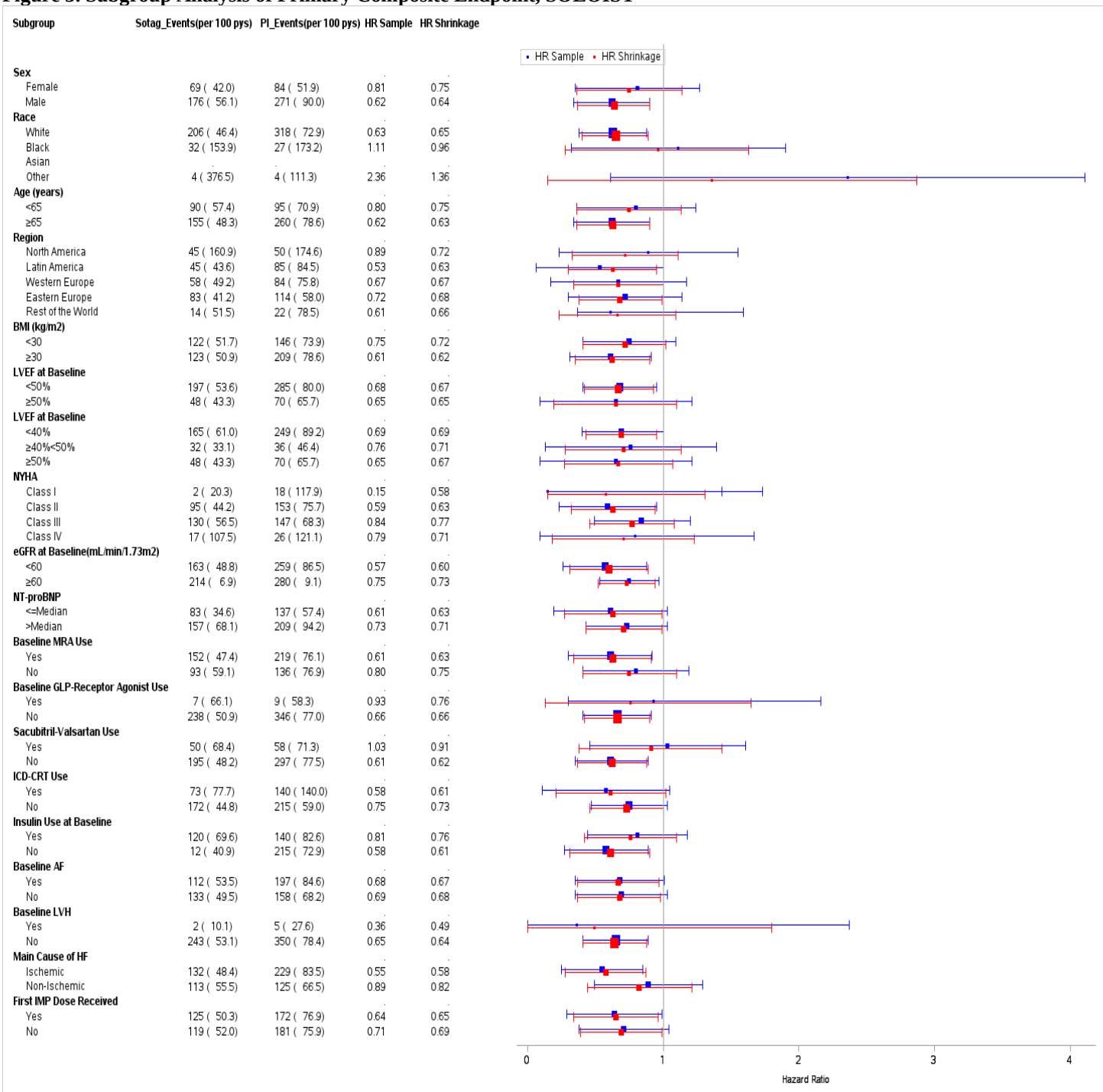
Subgroup	Sotag_Events(per 100 pys)	PI_Events(per 100 pys)	HR Sample	HR Shrinkage
Sex				
Female	162 (5.1)	210 (6.5)	0.77	0.76
Male	238 (6.1)	320 (8.3)	0.73	0.73
Race				
White	346 (5.7)	454 (7.7)	0.74	0.74
Black	17 (7.1)	26 (10.7)	0.82	0.75
Asian	23 (6.7)	22 (5.4)	1.17	0.87
Other	13 (3.1)	24 (6.0)	0.49	0.66
Age (years)				
<65	79 (3.8)	136 (6.3)	0.60	0.64
≥65	320 (6.4)	390 (7.9)	0.79	0.77
Region				
North America	61 (5.6)	64 (5.9)	0.92	0.81
Latin America	79 (3.8)	103 (5.0)	0.77	0.76
Western Europe	61 (6.1)	98 (9.8)	0.61	0.71
Eastern Europe	147 (6.8)	186 (8.6)	0.78	0.77
Rest of the World	51 (6.7)	75 (9.9)	0.68	0.73
BMI (kg/m2)				
<30	134 (5.4)	188 (7.3)	0.72	0.73
≥30	265 (5.8)	337 (7.5)	0.76	0.75
LVEF at Baseline				
<50%	199 (14.0)	254 (18.2)	0.78	0.76
≥50%	200 (3.5)	272 (4.8)	0.72	0.73
LVEF at Baseline				
<40%	130 (20.0)	143 (21.1)	0.94	0.82
≥40%<50%	69 (8.9)	112 (15.5)	0.57	0.69
≥50%	201 (3.6)	275 (4.9)	0.71	0.73
Major CV Risk Factor				
Yes	397 (5.8)	522 (7.7)	0.75	0.75
No	2 (0.8)	4 (1.4)	0.52	0.59
History of HF				
Yes	274 (12.6)	364 (16.8)	0.75	0.75
No	126 (2.6)	166 (3.4)	0.75	0.75
Presence of HF				
Present	200 (17.9)	256 (22.9)	0.79	0.78
Absent	200 (3.3)	274 (4.6)	0.72	0.73
eGFR at Baseline(mL/min/1.73m2)				
<30	51 (9.4)	71 (14.1)	0.68	0.72
≥30<45	214 (6.9)	280 (9.1)	0.75	0.75
≥45	135 (3.9)	179 (5.1)	0.76	0.75
NT-proBNP				
<=Median	42 (1.2)	69 (1.9)	0.59	0.63
>Median	353 (10.2)	459 (13.3)	0.78	0.77
History of CVD				
Yes	271 (7.8)	365 (10.6)	0.75	0.75
No	129 (3.6)	165 (4.6)	0.75	0.75
Baseline MRA in Patients with HF				
Yes	97 (20.8)	117 (26.2)	0.81	0.79
No	103 (15.8)	139 (20.7)	0.75	0.75
Baseline GLP-Receptor Agonist Use				
Yes	15 (3.3)	20 (4.5)	0.68	0.69
No	385 (5.8)	510 (7.7)	0.75	0.75
Sacubitril-Valsartan Use in Patients with HF				
Yes	21 (33.7)	15 (20.2)	1.00	0.86
No	179 (16.9)	241 (23.1)	0.73	0.73
ICD-CRT Use				
Yes	36 (15.8)	58 (21.0)	0.76	0.72
No	364 (5.3)	472 (7.0)	0.75	0.66
Insulin Use at Baseline				
Yes	291 (6.4)	393 (8.8)	0.70	0.69
No	109 (4.3)	137 (5.2)	0.84	0.78
Baseline LVH				
Yes	200 (5.7)	293 (8.4)	0.69	0.71
No	3196 (5.8)	227 (6.7)	0.84	0.82
UACR at Baseline (mg/g)				
<30	96 (4.1)	96 (4.0)	1.03	0.96
≥30	304 (6.4)	434 (9.3)	0.68	0.69



Source: Statistical reviewer analysis
HR sample: sample estimates from stratified Cox proportional hazard models with fixed effects of treatment, subgroup, treatment by subgroup interaction.

HR shrinkage: shrinkage estimates from the Bayesian hierarchical model.

Figure 5. Subgroup Analysis of Primary Composite Endpoint, SOLOIST



Source: Statistical reviewer analysis

HR sample: sample estimates from stratified Cox proportional hazard models with fixed effects of treatment, subgroup, treatment by subgroup interaction.

HR shrinkage: shrinkage estimates from the Bayesian hierarchical model.

Additional Analyses
This reviewer conducted additional analyses to address the following review issues:

1. Treatment effect in the HF population: In SOLOIST trial, all enrolled subjects had history of HF. However, in SCORED trial, only 16% of the total subjects had a history of HF. The results of subgroup analysis suggested that the benefit of sotagliflozin was consistent across all patients, regardless of HF status (Figure 13 Appendix 11). Refer to Section 5.4.2 for further discussion.

2. Treatment efficacy by LVEF: A linear model is commonly used to describe the relationship between baseline LVEF (as a continuous variable) and primary efficacy. However, there are some concerns that a linear model based on a linearity assumption may not be accurate to describe the relationship. We conducted analyses using LVEF as a categorical variable with different cut-off LVEF levels. The findings suggested that baseline LVEF was associated with outcome event —a higher baseline LVEF was associated with better outcome events (Figure 14 & Figure 15, Appendix 11). Refer to Section 5.4.3 for further discussion.

3. Treatment effect in the T2DM population: Analyses were performed to explore treatment effect in patients with T2DM and HF and to determine whether a specific HF claim (i.e., limited to patients with T2DM) should be granted. The findings (Figure 16, Appendix 11) suggested that patients with HF were likely to benefit from sotagliflozin regardless of the level of baseline HbA1c, supported by both trials. Therefore, a specific HF claim might not be granted. See Section 5.4.7 for further discussion.

Summary and Conclusion
In both trials, the primary endpoint analyses demonstrated that the primary endpoint event rate was statistically significantly lower in the sotagliflozin group compared with the placebo group. The primary efficacy results were robust, verified by sensitivity analyses. A consistent effect was shown across various subgroups defined by important baseline demographics and disease characteristics. Furthermore, the rate of missing data due to discontinuation of treatment/study and lost to follow-up appeared to be reasonably low in both trials (discontinuation of treatment/ study: 1%~2.6%; lost to follow-up: 0.2%~0.3%).
In conclusion, the efficacy of sotagliflozin is demonstrated in reducing the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit in adults with HF or type 2 diabetes mellitus and chronic kidney disease with other cardiovascular risk factors in both trials. Although the effect of individual components of the composite primary endpoint trends in a direction favorable to sotagliflozin, the overall effect appears to be driven by a large effect of hospitalization for HF.

Recommendations:

- Based on study findings, the proposed indication was modified as:

Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with:
    - heart failure
    - type 2 diabetes mellitus, chronic kidney disease, and other CV risk factors
- The secondary endpoints of MACE (SCORED) and KCCQ-12 score (SOLOIST) should not be claimed in the label because these endpoints were not formally tested, i.e., the type I error was not appropriately controlled in the analysis.

5.4. Review Issues Relevant to the Evaluation of Benefit

5.4.1. Diabetes Mellitus as an Enrichment Factor Predicting Benefit in a General Heart Failure Population

Both SOLOIST and SCORED had inclusion criteria requiring a known diagnosis of T2DM or laboratory data suggestive of a T2DM diagnosis (see Section 5.2.1, Eligibility Criteria). While the patient population predicted to benefit from sotagliflozin therapy could be restricted to patients with a T2DM diagnosis based solely on trial enrollment characteristics, we find that both published and current trial data support that T2DM represents an enrichment factor for HF, and that sotagliflozin is likely to provide benefit to a general HF population irrespective of baseline T2DM.

T2DM is an Enrichment Factor for Heart Failure Risk

In the case of HF and diabetes, there is a well-established bidirectional association between prevalence and incidence of the two conditions.[7] Large observational studies have consistently demonstrated a 2- to 4-fold increased risk of HF in individuals with T2DM compared to those without T2DM.[8,9] Furthermore, patients with comorbid HF and diabetes have worse clinical outcomes than HF patients without diabetes. Population-based HF studies, such as the ESC-HFA Heart Failure Long-Term Registry, have demonstrated that presence of diabetes confers adverse risk of death and hospitalization for chronic[10] and acute[11] heart failure patients.

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[7] Pop-Busui, R., et al., *Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association.* Diabetes Care, 2022. **45**(7): p. 1670-1690.

[8] Dunlay, S.M., V.L. Roger, and M.M. Redfield, *Epidemiology of heart failure with preserved ejection fraction.* Nat Rev Cardiol, 2017. **14**(10): p. 591-602.

[9] Dunlay, S.M., et al., *Type 2 Diabetes Mellitus and Heart Failure: A Scientific Statement From the American Heart Association and the Heart Failure Society of America: This statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update.* Circulation, 2019. **140**(7): p. e294-e324.

[10] Dauriz, M., et al., *Association Between Diabetes and 1-Year Adverse Clinical Outcomes in a Multinational Cohort of Ambulatory Patients With Chronic Heart Failure: Results From the ESC-HFA Heart Failure Long-Term Registry.* Diabetes Care, 2017. **40**(5): p. 671-678.

[11] Targher, G., et al., *In-hospital and 1-year mortality associated with diabetes in patients with acute heart failure: results from the ESC-HFA Heart Failure Long-Term Registry.* Eur J Heart Fail, 2017. **19**(1): p. 54-65.

HF Guideline Directed Medical Therapy is Mostly Agnostic to Underlying Etiology
Current recommendations for HF guideline directed medical therapy are largely agnostic to the underlying etiology of disease or presence of comorbid medical conditions.[12] Currently, patients with comorbid T2DM and HF are not considered to represent a distinct HF clinical entity. Instead, medical management recommendations focus on level of cardiac functional impairment, graded by LVEF, and the presence of symptoms. Therefore, the review team proposes that the indication statement for patients with HF should not be restricted to those with T2DM, in accordance with current guideline-based prescribing practices.

Conversely, in patients at risk of developing heart failure (ACC/AHA Stage A), clinical practice guidelines focus on addressing risk factors driving progression of the heart failure syndrome. Management recommendations in the at-risk population therefore include consideration for medications intended to treat underlying risk factors, such as hyperglycemia in patients with diabetes or elevated blood pressure in patients with hypertension. The intended population described in the second proposed indication statement captures this at-risk population, which is supported by the enrollment characteristics of the SCORED trial that included patients with "type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors." While it is possible that the glucose lowering potential of sotagliflozin may confer benefit for glycemic management, the mechanism of action by which sotagliflozin confers benefit for reduction HF morbidity and mortality captured by the primary composite endpoint is not well understood.

Sotagliflozin Demonstrates Benefit Across the HbA1c Spectrum
In the NDA 216203 mid-cycle communication (dated 17 November 2022), we requested that the Applicant provide further justification for an indication in "adults with heart failure," instead of adults with heart failure and T2DM. In response to our information request (SN0026; 15 December 2022), the Applicant provided a compelling sensitivity analysis describing the effect of sotagliflozin on the primary composite endpoint stratified by hemoglobin A1c (HbA1c) for both the SOLOIST (Table 14) and SCORED (Table 15. SCORED: Effect of sotagliflozin on the primary outcome by baseline HbA1c subgroup**Error! Reference source not found.**) pivotal clinical trials. Importantly, both trials demonstrated a beneficial effect on the primary composite endpoint regardless of HbA1c status as shown by the lack of a significant HbA1c subgroup interaction.

[12] Heidenreich, P.A., et al., 2022 AHA/ACC/HFSA *Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation,* 2022. **145**(18): p. e895-e1032.

Table 14. SOLOIST: Effect of sotagliflozin on the primary outcome by baseline HbA1c subgroup

	Sotagliflozin Event rate per 100 patient-years	Placebo Event rate per 100 patient-years	HR (95% CI)	p-value for treatment-by-HbA1c subgroup factor interaction
Overall, N = 1222	51.0	76.3	0.67 (0.52, 0.85)	
HbA1c subgroup				
≤median (7.1%), n = 590	48.4	63.9	0.73 (0.51, 1.04)	0.663
>median (7.1%), n = 573	55.3	87.7	0.65 (0.47, 0.92)	

Source: Applicant response to information request (SN0026), Table 1

In the SOLOIST trial, the median baseline value for HbA1c was 7.1%, a modest elevation considering that goal HbA1c for glycemic control in patients with T2DM is ≤ 7.0%.[13] The analysis indicated preservation of the beneficial effect on either side of the HbA1c median value. Additionally, it is possible to observe the effect of worsening glycemic control for enrichment on the primary composite endpoint event rate. There was both a higher incidence in the placebo arm (87.7 vs. 63.9 per 100PY) and greater absolute risk reduction (22.4 vs. 15.5 per 100PY) with sotagliflozin in patients with HbA1c > 7.1% versus ≤ 7.1%. While the point estimates in this analysis demonstrate attenuation of the effect on the primary composite endpoint in those with better glycemic control, the overlapping confidence limits for hazard ratio suggest against a significant HbA1c interaction. In summary, it is reasonable to extrapolate the presence of a treatment effect on trial subjects with HbA1c <7.1% as one that may be expected in an otherwise euglycemic population without a diagnosis of T2DM.

Table 15. SCORED: Effect of sotagliflozin on the primary outcome by baseline HbA1c subgroup

	Sotagliflozin Event rate per 100 patient-years	Placebo Event rate per 100 patient-years	HR (95% CI)	p-value for treatment-by-HbA1c subgroup factor interaction
Overall, N = 10,584	5.64	7.51	0.75 (0.63, 0.88)	
HbA1c subgroup				
<8%, n = 3976	5.61	6.99	0.80 (0.61, 1.05)	0.421
≥8 to <9%, n = 3092	5.25	6.68	0.81 (0.60, 1.09)	
≥9%, n = 3509	5.90	8.88	0.64 (0.49, 0.84)	

Source: Applicant response to information request (SN0026), Table 2

[13] American Diabetes, A., *6. Glycemic Targets: Standards of Medical Care in Diabetes-2021*. Diabetes Care, 2021. **44**(Suppl 1): p. S73-S84.

The trial population in SCORED had a lower primary composite endpoint event rate than what was shown in SOLOIST, which was to be expected in a study mainly designed to capture a population at risk for developing HF. Regardless, the analysis for SCORED demonstrated a similar relationship with preservation of the beneficial treatment effect across the range of HbA1c values (<8%, ≥8% to <9%, ≥9%). The analysis is notable in that point estimates for adverse CV outcomes captured in the primary composite endpoint remain positively correlated with increasing HbA1c values, but also notable for persistent lack of a significant HbA1c subgroup interaction. This relationship demonstrates how T2DM likely serves as an enrichment factor in an at-risk population, but also for the lack of a significant impact of HbA1c level on the overall treatment effect.

We verified the Applicant's preceding analyses by conducting sensitivity analysis evaluating treatment effect on the primary composite endpoint while treating HbA1c as a continuous variable (see Section 11, Figure 16). In our analysis, a trend remains for benefit across the range of baseline HbA1c values for each trial, and there is not a statistically significant treatment effect interaction between primary efficacy and HbA1c.

Nonclinical Data Suggesting Benefit in Non-Diabetic Animals
The clinical data obtained from the SOLOIST and SCORED trials provide sufficient evidence demonstrating the benefit of sotagliflozin treatment in patients with heart failure or in patients with T2DM, CKD, and other CV risk factors. However, we have also considered available nonclinical data to support our current justification for providing a nonspecific "adults with heart failure" claim. In an independently published study of normoglycemic mice treated with sotagliflozin versus control, there was a reduction in HF phenotypic measures, as generated by the transverse aortic constriction (TAC) pressure overload method.[14] The mechanism by which sotagliflozin conferred the beneficial effect in the TAC mouse model is unclear, but the authors documented significant glucosuria and diuresis in animals treated with sotagliflozin compared to control, despite being normoglycemic at baseline. While recognizing the limitations of translating findings from animal models to clinical medicine, these results are supportive to the proposed justification for a nonspecific HF claim.

5.4.2. Heart Failure Efficacy and Baseline Left Ventricular Ejection Fraction

Understanding the treatment effect for HF-targeted therapeutics across the range of baseline LVEF has been a topic of academic deliberation, clinical trial design and regulatory consideration. Recently, clinical trial data for ENTRESTO and JARDIANCE have led to efficacy labeling supplements demonstrating treatment benefits in adults with heart failure,

[14] Young, S.L., et al., *Sotagliflozin, a Dual SGLT1/2 Inhibitor, Improves Cardiac Outcomes in a Normoglycemic Mouse Model of Cardiac Pressure Overload.* Front Physiol, 2021. **12**: p. 738594.

including normal LVEFs. The design and conduct of SOLOIST and SCORED provided an opportunity to evaluate treatment effect across the range of baseline LVEF.

The SOLOIST trial enrolled patients with a known HF diagnosis and a range of baseline LVEF (median LVEF 35%; statistical reviewer analysis Section 11, Figure 15). The SCORED trial stratified patients in a pre-specified manner based on known HF diagnosis (~31%; n=3283). The HF patients in SCORED also had a range of baseline LVEFs but most trial subjects had normal, or mildly reduced LVEF (median LVEF 50%; statistical reviewer analysis Section 11, Figure 15). The referenced statistical reviewer sensitivity analyses for SOLOIST and SCORED demonstrate preservation of treatment effect on either side the median LVEF. Additionally, analysis by LVEF quartile in each trial shows a favorable trend for benefit for mildly reduced, and normal, LVEFs in both trials.

In the IND 135095 Type C Meeting Preliminary Responses (06 January 2021), the Agency recommended sensitivity analyses of pooled data for SOLOIST and SCORED to gauge treatment effect on patients with baseline HF diagnoses. The Applicant's pooled analysis demonstrated preservation of treatment effect across a wide range of baseline LVEF (Table 16). We performed our own sensitivity analyses to verify the Applicant's findings (Section 11, Figure 14Figure 1) which demonstrated preservation of effect on either side of the pooled median LVEF (45%) and quartile analysis showing a beneficial trend in higher range LVEFs (45%-57%; HR 0.73 [95%CI 0.47, 1.13] and 57%-85%; HR 0.72 [95%CI 0.41, 1.25]).

Table 16. Total Occurrences (Event Rate per 100-Patient Years) of CV Death, HHF, and UHFV in Patients with a History of HF Overall and in LVEF Subgroups (Investigator-Reported Events) – Pooled Analysis of SOLOIST and SCORED (ITT Analysis Set)

	Placebo	Sotagliflozin	HR (95% CI)
Overall	n = 2257	n = 2248	
	27.3	19.6	0.72 (0.61, 0.84) p <0.0001
LVEF <40%	n = 896	n = 862	
	41.0	32.0	0.78 (0.63, 0.96) p = 0.0207
LVEF ≥40 to <50%	n = 402	n = 409	
	27.0	16.0	0.57 (0.40, 0.83) p = 0.0027
LVEF <50%	n =1298	n = 1271	
	36.5	26.5	0.73 (0.60-0.87) P = 0.0006
LVEF ≥50%	n = 957	n = 975	
	16.8	11.8	0.67 (0.51, 0.89) p = 0.0057

Source: Module 5.3.5.3 ISE Tables 14.2.4.2.1 and 14.2.4.4.1

Source: Summary of Clinical Efficacy, Table 17

***Reviewer's Comment**: Analysis of data from SOLOIST and SCORED demonstrate preservation of benefit in adults with heart failure with a range of baseline LVEFs. I recommend an indication*

statement reflecting a treatment benefit in "adults with heart failure" that does not stipulate effect in specific LVEF patient categories.

5.4.3. Efficacy Driven by Heart Failure Hospitalization

The individual components of the common primary composite endpoint (CV death, HHF and UHFV) for SOLOIST and SCORED demonstrate a favorable trend toward benefit from sotagliflozin treatment versus placebo (See Section 5.3, Table 10 & Table 11). While the major driver of statistical significance for the primary composite endpoint was the HHF component, the concordance of benefit for the individual components supports a primary indication statement including a description of each. This recommendation follows the Agency's guideline document *Multiple Endpoints in Clinical Trials, Guidance for Industry*[15] which promotes consideration of the clinical significance of individual components with use of clinical judgement to decide whether the benefits are clinically meaningful and exceed risk.

Reviewer Conclusion: For the common primary composite employed in SOLOIST and SCORED, I have judged that the individual components of the composite endpoint are clinically meaningful with benefits outweighing risk. I recommend a description of each individual component (CV death, HHF and UHFV) in the indication statement for sotagliflozin.

5.4.4. Adjudicated vs. Investigator-Reported Events Demonstrate Concordance for Efficacy

Per the final SAPs for SOLOIST (09 August 2020) and SCORED (21 August 2020), analysis for the primary endpoint, and many of the secondary endpoints, changed *from* time-to-event analyses of adjudicated events *to* total (first and subsequent) analyses of investigator-reported events. The Applicant cites the early termination of both trials and the impending impact of the COVID-19 pandemic as the primary drivers of the pre-specified switch from adjudicated to investigator-reported events. Similarly, the Applicant cites loss of statistical power from reduced sample size (SOLOIST) and reduced follow-up time (SOLOIST and SCORED) to continue with time-to-event analyses. The Applicant states clearly that no unblinding of data or interim analyses were performed leading to the finalized SAPs.

There is precedent for utilizing investigator-reported events in lieu of adjudicated events for determination of substantial evidence of effectiveness. The Cardiovascular and Renal Drugs Advisory Committee (AC) of the Food and Drug Administration (FDA) met on 15 December 2020[16] to discuss data from the PARAGON-HF trial to support a supplemental HF indication for ENTRESTO (sacubitril-valsartan). The pre-specified analysis of the primary composite endpoint (adjudicated CV death and HHF) did not meet the stated statistical threshold (p=0.059), but post-

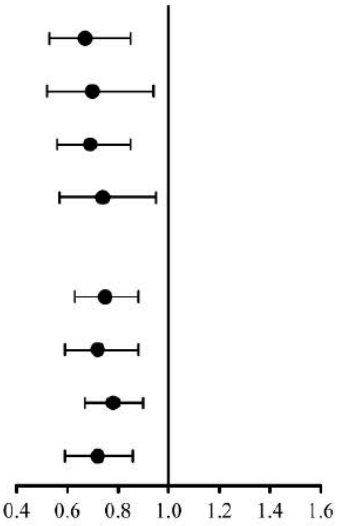
[15] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials-guidance-industry

[16] https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-time-and-public-participation-information-december-15-2020-meeting-cardiovascular-and-renal

hoc analysis of investigator-reported events and a graded adjudication process demonstrated results below the p=0.05 threshold. The AC voted 12 (yes) to 1 (no) that the post-hoc analyses were compelling and consistent and had little impact on how they interpreted relative risk in the PARAGON-HF trial. Additional commentary addressed that CVOTs including cardiovascular specialists as investigators lend support to their clinical reasoning when determining a reported clinical outcome.

Figure 6. Forest Plot of CV Death, HHF, and UVHF in SOLOIST and SCORED Studies: Summary of Primary (Investigator-Reported) and Sensitivity (Adjudicated) Analyses

	Hazard ratio (95% CI)	*P* value
SOLOIST[a]		
Total occurrences – investigator reported[b]	0.67 (0.53, 0.85)	0.001
Total occurrences – adjudicated	0.70 (0.52, 0.94)	0.018
Time to first occurrence – investigator reported	0.69 (0.56, 0.85)	0.0006
Time to first occurrence – adjudicated	0.74 (0.57, 0.95)	0.0169
SCORED[c]		
Total occurrences – investigator reported[b]	0.75 (0.63, 0.88)	0.0004
Total occurrences – adjudicated	0.72 (0.59, 0.88)	0.0012
Time to first occurrence – investigator reported	0.78 (0.67, 0.90)	0.0008
Time to first occurrence – adjudicated	0.72 (0.59, 0.86)	0.0004



[a]Placebo, N=614; sotagliflozin, N=608.
[b]Primary endpoint.
[c]Placebo, N=5292; sotagliflozin, N=5292.
CI, confidence interval.

Source: EFC15156 Table 14.2.1.1.1, Table 14.2.1.2, Table 14.2.1.8.1, Table 14.2.1.8.2 and EFC14875 Table 14.2.1.1.1, Table 14.2.1.2, Table 14.2.1.8.1, Table 14.2.1.8.2

Source: Clinical Summary of Efficacy, Figure 9 (SN0001)

In the conduct of SOLOIST, most investigators were cardiovascular specialists while investigators for SCORED included physicians practicing multiple specialties. Regardless, the protocols for each trial provide clear guidance on clinical endpoint definitions which point to the Clinical Events Classification Charter that appropriately referenced contemporary cardiovascular endpoint definition criteria.[17] In the IND 135095 Type C Meeting background package (SN0041; 18 December 2020), the Applicant provided analyses for investigator-reported events for the primary composite endpoint and 3-point MACE. In SOLOIST, of the investigator-reported events sent for adjudication, 174 of 225 (77.3%) events in the sotagliflozin group and 221 of 286 (77.3%) events in the placebo group were positively adjudicated. In SCORED, 337 of 501

[17] Hicks KA, Mahaffey KW, Mehran R, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation. 2018;137(9):961-972. doi:10.1161/CIRCULATIONAHA.117.033502

(67.3%) events in the sotagliflozin group and 460 of 664 (69.3%) events in the placebo group were positively adjudicated. Importantly, the positively and negatively adjudicated percentages in each treatment arm are not numerically imbalanced. In the NDA 216203 submission (SN0001), the Applicant's Clinical Summary of Efficacy provides further analysis, for both SOLOIST and SCORED, demonstrating concordance of effect on the primary composite efficacy endpoint for adjudicated versus investigator-reported events (Figure 6). The Applicant also extended this analysis for time-to-first occurrence in a sensitivity analysis intended to reflect originally proposed primary efficacy analyses.

Reviewer's Comment*: While there was a major change to the primary objectives for SOLOIST and SCORED, the Applicant's pre-specified plan to shift from time-to-event analyses of adjudicated events to total (first and potentially subsequent) investigator-reported events was reasonable and is sufficient to establish substantial evidence of effectiveness. There is Agency precedent for investigator-reported event reporting in CVOTs, and the concordance of treatment effect regardless of adjudication, along with sensitivity analysis of the original time-to-event strategy, is reassuring to this reviewer.*

5.4.5. Effect on Patients with Acute or Worsening Heart Failure

The Applicant proposed an indication statement which included a description of reduction of the primary composite endpoint in "*adults with heart failure, including those with acute or worsening heart failure*." However, we do not support an indication statement containing "including those with acute or worsening heart failure" given that the design and conduct of the SOLOIST and SCORED trials do not support use of sotagliflozin as a therapy for "acute"(or decompensated) heart failure nor is it clear that worsening heart failure (WHF) describes a specific heart failure patient population standing to benefit from sotagliflozin therapy.

We do find that the data from SOLOIST and SCORED support an indication statement showing benefit on the components of the primary composite endpoint in "adults with heart failure", as detailed in the preceding review issue sections. Review of treatment effect as a function of time from randomization does demonstrate early beneficial treatment effect, as seen through near-term separation of the hazard function curves. Additional sensitivity analyses (see statistical reviewer note Section 5.3, Efficacy), demonstrate HR 95%CIs falling below 1 around 4 months for SOLOIST and 8 months for SCORED. We also find that the data from SOLOIST demonstrate a reasonable safety profile, consistent with overall study population, for early initiation of sotagliflozin in hemodynamically stable heart failure patients. We will thus provide dosing guidance in the label (Section 2) stating ability to initiate sotagliflozin at time of hospitalization for hemodynamically stable heart failure patients.

To support their intended worsening heart failure (WHF) patient population, the Applicant references the design and conduct of SOLOIST which randomized patients with a known diagnosis of HF at time of an index HF Event (described in Section 5.2.2), which the Applicant defines as a WHF event. SOLOIST was originally planned to assess a time-to-event analysis for first and recurrent CV death, HHF and UHFV events. However, given the early termination of

the trials in March 2020, the Applicant made the decision to alter the primary endpoint analysis to total (first and recurrent) event analysis without a time-to-event component. In the NDA resubmission package (SOLOIST CSR Addendum 2; dated 18 May 2022), the Applicant subsequently provided post-hoc analysis of 30-day and 90-day readmission for HF-related events or CV death (Table 17) which demonstrated a significant risk reduction for patients treated with sotagliflozin versus placebo. One major limitation of this analysis is that <50% of trial subjects received IMP prior to or at time of discharge thus limiting the scope of the analysis to a partial subset of randomized participants. Furthermore, this post-hoc analysis lacks pre-specified inclusion in the formal alpha testing hierarchy for SOLOIST.

Table 17. Readmission for HF-related Events or CV Death Within 30- to 90-Days from Hospital Discharge

	Placebo N = 288	Sotagliflozin N = 275	Risk Ratio (95% CI) p-value
First Event within 30 days from discharge			
Readmission for non-fatal HF-related event	n=280 25 (8.9)	n=271 11 (4.1)	0.47 (0.24, 0.91) 0.023
CV death or readmission for HF-related event	n=285 30 (10.5)	n=274 14 (5.1)	0.48 (0.27, 0.88) 0.015
First Event within 90 days from discharge			
Readmission for non-fatal HF-related event	n=261 49 (18.8)	n=255 22 (8.6)	0.48 (0.30, 0.76) 0.002
CV death or readmission for HF-related event	n=270 58 (21.5)	n=260 27 (10.4)	0.49 (0.32, 0.75) <0.001

CI = confidence interval; CV = cardiovascular; HF = heart failure; N = total number of patients initiating therapy prior to or at hospital discharge; n = number of patients without missing data.
Patients who discontinued without an event within 30- or 90-days were considered as missing in the analysis.
[a]HF-related events include hospitalization for HF or urgent visit for HF.
Source: Table 1.1.1, Table 1.2.1, Table 2.1.1, and Table 2.2.1.

Source: SOLOIST CSR Addendum 2, Table 3

5.4.6. Effect on KCCQ-12 and 3-Point MACE

The Applicant formally included patient reported outcomes measures in the conduct of SOLOIST with inclusion of the KCCQ-12 test article in the pre-specified hierarchical alpha-spending plan for secondary endpoints (SAP dated 09 August 2020). In SCORED, the Applicant included 3-point MACE as a clinical outcomes measure in the pre-specified hierarchical alpha-spending plan for secondary endpoints (SAP dated 21 August 2020). It is notable that 3-point MACE had been listed as a primary clinical endpoint to assess non-inferiority against placebo early in the clinical development program to satisfy FDA guidance for assessing CV risk of new antidiabetic therapeutics. 3-point MACE was subsequently shifted to a primary efficacy endpoint in SAP v1.0 (dated 08 July 2019) before its eventual positioning as a secondary endpoint in the final SAP. The Applicant proposed inclusion of non-fatal MI and non-fatal stroke (components of 3-point MACE) in their second indication statement (b) (4)

Effect on KCCQ-12
SOLOIST included KCCQ-12 as a pre-specified secondary endpoint in the formal alpha-testing hierarchy (Table 12). Based on the ordering of the KCCQ-12 patient reported outcome measure in the pre-specified hierarchical alpha spending plan, there was no alpha remaining for Type 1 error control. While data analysis demonstrates a nominal improvement in KCCQ-12 (3.7 points; HR 3.75 [95%CI: 0.94, 6.56]) for subjects treated with sotagliflozin versus placebo, it is unclear if this is clinically meaningful. It is notable that both treatment arms demonstrated improvement in KCCQ-12 score (sotagliflozin – 17.7 points, placebo – 14 points). . (b) (4)
(b) (4)

Effect on 3-Point MACE
SCORED included a pre-specified secondary endpoint in the formal alpha-testing hierarch for 3-point MACE (Table 13). While analysis of the data demonstrates reduction in 3-point MACE risk (HR 0.79 [95%CI: 0.67, 0.93]) for subjects treated with sotagliflozin versus placebo, there is a lack of Type 1 error control given no alpha remaining based on its position in the secondary endpoint hierarchical order. (b) (4)

5.4.7. Effect on HbA1c, Weight and Blood Pressure

(b) (4)

Effect on HbA1c
SOLOIST demonstrated a modest mean HbA1c reduction (-0.27% [95%CI: -0.42, -0.11]) for subjects treated with sotagliflozin versus placebo. Similarly, SCORED demonstrated a modest mean HbA1c reduction (-0.42%, [95%CI: -0.47, -0.38]). We do not find these nominal changes to be clinically meaningful. (b) (4)

Effect on Blood Pressure
SOLOIST demonstrated equivocal findings for effect on SBP (-0.1 mmHg [95%CI: -1.4, 1.2]) for subjects treated with sotagliflozin versus placebo. SCORED demonstrated a modest reduction in SBP (-2.4 mmHg [95%CI: -2.9, -2.0]). We do not find the SBP reduction for SCORED to be clinically meaningful. (b) (4)

Effect on Weight
SOLOIST demonstrated a small mean between group difference in change in weight from baseline (-0.7 kg [95% CI: -1.1, -0.3]) for subjects treated with sotagliflozin versus placebo. Similarly, SCORED demonstrated a small mean between group difference in change in weight from baseline (-1.2 kg [95%CI: -1.4, -1.1] for subjects treated with sotagliflozin versus placebo. This effect is likely secondary to the osmotic diuretic effect of renal SGLT2 inhibition. We do not find the effect to be clinically meaningful from a primary weight loss perspective. (b) (4)

6. Risk and Risk Management

6.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Potential safety issues identified in the nonclinical program were derived from inhibition of sotagliflozin's intended pharmacological targets, SGLT1 and SGLT2, rather than from compound-specific toxicity. Highlighted here are notable nonclinical safety issues identified during review of the NDA.

In general, safety issues with sotagliflozin related to SGLT2 inhibition appear similar to that of other SGLT2 inhibitors. Most notably, these findings include tubule dilation and urinary tract inflammation secondary to high urinary glucose levels and subsequent osmotic-related fluid and electrolyte loss, and decreased body weight gain despite increased food consumption. Similar findings are recognized in patient populations exposed to SGLT2 inhibitors.

Central to the toxicity profile of SGLT1 inhibition is a state of calcium overload secondary to carbohydrate malabsorption (i.e., intestinal retention of glucose). The calcium disruption manifests in rats as trabecular bone accretion, calcification of soft tissues, hypercalciuria, complex changes in bone biomarkers and, in some cases, renal and adrenal neoplasms. An analogous pathway also appears to be operable in human subjects, although long-term outcomes are unknown. Contrary to the expectations for a mixed SGLT1/2 inhibitor, sotagliflozin resulted in a lower state of carbohydrate malabsorption in the nonclinical program compared with more 'SGLT2 selective' compounds and does not expect to present any greater clinical risk than already recognized for other compounds in the class, beyond mild gastrointestinal distress.

Of less certainty is the cause and relevance of toxicological findings in the prostate of rats. Briefly, prostatic inflammation was consistently observed across studies with an incidence and severity that was dose- and duration-dependent, culminating in a moderate to severe signal that occurs at approximately 3x clinical exposure from the 2-year rat study. The applicant plausibly argues that urinary tract infections (UTIs) are causative; however, these events are not always observed together. The prostate reportedly expresses SGLT1, though, its function remains undefined. Similar findings in the prostate have been reported in other programs, but not at the

incidence or severity observed with sotagliflozin. It is also reassuring that prostatic inflammation was not a feature of the toxicology studies with sotagliflozin in dogs and mice, and that the inflammation observed in rats did not progress to a more problematic state over 2 years of exposure (e.g., hyperplasia/hypertrophy, neoplasia, morbidity). Moreover, there were no important imbalances in prostatitis between sotagliflozin and placebo groups in the completed clinical trials.

Renal tubular and pelvic dilatation and/or dilated ureter were observed in the post-natal developmental and juvenile toxicology studies in rats with sotagliflozin, consistent with similar effects observed in the pre- and postnatal developmental and/or juvenile studies with other SGLT2 inhibitors, which are considered relevant to fetal renal development during the second and third trimesters of pregnancy in human. These findings were also observed in adult rat administered with sotagliflozin, although with a larger safety margin. This is considered secondary to the pharmacodynamic activity of this class of drugs and the increased sensitivity in juvenile animals is likely attributed to the reduced ability of the developing kidney to handle the increased urine volumes associated with SGLT2 inhibitor-induced osmotic diuresis. This risk should be properly disclosed in the risk summary for section 8.1 of the label.

6.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Potential safety concerns and laboratory changes based on drug class of SGLT2 inhibitors include the following:

- Ketoacidosis
- Volume depletion
- Urosepsis and pyelonephritis
- Hypoglycemia with concomitant insulin and insulin secretagogues
- Necrotizing fasciitis of the perineum (Fournier’s gangrene)
- Genital mycotic infections.
- Transient increase in serum creatinine and decrease in eGFR
- Increase in low density lipoprotein cholesterol (LDL-C)
- Increase in hematocrit

Potential safety concerns and laboratory changes for specific SGLT2 inhibitors include the following:

- Lower limb amputation (canagliflozin and ertugliflozin)
- Hypersensitivity reactions (canagliflozin and empagliflozin)
- Bone fracture (canagliflozin)
- Decrease in bone mineral density (canagliflozin)

6.3. Potential Safety Concerns Identified Through Postmarket Experience

There is no post marketing experience with sotagliflozin.

6.4. FDA Approach to the Safety Review

There are no concerns regarding submission quality, conduct of the studies with respect to assessment of safety, or the applicant's characterization of adverse events.

The clinical safety review was based on the data collected from two phase 3 studies, SOLOIST and SCORED (Table 3). Due to heterogeneity in the study population and different sizes and durations of the studies, the safety results were presented separately. The safety review was presented for the safety population (defined as randomized population who received at least 1 dose or part of a dose of the IMP and analyzed according to the treatment actually received) in both studies. AEs were presented as the number and percentage of patients with the AE and as the absolute risk difference (RD), which was calculated as the difference in the percentage of patients with AEs between sotagliflozin and placebo groups: negative RD values favor sotagliflozin and positive RD favor placebo.

AEs were primarily analyzed by Medical Dictionary for Regulatory Activities (MedDRA, version 23.0) preferred terms (PTs, same as the applicant's analyses) and by pooling similar AEs using FDA Medical Query [FMQ], Standard MedDRA Query [SMQ, version 23.0], and customized MedDRA query [CMQ]. Treatment-emergent adverse events (TEAEs) are AEs with an onset after the first IMP dose until 10 days (1 day for hypoglycemia) after the last IMP dose.

Adverse events of special interest (AESIs) were based on the approved product labels of SGLT2 inhibitors and the mechanism of action of sotagliflozin. In addition to performing additional queries (described in Table 18), the safety reviewer evaluated all applicant defined AESIs. Subgroup analyses were performed by age (<65 and >=65 years), sex, race, BMI (<30 and >=30 kg/m^2), eGFR (<30, >=30 to <45, and >=45 $mL/min/1.73m^2$), and LVEF (<40%, >=40 to <50%, and >=50%) for the AESI that occurred more frequently in the sotagliflozin group.

Table 18. AESI Approach for Sotagliflozin

AESI	Applicant's Approach	Reviewer's Additional Queries
Diabetic ketoacidosis	Investigator's opinion as collected on the eCRF form "Metabolic acidosis/suspected DKA" and adjudication by CEC	Broad FMQ "Diabetic ketoacidosis"
Volume depletion	Customized PT list	Broad FMQ "Volume depletion"
Urinary tract infections	Customized PT list	Customized PT list
Severe Hypoglycemia	eCRF "Hypoglycemic event information"	Narrow FMQ "Hypoglycemia"
Fournier's gangrene	Customized PT list	–
Genital mycotic infections	Customized PT list	Customized PT list
Diarrhea	Narrow SMQ "Noninfectious diarrhoea" and customized PT list	Broad FMQ "Diarrhea"
Acute kidney injury	Narrow SMQ "Acute Renal Failure" and/or eGFR decrease >25 mL/min from baseline, or initiation of dialysis or renal transplantation	Broad FMQ "Acute kidney injury"; broad SMQ "Acute renal failure"
Drug-Induced liver injury	Liver function test evaluation and adjudication of the etiology of potential cases of DILI by committee	Narrow FMQ "Hepatic injury"
Bone fractures	eCRF "Bone fracture" and adjudication by CEC	Customized PT list
Amputations	eCRF "Other procedures related to amputation"	–
AEs leading to amputation(s)	eCRF "Other procedures related to amputation"	–
Venous thrombotic events	Customized PT list	Narrow SMQ "Embolic and thrombotic events, venous"
Pancreatitis	Customized PT list	Narrow FMQ "Pancreatitis"; narrow SMQ "Acute pancreatitis"
Any malignancies of special interest	Narrow SMQ "Breast neoplasms, malignant and unspecified", Narrow SMQ "Prostate neoplasms, malignant and unspecified", and customized PT list	–
Hypersensitivity reactions	–	Broad FMQ "Anaphylactic reaction"; narrow and broad FMQ "Angioedema"

Source: Reviewer's table

Abbreviations: AE, adverse event; CEC, clinical endpoint committee; DILI, drug-induced liver injury; DKA, diabetic ketoacidosis; eCRF, electronic case report form; eGFR, estimated glomerular filtration rate; FMQ, FDA medical query; PT, preferred term; SMQ, standard MedDRA query

The statistical software R and JMP were used for safety analyses.

6.5. Adequacy of the Clinical Safety Database

Sotagliflozin was administered to a total of 5896 patients and placebo was administered to a total of 5897 patients (Table 19). Exposure was balanced between the sotagliflozin and the placebo groups in both studies. There were over 3600 patients who had exposure to sotagliflozin longer than 52 weeks.

Table 19. Duration of Exposure, Safety Population, SOLOIST and SCORED

	SOLOIST		SCORED	
	Sotagliflozin N=605	**Placebo N=611**	**Sotagliflozin N=5291**	**Placebo N=5286**
Exposure	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Duration of treatment, days				
Mean (SD)	252.1 (161.6)	241.3 (160.9)	440.8 (181.6)	440.1 (182.7)
Median (min, max)	238.0 (1.0, 645.0)	231.0 (1.0, 656.0)	432.0 (1.0, 881.0)	433.0 (1.0, 903.0)
Patients treated, by duration, n (%)				
>= 12 weeks	492 (81.3%)	478 (78.2%)	5075 (95.9%)	5066 (95.8%)
>= 36 weeks	290 (47.9%)	285 (46.6%)	4574 (86.4%)	4547 (86.0%)
>= 52 weeks	176 (29.1%)	159 (26.0%)	3437 (65.0%)	3414 (64.6%)
>= 78 weeks	23 (3.8%)	15 (2.5%)	1684 (31.8%)	1680 (31.8%)
>= 104 weeks	0 (0.0%)	0 (0.0%)	290 (5.5%)	292 (5.5%)

Source: Reviewer's analysis [adsl, adex]**; Software:** R
Abbreviations: N, number of patients in treatment group; n, number of patients with given treatment duration; SD, standard deviation
Sponsor's reference CSR table: 14.1.5.1

Reviewer's comment: *The safety exposure to sotagliflozin was adequate both in terms of the number of patients exposed to study drug and the duration of exposure to support the safety evaluation.*

There was a similar proportion of patients who up-titrated their dose in each treatment group (~54% in SOLOIST and ~75% in SCORED; applicant's reference CSR table: 14.1.5.2). The median time to up-titration was 16 days and 29 days in both treatment groups in SOLOIST and SCORED, respectively. A small percentage of patients down-titrated their dose following up-titration (SOLOIST: 4.1% and 3.1%; and SCORED: 5.5% and 5.1% in sotagliflozin and placebo groups, respectively).

6.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

The safety evaluation of sotagliflozin in SOLOIST and SCORED studies was adequate and acceptable for the proposed indication.

6.6.1. Overall Adverse Event Summary

There were no important imbalances in the incidence of deaths, serious TEAEs, and TEAEs leading to discontinuation between treatment groups in both studies (Table 20 and Table 21). In SOLOIST, there were more non-serious TEAEs overall for sotagliflozin treated patients, but the imbalance was only observed for mild AEs. There was no imbalance in non-serious TEAEs in SCORED.

Table 20. Overview of Treatment-Emergent Adverse Events,[1] Safety Population, SOLOIST

Event	Sotagliflozin N=605 n (%)	Placebo N=611 n (%)	Absolute Risk Difference[2] (95.0% CI)
Any AE	420 (69.4%)	411 (67.3%)	2.2 (-3.1, 7.4)
Severe	133 (22.0%)	157 (25.7%)	-3.7 (-8.5, 1.1)
Moderate	251 (41.5%)	266 (43.5%)	-2.0 (-7.6, 3.5)
Mild	288 (47.6%)	273 (44.7%)	2.9 (-2.7, 8.5)
SAE	235 (38.8%)	250 (40.9%)	-2.1 (-7.6, 3.4)
Death	49 (8.1%)	52 (8.5%)	-0.4 (-3.5, 2.7)
Life-threatening	22 (3.6%)	17 (2.8%)	0.9 (-1.1, 2.8)
Persistent or significant disability/incapacity	8 (1.3%)	4 (0.7%)	0.7 (-0.4, 1.8)
Requires or prolongs hospitalization	212 (35.0%)	232 (38.0%)	-2.9 (-8.3, 2.5)
Congenital anomaly or birth defect	0 (0.0%)	0 (0.0%)	0.0 (0.0, 0.0)
Other	28 (4.6%)	44 (7.2%)	-2.6 (-5.2, 0.1)
AE leading to permanent discontinuation	29 (4.8%)	23 (3.8%)	1.0 (-1.2, 3.3)
AE leading to interruption of study drug	109 (18.0%)	115 (18.8%)	-0.8 (-5.2, 3.6)

Source: Reviewer's analysis [adsl, adae]**; Software:** R
Abbreviations: AE, adverse event; IMP, investigational medical product; CI, confidence interval; N, number of patients in treatment group; n, number of patients with an event; SAE, serious adverse event
[1]Treatment-emergent AEs defined as AEs with an onset after the first IMP dose until 10 days (1 day for hypoglycemia) after the last IMP dose.
[2]Difference is shown between sotagliflozin and placebo.
Applicant's reference CSR table: 14.3.1.1.1

Table 21. Overview of Treatment-Emergent Adverse Events,[1] Safety Population, SCORED

Event	Sotagliflozin N=5291 n (%)	Placebo N=5286 n (%)	Absolute Risk Difference[2] (95.0% CI)
Any AE	3718 (70.3%)	3738 (70.7%)	-0.4 (-2.2, 1.3)
Severe	780 (14.7%)	845 (16.0%)	-1.2 (-2.6, 0.1)
Moderate	2089 (39.5%)	2161 (40.9%)	-1.4 (-3.3, 0.5)
Mild	2833 (53.5%)	2879 (54.5%)	-0.9 (-2.8, 1.0)
SAE	1234 (23.3%)	1334 (25.2%)	-1.9 (-3.5, -0.3)
Death	170 (3.2%)	188 (3.6%)	-0.3 (-1.0, 0.3)
Life-threatening	90 (1.7%)	79 (1.5%)	0.2 (-0.3, 0.7)
Persistent or significant disability/incapacity	22 (0.4%)	18 (0.3%)	0.1 (-0.2, 0.3)
Requires or prolongs hospitalization	1048 (19.8%)	1140 (21.6%)	-1.8 (-3.3, -0.2)
Congenital anomaly or birth defect	0 (0.0%)	0 (0.0%)	0.0 (0.0, 0.0)
Other	306 (5.8%)	324 (6.1%)	-0.3 (-1.2, 0.6)
AE leading to permanent discontinuation	228 (4.3%)	199 (3.8%)	0.5 (-0.2, 1.3)
AE leading to interruption of study drug	885 (16.7%)	806 (15.2%)	1.5 (0.1, 2.9)

Source: Reviewer's analysis [adsl, adae]**; Software:** R

Abbreviations: AE, adverse event; IMP, investigational medical product; CI, confidence interval; N, number of patients in treatment group; n, number of patients with an event; SAE, serious adverse event

[1]Treatment-emergent AEs defined as AEs with an onset after the first IMP dose until 10 days (1 day for hypoglycemia) after the last IMP dose.
[2]Difference is shown between sotagliflozin and placebo.
Applicant's reference CSR table: 14.3.1.1.1

6.6.2. Deaths

There was no imbalance in the incidence of deaths between treatment groups in SOLOIST or SCORED (Table 22). In both groups, common TEAEs that resulted in death were cardiac failure, sudden cardiac death, and myocardial infection (in SCORED). There was no imbalance in CV death (which was a part of the primary composite efficacy endpoint; see Section 5.3. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients) or non-CV death.

Table 22. TEAEs[1] Leading to Deaths with PTs >0.2% in any treatment group, Safety Population, SOLOIST and SCORED

	SOLOIST		SCORED	
	Sotagliflozin	**Placebo**	**Sotagliflozin**	**Placebo**
	N=605	**N=611**	**N=5291**	**N=5286**
Preferred Term[2]	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any TEAE leading to death	49 (8.1%)	52 (8.5%)	170 (3.2%)	188 (3.6%)
Cardiac failure	11 (1.8%)	14 (2.3%)	15 (0.3%)	19 (0.4%)
Sudden cardiac death	8 (1.3%)	9 (1.5%)	14 (0.3%)	8 (0.2%)
Cardiac failure acute	4 (0.7%)	0 (0.0%)	1 (<0.1%)	7 (0.1%)
Cardiogenic shock	2 (0.3%)	2 (0.3%)	3 (0.1%)	4 (0.1%)
Cerebrovascular accident	2 (0.3%)	1 (0.2%)	3 (0.1%)	2 (<0.1%)
Craniocerebral injury	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	2 (0.3%)	4 (0.7%)	9 (0.2%)	11 (0.2%)
Septic shock	2 (0.3%)	2 (0.3%)	1 (<0.1%)	1 (<0.1%)
Sudden death	2 (0.3%)	2 (0.3%)	7 (0.1%)	5 (0.1%)
Acute kidney injury	1 (0.2%)	2 (0.3%)	2 (<0.1%)	3 (0.1%)
Cardiac arrest	1 (0.2%)	0 (0.0%)	4 (0.1%)	11 (0.2%)
Pneumonia	1 (0.2%)	2 (0.3%)	3 (0.1%)	3 (0.1%)
Cardiac death	0 (0.0%)	2 (0.3%)	3 (0.1%)	0 (0.0%)
Cardiac failure chronic	0 (0.0%)	3 (0.5%)	2 (<0.1%)	2 (<0.1%)
Myocardial infarction	0 (0.0%)	2 (0.3%)	9 (0.2%)	22 (0.4%)

Source: Reviewer's analysis [adsl, adae]; **Software:** R

Abbreviations: AE, adverse event; IMP, investigational medical product; N, number of patients in treatment group; n, number of patients with a TEAE leading to death

[1]Treatment-emergent AEs defined as AEs with an onset after the first IMP dose until 10 days (1 day for hypoglycemia) after the last IMP dose.

[2]MedDRA version: 23.0

Applicant's reference CSR table: 14.3.1.2.8

6.6.3. Serious Adverse Events

There were no important imbalances in SAEs between treatment groups in SOLOIST (Table 20) or SCORED (Table 21). The SAEs reported with a RD >0.5% were hypotension and hypoglycemia in SOLOIST (Table 23); these SAEs were expected in the sotagliflozin group based on its mechanism of action. There were no SAEs reported with a RD >0.5% in SCORED (data not shown).

There were no unexpected SAEs grouped by FMQs or SMQs (narrow and broad) reported in SOLOIST and SCORED (data not shown).

Table 23. Serious Adverse Events[1] with Risk Difference >0.5%, Safety Population, SOLOIST

	Sotagliflozin	Placebo	Absolute Risk Difference[3]
Primary System Organ Class	**N=605**	**N=611**	
Preferred Term[2]	**n (%)**	**n (%)**	**(95.0% CI)**
Vascular disorders	13 (2.1%)	13 (2.1%)	0.0 (-1.6, 1.6)
Hypotension	6 (1.0%)	1 (0.2%)	0.8 (-0.0, 1.7)
Metabolism and nutrition disorders	20 (3.3%)	26 (4.3%)	-0.9 (-3.1, 1.2)
Hypoglycaemia	8 (1.3%)	4 (0.7%)	0.7 (-0.4, 1.8)
Cardiac disorders	131 (21.7%)	169 (27.7%)	-6.0 (-10.8, -1.2)
Angina unstable	8 (1.3%)	1 (0.2%)	1.2 (0.2, 2.1)

Source: Reviewer's analysis [adsl, adae]**; Software:** R
Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medical product; N, number of patients in treatment group; n, number of patients with an event
[1]Treatment-emergent AEs defined as AEs with an onset after the first IMP dose until 10 days (1 day for hypoglycemia) after the last IMP dose.
[2]MedDRA version: 23.0
[3]Difference is shown between sotagliflozin and placebo.
Applicant's reference CSR table: 14.3.1.2.1

Reviewer's comment*: The SAE of angina unstable was numerically higher in the sotagliflozin group in SOLOIST, but not in the larger, SCORED study. We strongly suspect this to be a chance finding and, hence, was not considered clinically relevant.*

6.6.4. Dropouts and/or Discontinuations Due to Adverse Events

In both studies, less than 5% of patients had TEAEs that led to study drug discontinuation (Table 20 and Table 21). None of the TEAEs leading to study drug discontinuation in sotagliflozin had RD > 0.5% in SOLOIST (Table 24) or SCORED study (data not shown).

Although 3 patients in the sotagliflozin group in SOLOIST reported a cerebrovascular accident (CVA) that led to treatment discontinuation (Table 24), there was no imbalance in the overall incidence of CVA between treatment groups (5 [0.8%] patients in sotagliflozin vs. 4 [0.7%] in placebo). There was also no imbalance in the incidence of CVA in SCORED.

Table 24. Adverse Events Leading to Discontinuation[1] with Risk Difference >0.2%, Safety Population, SOLOIST

	Sotagliflozin	Placebo	Absolute Risk Difference[3]
Primary System Organ Class	**N=605**	**N=611**	
Preferred Term[2]	**n (%)**	**n (%)**	**(95.0% CI)**
Nervous system disorders	8 (1.3%)	2 (0.3%)	1.0 (-0.0, 2.0)
Cerebrovascular accident	3 (0.5%)	0 (0.0%)	0.5 (-0.1, 1.1)
Investigations	2 (0.3%)	0 (0.0%)	0.3 (-0.1, 0.8)
Alanine aminotransferase increased	2 (0.3%)	0 (0.0%)	0.3 (-0.1, 0.8)
Gastrointestinal disorders	3 (0.5%)	2 (0.3%)	0.2 (-0.6, 0.9)
Intestinal ischaemia	2 (0.3%)	0 (0.0%)	0.3 (-0.1, 0.8)

Source: Reviewer's analysis [adsl, adae]**; Software:** R
Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medical product; N, number of patients in treatment group; n, number of patients with an event
[1]Treatment-emergent AEs defined as AEs with an onset after the first IMP dose until 10 days (1 day for hypoglycemia) after the last IMP dose.
[2]MedDRA version: 23.0
[3]Difference is shown between sotagliflozin and placebo.
Applicant's reference CSR table: 14.3.1.2.6

6.6.5. Treatment-Emergent Adverse Events

The TEAEs with RD >1% are shown for SOLOIST in Table 25. There were no TEAEs with RD >1% in SCORED (data not shown). No new TEAEs were identified in these studies.

Table 25. Treatment-Emergent Adverse Events[1] by Preferred Term with Risk Difference >1%, Safety Population, SOLOIST

	Sotagliflozin	Placebo	Absolute Risk Difference[3]
Primary System Organ Class	**N=605**	**N=611**	
Preferred Term[2]	**n (%)**	**n (%)**	**(95.0% CI)**
Gastrointestinal disorders	90 (14.9%)	81 (13.3%)	1.6 (-2.3, 5.5)
Diarrhoea	37 (6.1%)	21 (3.4%)	2.7 (0.3, 5.1)
Vascular disorders	65 (10.7%)	62 (10.1%)	0.6 (-2.8, 4.0)
Hypotension	35 (5.8%)	28 (4.6%)	1.2 (-1.3, 3.7)
General disorders and administration site conditions	60 (9.9%)	60 (9.8%)	0.1 (-3.3, 3.5)
Fatigue	13 (2.1%)	3 (0.5%)	1.7 (0.4, 2.9)
Metabolism and nutrition disorders	112 (18.5%)	115 (18.8%)	-0.3 (-4.7, 4.1)
Hypoglycaemia	26 (4.3%)	17 (2.8%)	1.5 (-0.6, 3.6)
Renal and urinary disorders	69 (11.4%)	75 (12.3%)	-0.9 (-4.5, 2.8)
Dysuria	10 (1.7%)	2 (0.3%)	1.3 (0.2, 2.4)

Source: Reviewer's analysis [adsl, adae]**; Software:** R
Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medical product; N, number of patients in treatment group; n, number of patients with an event
[1]Treatment-emergent AEs defined as AEs with an onset after the first IMP dose until 10 days (1 day for hypoglycemia) after the last IMP dose.
[2]MedDRA version: 23.0
[3]Difference is shown between sotagliflozin and placebo.
Applicant's reference CSR table: 14.3.1.1.2

No new or unexpected events were identified when TEAEs were analyzed using both narrow and broad FMQs and SMQs (Table 26 and Table 27; data not shown for broad FMQs and narrow or broad SMQs). The FMQs with RD >1% in SOLOIST and SCORED were diarrhea, hypoglycemia, hypotension, UTI, and genital mycotic infection (GMI).

Table 26. FDA MedDRA Queries[1] with Risk Difference >1%, Safety Population, SOLOIST

	Sotagliflozin	**Placebo**	**Absolute Risk Difference[3]**
System Organ Class	**N=605**	**N=611**	
FDA Medical Query (Narrow)[2]	**n (%)**	**n (%)**	**(95% CI)**
Preferred Term			
Gastrointestinal disorders			
Diarrhea	38 (6.3%)	21 (3.4%)	2.8 (0.4, 5.3)
Diarrhoea	37 (6.1%)	21 (3.4%)	2.7 (0.3, 5.1)
Musculoskeletal and connective tissue disorders			
Arthritis	23 (3.8%)	13 (2.1%)	1.7 (-0.2, 3.6)
Osteoarthritis	7 (1.2%)	3 (0.5%)	0.7 (-0.4, 1.7)
General disorders and administration site conditions			
Fatigue	22 (3.6%)	11 (1.8%)	1.8 (0.0, 3.7)
Fatigue	13 (2.1%)	3 (0.5%)	1.7 (0.4, 2.9)
Asthenia	10 (1.7%)	6 (1.0%)	0.7 (-0.6, 2.0)
Skin and subcutaneous tissue disorders			
Rash	12 (2.0%)	4 (0.7%)	1.3 (0.0, 2.6)
Endocrine disorders			
Hypoglycemia	28 (4.6%)	18 (2.9%)	1.7 (-0.5, 3.8)
Hypoglycaemia	26 (4.3%)	17 (2.8%)	1.5 (-0.6, 3.6)
Renal and urinary disorders			
Renal & Urinary Tract Infection	51 (8.4%)	42 (6.9%)	1.6 (-1.4, 4.5)
Vascular disorders			
Hypotension	42 (6.9%)	34 (5.6%)	1.4 (-1.3, 4.1)
Hypotension	35 (5.8%)	28 (4.6%)	1.2 (-1.3, 3.7)
Blood and lymphatic system disorders			
Thrombosis (Arterial)	32 (5.3%)	24 (3.9%)	1.4 (-1.0, 3.7)
Angina unstable	8 (1.3%)	2 (0.3%)	1.0 (-0.0, 2.0)
Transient ischaemic attack	4 (0.7%)	0 (0.0%)	0.7 (0.0, 1.3)
Hemorrhage	22 (3.6%)	15 (2.5%)	1.2 (-0.8, 3.1)

Source: Reviewer's analysis [adsl, adae]**; Software:** R
Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA MedDRA Query; IMP, investigational medical product; N, number of patients in treatment group; n, number of patients with an event; PT, preferred term
[1]Treatment-emergent AEs defined as AEs with an onset after the first IMP dose until 10 days (1 day for hypoglycemia) after the last IMP dose.
[2]Coded as MedDRA preferred terms (FMQ version v2.0 and MedDRA version: 23.0)
[3]Difference is shown between sotagliflozin and placebo.
Note: all PTs with RD > 0.5 % are shown.

Table 27. FDA MedDRA Queries[1] with Risk Difference >1%, Safety Population, SCORED

	Sotagliflozin	Placebo	Absolute Risk Difference[3]
System Organ Class	**N=5291**	**N=5286**	
FDA Medical Query (Narrow)[2]	**n (%)**	**n (%)**	**(95% CI)**
Preferred Term			
Gastrointestinal disorders			
Diarrhea	378 (7.1%)	258 (4.9%)	2.3 (1.4, 3.2)
Diarrhoea	376 (7.1%)	257 (4.9%)	2.2 (1.3, 3.1)
Infections and infestations			
Fungal Infection	183 (3.5%)	103 (1.9%)	1.5 (0.9, 2.1)
Vulvovaginal mycotic infection	36 (0.7%)	4 (0.1%)	0.6 (0.4, 0.8)

Source: Reviewer's analysis [adsl, adae]**; Software:** R
Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA MedDRA Query; IMP, investigational medical product; N, number of patients in treatment group; n, number of patients with an event; PT, preferred term
[1]Treatment-emergent AEs defined as AEs with an onset after the first IMP dose until 10 days (1 day for hypoglycemia) after the last IMP dose.
[2]Coded as MedDRA preferred terms (FMQ version v2.0 and MedDRA version: 23.0)
[3]Difference is shown between sotagliflozin and placebo.
Note: all PTs with RD > 0.5 % are shown.

6.6.6. Adverse Events of Special Interest

Table 28 summarizes applicant defined AESIs and reviewer's additional queries in both SOLOIST and SCORED studies. There were no incidences of pregnancy and no imbalance in the incidence of alanine aminotransferase (ALT) increase ≥3x upper limit of normal (ULN) between treatment groups in SOLOIST and SCORED studies. There was only one incidence of symptomatic overdose (a non-serious event of postural hypotension) reported in sotagliflozin group in SCORED, but upon further review, it was found that overdose definition of twice the recommended dose was not met.

Commonly reported AESIs (>5%) in either treatment group were acute kidney injury (AKI), volume depletion, UTI, diarrhea, and hypoglycemia (in SCORED). Volume depletion, UTI, GMI, and diarrhea occurred at an increased frequency in patients treated with sotagliflozin in SOLOIST and/or SCORED study. These AEs, except diarrhea, are consistent with the known clinical profile of selective SGLT2 inhibitors. There were no imbalances in the other AESIs between treatment groups.

Sensitivity analyses using reviewer's additional queries for AESIs provided similar results as applicant defined AESIs, and hence, AESIs are presented based on applicant's definition. In addition to AESIs that occurred at an increased frequency with sotagliflozin, DKA, severe hypoglycemia, amputations and AEs leading to amputation, bone fractures, drug-induced liver injury (DILI), Fournier's gangrene, and hypersensitivity reactions are discussed in the section below. As hypersensitivity reaction was not an AESI per protocol, it is presented using FMQ.

Table 28. Adverse Events of Special Interest,[1] Safety Population, SOLOIST and SCORED

	SOLOIST		SCORED	
AESI	Sotagliflozin N=605 n (%)	Placebo N=611 n (%)	Sotagliflozin N=5291 n (%)	Placebo N=5286 n (%)
Pregnancy (Applicant defined)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Symptomatic overdose with IMP (Applicant defined)	0 (0.0%)	0 (0.0%)	1 (<0.1%)	0 (0.0%)
ALT increase ≥ 3x ULN (Applicant defined)	12 (2.0%)	13 (2.1%)	48 (0.9%)	46 (0.9%)
Diabetic ketoacidosis				
Applicant defined	4 (0.7%)	7 (1.1%)	47 (0.9%)	30 (0.6%)
FMQ, broad	4 (0.7%)	6 (1.0%)	46 (0.9%)	34 (0.6%)
Volume depletion				
Applicant defined	56 (9.3%)	54 (8.8%)	277 (5.2%)	213 (4.0%)
FMQ, broad	15 (2.5%)	15 (2.5%)	70 (1.3%)	59 (1.1%)
Urinary tract infections				
Applicant defined	52 (8.6%)	44 (7.2%)	611 (11.5%)	584 (11.0%)
CMQ	52 (8.6%)	44 (7.2%)	635 (12.0%)	594 (11.2%)
Hypoglycemia				
Applicant defined	26 (4.3%)	17 (2.8%)	406 (7.7%)	416 (7.9%)
FMQ, narrow	28 (4.6%)	18 (2.9%)	417 (7.9%)	431 (8.2%)
Severe hypoglycemia (Applicant defined)	10 (1.7%)	6 (1.0%)	61 (1.2%)	70 (1.3%)
Fournier's gangrene (Applicant defined)	3 (0.5%)	0 (0.0%)	15 (0.3%)	16 (0.3%)
Genital mycotic infections				
Applicant defined	5 (0.8%)	1 (0.2%)	125 (2.4%)	45 (0.9%)
CMQ	14 (2.3%)	4 (0.7%)	247 (4.7%)	93 (1.8%)
Diarrhea				
Applicant defined	42 (6.9%)	25 (4.1%)	447 (8.4%)	315 (6.0%)
FMQ, broad	47 (7.8%)	26 (4.3%)	497 (9.4%)	363 (6.9%)
Acute kidney injury				
Applicant defined	82 (13.6%)	93 (15.2%)	300 (5.7%)	346 (6.5%)
FMQ, broad	57 (9.4%)	70 (11.5%)	338 (6.4%)	366 (6.9%)
SMQ, broad (Acute renal failure)	58 (9.6%)	70 (11.5%)	339 (6.4%)	374 (7.1%)

	SOLOIST		SCORED	
AESI	Sotagliflozin N=605 n (%)	Placebo N=611 n (%)	Sotagliflozin N=5291 n (%)	Placebo N=5286 n (%)
Drug-Induced liver injury				
Applicant defined	11 (1.8%)	14 (2.3%)	36 (0.7%)	34 (0.6%)
FMQ, narrow (Hepatic injury)	13 (2.1%)	10 (1.6%)	55 (1.0%)	57 (1.1%)
Bone fractures				
Applicant defined	12 (2.0%)	9 (1.5%)	112 (2.1%)	115 (2.2%)
CMQ	11 (1.8%)	9 (1.5%)	110 (2.1%)	113 (2.1%)
Amputations (Applicant-defined)	4 (0.7%)	0 (0.0%)	30 (0.6%)	28 (0.5%)
AEs leading to amputation (Applicant-defined)	4 (0.7%)	1 (0.2%)	32 (0.6%)	33 (0.6%)
Venous thrombotic events				
Applicant-defined	0 (0.0%)	7 (1.1%)	31 (0.6%)	37 (0.7%)
SMQ, narrow (Embolic and thrombotic events, venous)	0 (0.0%)	7 (1.1%)	33 (0.6%)	38 (0.7%)
Pancreatitis				
Applicant-defined	0 (0.0%)	3 (0.5%)	12 (0.2%)	20 (0.4%)
FMQ, narrow	0 (0.0%)	3 (0.5%)	15 (0.3%)	22 (0.4%)
SMQ, narrow (Acute pancreatitis)	0 (0.0%)	2 (0.3%)	8 (0.2%)	17 (0.3%)
Any malignancies of special interest				
Applicant-defined	4 (0.7%)	4 (0.7%)	47 (0.9%)	42 (0.8%)
Hypersensitivity reactions				
FMQ, broad (Anaphylactic reaction)	2 (0.3%)	0 (0.0%)	8 (0.2%)	12 (0.2%)
FMQ, narrow (angioedema)	0 (0.0%)	0 (0.0%)	9 (0.2%)	6 (0.1%)
FMQ, broad (Angioedema)	2 (0.3%)	0 (0.0%)	19 (0.4%)	21 (0.4%)

Source: Reviewer's analysis [adsl, adae, adevsi]**; Software:** R
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; CMQ, customized MedDRA query; FMQ, FDA medical query; IMP, investigational medical product; N, number of patients in treatment group; n, number of patients with an event; SMQ, standard MedDRA query; ULN, upper limit of normal
[1]Treatment-emergent AESIs defined as AEs with an onset after the first IMP dose until 10 days (1 day for hypoglycemia) after the last IMP dose.
Applicant's reference CSR table: 14.3.1.3.1, 14.3.1.4.1, and 14.3.1.4.6.1

6.6.6.1. Volume Depletion

Volume depletion events were more frequently reported in the sotagliflozin group in both studies (Table 28).

In SCORED, volume depletion events were reported in 5.2% (328 events in 277 patients) and 4.0% (242 events in 213 patients) of the sotagliflozin and placebo groups, respectively. Serious

events (0.8% and 0.9%, respectively) and events leading to permanent treatment discontinuation (0.1% and 0.1%, respectively) were uncommon in both sotagliflozin and placebo patients.

In SOLOIST, volume depletion events were reported in 9.3% (68 events in 56 patients) and 8.8% (68 events in 54 patients) of the sotagliflozin and placebo groups, respectively. Serious events (2.1% and 3.1%, respectively) and events leading to permanent treatment discontinuation (0% and 0.2%, respectively) were uncommon in both sotagliflozin and placebo patients. Most commonly reported PT (>2%) was hypotension in both studies.

There was a case of volume depletion with a fatal outcome reported in sotagliflozin group in SOLOIST.

> *Patient (b) (6), a 66-year-old Native Hawaiian or other Pacific Islander male with a 34-year history of T2DM at the time of enrollment ((b) (6)), experienced circulatory collapse on day 102 (b) (6)) and was found dead on the toilet in his home. The primary cause of death was sudden cardiac death. The event of circulatory collapse was sent to the Clinical Endpoint Adjudication Committee who assessed it as positively adjudicated as an undetermined death.*

***Reviewer's comment**: The death was adjudicated, and the primary cause of death was sudden cardiac death. As circulatory collapse was part of the AE grouping related to AESI of volume depletion, the fatal outcome was reported under volume depletion, but the death was not due to volume depletion.*

In both studies, volume depletion events were more likely to occur in elderly patients and in patients with lower baseline eGFR (<30 mL/min/1.73m^2 in SCORED and <60 mL/min/1.73m^2 in SOLOIST). In SCORED, there was no imbalance in the incidence of volume depletion events in sotagliflozin treated patients with HF compared to those without HF (5.0% vs. 5.3%, respectively).

6.6.6.2. Urinary Tract Infections

Urinary tract infections were more frequently reported in the sotagliflozin group than placebo in SOLOIST, but in a larger study (SCORED), it was not reported at a higher rate than placebo (Table 28). In both SOLOIST and SCORED studies, majority of the UTI events in both treatment groups were non-serious, mild or moderate in severity, and rarely resulted in treatment discontinuation. Most commonly reported PTs (>1%) were cystitis bacterial, cystitis, UTI bacterial, and UTI in SCORED and cystitis in SOLOIST.

Urinary tract infections occurred more frequently in female patients in both sotagliflozin and placebo groups.

6.6.6.3. Genital Mycotic Infections

Genital mycotic infections were reported more frequently in patients treated with sotagliflozin in both studies (Table 28). The majority of events were mild or moderate in severity. One patient in SCORED had a serious event that led to treatment discontinuation.

> *Patient (b) (6), a 68-year-old female weighing 84.3 kg with T2DM for 13 years, developed frequent vulvovaginitis after initiation of IMP. The patient went to emergency room with her third episode which occurred 2 months after randomization. The sotagliflozin dose was reduced to 200 mg. Following another episode of vulvovaginitis 8 months after randomization (on (b) (6)), sotagliflozin dose was withdrawn. All episodes of vulvovaginitis were treated with miconazole cream.*

***Reviewer's comment**: Genital mycotic infections are a known safety concern with the approved SGLT2 inhibitors and adequately described in the Warnings and Precautions section of the applicant's proposed product labeling of sotagliflozin.*

GMI occurred more frequently in female patients, with a relative risk (95% CI) of 2.9 (1.9, 4.4) and 3.2 (0.3, 30.6) in SCORED and SOLOIST, respectively.

6.6.6.4. Diarrhea

Diarrhea occurred at an increased frequency in patients treated with sotagliflozin (Table 28). Most events were mild or moderate in severity. Serious events and events leading to permanent treatment discontinuation were uncommon in both studies.

There were a few more AEs of diarrhea reported in elderly patients in SOLOIST; however, there were no between group differences in the incidences of diarrhea by age in SCORED. In both studies, incidence of diarrhea was slightly higher in female patients.

6.6.6.5. Diabetic Ketoacidosis

An independent CEC reviewed and adjudicated all events of DKA. The incidence of DKA events is shown in Table 28. Incidence rates of DKA events were low in SCORED (0.7 and 0.5 per 100 patient-years in sotagliflozin and placebo groups, respectively) and SOLOIST (1.0 and 1.7 per 100 patient-years in sotagliflozin and placebo groups, respectively); however, the risk of DKA was slightly higher for sotagliflozin treated patients in SCORED. The relative risk (95% CI) was 1.6 (1.0, 2.5) and 0.5% of events were serious in SCORED. There were no imbalances in serious DKA events between treatment groups in SOLOIST.

There was a case of DKA with a fatal outcome reported in the sotagliflozin group in SCORED.

> *Patient (b) (6), a 70-year-old White male, developed a pressing chest pain in the early morning at 05:30. During the day, his condition deteriorated, and he was*

hospitalized at 22:49 with DKA after 5.5 months of IMP and diagnosed with cardiopulmonary insufficiency (assisted ventilation), asystole, acute septal-apical MI, hyperglycemia, metabolic acidosis, generalized arteriosclerosis, angina pectoris, cerebral arteriosclerosis, and vertebrobasilar insufficiency. The patient was found in tachycardia with arrhythmic heart sounds with no murmurs. Heart rate: 100/min, BP: 110/70 mmHg (while on noradrenaline 3 mg/h), peripheral oxygen saturation: 100%, fraction of inspired oxygen: 40%, positive end-expiratory pressure: 6 cm water, serum glucose 28 mmol/L (504 mg/dL), blood acidity level was pH 6.7, and blood ketone level was unknown. Over the next 12 hours, he deteriorated hemodynamically and expired on day 173. On day 172 (b) (6)), the patient had elevated cardiac biomarkers (creatine kinase MB 125 IU/L and high sensitivity troponin T 5.07 ng/mL). The event was sent to the Clinical Endpoint Adjudication Committee who assessed it as positively adjudicated as a myocardial infarction.

Reviewer's comment: *The death was adjudicated, and the primary cause of death was myocardial infarction.*

In both SOLOIST and SCORED studies, there were no meaningful differences between treatment groups in the incidences of DKA by age, sex, race, BMI, eGFR and LVEF subgroups.

6.6.6.6. Severe Hypoglycemia

Severe hypoglycemia was identified based on investigator's opinion as an event where all the following criteria were met: (1) external assistance is required; (2) subject was not capable of treating self and required assistance by ambulance or an emergency room visit or hospitalization; and (3) symptoms such as seizures, coma, or loss of consciousness present.

The incidence of severe hypoglycemia was similar in both sotagliflozin and placebo groups in both studies (Table 28). One patient in SCORED had a serious event that led to treatment discontinuation.

In SOLOIST, serious events were reported in 1.2% and 0.5% of patients in the sotagliflozin and placebo groups, respectively. No events of hypoglycemic coma or hypoglycemic unconsciousness were reported. In elderly patients, there was higher incidence for severe hypoglycemia in SOLOIST, but the difference was not seen in a larger, SCORED study. In both studies, severe hypoglycemia was most frequently reported in patients with duration of T2DM >10 years and baseline insulin use, regardless of treatment.

Reviewer's comment*: In summary, based on the available data, there did not appear to be an increased risk of severe hypoglycemia with sotagliflozin.*

6.6.6.7. Amputations and AEs leading to amputation

In SCORED, amputations were reported for 0.6% (35 events in 30 patients) and 0.5% (28 events in 28 patients) in the sotagliflozin and of placebo groups, respectively (Table 28). The incidence rate was 0.5 and 0.4 per 100 patient-years in sotagliflozin and placebo groups, respectively, in SCORED; the hazard ratio (95% CI) was 1.07 (0.64, 1.79) indicating no significant difference in the risk of amputation events between sotagliflozin and placebo.

In SOLOIST, the sotagliflozin group had a numerically higher incidences of amputation events compared to placebo (Table 28), but the difference was too small to make a definitive conclusion; all four amputations were reported in elderly patients in SOLOIST.

The incidence of events leading to amputation are shown in Table 28. Most common precipitating events leading to amputation were diabetic foot, osteomyelitis, gangrene, skin ulcer, diabetic foot infection, or peripheral artery thrombosis in SCORED and osteitis, osteomyelitis, skin ulcer, gouty arthritis, or gangrene in SOLOIST.

***Reviewer's comment**: There is a concern that SGLT2 inhibitors, via their diuretic effect, could lead to hypoperfusion of distal extremities, triggering ischemia and necrosis, eventually leading to amputation. Lower limb amputation is a labeled warning for canagliflozin and ertugliflozin, other members of the SGLT2 inhibitors drug class. However, the available data from SOLOIST and SCORED do not show meaningful between group differences in amputation or events leading to amputation.*

6.6.6.8. Bone Fractures

An independent CEC reviewed and adjudicated bone fractures. There was no difference in the incidence of bone fractures between treatment groups in SOLOIST (sotagliflozin: 2.0% vs. placebo: 1.5%) or SCORED (2.1% vs. 2.2%) (Table 28). The incidence rate was 2.9 and 2.2 per 100 patient-years in sotagliflozin and placebo groups, respectively, in SOLOIST, and 1.8 per 100 patient-years in both sotagliflozin and placebo groups in SCORED.

Majority of the bone fractures were serious in both treatment groups. One patient in SCORED had a serious event that led to treatment discontinuation.

> *Patient (b) (6), a 51-year-old Asian male, experienced femoral neck fracture on day 299 ((b) (6)) due to an accidental fall and was hospitalized to emergency department. The patient reported pain in the right hip joint, restricted movement, and inability to stand. X-ray examination revealed right femoral neck fracture. The type of fracture was reported as high trauma. Sotagliflozin dose was withdrawn due to the event. Patient was treated with remedial therapies and on (b) (6), he underwent right total hip arthroplasty. The bone mineral density and bone scintigraphy tests were not performed. On (b) (6), the patient was discharged from the hospital.*

Reviewer's comment: *The femoral neck fracture was a high trauma event due to fall and not related to sotagliflozin treatment.*

Bone fractures were more frequently reported in females and elderly, regardless of treatment, and were mostly low trauma events (<2% in both studies).

6.6.6.1. Drug-Induced Liver Injury

The DILI committee reviewed and adjudicated the etiology of potential cases of DILI in a treatment-blinded manner. Potential cases of DILI were reported in sotagliflozin and placebo groups in both studies at similar frequencies (Table 29). There was only one case in sotagliflozin group in SCORED that met the criteria for Hy's Law.

> *Patient (b) (6), a 72-year-old male weighing 96.3 kg, had a 23-year history of T2DM at the time of enrollment ((b) (6)). IMP was discontinued on (b) (6) proximate to beginning peritoneal dialysis. Four months later ((b) (6)) the patient developed a common bile duct obstruction secondary to gallstones. The obstruction was associated with elevated bilirubin and ALT. Endoscopic ultrasound showed distended gallbladder with a large amount of sludge and two stones. On (b) (6), patient underwent bile duct stone extraction with biliary sphincterotomy, and liver function tests improved.*

Reviewer's comment*: This was a case of obstructive jaundice related to cholelithiasis and not liver injury caused by sotagliflozin treatment.*

Table 29. Events of Special Interest,[1] Overview of Potential Drug-Induced Liver Injury, Safety Population, SOLOIST and SCORED

	SOLOIST		SCORED	
	Sotagliflozin N=605	**Placebo N=611**	**Sotagliflozin N=5291**	**Placebo N=5286**
Event	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any Event	11 (1.8%)	14 (2.3%)	36 (0.7%)	34 (0.6%)
Adjudicated	11 (1.8%)	14 (2.3%)	36 (0.7%)	34 (0.6%)
Positively adjudicated	4 (0.7%)	8 (1.3%)	21 (0.4%)	19 (0.4%)
Negatively adjudicated	7 (1.2%)	5 (0.8%)	13 (0.2%)	14 (0.3%)
Not evaluable	0 (0.0%)	1 (0.2%)	3 (0.1%)	4 (0.1%)
Possible Hy's Law cases by CEC	10 (1.7%)	14 (2.3%)	34 (0.6%)	34 (0.6%)
Yes	0 (0.0%)	0 (0.0%)	1 (<0.1%)	0 (0.0%)
No	10 (1.7%)	13 (2.1%)	32 (0.6%)	30 (0.6%)
Not evaluable	0 (0.0%)	1 (0.2%)	1 (<0.1%)	4 (0.1%)
Drug induced liver injury	11 (1.8%)	14 (2.3%)	36 (0.7%)	34 (0.6%)
Yes	10 (1.7%)	13 (2.1%)	34 (0.6%)	33 (0.6%)
No	1 (0.2%)	0 (0.0%)	1 (<0.1%)	0 (0.0%)
Not evaluable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Reviewer's analysis [adsl, adevsi]**; Software:** R
Abbreviations: AE, adverse event; CEC, clinical endpoint committee; IMP, investigational medical product; N, number of patients in treatment group; n, number of patients with an event
[1]Treatment-emergent EOSIs defined as AEs with an onset after the first IMP dose until 10 days after the last IMP dose.
Sponsor's reference CSR table: 14.3.1.4.6.1

6.6.6.2. Fournier's Gangrene

Cases of Fournier's gangrene were identified in accordance with a signal issued by FDA in 2018 about rare occurrences of serious infections of the genitals and area around the genitals with SGLT2 inhibitors for diabetes. Fournier's gangrene was reported in the sotagliflozin group at an incidence of 0.5% (3 events in 3 patients) in SOLOIST; however, it did not occur at higher rates in patients treated with sotagliflozin compared to placebo in a larger, SCORED study (Table 28). Two of the three events were serious in SOLOIST and majority of the events were serious in both treatment groups in SCORED. None of the events led to treatment discontinuation in SOLOIST and <0.1% events in both treatment groups led to discontinuation in SCORED.

All three cases in SOLOIST and majority of the cases in SCORED were identified using applicant's customized PT list for Fournier's gangrene did not involve perineum. There was one event of confirmed Fournier's gangrene which led to treatment discontinuation in SCORED.

> *Patient (b) (6) a 67-year-old Native Hawaiian or Other Pacific Islander male with a history of T2DM, presented to emergency department on day 400 ((b) (6)) with spiking fevers, perianal pain, tachycardia, and dehydration. On the basis of clinical data, patient was diagnosed with DKA. The CEC positively adjudicated the event as DKA. On day 402 ((b) (6)), patient had erythema with perianal hemorrhoids and*

perianal tenderness. Based on the blood work-up, the patient was found to have raised inflammatory markers including CRP (200mg/mL). Magnetic resonance imaging (MRI) of the patient's pelvic region revealed extensive superficial edema with fluid collections surrounding the superficial anus and suspected soft tissue gas locules. The sotagliflozin dose was withdrawn on (b) (6) due to the event. On day 405 ((b) (6)), the patient was taken to surgery and perineal debridement of necrotizing fasciitis and packing was performed. On day 406 ((b) (6)), based on the sections of perineal skin to subcutis, severe extensive necrotizing fasciitis was confirmed.

***Reviewer's comment**: Fournier's gangrene is a rare, but serious, necrotizing infection of perineum observed across the SGLT2 inhibitor class and adequately described in the Warnings and Precautions section of the applicant's proposed product labeling of sotagliflozin.*

6.6.6.3. Hypersensitivity reactions

Table 28 summarizes FMQs for anaphylactic reaction and angioedema in both SOLOIST and SCORED studies. In SOLOIST, there were two cases of anaphylactic reactions (broad FMQ) reported in sotagliflozin group. Of the two, one resulted in a fatal outcome (PT circulatory collapse) – see Section 6.6.7.2 Volume Depletion for a patient narrative, and the other had a reported PT of pharyngeal swelling.

***Reviewer's comment**: The death was adjudicated, and the primary cause of death was sudden cardiac death. As circulatory collapse was part of the AE grouping related to broad FMQ of anaphylactic reaction, the fatal outcome was reported under the FMQ, but the death was not due to anaphylactic reaction.*

In SCORED, there were three serious cases of angioedema (narrow FMQ) reported. Of the three, one was a life-threatening angioedema, second one resulted in a hospitalization, and third one was categorized as other medically important serious event. Two cases of non-serious angioedema led to study drug discontinuation.

Patient (b) (6) was an 80-year-old White male with a past medical history of T2DM, arterial hypertension, chronic obstructive pulmonary disease, four episodes of myocardial infarction, ischemic stroke, dyslipidemia, coronary artery disease, congestive heart failure, and chronic kidney disease. Concomitant medications include atorvastatin, aspirin, and antihypertensive medications including ramipril. On (b) (6) (4 months after first administration of IMP), patient visited to emergency room (ER) due to tongue edema. The patient was diagnosed with angioedema of tongue and received methylprednisolone, sodium chloride, clemastine, glucose, hydrocortisone and ranitidine as corrective treatment. The patient was recovered on the same day and was discharged from the ER. The sotagliflozin dose was not changed due to the event.

Patient (b) (6) a 63-year-old White female, visited ER due to swollen tongue and anterior neck on (b) (6) (1.2 years after the first IMP administration).

The patient reported that the swelling was not painful, but felt tight, and she was able to swallow. The patient has taken cilazapril on the day before the event and was on this medication for months. The patient was diagnosed with angioedema. The sotagliflozin dose was not changed with respect to the event. The patient received hydrocortisone, loratadine and prednisone as corrective treatment for angioedema and was advised to stop ACE inhibitor cilazapril. On (b) (6), the event was resolved.

Patient (b) (6), a 70-year-old White female, suddenly experienced difficulty breathing and swelling of the face and neck on (b) (6) (1.1 years after the first administration of IMP). The patient was hospitalized on the same day; hematology test results showed: hemoglobin 125 g/l, red blood cell 4.5 x 10^{12}/l, white blood cell 14.3 x 10^{9}/l, eosinophil 4%, neutrophil 71%, lymphocyte 19%, monocytes 6%, and platelet 205 x 10^{9}/l. Skin prick test and other allergy tests were not done. Patient was diagnosed with quincke's edema on unspecified allergen (angioedema). Sotagliflozin dose was not changed with respect to the event. During hospitalization, desensitizing therapy was done using activated charcoal, clemastine fumarate, and dexamethasone. The event resolved on (b) (6) and the patient was discharged from the hospital.

***Reviewer's comment**: Sotagliflozin treatment was not discontinued in any of these three patients with respect to the event. The two reported cases of angioedema were possibly due to intake of angiotensin-converting enzyme (ACE) inhibitor, ramipril and cilazapril, and the other case of angioedema was possibly due to unknown allergen. These events didn't appear to be related to sotagliflozin treatment.*

6.6.7. Laboratory Findings

In SOLOIST and SCORED, several laboratory parameters including chemistry, hematology, and renal function were collected at all visits and other parameters including lipids were collected at baseline visit and at the last study visit (i.e., either at premature treatment discontinuation visit or study closure visit).

Mean change from baseline for all clinical laboratory parameters analyzed were relatively similar between treatment groups in both studies and generally stable throughout the duration of treatment except for those parameters that are known to be impacted by SGLT2 inhibition (Figure 7, Figure 8, Figure 9, and Figure 10). Mean values for these parameters at baseline and the change from baseline to last on-treatment visit are summarized in Table 30Table 30below.

Table 30. Mean Changes in Laboratory Parameters from Baseline to Last On-Treatment Visit, Safety Population, SOLOIST and SCORED

	SOLOIST		SCORED	
Lab Parameter (unit), mean (SD)	**Sotagliflozin N=605**	**Placebo N=611**	**Sotagliflozin N=5291**	**Placebo N=5286**
eGFR (mL/min/1.73m^2)				
Baseline	52.5 (18.6)	54.0 (18.7)	44.6 (11.4)	44.6 (11.2)
Change from BL to last on-treatment visit	-0.4 (13.6)	-1.2 (13.7)	-2.6 (10.0)	-2.1 (9.9)
Serum creatinine (mg/dL)				
Baseline	1.2 (0.4)	1.2 (0.4)	1.3 (0.4)	1.3 (0.4)
Change from BL to last on-treatment visit	0.04 (0.4)	0.05 (0.4)	0.1 (0.4)	0.1 (0.4)
Hematocrit (%)				
Baseline	40.9 (6.2)	41.4 (6.2)	40.4 (4.8)	40.4 (4.8)
Change from BL to last on-treatment visit	0.5 (4.7)	-1.3 (4.3)	1.3 (3.7)	-0.9 (3.5)
LDL-C (mg/dL)				
Baseline	73.1 (33.1)	72.2 (32.1)	81.6 (36.8)	81.2 (36.5)
Change from BL to last on-treatment visit	7.8 (30.0)	1.9 (29.2)	4.2 (33.2)	2.6 (32.9)

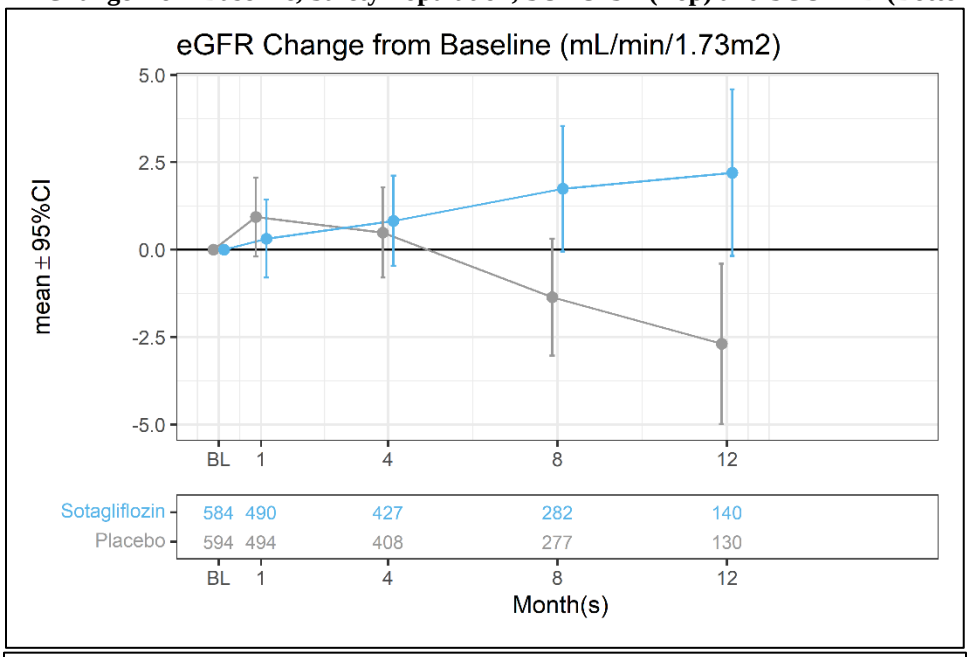
Source: Reviewer's analysis [adsl, adlb]**; Software:** JMP
Abbreviations: BL, baseline; eGFR, estimated glomerular filtration rate; IMP, investigational medical product; LDL-C, low density lipoprotein cholesterol; N, number of patients in treatment group; SD, standard deviation
Note: Last on-treatment value is defined as the last value collected (including unscheduled evaluations) up to 2 days after last IMP intake. Only central laboratory values are included in this summary.
Applicant's reference CSR table: 14.3.2.1.1, 14.3.2.2.1, 14.3.2.3.1, and 14.3.2.5.1

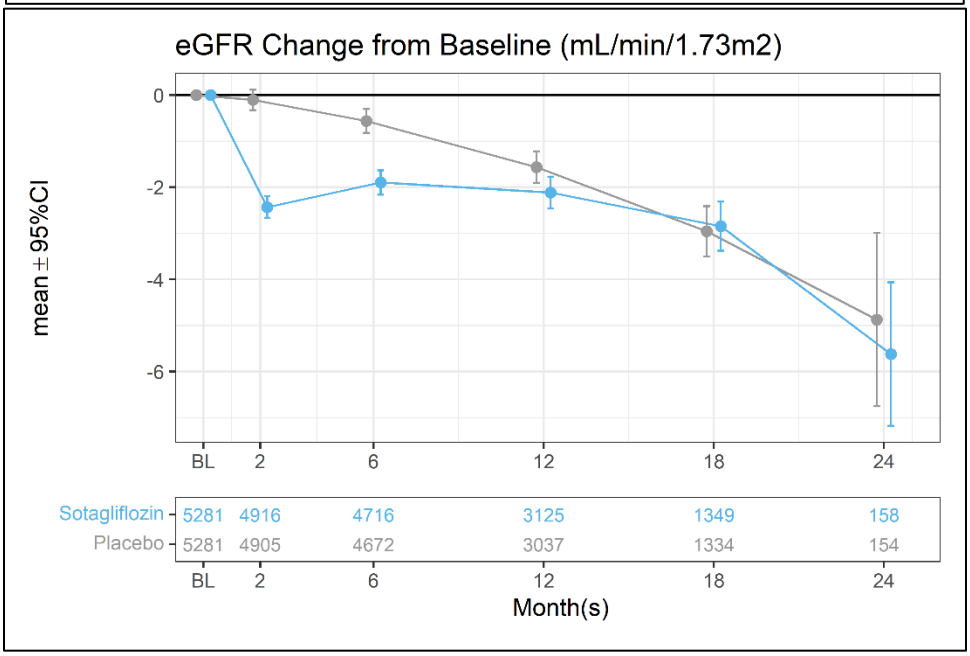
6.6.7.1. Renal Function

In SCORED, mean serum creatinine increased and eGFR decreased acutely after the start of the treatment and remained steady throughout the study in the sotagliflozin group (Figure 7 and Figure 8, bottom). In SOLOIST, there were no important between group differences in mean serum creatinine and eGFR (Figure 7 and Figure 8, top).

Mean changes from baseline in other renal function parameters (e.g., urea nitrogen and urate) were similar between treatment groups and relatively stable over time in both studies.

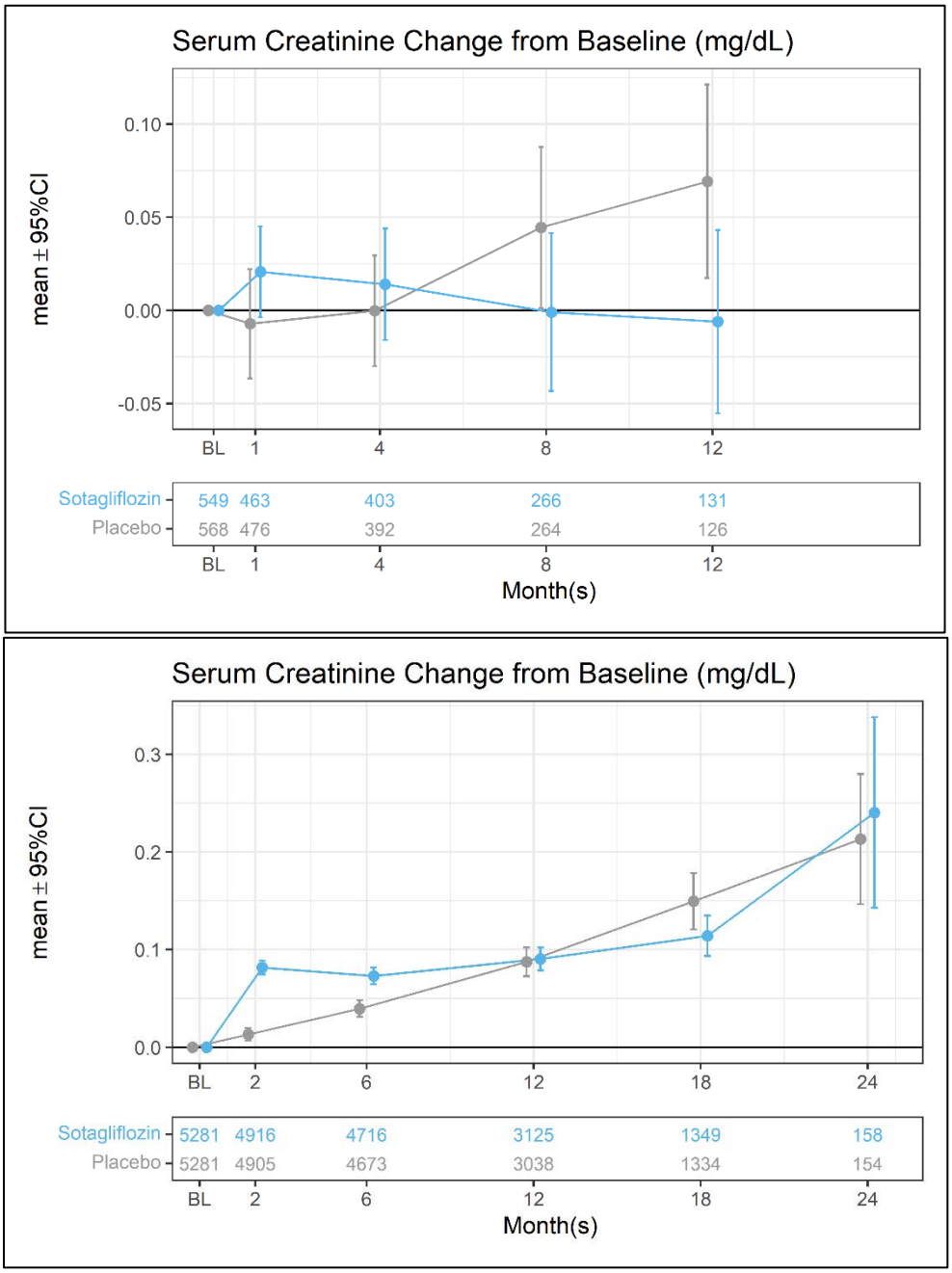
Figure 7. eGFR Change from Baseline, Safety Population, SOLOIST (Top) and SCORED (Bottom)





Source: Reviewer's analysis [adsl, adlb]**; Software:** R

Figure 8. Serum Creatinine Change from Baseline, Safety Population, SOLOIST (Top) and SCORED (Bottom)



Source: Reviewer's analysis [adsl, adlb]**; Software:** R

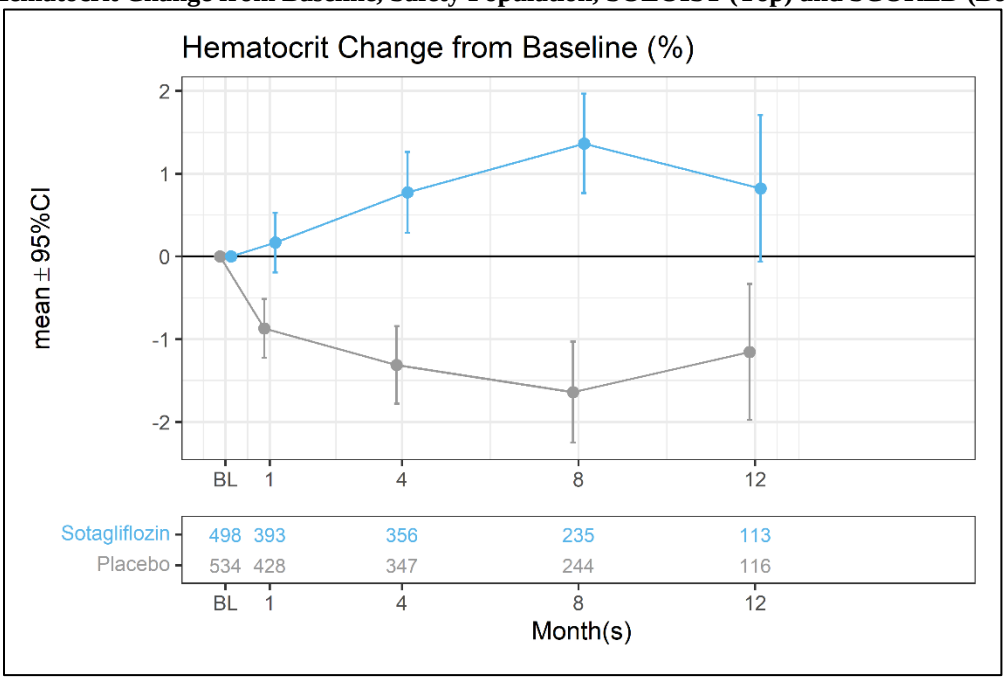
Reviewer's comment: *The observed small early changes in eGFR and creatinine are transient and likely related to hemodynamic changes. There were no corresponding clinical findings based on the AE data. These changes have been consistent across the SGLT2 inhibitor class.*

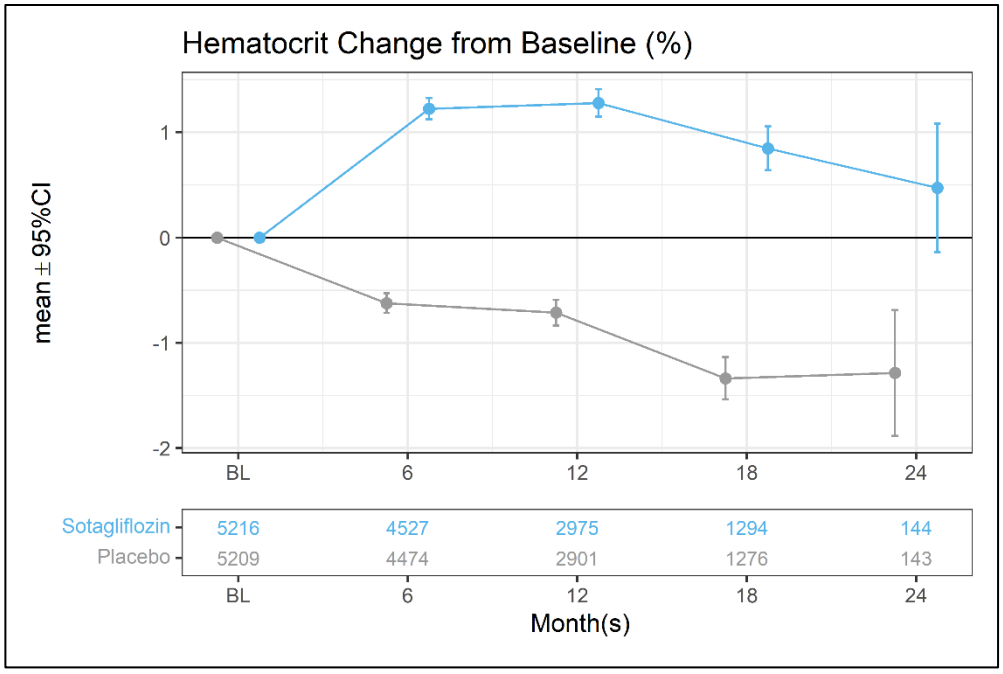
6.6.7.2. Hematology

Mean changes from baseline in hematology parameters (e.g., hemoglobin, platelets, and leukocytes) were similar between treatment groups and relatively stable over time with the exception of slight increase in mean change from baseline over time in hematocrit in the sotagliflozin group compared to placebo group in both studies (Figure 9).

Reviewer's comment: *Increases in hematocrit were observed consistently across the SGLT2 inhibitor class which may be related to the volume depletion class effects. Increases in hematocrit could theoretically increase the risk of thromboembolic events, however, in both SOLOIST and SCORED, these small increases in hematocrit did not result in any significant clinical findings.*

Figure 9. Hematocrit Change from Baseline, Safety Population, SOLOIST (Top) and SCORED (Bottom)





Source: Reviewer's analysis [adsl, adlb]**; Software:** R

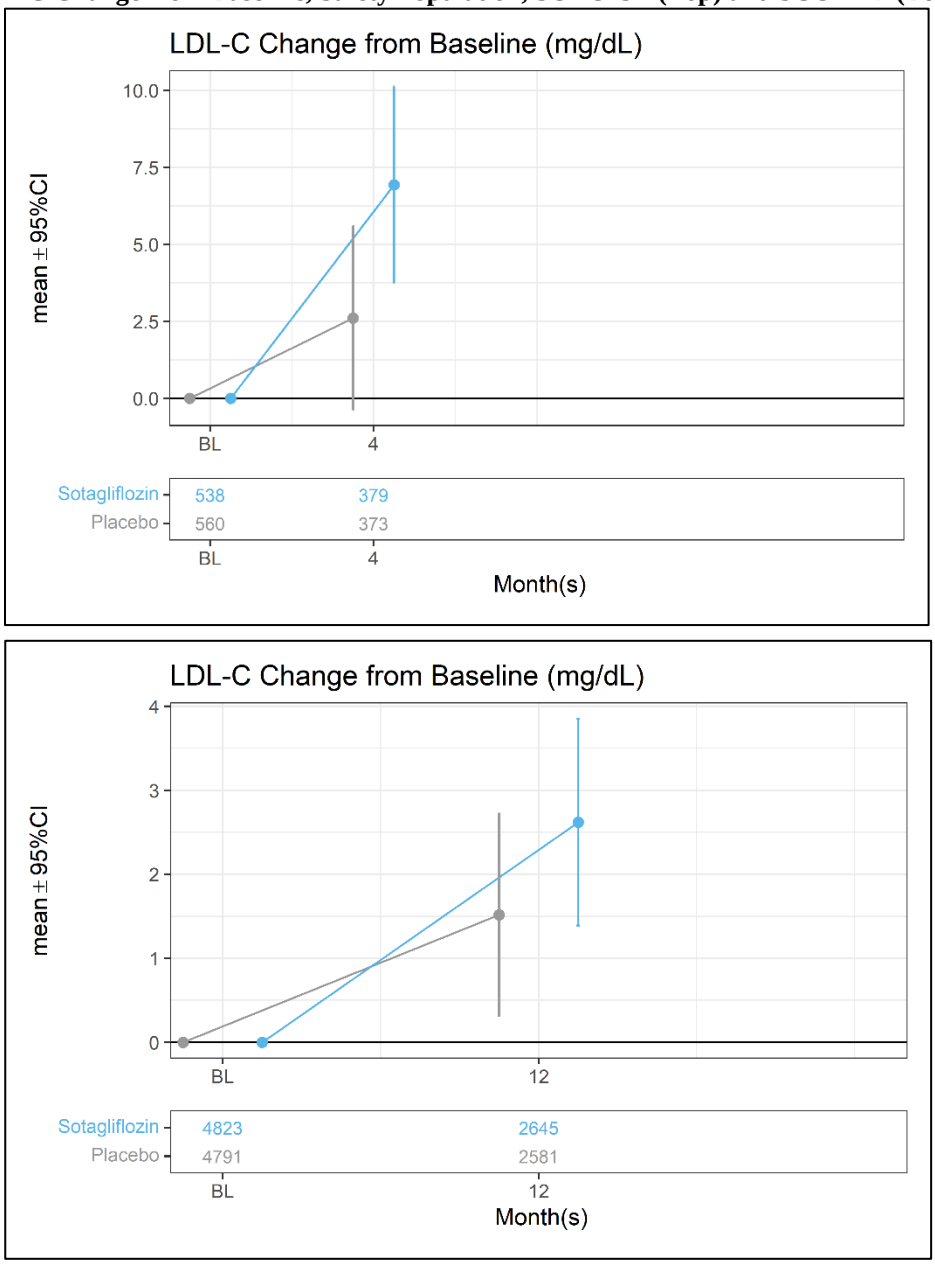
6.6.7.3. Lipids

Mean changes from baseline in lipid values (e.g., high density lipoprotein cholesterol [HDL-C], non-HDL-C, and triglycerides) were similar between the treatment groups and generally stable during treatment with the exception of slight increase in mean change from baseline over time in LDL-C in the sotagliflozin group compared to the placebo group in both studies (Figure 10).

A customized MedDRA query for TEAEs related to dyslipidemia shows a slight numerical increase in the incidences of dyslipidemia in sotagliflozin group compared to placebo (70[1.3%] vs. 57[1.1%]) in SCORED.

Reviewer's comment: *Increases in LDL-C were observed consistently across the SGLT2 inhibitor class, which may be related to the reduced LDL-C clearance. Dyslipidemia is often seen in conjunction with diabetes mellitus, and a risk factor for cardiovascular disease. However, these small increases in LDL-C did not result in any significant cardiovascular findings.*

Figure 10. LDL-C Change from Baseline, Safety Population, SOLOIST (Top) and SCORED (Bottom)



Source: Reviewer's analysis [adsl, adlb]**; Software:** R

6.6.7.4. Electrolytes

In both studies, mean changes from baseline in electrolyte values (e.g., sodium, bicarbonate, potassium, calcium, phosphate, and magnesium) were similar between the treatment groups and generally stable during treatment.

6.6.7.5. Glucose

Mean reduction from baseline in serum glucose was of greater magnitude in the sotagliflozin group compared to placebo group in SCORED (-18.3 vs. -2.8 mg/dL, respectively) and in SOLOIST (-15.0 vs. 1.1, respectively).

As discussed in Section 5.4.7. Effect on HbA1c, Weight and Blood Pressure, mean HbA1c reduction was modest and not clinically meaningful in SOLOIST and SCORED.

Reviewer's Comment: *The observed changes in serum glucose were consistent with the inhibitory effect of sotagliflozin on SGLT1 (inhibiting intestinal glucose absorption) and SGLT2 (inhibiting renal tubular glucose reabsorption).*

6.6.8. Vital Sign Findings

In both studies, baseline vital signs (e.g., SBP and DBP [siting], heart rate, and weight) were similar between treatment groups and mean changes from baseline over time were modest, not clinically meaningful, and consistent with those associated with other SGLT2 inhibitors.

Mean changes from baseline in blood pressure and weight were discussed as review issues relevant to the evaluation of benefit in Section 5.4.7. Effect on HbA1c, Weight and Blood Pressure.

Reviewer's Comment: *The observed changes in vital signs including SBP and weight were consistent with the volume depletion/diuretic effect of sotagliflozin.*

6.7. Review Issues Relevant to the Evaluation of Risk

There were no review issues identified, and all AEs can be managed through the product labeling.

7. Therapeutic Individualization

7.1. Pediatric Labeling/Plans for Pediatric Drug Development

The initial pediatric study plan (iPSP) was originally submitted to IND135095 (SN0052) and agreed upon by the Agency in its correspondence dated 03 November 2021. A copy of the agreed iPSP was included with the original NDA 216203 submission (SN0001). The Applicant submitted their pediatric study plan with NDA 216203 re-submission (SN0021) in which they requested a full waiver for all pediatric age groups (0 to <18 years old). The justification for a full pediatric waiver is that necessary studies are impossible or highly impracticable because the number of patients is so small. The Division supports the rationale for full waiver of pediatric studies.

8. Human Subjects Protections/Clinical Site and Other GCP Inspections/Financial Disclosure

Human Subjects Protections
SOLOIST and SCORED were conducted in accordance with the principles of the Declaration of Helsinki, International Conference for Harmonization (ICH)/Good Clinical Practice (GCP) and was approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) prior to the start of the trial.

Financial Disclosure
The overall number of investigators reporting disclosable financial interests was low for both trials, approximately 0.1%. However, there was a large proportion of investigators/sub-investigators who did not submit financial disclosures (approximately 35%), despite Lexicon's repeated attempts[18] of collecting this information. Despite the lack of adequate financial disclosures in both trials, this finding is unlikely to affect the efficacy results from either trial since most sites enrolled few subjects. For SCORED, the largest enrolling site enrolled 105 subjects (1% of the total enrollment), whereas for SOLOIST, the largest enrolling site enrolled 30 subjects (2.5% of the total enrollment). In addition, the trial designs (i.e., randomized, double blinded, use of an adjudication for efficacy endpoints), helped to minimize a bias in both trials.

III. Appendices

9. Summary of Regulatory History

9.1. U.S. Regulatory Actions and Marketing History

Sotagliflozin is not currently marketed in the United States. The Agency has previously reviewed sotagliflozin for an indication to treat Type 1 Diabetes Mellitus (T1DM) under NDA 210934. On 22 March 2019, the Applicant received a Complete Response given an unfavorable benefit-risk assessment. Sotagliflozin demonstrated a modest reduction in hemoglobin A1c (0.3-0.4%) but a significant and dose-responsive, increase in risk of DKA .

On 26 April 2019, sotagliflozin received initial EMA market approval for a T1DM indication (Zynquista; Product# EMEA/H/C/004889). However, on 22 March 2022, the European

[18] Lexicon completed 5 attempts for obtaining financial disclosure information, including the following: 3 emails were sent by Lexicon (on June 16, 2021, June 29, 2021 and July 12, 2021) asking investigators to fill out the financial information survey. A fourth attempt included a phone call to non-responding investigators (occurring between August 10, 2021 to September 30, 2021) and a final attempt was a certified letter which was sent between August 30, 2021 and September 3, 2021.

Commission (EU) withdrew marketing authorization for Zynquista in the EU at the request of the marketing authorization holder based on a decision to not market the product in the EU for commercial reasons. The Applicant also received market approval from the Great Britain Medicines and Healthcare products Regulatory Agency on 25 January 2022. Per the Applicant's report, this market approval remains active, but the product has not yet been marketed in Great Britain.

9.2. U.S. Summary of Presubmission/Submission Regulatory Activity

On 21 November 2008, the Applicant submitted Investigational New Drug (IND) 102191 which pertained to a clinical development program for sotagliflozin for a glycemic control indication. Under this IND, the Applicant developed the SCORED clinical trial to gather evidence of potential cv benefit and risk pursuant to Agency *Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (December 2008)[19]. The Applicant subsequently opened IND 135095 for a HF indication under which the SOLOIST trial was submitted. The key regulatory history of the clinical development program for sotagliflozin is summarized in Table 31 below:

Table 31. Summary of Key Regulatory History

Source	Advice from Agency
21 December 2012 IND 102191 Type B End of Phase 2 Meeting Minutes	The Agency provided guidance on acceptable primary composite endpoints for a planned phase 3 CVOT. The Agency stated that 3-point MACE (CV death, nonfatal MI and nonfatal stroke) combined with hospitalization for unstable angina could be an acceptable primary composite endpoint in a study designed to show superiority against placebo.
06 November 2013 IND 102191 Type C Written Response Only Meeting	The Agency agreed with the proposed CVOT patient population and primary/secondary endpoints. The Agency also noted that the proposed phase 3 CVOT would be inadequate to determine the safety and efficacy of sotagliflozin co-administered with other commonly used anti-diabetic agents given dose differences for co-administered drugs confounding interpretation. The Agency provided further guidance on proposed indication statements stating that support for claims would be a review issue and that guidance for CV claims would be sought from the Division of Cardiovascular and Renal Products.
09 July 2014 IND 102191	The Agency stated that the Applicant will need to establish that sotagliflozin carries an acceptable cardiovascular risk profile, as

[19] Guidance withdrawn and replaced by *Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control, Guidance for Industry* on 25 February 2020: https://www.fda.gov/media/135936/download

Type B End of Phase 2 Meeting Minutes	described in the FDA Guidance "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" (b) (4).
23 December 2016 IND 102191 IRB Waiver Request	The Agency agreed with the IRB waiver request for the use of sotagliflozin tablets in all foreign investigational studies conducted under IND 102191.
09 February 2017 IND 102191 Type C Written Response Only Meeting	The Applicant sought guidance on performing meta-analysis of 4-point MACE in Phase 2/3 trials for T1DM/T2DM indications, or an interim analysis of EFC14875 if needed, to demonstrate pre-market CV safety of sotagliflozin. The Agency stated that a pre-specified meta-analysis of Phase 2/3 trials without reliance on interim analysis of the CVOT would be preferred. The Agency suggested submission of an SAP for review prior to breaking blinding in any referenced trials. The Applicant sought guidance on the design of EFC14875, including the addition of hospitalization for heart failure as a component of the primary composite, but the Agency stated that a heart failure endpoint would be best suited as a secondary endpoint. Overall guidance regarding EFC14875 was that the Applicant should submit a finalized protocol for review.
26 July 2017 IND 135095 Type B Pre-IND Meeting Minutes	Opening PIND meeting for IND 135095 to establish consensus on baseline characteristics for the EFC15156 phase 3 pivotal trial seeking an indication for reduction in CV death and HHF. The Agency agreed with the proposed dosing regimen, event-driven design, and plan to control type 1 error. Additional guidance was provided for applicability to US population including appropriate documentation of baseline background heart failure therapies. The Agency also commented on the sufficiency of safety data generated from both pivotal CVOTs (EFC15156, EFC14875) to meet guidance for development of new antidiabetic drugs again suggesting against use of interim analysis of EFC14875. Further discussion was held on inclusion of secondary renal endpoints that could lead to a renal claim; The Agency clarified that secondary renal endpoints should be limited to renal components and should not include CV death. A robust p-value for a secondary renal endpoint would likely be required to support a renal claim.
26 March 2018 IND 135095 Study May Proceed Letter	Study may proceed letter for IND 135095 in support of EFC15156. Clinical non-hold comments included clarification on eligibility criteria including documentation of baseline volume status, appropriate supportive documentation for baseline heart failure and T2DM diagnoses, and definitions for hospitalization for heart failure and urgent heart failure visit. The Agency further requested the submission of key trial documents including the Clinical Events Committee charter, statistical analysis plan, Data

	Monitoring Committee charter, and informed consent form clearly documenting that there is an existing drug approved to reduce CV mortality in patients with T2DM and established CV disease.
02 March 2020 IND 135095 Type C Meeting Preliminary Comments	The Applicant proposed to change the primary endpoint for both EFC14875 and EFC15156 to a composite including CV death and HHF based on emerging data from other SGLT2i clinical development programs. The Agency stated that this plan was acceptable. The Agency further stated that exploration of treatment effect of EF would be necessary to determine scope of potential claims. The Agency replied to the Applicant's proposal for a claim on the primary composite at 90 days that the label would include the Kaplan-Meier curve for the observed treatment effect over time, but not a description of the endpoint at a specific time-point. The Agency also stated that data from EFC14875 and EFC15156 could support an indication for the primary composite regardless of achieving a claim in T1DM or T2DM.
19 March 2020 Early Trial Termination	The Applicant announced early termination of EFC14875 and EFC15156 for business reasons and challenges of operations from the start of the COVID-19 pandemic.
06 January 2021 IND 135095 Type C Meeting Preliminary Comments	The Agency agreed with the Applicant's proposal to change the SAPs for both EFC14875 and EFC15156 to include a primary composite endpoint of CV death, HHF, and UHFV with a plan to shift from a time-to-event analysis to total occurrences. The Agency stated that the provided analysis for the two trials could support NDA submission for an indication statement reflecting the primary composite endpoint. The Agency further requested for consideration of pooled analyses from EFC14875 and EFC15156 intended to evaluate treatment effect by EF and treatment effect on the primary endpoint (total occurrence and time-to-event). The Agency also requested specific analyses for KCCQ-12 from EFC15156 including proposed anchoring of symptom assessments and reporting additional result characteristics (score variability and the cumulative distribution function) from Baseline to Months 4 & Month 8.
14 July 2021 IND 135095 Type B Pre-NDA Meeting Minutes	The Agency stated that the three pre-specified secondary renal endpoints did not reach statistical significance (b) (4) (b) (4) The Agency also found the plan for conducting the requested pooled analyses for EFC14875 and EFC15156 acceptable. The Agency further commented that a formal risk evaluation and mitigation strategy will likely not be necessary. The Agency stated that priority review designation would likely be successful given that there were no contemporary approved therapies for treatment of heart failure patients with EF >50%.

30 December 2021 NDA Submission	The Applicant submits NDA 216203 for sotagliflozin for the treatment of heart failure.
28 February 2022 NDA Withdrawal Letter	The Agency was informed by the Applicant that they had discovered significant discrepancies for reported protocol deviations during an internal audit. The likely root cause for the issue was a database transfer error during migration of data from the prior Sponsor of the sotagliflozin clinical development program to the current Applicant. The Applicant also informed the Agency of discovery of additional closed session data outputs from the Data Monitoring Committee. The Agency requested that the Applicant present a plan to recertify the data quality of the NDA submission prior to consideration of NDA resubmission.
28 February 2022 **IND 160506** Type B Pre-IND Meeting Preliminary Comments	The Applicant filed IND 160506 to support an additional clinical phase 3b trial mirroring the population from EFC15156, but without a baseline T2DM diagnosis. The Agency stated that the Applicant should submit a rationale for why the proposed indication in NDA 216203 should be restricted to patients with T2DM. Furthermore, the Agency proposed whether it would be ethical to conduct a placebo-controlled trial when the benefits of sotagliflozin to patients with heart failure are known.
25 April 2022 Type A Meeting Preliminary Comments	The Applicant presented the components of the plan to recertify the data integrity of their NDA resubmission. Components of the plan included a Data Transfer Integrity and Quality Control Plan, Trial Master File Quality Control Plan and Protocol Deviation QC Plan. The Agency stated that the proposed plan was acceptable.
27 May 2022 NDA Resubmission	The Applicant filed a resubmission after withdrawal for NDA 216203.

10. Trial Design: Additional Information and Assessment

10.1. Protocol Amendments and SAP Revisions

10.1.1. Protocol Amendments

SOLOIST Protocol Amendments

The original SOLOIST (EFC15156) v1 protocol was dated 05 January 2018. The Applicant amended the clinical trial protocol twice. Amended Clinical Trial Protocol No. 01, v1 was dated 17 December 2018 and Amended Clinical Trial Protocol No. 02, v1 was dated 10 December 2019. No trial subjects were enrolled under Amended Clinical Trial Protocol No. 02, v1.

Table 32. Protocol Amendments – SOLOIST

Protocol Version	Rationale / Significant Amendments
Amended Clinical Trial Protocol No. 01, v1 17 December 2018	**Rationale:** 1) The procedures related to the endpoint of detection of premature ventricular complexes (PVCs) in the subgroup of patients with an implantable cardioverter defibrillator or cardiac resynchronization therapy device are not operationally feasible. Therefore, the protocol was amended to remove this endpoint. 2) Following advice from the external steering committee, a new objective and endpoint were added -to compare sotagliflozin versus placebo on the time of first occurrence of cardiovascular death and hospitalization for heart failure, in subgroups of patients who started first IMP dose before and after hospital discharge. 3) The order of secondary endpoints was revised, and the multiplicity testing procedure was updated from fixed sequence approach to graphical approach in response to U.S. FDA recommendation.
Amended Clinical Trial Protocol No. 02, v1 10 December 2019 *No patients enrolled*	**Rationale:** The inclusion/exclusion criteria for the EFC15156 study (SOLOIST-WHF) were updated to broaden the eligible patient population based on recent data supporting efficacy and safety of SGLT2 inhibitors in patients with chronic heart failure without diabetes, as well as data from the study of sotagliflozin in patients with severe kidney disease. The revisions also address feedback from the Steering Committee and Investigators following study initiation and are expected to facilitate recruitment. **Significant Line-Item Amendment**s: • Randomization window after hospital discharge has been extended from 3 days to 1 week • Added new secondary endpoint, "CV death and HHF in patients with LVEF <50% with and without T2DM" and moved secondary endpoints to other endpoints: o All-cause mortality in patients with LVEF <50% o All-cause mortality in the total patient population • Removed T2DM inclusion criterion and updated study design and background to study a broader population at increased risk of HF based on results of the DAPA-HF trial which indicated patients without diabetes may benefit equally from SGLT inhibition • Patient's diagnosis of HF modified from 3 months prior to Screening to 1 month prior to Index HF Event • Limited exclusion criteria to exclude on WHF due specifically to STEMI instead of the prior exclusion criteria that broadly

	applied to all MI. Limited to STEMI within 1 month, rather than all MI within 3 months • Modified to decrease eGFR exclusion range <30 to <20 mL/min/1.73m^2 for patients with severe kidney disease • Modification to treatment discontinuation criteria for dialysis or renal transplant rather than sustained eGFR criteria <15 mL/min/1.73m^2

SCORED Protocol Amendments

The original SCORED (EFC14875) v2 protocol was dated 17 September 2017. The Applicant subsequently amended the clinical protocol twice. Amended Clinical Trial Protocol No. 01, v1 (Local Amendment US and Canada Only) was dated 12 January 2018 and Amended Clinical Trial Protocol No. 01, v1 (India Only) was dated 29 August 2018.

Table 33. Protocol Amendments – SCORED

Protocol Version	Rationale / Significant Amendments
Amended Clinical Trial Protocol No. 01, v1 US & Canada Only 12 January 2018	In order to secure the reliability of the markers of bone turnover, the study protocol was amended to secure that this testing is performed under controlled conditions.
Amended Clinical Trial Protocol No. 01, v1 India Only 29 August 2018	In order to meet the requirement of the health authority of India, the study protocol was amended to exclude *patients* with HbA1c greater than 10% at Screening and to add rescue criteria for patients with uncontrolled hyperglycemia. •

10.1.2. SAP Versions and Revisions

SOLOIST SAP Revisions
The original and final SAP v1.0 for SOLOIST was filed on 09 August 2020. The finalized SAP was agreed to, in principle, in the Type C Meeting Preliminary Comments dated 06 January 2021.

SCORED SAP Revisions
The original SAP v1.0 (Sanofi) for SCORED was filed on 19 July 2019. The final SAP v1.0 (Lexicon) was filed on 21 August 2020. The finalized SAP was agreed to, in principle, in the Type C Meeting Preliminary Comments dated 06 January 2021.

Table 34. SAP Revisions – SCORED

SAP Version	Rationale / Significant Revisions
Statistical Analysis Plan v1.0 21 August 2020	**Rationale:** 1) This plan describes statistical efficacy analyses to be conducted by an independent academic statistician and separately verified by the Lexicon statistical team. It addresses issues related to the early termination of SCORED. These issues have been reviewed and the recommended steps have been chosen in a blinded fashion, without the use of any unblinded interim analysis. 2) The termination of follow-up in SCORED did not allow enough time to amend the study protocol. Changes to the intended analysis plan are reflected in this document, rather than the protocol, and this plan takes precedence where there are differences between the two documents. 3) The key efficacy focus is on total (first and potentially subsequent) investigator-reported events. This focus captures the impact of treatment in actual practice. Recurrent hospitalization for heart failure, and urgent heart failure visits, as recognized and treated by the medical community, are very frequent and have a significant clinical and societal impact. In contrast, a standard assessment of time to a first event may not capture the totality of the effects of treatment. The number of total investigator-reported events in SCORED is a measure of high clinical relevance, and consequently it is appropriate to summarize the effects of sotagliflozin in SCORED. **Significant Revisions:** • Primary Objective: Updated from two primary objectives comparing the effect of sotagliflozin versus placebo in patients with T2DM, CV risk factors and moderately impaired renal function From: o Is non-inferior on the composite endpoint of CV death, non-fatal MI or non-fatal stroke (3-point MACE) o Reduces the composite endpoint of CV death or HHF To: o Reduces the total occurrences of CV death, HHF and UHFV • Sample Size: The originally assumed sample size and projected duration of follow-up were based on a hazard ratio of 0.80 for a composite of CV death and HHF, plus the aim of demonstrating superiority in the composite endpoint of CV death, non-fatal stroke, and non-fatal myocardial infarction. Given the early termination of SCORED, the study is not

	powered for these assumptions. However, an examination of efficacy is relevant because hazard ratios less than 0.80 have been reported with SGLT inhibition in cardiovascular outcomes studies, and the profile of sotagliflozin (with gastrointestinal SGLT1 inhibition in addition to SGLT2 inhibition) may differ from that of selective SGLT2 inhibitors. Analyses are therefore conducted without any new sample size calculations.

10.2. Recommended Source Documents for Primary Composite Endpoint

Recommended event-specific source documents for the following primary endpoints in both SOLOIST (**EFC15156**) and SCORED (**ECF14875**) are as follows:

Cardiovascular Death:

- Clinical Narrative in CEC Format
- Death Summary
- Discharge Summary
- ER/Ambulance Service Reports
- Autopsy/Forensic Report
- Death Certificate

Hospitalization for Heart Failure / Urgent Visit for Heart Failure:

- Clinical Narrative in CEC Format
- Discharge Summary
- Admission H&P, ER/UC Visit Notes
- Medication Records
- Imaging Reports
- BNP/NT-pro-BNP Lab Results
- Pulmonary Wedge Pressure Results.

10.3. Endpoint Reporting and Adjudication Criteria

The CEC adjudication charter states that Death, Myocardial Infraction, Unstable Angina & Heart Failure events will be adjudicated in Phase 1 by two independent cardiologists with the caveat that Phase 1 review in the SOLOIST trial will be "by at least 1 Faculty-level Reviewer, and 1 Reviewer may be a DCRI Fellow Reviewer." Phase 2 reviews will address discrepancies in

adjudication between the two independent reviewers in Phase 1 with the final result being the majority decision of Phase 2 Committee members (minimum three members).

Criteria for positive adjudication of primary endpoints are standardized between SOLOIST **(ECF15156)** and SCORED **(ECF14875)** as follows:

Cardiovascular Death as that occurring from

[a] Acute Myocardial Infarction

[b] Sudden Cardiac Death

[c] Heart Failure

[d] Stroke

[e] Cardiovascular Procedure

[f] Cardiovascular Hemorrhage

[g] Other Cardiovascular (i.e., Pulmonary Embolism or Peripheral Arterial Disease)

Hospitalization for Heart Failure as having

[a] an inpatient admission with HF primary diagnosis of >24h duration or change in calendar date **with**

[b] at least ***one*** significant symptom (dyspnea, decreased exercise tolerance, fatigue and decreased end-organ perfusion consistent with volume overload) **and**

[c] objective evidence of HF **with**

[i] ***two*** positive physical exam findings

- peripheral edema
- abdominal distension
- pulmonary rales
- increased JVP
- S3 gallop or rapid weight gain >3-4lbs in 3-4 days **or**

[ii] ***one*** of the prior physical exam findings **with**

one piece of laboratory evidence

- increased BNP >500 pg/mL
- increased NT-pro-BNP >2,000 pg/mL
- radiological evidence of pulmonary congestion
- non-invasive diagnostic imaging consistent with elevated left-or-right-sided ventricular filling pressure or decreased cardiac output

-or-

- diagnostic invasive right heart catheterization (PCWP ≥18 mmHg, CVP ≥12 mmHg or a CI ≤2.2 L/min/min^2) **and**

[d] receives intensification of treatment specifically for HF with at least ***one*** intervention

[i] augmentation in oral diuretic therapy

[i] intravenous diuretic or vasoactive agent

[iii] mechanical circulatory support

[iv] mechanical fluid removal specifically for HF

Urgent Visit for Heart Failure as having

[a] an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF not meeting inpatient HF hospitalization criteria above **with**

[b] at least ***one*** significant symptom (dyspnea, decreased exercise tolerance, fatigue and decreased end-organ perfusion consistent with volume overload) **and**

[c] objective evidence of HF **with**

[i] ***two*** positive physical exam findings

- peripheral edema
- abdominal distension
- pulmonary rales
- increased JVP
- S3 gallop or rapid weight gain >3-4lbs in 3-4 days **or**

[ii] ***one*** of the prior physical exam findings **with**

one piece of laboratory evidence

- increased BNP >500 pg/mL
- increased NT-pro-BNP >2,000 pg/mL
- radiological evidence of pulmonary congestion
- non-invasive diagnostic imaging consistent with elevated left-or-right-sided ventricular filling pressure or decreased cardiac output

-or-

- diagnostic invasive right heart catheterization (PCWP ≥18 mmHg, CVP ≥12 mmHg or a CI ≤2.2 L/min/min^2) **and**

[d] receives intensification of treatment specifically for HF with at least ***one*** intervention

[i] doubling of oral diuretic therapy

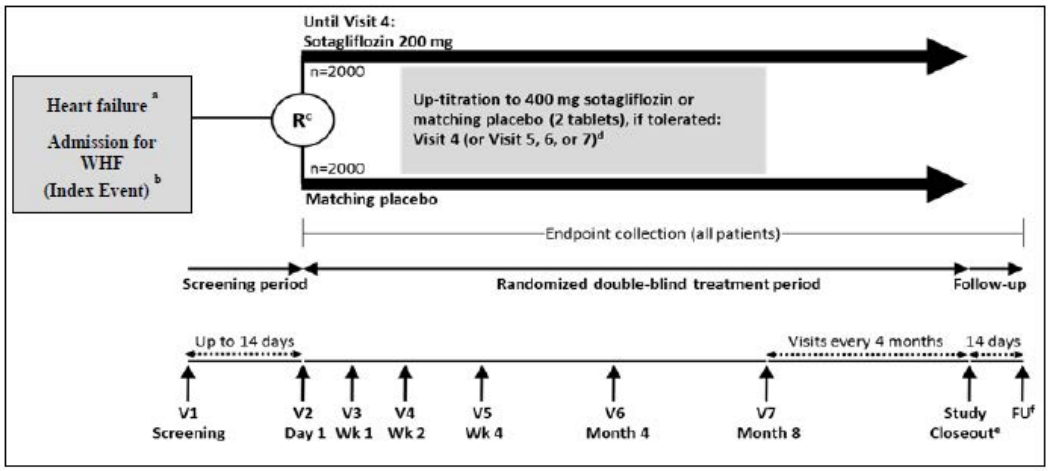
[ii] intravenous diuretic or vasoactive agent

[iii] mechanical circulatory support

[iv] mechanical fluid removal specifically for HF

10.4. Trial Design Diagrams

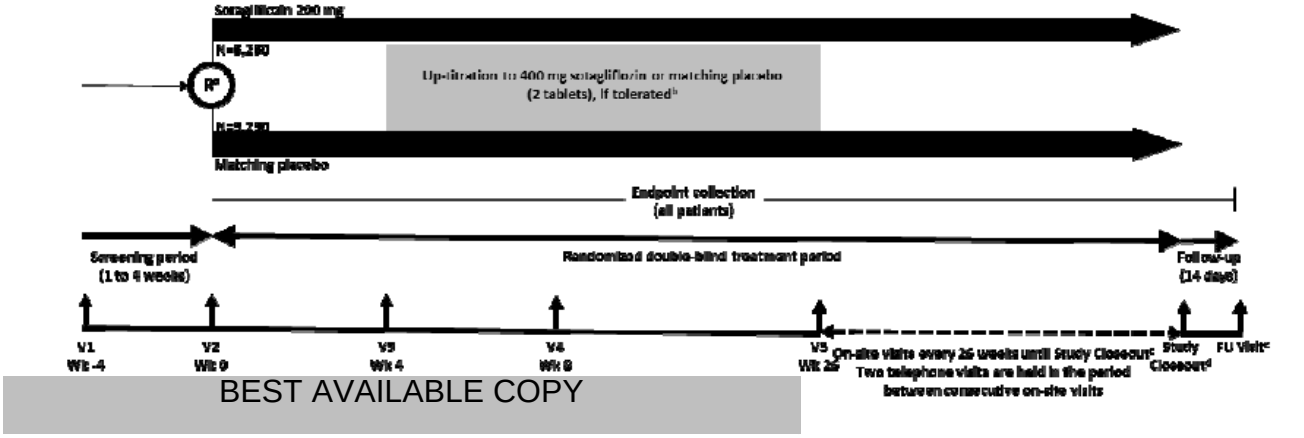
Figure 11. SOLOIST Trial Design



a Prior diagnosis of HF ≥1 month prior to the Index Event based on appropriate supportive documentation.
b Index Event: Patient admitted to the hospital or had urgent HF visit to ED, HF Unit, or infusion center for WHF with intravascular volume overload, including clinical sign/symptom(s) of fluid overload as determined by Investigator based on appropriate supportive documentation and further defined in I02.
d For titration details, please refer to Section 8.1.1.
e This is an event-driven study. All randomized patients will be asked to return to the study site for a Study Closeout Visit once the date the required number of events are projected to be positively adjudicated has been determined. The timing and window of this visit will be communicated to sites.
f A FU Visit will take place 14 days (±4 days) after the Study Closeout Visit for patients who do not prematurely and permanently discontinue IMP.
ED = Emergency Department; FU = Follow-up; HF = heart failure; IMP = investigational medicinal product; T2D = type 2 diabetes; R = Randomization; V = visit; WHF = worsening heart failure; Wk = Week.

Source: SOLOIST Protocol Version 2.0, page 20.

Figure 12. SCORED Trial Design



a: The Randomization Day is always Day 1. The Randomization is stratified by region and heart failure-related criteria (see Section 6.1.2).

b: At Visit 3 (Week 4), the dose of IMP will be increased to 400 mg or matching placebo (2 tablets) unless, in the opinion of the Investigator, up-titration is not appropriate for safety reasons. If up-titration does not occur at Visit 3 for safety reasons, all attempts will be made to up-titrate at Visit 4 (Week 8) or Visit 5 (Week 26). The 400 mg dose (or 200 mg in those who cannot tolerate up-titration by Visit 5) or corresponding matching placebo will be maintained for the duration of the remaining Double-blind Treatment period.

c: The study is event driven. Therefore, the study will continue until approximately 844 positively-adjudicated primary CV events of CV death or HHF and approximately 1189 positively-adjudicated 3-point MACEs have occurred.

d: All randomized patients will be asked to return to the study site for a Study Closeout Visit when approximately 844 primary CV events of CV death or HHF and approximately 1189 3-point MACE are positively adjudicated. Patients who prematurely permanently discontinue IMP will also attend a pEOT Visit as soon as possible after the last dose of IMP and will then continue study visits as per the original study schedule. Patients will continue to be followed after a CV or renal endpoint occurs irrespective of whether they are receiving IMP. If the patient does not agree to site visits, he/she will be contacted by telephone to inquire about safety status (including hospitalizations and endpoints).

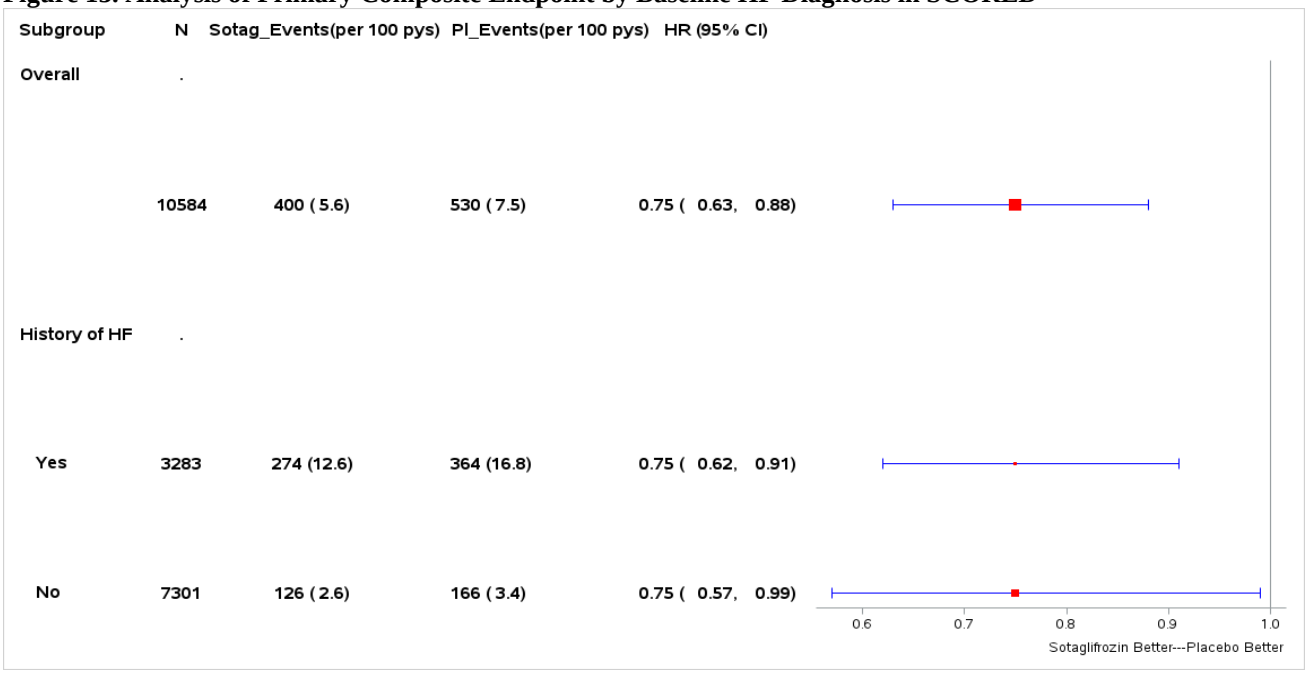
e: A FU Visit will take place 14 days (±4 days) after the Study Closeout Visit for patients who do not prematurely permanently discontinue IMP.

CV cardiovascular; FU follow-up; HHF hospitalization for heart failure; IMP investigational medicinal product; MACE major adverse cardiovascular event; pEOT Premature End-Of-Treatment; R Randomization V visit; Wk week.

Source: SCORED Protocol, Version 2, page 14

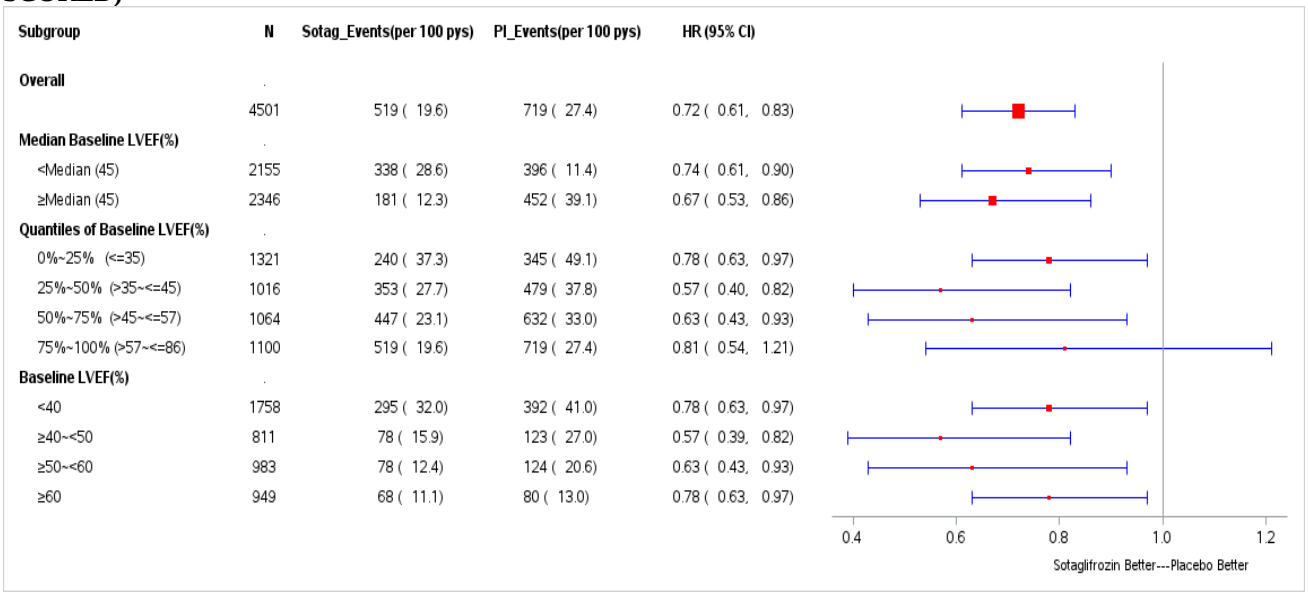
11. Efficacy Assessment Additional Information and Assessment

Figure 13. Analysis of Primary Composite Endpoint by Baseline HF Diagnosis in SCORED



Source: Statistical reviewer analysis

Figure 14. Analysis of Primary Composite Endpoint by Baseline LVEF (Pooled Data from SOLOIST and SCORED)

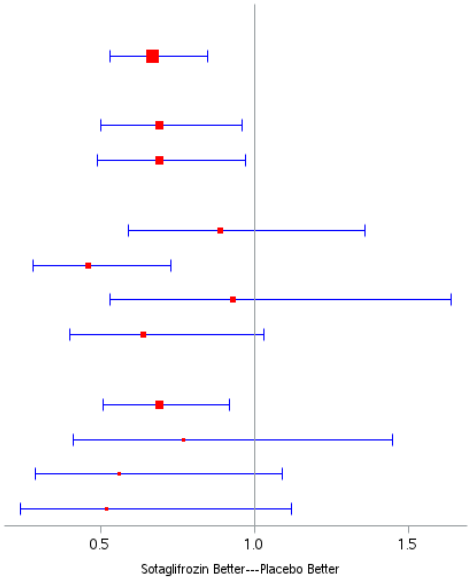


Source: Statistical reviewer analysis

Figure 15. Analysis of Primary Composite Endpoint in Patients with HF Diagnosis by Baseline LVEF (SOLOIST and SCORED)

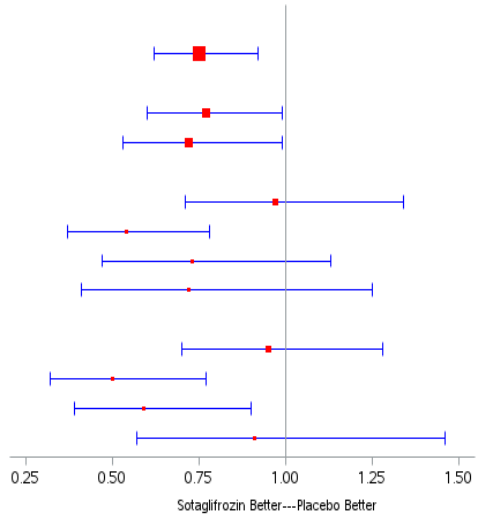
SOLOIST

Subgroup	N	Sotag_Events(per 100 pys)	Pl_Events(per 100 pys)	HR (95% CI)
Overall				
	1222	245 (51.3)	355 (76.4)	0.67 (0.53, 0.85)
Median Baseline LVEF(%)				
<Median (35)	543	133 (70.8)	219 (101)	0.69 (0.50, 0.96)
≥Median (35)	677	112 (38.6)	136 (55.3)	0.69 (0.49, 0.97)
Quantiles of Baseline LVEF(%)				
0~25% (<=28)	321	88.0 (74.2)	103 (83.6)	0.89 (0.59, 1.36)
25%~50% (>28~<=35)	308	59.0 (52.2)	138 (114)	0.46 (0.28, 0.73)
50%~75% (>35~<=46)	288	41.0 (35.1)	39.0 (38.3)	0.93 (0.53, 1.64)
75%~100% (>46~<=79)	303	57.0 (44.0)	75.0 (63.9)	0.64 (0.40, 1.03)
Baseline LVEF(%)				
<40	725	165 (61.0)	249 (89.2)	0.69 (0.51, 0.92)
≥40~<50	230	32.0 (33.1)	36.0 (46.4)	0.77 (0.41, 1.45)
≥50~<60	162	30.0 (45.8)	46.0 (66.8)	0.56 (0.29, 1.09)
≥60	103	18.0 (16.3)	24.0 (22.5)	0.52 (0.24, 1.12)



SCORED

Subgroup	N	Sotag_Events(per 100 pys)	Pl_Events(per 100 pys)	HR (95% CI)
Overall				
	3283	274 (12.6)	364 (16.8)	0.75 (0.62, 0.92)
Median Baseline LVEF(%)				
<Median (50)	1614	176 (16.9)	230 (21.8)	0.77 (0.60, 0.99)
≥Median (50)	1667	98 (8.7)	134 (12.1)	0.72 (0.53, 0.99)
Quantiles of Baseline LVEF(%)				
0%~25% (<=38)	958	122 (20.4)	132 (21.1)	0.97 (0.71, 1.34)
25%~50% (>38~<=50)	794	64 (12.2)	113 (21.7)	0.54 (0.37, 0.78)
50%~75% (>50<=60)	900	57 (9.0)	71 (12.3)	0.73 (0.47, 1.13)
75%~100% (>60~<=86)	629	31 (7.5)	48 (10.9)	0.72 (0.41, 1.25)
Baseline LVEF(%)				
<40	1033	130 (20.0)	143 (21.2)	0.95 (0.70, 1.28)
≥40~<50	581	46 (11.8)	87 (23.0)	0.50 (0.32, 0.77)
≥50~<60	821	48 (8.5)	78 (14.7)	0.59 (0.39, 0.90)
≥60	846	50 (8.9)	56 (9.7)	0.91 (0.57, 1.46)

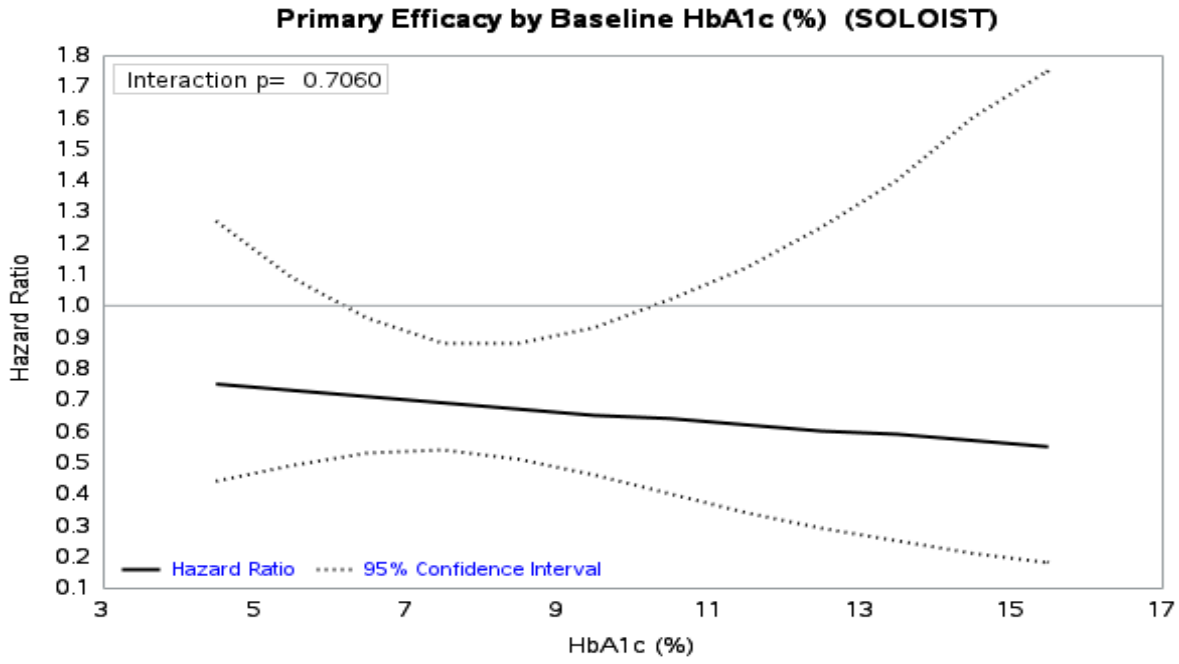


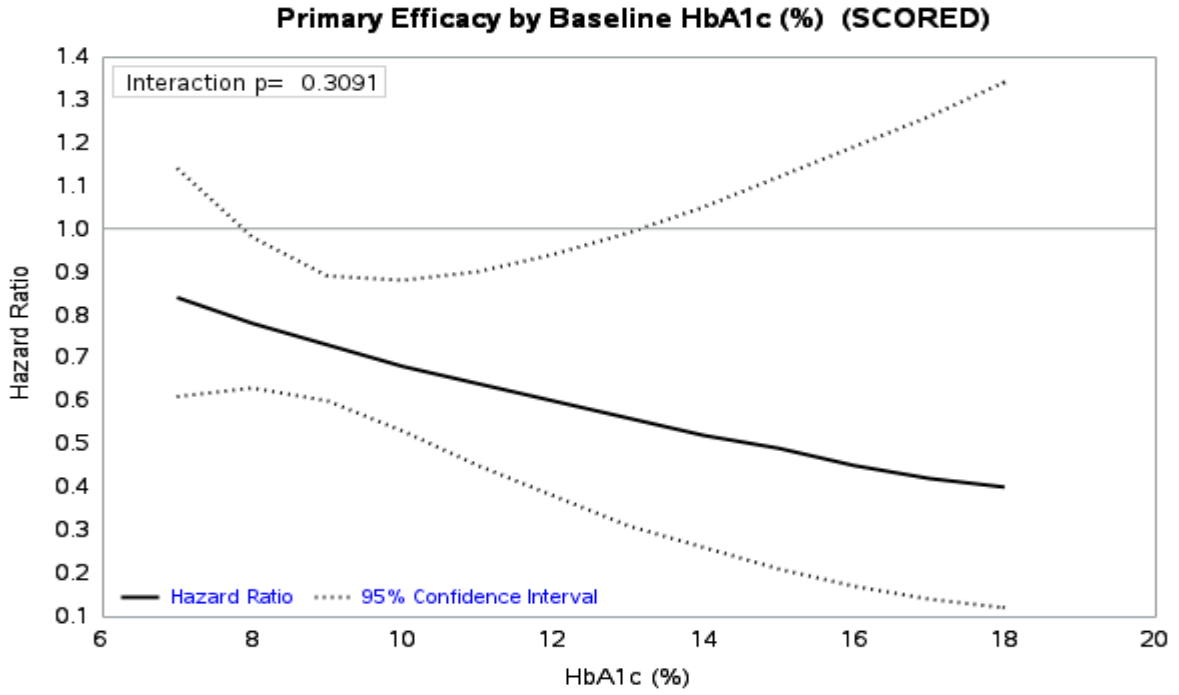
Source: Statistical reviewer analysis

*Time to first event analysis

Source: Statistical reviewer analysis

Figure 16. Analysis of Primary Composite Endpoint by Baseline HbA1c (SOLOIST and SCORED)





Source: Statistical reviewer analysis

12. Data Integrity-Related Consults (OSI, Other Inspections)

No inspections were conducted.

13. Labeling Summary of Considerations and Key Additional Information

13.1. Justification for Proposed Versus Final Indication Statement

The Applicant proposed the following two indication statements at time of NDA resubmission (27 May 2022):

- *Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure.*
- *Reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.*

After deliberation within the Division and Office (OCHEN), we consolidated and revised to a single indication statement which reflects the unified primary composite endpoint in SOLOIST and SCORED and the two patient populations most likely to benefit from sotagliflozin treatment based on the totality of data presented from each trial:

Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with:

- *heart failure - or-*
- *type 2 diabetes mellitus, chronic kidney disease, and other CV risk factors*

We find that the data from SOLOIST and SCORED demonstrate substantial evidence of effectiveness for a reduction in the risk of the primary composite endpoint of CV death, HHF and UHFV. We also support a description of the individual components of the primary composite given that they represent clinically meaningful endpoints and that the benefits exceed the risk (see Section 5.4.3). While both pivotal trials exclusively enrolled patients with a baseline diagnosis of T2DM, we consider comorbid T2DM to be an enrichment factor for the primary composite clinical endpoint rather than a clinically distinct heart failure entity (see Section 5.4.1). Accordingly, we granted a nonspecific claim for all “adults with heart failure” without a restriction to patients with a comorbid T2DM diagnosis. The nonspecific claim for “adults with

heart failure" also accounts for the preservation of primary efficacy across the spectrum of baseline LVEFs for patients enrolled in SOLOIST and SCORED (see Section 5.4.2). While the Applicant provided post-hoc analysis to support a claim for "worsening heart failure" we found the lack of pre-specification and overall strength of this analysis was insufficient to support a claim (see Section 5.4.5). When evaluating the data from SCORED, patients without a baseline HF diagnosis represented the majority of enrolled subjects. We performed a sensitivity analysis of the primary composite endpoint which demonstrated preservation of benefit in this non-HF population (see Section 11, Figure 13). We thus support a labeled indication in this second population. However, we did not grant a claim for the nonfatal MI and nonfatal stroke components of 3-point MACE given lack of remaining alpha in the prespecified hierarchical testing of this secondary endpoint in the SCORED trial (see Section 5.4.6).

13.2. (b) (4)

A (b) (4) is unlikely to be necessary because sotagliflozin is not (b) (4) Section 5 of the label will describe the risk of ketoacidosis.

14. Postmarketing Requirements and Commitments

None planned.

15. Financial Disclosure

Table 35. Covered Clinical Studies: SOLOIST and SCORED

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1371 (for SOLOIST) and 2528 (for SCORED)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 (SOLOIST) and 3 (SCORED) Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 487 (SOLOIST) and 487 (SCORED)		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

16. Review Team Acknowledgements

Table 36. Reviewers of Interdisciplinary Assessment

Role	**Name**
Regulatory Project Manager	Bridget Kane
Clinical Reviewer	Jordan Pomeroy
Safety Reviewer	Tejas Patel
Safety Team Leader	Christine Garnett
Statistical Reviewer	Ququan Liu
Statistical Team Leader	Jialu Zhang
Cross-Disciplinary Team Leader	Charu Gandotra
Division Director (DCN)	Norman Stockbridge
Division Director (OB)	Mark Rothman
Office Director (or designated signatory authority)	Lisa Yanoff

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JORDAN E POMEROY
03/22/2023 10:43:40 AM

QUQUAN LIU
03/22/2023 10:58:27 AM

JIALU ZHANG
03/22/2023 11:47:57 AM

MARK D ROTHMANN
03/22/2023 12:05:45 PM

TEJAS PATEL
03/22/2023 12:12:56 PM

CHRISTINE E GARNETT
03/22/2023 12:13:59 PM

CHARU GANDOTRA
03/23/2023 02:49:40 PM

Cross-Discipline Team Leader Review

Date	April 4, 2023
From	Charu Gandotra MD, MS
Subject	Cross-Discipline Team Leader Review
NDA#	216203
Applicant	Lexicon Pharmaceuticals, Inc
Date of Submission	May 27, 2022
PDUFA Goal Date	May 27, 2023
Proprietary Name	(b) (4)
Established or Proper Name	Sotagliflozin
Dosage Form(s)	Tablet
Applicant Proposed Indication(s)/Population(s)	• Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure. • Reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.
Applicant Proposed Dosing Regimen(s)	200 mg orally once daily increased to 400 mg orally once daily, as tolerated
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with: • Heart failure • Type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors
Recommended Dosing Regimen(s) (if applicable)	200 mg orally once daily increased to 400 mg orally once daily, as tolerated

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress. HF is a chronic condition that is associated with significant morbidity due to recurrent hospitalizations or urgent visits for worsening HF, and premature mortality. It afflicts 1 to 3% of the population worldwide, with annual incidence of > 650,000 in the United States (US). • Patients with history HF or risk factors for HF such as of type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), coronary artery disease (CAD), hypertension, obesity, etc. are at increased risk for adverse HF related outcomes.	HF is a chronic and debilitating disease that is associated with recurrent hospitalizations for HF (HHF) and premature mortality.
Current Treatment Options	• Current treatment options for patients with HF are based on left ventricular ejection fraction (LVEF). The American Society of Echocardiography (ASE) defines normal mean LVEF ± 2-Standard Deviation (SD) as 62 ± 5 % (52-72%) in males and 64 ± 5 % (54-74 %) in females. Patients with HF with below normal LVEF are treated with pharmaco- and device-therapies to improve symptoms and reduce the risk of hospitalization and cardiovascular (CV) death. Pharmacotherapy includes drugs such as loop diuretics, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin-receptor neprilysin inhibitors (ARNI), beta blockers (BB), mineralocorticoid receptor antagonists (MRAs), digoxin,	Currently, patients with HF are treated based on LVEF. Patients with HF and below normal LVEF have several pharmacotherapy options and also receive device therapies. Patients with HF with normal LVEF have more limited pharmacotherapy options, with only SGLT2i being FDA approved. SGLT2i, dapagliflozin, is the only pharmacotherapy approved to reduce the risk of hospitalization for HF in adults with

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	ivabradine, sodium-glucose co-transporter 2 inhibitors (SGLT2i), and vericiguat. FDA approved SGLT2i to treat HF include Jardiance (empagliflozin) and Farxiga (dapagliflozin). Device therapies include implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy defibrillator (CRT-D). Patients with HF with normal LVEF are treated with pharmacotherapy to improve symptoms and reduce the risk of hospitalization and cardiovascular (CV) death. Pharmacotherapy includes drugs such as loop diuretics, angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRAs), and SGLT2i. Of these, SGLT2i are the only drugs that are FDA approved to treat patients with HF with normal LVEF. • Patients with risk factors for HF are treated for the respective risk factors. SGLT2i, dapagliflozin, is approved to reduce the risk of hospitalization for HF in adults with T2DM and established CV disease or multiple CV risk factors.	T2DM and established CV disease or multiple CV risk factors.
Benefit	• The Applicant conducted two pivotal, randomized-controlled, double-blinded, phase 3 trials, SOLOIST and SCORED, to evaluate the efficacy and safety of sotagliflozin versus placebo to reduce the risk of the primary composite endpoint of total (first and recurrent) HHF, urgent HF visit (UHFV) and CV death. • SOLOIST randomized 1222 patients with HF and T2DM in 1:1 to sotagliflozin vs. placebo. The incidence rate for the primary composite endpoint was 51.3 versus 76.4 per 100 patient years in sotagliflozin versus placebo groups, respectively; hazard ratio (HR) 0.67 (95%CI 0.53, 0.85); p-value <0.001 favoring sotagliflozin. In SOLOIST, T2DM is considered an enrichment factor for risk HF, not a requisite to derive treatment benefit with sotagliflozin. • SCORED randomized 10,584 patients with T2DM, CKD with estimated glomerular filtration rate (eGFR) ≥25 to ≤60 mL/min/1.73 m^2) and either a major CV risk factor or age ≥55 years or with at least 2 minor CV risk factors	SOLOIST and SCORED provided substantial evidence of effectiveness of sotagliflozin to reduce the risk of HHF, UHFV and CV death in adults with HF or T2DM, CKD and other CV risk factors, respectively.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	in 1:1 ratio to sotagliflozin vs. placebo. The incidence rate for the primary composite endpoint was 5.6 versus 7.5 per 100 patient years in sotagliflozin versus placebo groups, respectively; HR 0.75 (95% CI 0.63, 0.88); p-value <0.0004 favoring sotagliflozin.	
Risk and Risk Management	• In SOLOIST and SCORED, there was no important imbalance in the incidence of deaths, serious treatment emergent adverse events (TEAEs), or TEAEs leading to treatment discontinuation between the treatment groups. Volume depletion, urinary tract infection (UTI), genital mycotic infection (GMI), and diarrhea occurred at an increased frequency in patients treated with sotagliflozin versus placebo in both studies. The incidence rates of diabetes ketoacidosis (DKA) events were low in SCORED (0.7 and 0.5 per 100 patient-years in sotagliflozin and placebo groups, respectively) and SOLOIST (1.0 and 1.7 per 100 patient-years in sotagliflozin and placebo groups, respectively).	The safety profile of sotagliflozin is generally consistent with other approved SGLT2i, except for increased incidence of diarrhea which is likely attributable to SGLT1 activity.

Benefit-Risk Integrated Assessment

Sotagliflozin is a new molecular entity (NME) purported to be a dual sodium glucose co-transporter 1 (SGLT1) and SGLT2 inhibitor. On May 27, 2022, Lexicon Pharmaceuticals, Inc. (the Applicant) submitted a new drug application (NDA) for the following proposed indications: 1) to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure and 2) to reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure. Despite currently available therapeutic options, heart failure (HF) is a highly prevalent condition with significant morbidity and mortality, thus representing unmet need.

To support the proposed indications, the Applicant submitted results of two pivotal phase 3 trials, SOLOIST and SCORED. SOLOIST and SCORED were randomized, placebo-controlled, multi-center, double-blind, trials of sotagliflozin in patients with T2DM. SOLOIST randomized 1222 patients with a history of HF in 1:1 ratio to sotagliflozin versus placebo. SCORED randomized 10,584 patients with eGFR ≥25 to ≤60 mL/min/1.73 m2 with either a major CV risk factor or age ≥55 years with at least 2 minor CV risk factors in 1:1 ratio to sotagliflozin versus placebo. The primary composite endpoint for SOLOIST and SCORED was total (first and recurrent) CV death, HHF and UHFV.

SOLOIST demonstrated a reduction in risk of the primary composite endpoint compared to placebo with a respective incidence rate of 51.3 versus 76.4 per 100 patient years; hazard ratio 0.67 (95% CI 0.53, 0.85); p-value <0.001. Although SOLOIST enrolled patients with HF and T2DM, T2DM is considered an enrichment factor for risk of adverse outcomes in a HF population, and the study data suggest it not to be a requisite to derive treatment benefit with sotagliflozin. SCORED demonstrated a reduction in risk of the primary composite endpoint compared to placebo with a respective incidence rate of 5.6 versus 7.5 per 100 patient years; hazard ratio 0.75 (95%CI 0.63, 0.88); p-value <0.0004. The data from SOLOIST and SCORED provide substantial evidence of effectiveness of sotagliflozin to reduce the risk of CV death, HHF and UHFV in patients with HF or with T2DM, CKD and other CV risk factors.

In SOLOIST and SCORED, sotagliflozin was administered to a total of 5896 patients, with approximately 3600 patients exposed to sotagliflozin for ≥52 weeks. There were no important unfavorable imbalances in the incidence of deaths, serious treatment emergent adverse events (TEAEs), and TEAEs leading to discontinuation between treatment groups in both studies. In SOLOIST, there were more non-serious TEAEs overall for sotagliflozin treated patients, but the imbalance was only observed for mild adverse events (AEs). In SCORED, there was no imbalance in non-serious TEAEs. In both studies, volume depletion, urinary tract infection (UTI), genital mycotic infection (GMI), and diarrhea occurred at an increased frequency in patients treated with sotagliflozin versus placebo.

Incidence rates of AE of diabetic ketoacidosis (DKA) were low in SCORED (0.7 and 0.5 per 100 patient-years in sotagliflozin and placebo groups, respectively) and SOLOIST (1.0 and 1.7 per 100 patient-years in sotagliflozin and placebo groups, respectively); however, the risk of DKA was slightly higher for sotagliflozin treated patients in SCORED. These AEs, except diarrhea, are consistent with the known safety profile of other SGLT2 inhibitors.

DKA is a particular concern with SGLT2 inhibitors in patients with type 1 diabetes. In sotagliflozin glycemic control clinical trials in patients with type 1 diabetes, the incidence of DKA was markedly increased vs placebo. The NDA for sotagliflozin for glycemic control in patients with type 1 diabetes received a complete response action because the benefits(s) were considered to not outweigh the DKA risk. In the setting of glycemic control, it is reasonable to state that the risk of ketoacidosis does not outweigh the glycemic control benefit in patients with T1DM, especially when there are other effective approved agents for glycemic control, including insulin. However, when comparing the ketoacidosis risk against potential benefit for reduction of CV death, HHF and UHFV, the benefit of treating patients with comorbid T1DM and HF is considered to outweigh the risk of ketoacidosis. Nevertheless, reasonable efforts to reduce risk further through labeling is appropriate.

In conclusion, the overall benefit-risk assessment is favorable and supports the approval of sotagliflozin to reduce the risk of CV death, HHF, and UHFV in adults with HF, or T2DM, CKD and other CV risk factors.

2. Background

On May 27, 2022, the Applicant submitted NDA 216203 for sotagliflozin, a New Molecular Entity (NME), purported to be a dual sodium-glucose cotransporter (SGLT) 1 and 2 inhibitor for the following proposed indications:

- To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure.
- To reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.

To support the proposed indications, the Applicant submitted two pivotal randomized controlled trials – SOLOIST and SCORED – with the same primary composite endpoint of cardiovascular (CV) death, total (first and recurrent) hospitalization for heart failure (HHF) and urgent heart failure visit (UHFV).

Past regulatory history of sotagliflozin includes issuance of a Complete Response letter dated March 22, 2019, under NDA 210934, due to increased severity and eight-fold the risk of diabetic ketoacidosis (DKA) associated with sotagliflozin (200 mg and 400 mg) as compared to placebo leading to an unfavorable benefit-risk assessment of sotagliflozin for glycemic control indication in patients with type 1 diabetes mellitus (TIDM).

3. Product Quality

- *General product quality considerations:* CMC review by Theodore Carver, dated January 27, 2023, recommended approval of NDA 216203. Key elements of CMC review are listed below:

    - Sotagliflozin *drug substance* has a molecular formula of $C_{21}H_{25}ClO_5S$ and a molecular weight of 424.9 g/mol. It is a small, neutral (non-salt) compound isolated as a white to off-white solid and is not hygroscopic or light sensitive. It is

synthesized as a (b) (4). Risk assessments provided for elemental impurities, potential genotoxic impurities, and potential (b) (4) support a low risk for presence of these impurities in the drug substance.

- The *drug product* is immediate release, film-coated tablets provided in two strengths, 200 mg and 400 mg. All excipients are compendial (USP/NF), including components of the printing ink. The drug product specification includes adequate tests to ensure the potency, purity, and quality of the drug product. All potential drug product degradants are controlled at the ICH Q3B-recommended limit of 0.2% and there are no specified related substances.

- The Biopharmaceutics review concluded that adequate in vitro data were provided to support bridging of the 200 mg and 400 mg formulations.

- *Facilities review/inspection:*

  - According to CMC review, all manufacturing facilities have been found acceptable to perform their intended functions for commercial manufacture under this NDA.

  - According to review by Sarmistha Sanyal, Office of Study Integrity and Surveillance (OSIS), dated February 28, 2023, the remote regulatory assessment (RRA)[1] of the analytical portion of Study BEQ 14993 (NDA 216203, sotagliflozin), conducted at (b) (4) did not reveal any objectionable conditions. The reviewer concluded that the data from the audited study are reliable.

[1] One set of tools for oversight of regulated products used during the pandemic has been remote regulatory assessments (RRAs). The term "RRA" describes a category of activities for which FDA may use different terminologies, but all are considered to be types of RRAs, including "remote record reviews" and "remote interactive evaluations."

4. Nonclinical Pharmacology/Toxicology

The nonclinical program of sotagliflozin under NDA 210934 was considered supportive of approval of sotagliflozin (primary review by Dr. Brundage dated November 28, 2018 and secondary review by Dr. Bourcier dated February 22, 2022 in DARRTS). Under NDA 216203, primary review by Dr. Baichun Yang dated October 28, 2022, and secondary review by Dr. Xuan Chi dated February, 10, 2023 in DARRTS, concluded that the pharmacology and toxicology data support approval of sotagliflozin. Key elements of pharm/tox review are listed below:

- Sotagliflozin is a potent dual inhibitor of human SGLT2 (IC_{50} 1.8 nM) and SGLT1 (IC_{50} 36.3 nM). SGLT2 inhibition blocks glucose reabsorption in the renal proximal tubules resulting in increased urinary glucose excretion. SGLT1 inhibition in the intestines may improve glucose control by reducing or delaying postprandial glucose absorption delivering more glucose distally and increasing the release of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) levels into the portal circulation, which in turn increase insulin secretion.

- The pharmacokinetics (PK) of sotagliflozin has been assessed in mice, rats, dogs, and monkeys after both intravenous (IV) and oral dosing. Sotagliflozin is rapidly absorbed across species after oral dosing with a bioavailability in rats and dogs (50-71%) that is comparable to that in the human (63%). Sotagliflozin is extensively distributed throughout the body in the rat, although levels in brain, spinal cord, eye, bone, and bone marrow are relatively low. Plasma protein binding of sotagliflozin is high across species including humans (>91%).

  In humans, direct glucuronidation is the predominant route of metabolism; while in the rat and mouse, there is more oxidative metabolism in addition to glucuronidation. The sotagliflozin glucuronide conjugate, sotagliflozin-3-O-glucuronide, accounts for 94% of total radioactivity in human plasma and is higher than in the rat and the mouse. As sotagliflozin-3-O-glucuronide has minimal pharmacological activity at SGLT1 and SGLT2 and is not an acyl glucuronide of sotagliflozin, there is no toxicological concern at clinical exposure. UGT1A9 and, to a lesser extent, CYP3A4 are responsible enzymes for the metabolism of sotagliflozin in humans. In rats, excretion of an orally administered dose was primarily recovered in the feces (82%) with 13% excreted in the urine. Whereas, in humans, the main route of elimination was through the urine (57%) with 37% excreted in the feces.

- The toxicity profile of sotagliflozin was evaluated by a nonclinical development program conducted in accordance with international guidance appropriate for a novel, small molecule therapeutic intended for chronic use. This includes a single-dose rat study, a battery of definitive repeat-dose general toxicity studies in rats (up to 26 weeks) and dogs (up to 39 weeks), a full battery of genetic toxicity studies, mouse and rat carcinogenicity studies, and a battery of exploratory and definitive reproductive and developmental toxicity studies in rats and rabbits. Other toxicity studies were performed as needed.

  In general toxicity studies, the rat was the more sensitive one of the two species used. Target organs include the kidney (cortical tubule dilation and inflammation/hyperplasia), bladder (inflammation/hyperplasia), prostate (inflammation), bone (increased trabecular bone), and stomach (nonglandular hyperplasia/hyperkeratosis and ulcers), most of which were identifiable after 4 weeks of dosing in the rat. Adverse effects in the dog were generally limited to gastrointestinal-related clinical signs and an increase in heart rate. Thyroid (follicular cell hyperplasia/adenoma/carcinoma) was an additional target organ identified in the 2-year carcinogenicity study in rats.

  Renal tubule dilation observed in 6-month and 2-year rat study, at 3 to 8 x maximal human recommended dose (MHRD), was reversible and considered to be an adaptive change to polyuria, consistent with the findings of other SGLT2 inhibitors. In the 2-year rat study, dose-related increases in urinary tract inflammation/infection were considered secondary to pharmacodynamically mediated glucosuria, and/or calculi formation, and were not associated with any neoplastic changes in the urinary tract at exposures up to 15X MHRD in males (AUC_{0-24} 28500 ng·h/ml) and 45X MHRD in females (AUC_{0-24} 87800 ng·h/ml). In dog, renal changes were limited to reversible increases in kidney weight.

  In the 6-month rat study, dose-related increase in trabecular bone of the sternum (mild to moderate) and a decrease in calciotropic hormones 1,25-dihydroxyvitamin D and parathyroid hormone (PTH) in all dose groups (≥30 mg/kg/day, 8X MHRD), likely due to changes in calcium homeostasis as a result of intestinal SGLT1 inhibition. Reduction in 1,25-dihydroxyvitamin D levels were also observed in the 9-month dog study at the mid and high dose.

- Safety pharmacology studies assessing the CV, neurological, respiratory, renal, and gastrointestinal effects of sotagliflozin did not identify any acute safety concerns at clinical exposure levels [NOAELs 100 mg/kg in dogs or rats, ≥24X MHRD].

- Reproductive and developmental toxicity assessments demonstrated that sotagliflozin had no effects on reproductive performance or fertility indices in rat, was not teratogenic in rate or rabbit, caused maternal and fetal toxicity at 350 mg/kg dose (161X MHRD) in rat, and reduced maternal weight gain in rabbit at 200 mg/kg dose without effect on the fetus. In the post-natal development study in the rat, sotagliflozin had no effect on developmental landmarks, sexual maturation, neural behavior development, or reproductive performance of the F1 generation (up to 19-25X MRHD). However, sotagliflozin caused dilation of the renal pelvis in F1 pups exposed at ≥30 mg/kg (4-7X MHRD) in utero and during lactation, resulting in a NOAEL of 10 mg/kg/day (1.3-2.5X MHRD) for the F1 generation.

  The kidney was also identified as a target organ in male and female juvenile rats with renal tubular and pelvis dilatation at 5-11X MHRD in the juvenile animal study. Increases in kidney weights and renal mineralization (males only) across all dose groups (~1X MHRD) were observed as well. All treatment-related renal changes demonstrated full or partial reversibility following the 4-week recovery period. The renal changes in rats in the post-natal development and juvenile animal studies are considered secondary to the pharmacodynamic activity of the drug and are consistent with the effects of other SGLT2 inhibitors. The morphological and functional renal development in the juvenile rat corresponds to renal development in humans during the late second and third trimester through approximately 2 years of age. Lactational exposure may also pose a risk to the developing human kidney as sotagliflozin was excreted in maternal milk (30% higher than plasma; on AUC basis) in rats.

- Sotagliflozin was not mutagenic or clastogenic in a standard battery of two in vitro and one in vivo GLP genetic toxicology studies. The Executive Carcinogenicity Assessment Committee (ECAC) concluded that there were no treatment-related increases in neoplasms in rats at doses up to 75 mg/kg (18-54X MHRD).

- The reviewer concluded that nonclinical data support market approval of sotagliflozin. The reviewer comments indicate that,

  - Increased susceptibility to urinary tract inflammation and infection due to glucosuria and osmotic diuresis secondary to renal SGLT2 inhibition is expected.
  - Clinical implication of prostate inflammation observed in rats is unclear and may become apparent with post-market experience.

- Long term clinical consequences of increased glucose/water residence time in the gastrointestinal tract must also await post-market experience. The nonclinical program identified pathological changes to the gastrointestinal tract and to bone (secondary to altered calcium homeostasis) at exposures higher than the therapeutic dose. The degree of effect in clinical trials thus far has resulted in diarrhea, but no other gastrointestinal or bone-related adverse events as observed in the nonclinical program.

5. Clinical Pharmacology

Under NDA 210934, clinical pharmacology review dated February 20, 2019, relied on 12 clinical and clinical pharmacology studies and one population pharmacokinetics (PK) study and recommended approval. Under NDA 216203, clinical pharmacology review by Mohamed Ismail Nounou and Snehal Samant, Office of Clinical Pharmacology (OCP), dated March 16, 2023, recommended approval of sotagliflozin. Key elements of clinical pharmacology review are listed below:

- *General clinical pharmacology considerations:* Sotagliflozin has linear pharmacokinetics (PK) across 50 to 400 mg dose range. The absolute bioavailability of oral sotagliflozin tablets was approximately 25% (90% CI: 16% to 39%) for AUC_{last}. The median T_{max} of the tablet formulation was 1.25 to 3 hours, for single doses of 200 to 2000 mg, and 2.5 to 4 hours for multiple doses (400 and 800 mg). Following once daily dose, steady state was achieved by 5 days and the accumulation ratios for C_{max} and $AUC_{0\text{-}24h}$ on Day 10 were approximately 1.5- to 2.0-fold for both.

  When a single dose sotagliflozin was administered with high-fat and high-calorie meal, sotagliflozin was absorbed with the median T_{max} (range) of 1.5 (1.5-5.0) hours, and sotagliflozin C_{max} and $AUC_{0\text{-}inf}$ increased by 149% and 50%, respectively. Multiple doses of sotagliflozin 400 mg given immediately before breakfast; 30 minutes prior to breakfast; and 1- hour before breakfast in healthy subjects showed consistent effect of sotagliflozin on urine glucose excretion (UGE), insulin, and postprandial glucose (PPG) across all dose schedules.
  Labeling implication: It is recommended that sotagliflozin be taken not more than one hour before the first meal of the day.

  Both sotagliflozin and its major human metabolite 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 [14C]-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.

In vitro metabolism studies indicated that the key enzymes responsible for the metabolism of sotagliflozin were UGT1A9 and, to a lesser extent, CYP3A4. Sotagliflozin is extensively metabolized to its 3-O-glucuronide (M19), that represented 94% of the radioactivity in plasma following administration of single dose of 400 mg [14C]-sotagliflozin in healthy subjects. Compared with sotagliflozin, M19 has significantly diminished (> 275-fold) activity toward SGLT1 and SGLT2.

The main route of elimination of sotagliflozin and its metabolites is through urine. Following administration of 200 mg and 400 mg sotagliflozin in healthy volunteers, mean CL/F of sotagliflozin ranged from 261 to 374 L/hr. Effective half-life ($t_{1/2}$) of sotagliflozin ranges from 5 to 10 hours. Mean terminal $t_{1/2}$ ranges from 21 to 35 hours for sotagliflozin and from 19 to 26 hours for M19.

- *Intrinsic factors potentially affecting elimination:* Exposure of sotagliflozin was evaluated in a dedicated PK study in subjects with mild (eGFR 60 to <90 mL/min/1.73 m²) and moderate (eGFR 30 to <60 mL/min/1.73 m²) renal impairment and subjects with normal renal function (eGFR ≥90 mL/min/1.73 m²). Exposure to sotagliflozin following a single dose of 400 mg was approximately 70% higher in subjects with mild and up to 170% higher in subjects with moderate renal impairment compared to subjects with normal renal function. In the pivotal trials (SCORED and SOLOIST), no apparent trends were observed for fraction of patients anytime up-titrated, down-titrated following up-titration, and dose at end of the trial when stratified by renal function.
  Labeling implication: The recommended dose of sotagliflozin for patients (b) (4) (b) (4) is 200 mg once daily, up titrated to 400 mg once daily, as tolerated. (b) (4) (b) (4) .

  In a study with subjects with reduced hepatic function, AUC of sotagliflozin was not increased in mild (Child Pugh A) hepatic impaired subjects but was increased by approximately 3-fold in moderate (Child Pugh B) and approximately 6-fold in severe (Child Pugh C) hepatic impaired subjects compared to subjects with normal hepatic function.

Labeling implication: No dosage adjustment is necessary in patients with mild hepatic impairment. Sotagliflozin is not recommended in patients with moderate or severe hepatic impairment since the available dose strengths do not permit adequate dose adjustments. Also, the safety and efficacy of 3-fold and 6-fold lower doses of sotagliflozin have not been established in patients with moderate or severe hepatic impairment.

- *Drug-drug interactions:* Rifampicin (UGT inducer) decreases exposure to sotagliflozin. If an inducer of UGT1A9 is required to be co-administered with sotagliflozin, frequent monitoring of glucose levels is recommended. The increase in exposure (C_{max} and AUC) of digoxin, a P-gp substrate, when co-administered with sotagliflozin requires monitoring of patients. The observed changes in overall exposure (AUC) of sotagliflozin following coadministration with hydrochlorothiazide, ramipril, metformin, mefenamic acid, oral contraceptives, metoprolol, rosuvastatin and midazolam are not considered to be clinically relevant. Based on class labeling, concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations. Monitor serum lithium concentration more frequently during sotagliflozin initiation and dosage changes.

- *Demographic interactions/specific populations:* Based on population PK analysis, age, body weight, sex, and race (non-white versus primarily whites) do not have a clinically meaningful effect on PK of sotagliflozin.

- *QT assessment:* In a randomized, placebo-controlled, active-comparator, crossover study, 58 healthy subjects were administered a single oral dose of sotagliflozin 800 mg or sotagliflozin 2000 mg (5 times the maximum recommended dose), moxifloxacin, and placebo. The maximum mean ΔΔQTc for sotagliflozin 800 mg and 2000 mg was 1.9 and 1.3 msec with an associated upper confidence boundary (UCB) of 3.7 and 2.4 msec respectively. At a dose 5 times the maximum recommended dose (400 mg QD), sotagliflozin does not prolong QTc interval to any clinically relevant extent.

- *Bridge between the to-be marketed and clinical trial formulations:* Based on the results of the bioequivalence Study BEQ14993, to-be marketed 400 mg oral tablet formulation has similar bioavailability to the Phase 3 clinical trial tablet formulation (2 x 200 mg tablets). Inspection of the clinical and analytical sites determined the findings to be reliable.

- *Other notable issues:* Based on the lack of sotagliflozin exposure data from the two pivotal trials (SCORED and SOLOIST) and the very low incidence rate of the CV events of special interest (CV EOSI; CV death, myocardial infarction, stroke, and

hospitalization due to HF) in the core T2DM studies with sotagliflozin exposure data, no exposure-response analysis was conducted for efficacy. FDA had previously agreed to this proposal (FDA response letter dated September 30, 2021).

Lack of independent treatment arms for the 200 mg and 400 mg sotagliflozin doses and a titrated dosing regimen implemented in the pivotal Phase 3 trials limited any direct comparison between the 200 and 400 mg doses.

6. Clinical Microbiology

Not Applicable.

7. Clinical/Statistical- Efficacy

Summary of efficacy and safety presented in Sections 1, 7 and 8 of this CDTL review largely relies on the joint clinical and statistical review by Jordan E Pomeroy, Ququan Liu and Tejas Patel, dated March 23, 2023 in DARRTS.

SOLOIST was a phase 3, placebo-controlled, double-blind trial designed to evaluate the efficacy and safety of sotagliflozin to reduce the risk of CV death, HHF and UHV in patients with heart failure (HF) and type 2 diabetes mellitus (T2DM). SOLOIST randomized 1222 patients in 1:1 ratio to sotagliflozin versus placebo and demonstrated decreased incidence of the primary composite endpoint with sotagliflozin with a hazard ratio (HR) 0.67 (95% CI 0.53, 0.85); P-value <0.001.

SCORED was a phase 3, placebo-controlled, double-blind trial designed to evaluate the efficacy and safety of sotagliflozin to reduce the risk of CV death, HHF, and UHV in patients with T2DM, chronic kidney disease with estimated glomerular filtration rate (eGFR) ≥25 to ≤60 mL/min/1.73 m2, and either a major CV risk factor or age ≥55 years with at least 2 minor CV risk factors. SCORED randomized 10,584 patients in 1:1 ratio to sotagliflozin versus placebo and demonstrated decreased incidence of the primary composite endpoint with a HR 0.75 (95%CI 0.63, 0.88); p-value <0.0004.

In both trials, all components of the primary composite endpoint contributed to the overall results. For the planned secondary endpoints, only the first endpoint of HHF and UVHF was formally tested. Tables 1 and 2 display the treatment effect for the composite endpoint, its components and the first secondary endpoint in SOLOIST and SCORED, respectively.

Table 1 Treatment Effect for the Primary Composite Endpoint, Components of the Primary Endpoint, and First Secondary Endpoint in the SOLOIST Study

	Event Rates per 100 Patient-years		
Efficacy Endpoint[a]	**Sotagliflozin N = 608**	**Placebo N = 614**	**Hazard Ratio (95% CI)**
Total occurrence of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit[b]	51.3	76.4	0.67 (0.53, 0.85) p=0.001
Hospitalization for heart failure	33.7	51.9	0.65 (0.49, 0.87)
Urgent heart failure visit	6.9	12.1	0.60 (0.34, 1.06)
Cardiovascular death[c]	8.4	9.4	0.84 (0.58, 1.23)
Secondary Endpoint[d]			
Hospitalization for heart failure and urgent heart failure visit[d]	40.6	63.9	0.64 (0.50, 0.84)

[a] Based-on investigator-reported events in all randomized patients, analyzed according to the treatment group allocated by randomization.
[b] Predefined primary endpoint.
[c] Time-to-event analysis was performed; event rates are percentages of patients with events.
[d] Predefined secondary endpoint and tested with multiplicity control.

Table 2 Treatment Effect for the Primary Composite Endpoint, Components of the Primary Endpoint, and First Secondary Endpoint in the SCORED study

Efficacy Endpoint[a]	Event Rates (per 100 Patient-years)		Hazard Ratio (95% CI)
	Sotagliflozin N = 5,292	Placebo N = 5,292	
Total occurrence of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit[b]	5.6	7.5	0.75 (0.63, 0.88) $p < 0.001$
Hospitalization for heart failure	2.8	4.2	0.66 (0.53, 0.82)
Urgent heart failure visit	0.7	0.9	0.73 (0.48, 1.11)
Cardiovascular death[c]	2.9	3.2	0.90 (0.73, 1.12)
Secondary Endpoint[d]			
Hospitalization for heart failure or urgent heart failure visit[d]	3.5	5.1	0.67 (0.55, 0.82)

[a] Based-on investigator-reported events in all randomized patients, analyzed according to the treatment group allocated by randomization.
[b] Predefined primary endpoint.
[c] Time-to-event analysis was performed; event rates are percentages of patients with events.
[d] Predefined secondary endpoint and tested with multiplicity control.

Prespecified subgroup analyses for SOLOIST and SCORED demonstrated consistent treatment benefit with sotagliflozin on the primary composite endpoint across key subgroups, including left ventricular ejection fraction (LVEF) at screening, presence of HF, and main etiology of HF. Background therapies used for the treatment of HF were consistent with standard of care at the time of trial conduct. Treatment effect was observed across the range of baseline HbA1c values, with no statistically significant treatment effect interaction between primary endpoint results and HbA1c.

Conclusions on the Substantial Evidence of Effectiveness: Data submitted in support of NDA 216203 meets the statutory requirement for substantial evidence of effectiveness and supports a favorable benefit-risk assessment of sotagliflozin "to reduce the risk of

cardiovascular death, hospitalization for heart failure and urgent heart failure visits in adults with heart failure or type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors." The review team recommends approval of sotagliflozin for this indication statement, and I concur.

8. Safety

The mean duration of exposure to sotagliflozin was 252 (± 161) and 441 (± 182) days in SOLOIST and SCORED, respectively and was similar to placebo. Safety analyses of SOLOIST and SCORED did not demonstrate any unfavorable imbalance in the incidence of deaths or serious treatment emergent adverse events (TEAEs). The absolute risk difference for TEAEs leading to permanent treatment discontinuation between sotagliflozin and placebo was small, 1 (-1.2, 3.3) in SOLOIST and 0.5 (-0.2, 1.3) in SCORED. In these trials, the most commonly reported TEAE by preferred term was diarrhea. In both studies, TEAEs related to volume depletion were more likely to occur in elderly patients and in patients with lower baseline eGFR (<30 mL/min/1.73m2 in SCORED and <60 mL/min/1.73m2 in SOLOIST). Genital mycotic infections occurred more frequently in female patients, with a relative risk (95% CI) of 3.2 (0.3, 30.6) and 2.9 (1.9, 4.4) in SOLOIST and SCORED, respectively. The incidence rate of diabetic ketoacidosis (DKA) and amputations was low in both trials, with no clinically relevant imbalance between the treatment groups. The TEAEs observed with sotagliflozin, except diarrhea, are consistent with the known safety profile of other approved SGLT2 inhibitors.

9. Advisory Committee Meeting

No Advisory Committee meeting was convened because no controversial issues related to pivotal study design, efficacy or safety results and overall determination of benefit-risk were identified.

10. Pediatrics

The Applicant has requested a full waiver for pediatric studies according to the agreed initial Pediatric Study Plan (iPSP) for all pediatric age groups (0 to <18 years old) on the grounds that necessary studies are impossible or highly impractical because the number of patients is so small and there is no established/agreed upon bridging biomarker for SGLT2i for HF benefit.

11. Other Relevant Regulatory Issues

None.

12. Labeling

Prescribing Information

Major labeling issues that were addressed during the review are summarized below.

- INDICATIONS AND USAGE:
  - (b) (4) In vitro studies demonstrate that sotagliflozin inhibits human SGLT2 with similar potency (IC_{50}) as do other SGLT2 inhibitors (e.g., dapagliflozin, canagliflozin, and empagliflozin). Unlike the other approved SGLT2 inhibitors, sotagliflozin inhibits SGLT1 with higher potency and achieves functional inhibition of SGLT1 at the proposed clinical dose, most readily apparent as gastrointestinal adverse effects observed clinically and nonclinically.[2] Available data are inadequate to conclude contribution of SGLT1 inhibition to sotagliflozin' s cardiovascular benefit. (b) (4) SGLT1 inhibition will be described in Section 12 in the context of adverse gastrointestinal events.

  - The Applicant's proposed indication in HF population was restricted to patients with T2DM because of the enrollment criteria used in SOLOIST. However, T2DM is a risk factor for HF, and sotagliflozin demonstrated benefit across the HbA1c spectrum in SOLOIST and SCORED. In the context of the submitted studies, T2DM is an enrichment factor for HF, not a requisite to derive treatment benefit with sotagliflozin. Hence, the indicated HF population will not be restricted to those with T2DM.
  - The Applicant's proposed indication included a description of reduction of the primary composite endpoint in "adults with heart failure, including those with acute or worsening heart failure." However, the design and conduct of the

[2] Secondary Pharmacology Toxicology Review by Dr. Xuan Chi dated December 10, 2023 in DARRTS

SOLOIST and SCORED trials do not support use of sotagliflozin as a therapy for "acute" heart failure nor does worsening heart failure (WHF) describe a specific HF patient population standing to benefit from sotagliflozin therapy. Hence, the indication statement will not include "acute or worsening heart failure."

- The Applicant's proposed indication included reduction of nonfatal myocardial infarction (MI) and nonfatal stroke in adults with T2DM. SCORED included 3-point major adverse cardiovascular events (MACE) i.e., CV death, nonfatal MI and nonfatal stroke as a secondary endpoint to be tested within the pre-specified hierarchical alpha spending plan. However, at study result analysis, there was no alpha remaining to be assigned to MACE. Hence, nonfatal MI and nonfatal stroke will not be included in the indication statement, (b) (4) (b) (4)

- Use in patients with type 1 diabetes mellitus (T1DM).
  The Applicant (b) (4) In the pivotal trials submitted to support NDA 210934 for sotagliflozin for treatment of T1DM [Study 309 (N=793), study 310 (N=782), and study 312 (N=1405)], an 8 times the risk of ketoacidosis was observed in patients with T1DM treated with sotagliflozin versus placebo [4.06 per 100 patient years (PY) vs. 0.57 per 100 PY, respectively; ~3.5 events per 100 PY absolute risk increase]. This safety risk, weighed against the observed benefits, led to a Complete Response of NDA 210934.

  Under NDA 216203, the primary composite endpoint for SOLOIST and SCORED trials was total occurrence of CV death, HHF, and UHFV. SOLOIST trial demonstrated an absolute risk reduction of 25.1 events per 100 PY for the primary composite endpoint in patents with T2DM and heart failure. SCORED trial demonstrated a more limited absolute risk reduction of 1.9 events per 100PY for the primary composite endpoint in patients with T2DM, CKD and other CV risk factors. SCORED trial population included about 16 to 20% patients with history of heart failure at baseline. Neither of these trials enrolled patients with T1DM.

  The Division believes that the observed benefit of absolute risk reduction for the primary composite endpoint of total occurrence of CV death, HHF, and UHV in SOLOIST and SCORED trials, especially in patients with HF likely outweighs the increase in absolute risk of 3.5 events per 100PY for ketoacidosis in a subpopulation of patients with T1DM. In the setting of glycemic control, it is reasonable to state that the risk of ketoacidosis does not outweigh the glycemic

control benefit in patients with T1DM, especially when there are other effective approved agents for glycemic control, including insulin. However, when comparing the ketoacidosis risk against potential benefit for reduction of CV death, HHF and UHFV, we believe that the benefit of treating patients with comorbid T1DM, and HF outweighs the risk of ketoacidosis.

(b) (4)

(b) (4). To help mitigate risk, a description of increased risk of ketoacidosis in patients with T1DM will be included in Section 5.1 of the PI (discussed below).

- WARNINGS and PRECAUTIONS section-Diabetic Ketoacidosis in Patients with Type 1 Diabetes and Other Ketoacidosis:
  The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) has drafted revised class labeling for SGLT2 inhibitors regarding diabetic ketoacidosis (DKA) in patients with type 1 diabetes (T1DM) and other ketoacidosis. This revised language will be included in the sotagliflozin labeling. Because sotagliflozin and certain other SGLT2 inhibitors may be used in patients with type 1 diabetes for non-glycemic control indications, the title and information in the warning and precaution were revised to highlight the markedly increased DKA risk in patients with T1DM. Overall, DDLO reorganized and streamlined existing information in the warning and precaution to convey the risk and mitigation more clearly and succinctly. Additional new labeling revisions include:
  - Instructions for temporarily withholding drug at least 3 days, if possible, prior to major surgery or procedures associated with prolonged fasting in the Dosage and Administration section,
  - New safety information regarding post marketing cases of prolonged ketoacidosis and glucosuria, and
  - Consideration of ketone monitoring in patients with T1DM and consideration of ketone monitoring in others at risk for ketoacidosis if indicated by the clinical situation to further highlight the increased risk of DKA in patients with T1DM and to provide a possible mechanism for earlier identification of impending DKA for mitigation.

It is important to note that ketone monitoring was not shown to sufficiently lower sotagliflozin' s DKA risk in patients with T1DM in clinical trials for glycemic control, and the (b) (4) (b) (4) for the heart failure indication, we have determined that sotagliflozin' s benefit(s) outweighs its overall risks, including the significant DKA risk for T1DM patients (see benefit risk assessment in this memo). Nevertheless, the DKA risk should be mitigated to the extent possible and instructing prescribers to consider ketone monitoring for T1DM patients receiving sotagliflozin for the heart failure indication may help prescribers identify some patients with impending DKA earlier and mitigate some of this known risk, possibly to a meaningful extent, although it is not expected that ketone monitoring will fully mitigate these patients' DKA risk.

- CLINICAL STUDIES section:
  - (b) (4)
  -

Other Labeling

- The Applicant was advised to include description of renal changes observed in rats from the post-natal developmental and juvenile toxicology studies with sotagliflozin in Section 8.1 because these findings are relevant to reproductive toxicities.

DMEPA Review

Labeling Review by Janine Stewart, Division of Medication Error Prevention and Analysis 2 (DMEPA 2), dated November 28, 2022, for (b) (4) (sotagliflozin) tablets, concluded that the proposed (b) (4) prescribing information (PI), Medication Guide, container label,

and carton labeling can be improved to promote the safe and effective use of the product. Recommendations by DMEPA were incorporated into the Label.

DPMH Review

Review by Wenjie Sun, Division of Pediatrics and Maternal Health (DPMH), dated November 22, 2022, concluded that available human data regarding the use of sotagliflozin in pregnancy are insufficient to assess a drug-related risk of congenital malformations, miscarriage, or adverse maternal or fetal outcomes. The reviewer indicated that in the limited number of reports received involving pregnancy (4 paternal and 10 maternal exposures to sotagliflozin, 11 exposures to placebo), there were no safety issues identified with sotagliflozin. Review of literature by the applicant and the DPMH reviewer did not find any published data on use of sotagliflozin during pregnancy. Due to finding of renal tubular dilation in juvenile rats with sotagliflozin, and similar findings with other SGLT2 inhibitors, DPMH recommended that sotagliflozin not be used during the second and third trimesters of pregnancy.

DPMH recommended a post market pregnancy registry. The Division questions the feasibility and interpretability of a single armed safety study and will not mandate a post market pregnancy registry for sotagliflozin.

Sotagliflozin is present in animal milk. When a drug is present in animal milk, it is likely to be present in human milk. Use of SGLT2 inhibitors is not recommended during breast feeding. DMPH recommended a post marketing clinical lactation study (a milk-only study in lactating volunteer to determine the concentration of sotagliflozin in milk) to inform the lactation labeling. The Division considers available nonclinical data with sotagliflozin, which is consistent with other SGLT2 inhibitors, adequate to inform lactation labeling at this time and is not recommending that the Applicant conduct a post marketing clinical lactation study.

DPMH revised subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR.

13. Post marketing Recommendations

None.

14. Recommended Comments to the Applicant

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHARU GANDOTRA
05/12/2023 04:51:48 PM

NORMAN L STOCKBRIDGE
05/13/2023 05:43:21 AM

LISA B YANOFF
05/13/2023 09:00:32 AM
I agree with the review conclusions and recommended regulatory action in this memo. This memo serves as the summary basis for regulatory action for this NDA

Office of Clinical Pharmacology Review

NDA Number	216203
Link to EDR	\\CDSESUB1\evsprod\NDA216203\0021
Submission Date	5/27/2022
Submission Type	505 (b)(1) Type 1- New Molecular Entity
Brand Name	(b) (4)
Generic Name	Sotagliflozin
Dosage Form and Strength	Tablet 200 mg and 400 mg
Route of Administration	Oral
Proposed Indication	• Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure • Reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.
Applicant	Lexicon Pharmaceuticals Inc.
Associated INDs	102191 (DDLO), 135095 & 160506 (DCN)
OCP Review Team	Mohamed Ismail Nounou, Ph.D., Ye Yuan, Ph.D., Hao Zhu, Ph.D. & Snehal Samant, MS, Ph.D.
OCP Final Signatory	Doanh Tran, Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY

Sotagliflozin is a Sodium-glucose Cotransporter-2 (SGLT2) and Sodium-glucose Cotransporter-1 (SGLT1) inhibitor new molecular entity (NME). The role of SGLT1 inhibition effect on efficacy of sotagliflozin is not clear. The Applicant submitted a New Drug Application (NDA 216203) on 27 May 2022 for sotagliflozin (200 mg and 400 mg tablets for oral administration) for the following proposed indications:

- To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure and
- To reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.

The Applicant is primarily relying on the efficacy and safety results from two pivotal phase 3 trials, SOLOIST (SOLOIST-WHF, SOLOIST: EFC15156) and SCORED (SCORED: EFC14875). Additionally, the Applicant submitted 8 Phase 1 studies (pharmacokinetic (PK), relative bioavailability, and drug-drug interaction (DDI) studies), and 2 Phase 2 studies (PK/Pharmacodynamic (PD) in patients with type 2 diabetes mellitus (T2DM) and heart failure).

On 22 March 2018, the Applicant submitted NDA 210934 seeking an indication to improve glycemic control when used with insulin in adult patients with type 1 diabetes mellitus (T1DM). On 22 March 2019, FDA issued a Complete Response letter due to an unfavorable benefit-risk assessment. Clinical pharmacology of sotagliflozin previously reviewed under NDA 210934 (*Clinical Pharmacology Review, 20 March 2019*) is summarized in the current review.

The key issues addressed in this clinical pharmacology review are:
1) Appropriateness of the proposed dose of sotagliflozin.
2) Appropriateness of the proposed dosing for patients with renal impairment.
3) Assessment of the relative bioavailability of Phase 3 clinical trial formulation to the to-be-marketed formulation of sotagliflozin.
4) Assessment of the drug interaction potential of sotagliflozin with hydrochlorothiazide and ramipril.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (DCEP) has reviewed NDA 216203 Clinical Pharmacology data submitted on May 27, 2022 and recommends approval of this NDA. The key review issues with specific recommendations / comments are summarized below.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The pivotal evidence of effectiveness and safety are provided by two phase 3 studies (SOLOIST and SCORED studies). SOLOIST provided evidence of effectiveness for reduction of CV death, hospitalization for heart failure (HHF) and urgent heart failure visit (UHFV) in adults with heart failure, regardless of T2DM status. SCORED provided evidence of effectiveness for reduction of CV death, HHF and UHFV in adults with T2DM, CKD and other CV risk factors.
General dosing instructions	• The recommended starting dose of sotagliflozin is 200 mg orally once daily not more than one hour before the first meal of the day. • Uptitrate after at least 2 weeks to 400 mg orally once daily as tolerated. Downtitrate to 200 mg as necessary.
Dosing in patient subgroups (intrinsic and extrinsic factors)	(b) (4)
Labeling	The proposed labeling language pertaining to clinical pharmacology is generally acceptable. In accordance with the labels for the other SGLT2 inhibitors, the following class labeling recommendation was added to the Drug Interactions Section of the label: 7.3 Lithium Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations. Monitor serum lithium concentration more frequently during TRADENAME initiation and dosage changes.
Bridge between the to-be-marketed and clinical trial formulations	To-be marketed 400 mg oral tablet formulation has similar bioavailability to the Phase 3 clinical trial tablet formulation (2 x 200 mg tablets). Inspection of the clinical and analytical sites determined the findings to be reliable.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

Sotagliflozin is an inhibitor of SGLT2 and SGLT1. The data are inadequate to conclude that SGLT1 contributes to the mechanism of efficacy in heart failure beyond inhibition of SGLT2. Inhibiting SGLT2 reduces renal reabsorption of glucose and sodium. Inhibiting SGLT1 reduces intestinal absorption of glucose and sodium which likely contributes to diarrhea. The mechanism for sotagliflozin's cardiovascular benefits has not been established.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, crossover study, 58 healthy subjects were administered a single oral dose of sotagliflozin 800 mg or sotagliflozin 2000 mg (5 times the maximum recommended dose), moxifloxacin, and placebo. The maximum mean ΔΔQTc for sotagliflozin 800 mg and 2000 mg was 1.9 and 1.3 msec with an associated upper confidence boundary (UCB) of 3.7 and 2.4 msec respectively. At a dose 5 times the maximum recommended dose (400 mg QD), sotagliflozin does not prolong QTc interval to any clinically relevant extent. (*Clinical Pharmacology Review, 20 March 2019*)

The following is a summary of the clinical pharmacokinetics of sotagliflozin:

Pharmacokinetics

Peak plasma concentration (C_{max}) and area under the concentration-time curve (AUC) of sotagliflozin increased in a dose-proportional manner in the therapeutic dose range of 200 to 400 mg QD. The absolute bioavailability of oral sotagliflozin tablets was approximately 25% (90% CI: 16% to 39%) for AUClast Accumulation of sotagliflozin was observed with approximately 50 – 100% increase in C_{max} and area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24h}) values observed at steady state when compared to the first day of dosing (*Study 110, Clinical Pharmacology Review, 20 March 2019*).

Absorption

- The median T_{max} of the tablet formulation ranged from 1.25 to 3 hours, over a single-dose range of 200 mg to 2000 mg. Following administration of multiple doses (400 and 800 mg dose), the median T_{max} values ranged from 2.5 to 4 hours.
- When a single dose sotagliflozin was administered with high-fat and high-caloric meal, sotagliflozin was rapidly absorbed with the median T_{max} (range) of 1.5 (1.5-5.0) hours, and sotagliflozin C_{max} and AUC_{0-inf} increased by 149% and 50%, respectively. Multiple doses of sotagliflozin 400 mg given immediately before breakfast; 30 minutes prior to breakfast; and 1-hour before breakfast in healthy subjects showed consistent effect of sotagliflozin on urine glucose excretion (UGE), insulin, and postprandial glucose (PPG) across all dose schedules. It is

recommended that TRADENAME be taken not more than one hour before the first meal of the day.

Distribution

• Both sotagliflozin and its major human metabolite 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.
• Sotagliflozin is extensively metabolized to its 3-O-glucuronide (M19). Following the administration of single dose of 400 mg [^{14}C]-sotagliflozin in healthy subjects, the predominant metabolite in the plasma was sotagliflozin-3-O-glucuronide (M19) and represented a mean of 94.3% of the radioactivity in plasma.
• M19 has significantly diminished (> 275-fold) activity toward SGLT1 and SGLT2 compared with sotagliflozin.

Elimination

• As indicated by the metabolism data above, the primary route of elimination of sotagliflozin is via metabolism.
• Following the administration of single dose of 400 mg [^{14}C]-sotagliflozin in healthy subjects, the mean cumulative radioactive dose recovered in the urine and feces were 57.4% and 36.7%, respectively, suggesting that the main route of elimination of radioactivity associated with sotagliflozin and metabolites was through the urine. The predominant metabolite detected in urine was M19, representing a mean of 33.2% of the administered radioactive dose. Unchanged [^{14}C] sotagliflozin was the predominant radioactive peak detected in fecal extracts representing a mean of 23.4% of the total administered radioactive dose.
• Following administration of 200 mg and 400 mg sotagliflozin in healthy volunteers, mean CL/F of sotagliflozin ranged from 261 to 374 L/hr. The median population PK model predicted CL/F in type 2 diabetes mellitus patients with normal renal function was about 300 L/hr.
• Effective half-life ($t_{1/2}$) of sotagliflozin ranges from 5 to 10 hours. Mean terminal $t_{1/2}$ ranges from 21 to 35 hours for sotagliflozin and from 19 to 26 hours for M19.

Intrinsic factors

Renal impairment

Exposure of sotagliflozin was evaluated in a dedicated PK study in subjects with mild (eGFR 60 to <90 mL/min/1.73 m²) and moderate (eGFR 30 to <60 mL/min/1.73 m²) renal impairment and subjects with normal renal function (eGFR ≥90 mL/min/1.73 m²). Exposure to sotagliflozin following a single dose of 400 mg was approximately 70% higher in subjects with mild and up to 170% higher in subjects with moderate renal impairment compared to subjects with normal renal function.

Hepatic impairment

In a study with subjects with reduced hepatic function, AUC of sotagliflozin was not increased in mild (Child Pugh A) hepatic impaired subjects but was increased by approximately 3-fold in moderate (Child Pugh B) and approximately 6-fold in severe (Child Pugh C) hepatic impaired subjects compared to subjects with normal hepatic function.

Effects of Age, Sex, Race, and Body Weight on Pharmacokinetics

Based on population PK analysis, age, body weight, sex, and race (non-white versus primarily whites) do not have a clinically meaningful effect on PK of sotagliflozin.

Drug-drug interactions

The observed changes in overall exposure (AUC) of sotagliflozin following coadministration with hydrochlorothiazide, ramipril, metformin, mefenamic acid, and oral contraceptives are not considered to be clinically relevant. Rifampicin (UGT inducer) decreases exposure to sotagliflozin. If an inducer of UGT1A9 is required to be co-administered with sotagliflozin, frequent monitoring of glucose levels is recommended.
The increases in exposure (AUC) of metoprolol (CYP2D6 substrate) and rosuvastatin (BCRP substrate), as well as the decrease in exposure to midazolam (CYP3A4 substrate) are not considered to be clinically relevant. The increased exposure (C_{max} and AUC) in ramipril is not considered clinically significant because the exposure of ramiprilat, the primary active metabolite, is minimally increased.
The increase in exposure (C_{max} and AUC) of digoxin, a P-gp substrate, when coadministered with sotagliflozin requires monitoring of patients.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended starting dose of sotagliflozin is 200 mg orally once daily not more than one hour before the first meal of the day. Uptitrate after at least 2 weeks to 400 mg orally once daily as tolerated. Downtitrate to 200 mg as necessary.

2.2.2 Therapeutic individualization

No dose adjustment is needed in patients based on age, body weight, gender, and race/ethnicity. Dosing recommendations based on renal function is shown in **Table 1**.

Table 1: Recommended dosage based on renal function

Estimated Glomerular Filtration Rate (eGFR) (mL/min/1.73 m^2)	**Dosing recommendation**
[redacted]	(b) (4)

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

The clinical pharmacology section of the proposed label was updated to reflect the current Guidance on Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products. In accordance with the labels for the other SGLT2 inhibitors, the following class labeling recommendation was added to Drug Interactions Section 7.3, regarding the drug-drug interaction of sotagliflozin with lithium.

7 DRUG INTERACTIONS

7.3 Lithium

Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations. Monitor serum lithium concentration more frequently during TRADENAME initiation and dosage changes.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

3.1.1. Drug Product

Sotagliflozin is a small molecule drug (**Figure 1**). Sotagliflozin drug product will be supplied as an immediate release tablet at 200 mg and 400 mg strengths.

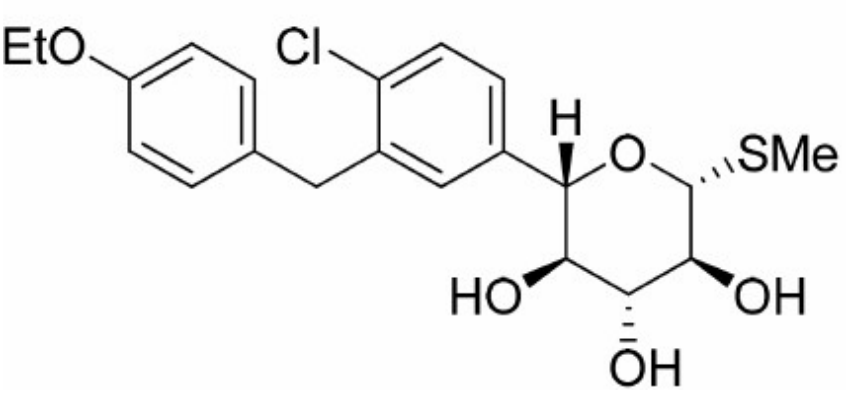

Figure 1: Sotagliflozin molecular structure
(Source: Page 8 of Quality Overall Summary)

Its molecular formula is $C_{21}H_{25}ClO_5S$, and the molecular weight is 424.94. Sotagliflozin is a white to off-white solid. It is practically insoluble in water.

3.1.2. Regulatory Background

Lexicon Pharmaceuticals, Inc re-submitted NDA 216203 for sotagliflozin on May 27, 2022. NDA 216203 was initially filed on 30 December 2021. The Applicant withdrew the NDA on 28 February 2022 after the Applicant notified the Agency of (b) (4) (b) (4) The Agency later agreed with the Applicant's (b) (4) which facilitated the resubmission of the NDA.

The Applicant submitted NDA 210934 on 22 March 2018 seeking an indication to improve glycemic control when used with insulin in adult patients with T1DM. Due to an unfavorable benefit-risk assessment the Agency issued a Complete Response letter on 22 March 2019. For NDA 216203, the Applicant submitted results from SOLOIST and SCORED studies as the pivotal Phase 3 studies to support the proposed indication. The proposed to-be marketed formulation is an immediate release film-coated tablet available in 200 mg and 400 mg strengths.

Clinical pharmacology of sotagliflozin previously reviewed under NDA 210934 is summarized in this review. Refer to the original Clinical Pharmacology Review (*DARRTS, NDA 210934, 02/20/2019*) for details. Twelve clinical and clinical pharmacology studies and one population PK report are reviewed under NDA 216203.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Sotagliflozin is an inhibitor of SGLT2 and SGLT1. Inhibiting SGLT2 reduces renal reabsorption of glucose and sodium. Inhibiting SGLT1 reduces intestinal absorption of glucose and sodium which likely contributes to diarrhea. The mechanism for sotagliflozin's cardiovascular benefits has not been established.
General Information	
Bioanalysis	Sotagliflozin plasma concentrations were measured by a validated liquid chromatography- tandem mass spectrometry assay (Refer to Appendix 4.3)
Dose proportionality	Following single and multiple doses sotagliflozin PK appeared to be dose proportional across the 50 to 400 mg range.
Absorption	
T_{max}	The median T_{max} of the tablet formulation ranged from 1.25 to 3 hours, over a single-dose range of 200 to 2000 mg. Following administration of multiple doses (400 and 800 mg dose), the median T_{max} values ranged from 2.5 to 4 hours.
Accumulation	Following QD dose, steady state was generally achieved by 5 days and the accumulation ratios for C_{max} and AUC_{0-24h} on Day 10 were approximately 1.5- to 2.0-fold for both.
Food effect	When a single dose sotagliflozin was administered with high-fat and high-calorie meal, sotagliflozin was absorbed with the median T_{max} (range) of 1.5 (1.5-5.0) hours, and sotagliflozin C_{max} and AUC_{0-inf} increased by 149% and 50%, respectively.
Distribution	
Volume of distribution	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.
Protein binding	Both sotagliflozin and its major human metabolite M19, exhibited high binding to human plasma proteins *in vitro* (>93% bound) which was not dependent on the concentration of sotagliflozin and M19.
Mean whole blood to plasma concentration ratio	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.
Elimination	
Half-life	Following sotagliflozin administration, mean terminal $t_{1/2}$ ranged from 21 to 35 hours for sotagliflozin and from 19 to 26 hours for M19.
Metabolism	
Metabolizing enzymes	• *In vitro* metabolism studies indicated that the key enzymes responsible for the metabolism of sotagliflozin were UGT1A9 and, to a lesser extent, CYP3A4. • Sotagliflozin is extensively metabolized to its 3-O-glucuronide (M19).

Excretion	
Primary excretion pathways	• The primary route of elimination of sotagliflozin is via metabolism. • Following the administration of single dose of 400 mg [^{14}C]-sotagliflozin in healthy subjects, the mean cumulative radioactive dose recovered in the urine and feces were 57.4% and 36.7%, respectively, suggesting that the main route of elimination of radioactivity associated with sotagliflozin and metabolites was through the urine.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The primary evidence of efficacy for sotagliflozin is demonstrated by two pivotal Phase 3 trials SOLOIST and SCORED. SOLOIST is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the effects of sotagliflozin on clinical outcomes in hemodynamically stable patients post worsening heart failure. SCORED is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to demonstrate the effects of sotagliflozin on cardiovascular and renal events in patients with type 2 diabetes, cardiovascular risk factors and moderately impaired renal function.

The dose selection for SCORED and SOLOIST study was based on the results of the Phase 2b study LX4211.1 202 DM (submitted under NDA 210934), in which doses of sotagliflozin 75 mg QD, 200 mg QD, 200 mg twice daily (BID), and 400 mg QD were tested over a 12week, double-blind period. At 12 weeks, the 200 mg QD and 400 mg QD doses lowered hemoglobin A1c (HbA1c) by a mean of 0.52% and 0.92%, respectively ($p<0.001$ for both arms), while placebo lowered HbA1c by a mean of 0.09%. Sotagliflozin induces an acute, but modest, decrease in eGFR. Since the study population consisted of patients at increased risk of acute kidney injury (i.e., patients with moderately to severely impaired renal function and patients with acute HF), study treatment began with the low dose of sotagliflozin (200 mg QD) and was increased to the maintenance dose of 400 mg QD, once tolerability of the low dose was established by the Investigator.

SOLOIST enrolled n=1222 subjects (~1:1 sotagliflozin vs. placebo) with a history of HF who were hemodynamically stable after an admission to the hospital, urgent heart failure visit (UHFV) or emergency department (ED)/infusion center visit for worsening HF and requiring intravenous (IV) diuresis. The primary composite endpoint was total (first and recurrent) cardiovascular (CV) death, hospitalization for heart failure (HHF) and UHFV. Sotagliflozin reduced the primary composite endpoint compared to placebo with a respective incidence rate of 51.3 versus 76.4 per 100 patient years; hazard ratio 0.67 (95%CI 0.53, 0.85); p-value <0.001.

SCORED enrolled n=10584 subjects (1:1 randomization sotagliflozin vs. placebo) with eGFR≥25 to ≤60 mL/min/1.73 m^2 with either a major CV risk factor or age ≥55 years or with at least 2 minor CV risk factors (as detailed in section 5.2.2). The primary composite endpoint was total (first and recurrent) CV death, HHF and UHFV. Sotagliflozin reduced the primary composite endpoint compared to placebo with a respective incidence rate of 5.6 versus 7.5 per 100 patient years;

hazard ratio 0.75 (95% CI 0.63, 0.88); p-value <0.0004. Refer to the integrated clinical statistics review for detailed clinical study design and results pertaining to secondary endpoints of the Phase 3 studies.
Because of the early termination of the two studies, there were no plasma samples collected from SCORED, while a few sparse plasma samples were available from the month 12 timepoint in SOLOIST (approximately 120 samples from sotagliflozin arm). Population PK (PPK) model and exposure-response (ER) model for safety were developed using data from patients with type-2 diabetes mellitus (T2DM). Based on the lack of sotagliflozin exposure data from the two pivotal trials (SCORED and SOLOIST) and the very low incidence rate of the CV events of special interest (CV EOSI; CV death, myocardial infarction, stroke, and hospitalization due to HF) in the core T2DM studies with sotagliflozin exposure data, no exposure-response analysis was conducted for efficacy. FDA had previously agreed to this proposal. (*FDA response letter 30-Sep-2021*).

3.3.2 Is the proposed dosing regimen (200 mg once daily dose up titrated to 400 mg once daily based on tolerability) acceptable for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen is acceptable to support use of sotagliflozin for the proposed indications. The recommended starting dose of (b) (4) is 200 mg once daily (QD) not more than one hour before the first meal of the day. In patients tolerating (b) (4) it is recommended to up titrate after at least 2 weeks to 400 mg QD. Dose may be downtitrated to 200 mg QD if necessary. **Table 1** details dosage recommendation based on estimated glomerular filtration rate (eGFR).

The proposed dosing regimen was implemented in the two pivotal Phase 3 trials. In the SCORED trial, 74.4% and 75.4% of subjects in the sotagliflozin and placebo arms, respectively were successfully up titrated to the 400 mg dose. In the SOLOIST trial 55.5% and 53.3% of the subjects in the sotagliflozin and placebo arms, respectively, were successfully up titrated per protocol. Evaluating the difference between the two doses overall is not meaningful as any such evaluation would be highly confounded by the titrated regimen used in the trials. Overall, the lack of independent treatment arms for the 200 mg and 400 mg sotagliflozin doses and a titrated dosing regimen implemented in the pivotal Phase 3 trials limit any direct comparison between the 200 mg and 400 mg doses. The proposed dosing regimen is supported by the two pivotal Phase 3 trials which demonstrated efficacy and safety in the intended patient population compared to placebo.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

An alternate dosing regimen or management strategy is not required in patients based on age, body weight, sex, and race. Specific dosing recommendations are recommended for patients with renal or hepatic impairment, and they are discussed below.

3.3.3.1. Renal impairment

(b) (4)

(b) (4)

Effect of renal impairment on the PK of sotagliflozin was evaluated in subjects with mild (eGFR 60 to <90 mL/min/1.73 m²) and moderate (eGFR 30 to <60 mL/min/1.73 m²) renal impairment and subjects with normal renal function (eGFR ≥90 mL/min/1.73 m²) in a dedicated renal impairment study (LX4211.121) *(See NDA210934 original Clinical Pharmacology review in DARRTS)*. Systemic exposure (AUC) of sotagliflozin following a single 400 mg dose was approximately 70% higher in subjects with mild renal impairment and up to 170% higher in subjects with moderate renal impairment compared to subjects with normal renal function. The review team evaluated whether the proposed dosing regimen of 200 mg once daily dose up titrated to 400 mg once daily based on tolerability is acceptable for patients with renal impairment, who are expected to have a relatively higher sotagliflozin exposure compared to those with normal renal function. Using data from SCORED and SOLOIST trials, reviewer also performed independent exploratory analyses to evaluate whether the dose titration pattern varied for patients with varying degrees of renal function.

Per communication with the medical team, the common safety events are diarrhea, hypoglycemia, and volume depletion. The exposure-response model developed using patients with T2DM predicted an approximate 5% incidence of diarrhea in placebo group, compared to a 5% to 12% incidence in patients with sotagliflozin 400 mg once daily. However, the dose can be down titrated if patients are intolerant. No E-R relationships between sotagliflozin exposure and the occurrence of hypoglycemia or volume depletion were identified after the inclusion of covariate effects.
Per the trial design, the dose may be up titrated and down titrated based on tolerability. There appeared a trend for increasing fraction of patients down-titrated due to AE following the worsening of the renal function in SCORED (**Figure 2**). However, this was not observed in SOLOIST (**Figure 2**). Considering the small number of patients experiencing dose reduction and the limited number of patients with mild and severe renal impairment in SCORED, the trend was not considered clinically relevant. Overall, no apparent trends were observed for fraction of patients anytime up-titrated (**Figure 2**), down-titrated following up-titration (**Figure 2)**, and dose at end of the trial when stratified by renal function (**Figure 3**).
The review team finds the proposed dosing regimen for patients with renal impairment, which was also implemented in the pivotal Phase 3 trials, to be acceptable.

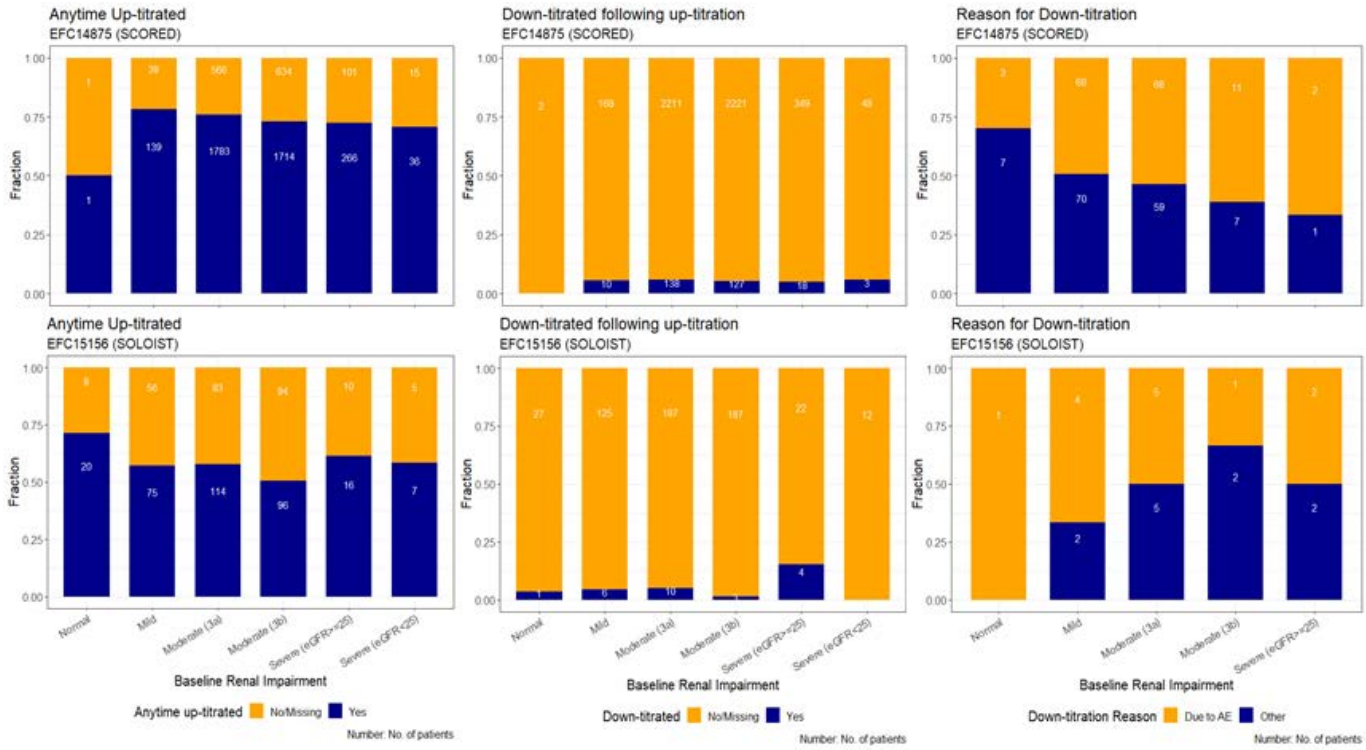

Figure 2: Fraction of patients up-titrated at any time (left panel), down-titrated following up-titration (center panel), and reason for down-titration (right panel) in SCORED (top panel) and SOLOIST (bottom panel) stratified by renal impairment categories

Source: Reviewer's analysis, Appendix 4.4 Pharmacometrics review

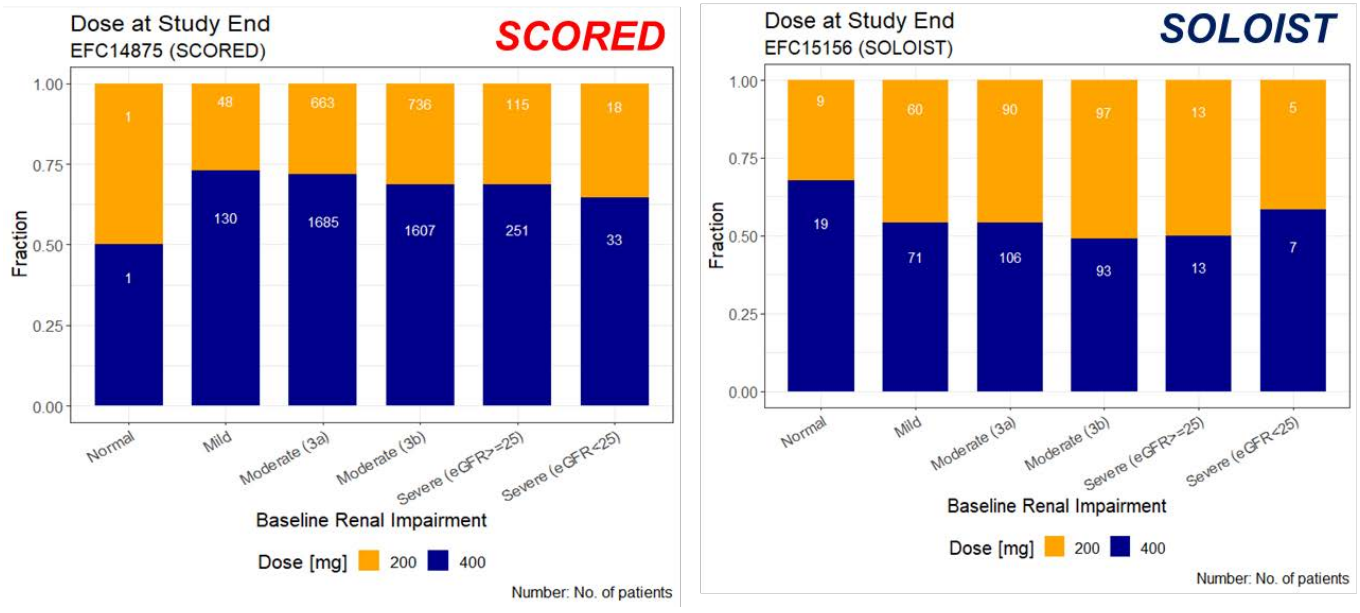

Figure 3: Fraction of patients on 200 mg and 400 mg dose at study end stratified by renal impairment (SCORED and SOLOIST studies)

Source: Reviewer's analysis, Appendix 4.4 Pharmacometrics review

3.3.3.2. Hepatic impairment

The impact of hepatic impairment on sotagliflozin and M19 PK was assessed in an open-label, parallel group, single dose study (Study LX4211.116) in subjects with mild (Child Pugh A), moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment and their matched control with normal hepatic function. *(See NDA210934 original Clinical Pharmacology review in DARRTS)*. Following a 400 mg single oral dose, AUC of sotagliflozin increased by approximately 3-fold in subjects with moderate (Child Pugh B) hepatic impairment and by approximately 6-fold in subjects with severe (Child Pugh C) hepatic impairment compared to subjects with normal hepatic function *(See NDA210934 original Clinical Pharmacology review in DARRTS)*. Exposure (mean change in AUC and C_{max}) of sotagliflozin in subjects with mild hepatic impairment was similar or up to 45% lower compared to those with normal hepatic function. No dosage adjustment is necessary in patients with mild hepatic impairment. Sotagliflozin is not recommended in patients with moderate or severe hepatic impairment since the available dose strengths do not permit adequate dose adjustments. Also, the safety and efficacy of 3-fold and 6-fold lower doses of sotagliflozin have not been established in patients with moderate or severe hepatic impairment *(See NDA210934 original Clinical Pharmacology review in DARRTS)*.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

3.3.4.1 Food-Drug Interaction

Effect of food on sotagliflozin PK has been previously reviewed under NDA 210934. Administration of 400 mg sotagliflozin following a high-fat high calorie meal increased sotagliflozin C_{max}, AUC_{0-t}, and AUC_{0-inf} by 149%, 49%, and 50%, respectively, compared to fasted state administration. The median T_{max} was 4.5 (range 0.50-5.00) hours and 1.5 (range 1.50- 5.00) hours under fasted and fed conditions respectively. Multiple doses of sotagliflozin 400 mg given immediately before breakfast; 30 minutes prior to breakfast; and 1-hour before breakfast in healthy subjects showed consistent effect of sotagliflozin on UGE, insulin, and PPG across all dose schedules (*Study 104, See Clinical Pharmacology review in DARRTS, 2/20/2019).* Sotagliflozin was administered before the first meal of the day in the pivotal Phase 3 trials SOLOIST and SCORED. Based on the consistent PD effect observed when sotagliflozin is administered up to 1-hour before meal, the review team for NDA216203 recommended that sotagliflozin be taken not more than one hour before the first meal of the day. The Applicant agreed with the review team's recommendation (**Table 2**).

Table 2: Summary of sotagliflozin PK comparison under fasted and fed conditions

Parameters	**Geometric means**		**Geometric mean ratio (90% CI) (Test/Reference)**
	Fed (Test)	**Fasted (Reference)**	
C_{max} (ng/mL)	133	52.2	2.49 (1.92, 3.24)
AUC_{0-t} (h*ng/mL)	1450	938	1.49 (1.29, 1.72)

$AUC_{0\text{-}inf}$ (h*ng/mL)	1650	1200	1.50 (1.31, 1.73)

(Source: Table 8, NDA210934 Original clinical Pharmacology review in DARRTS, Tables 15, 16 & 18 of Study PKM15047 CSR)

3.3.4.2 Drug-Drug Interaction (DDI)

Please refer to NDA210934 original Clinical Pharmacology review (*DARRTS 2/20/2019*) for details regarding results of in vivo drug-drug interaction studies of sotagliflozin with mefenamic acid (a UGT inhibitor), metformin, oral contraceptive Ortho-Cyclen, digoxin, rosuvastatin (a BCRP substrate), metoprolol (a CYP2D6 substrate) and midazolam (a CYP3A4 substrate).

Digoxin

When sotagliflozin was co-administered with digoxin (a P-gp substrate), the mean C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ 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, appropriate monitoring of digoxin concentration is recommended when sotagliflozin is coadministered with digoxin *(See NDA210934 original Clinical Pharmacology review, DARRTS 2/20/2019).*

Uridine 5'-diphospho-glucuronosyltransferase (UGT) Inducer

Glucuronidation by UGT1A9, to form the 3-O-glucuronide, was identified as a major metabolic pathway for sotagliflozin. The coadministration of rifampicin, an inducer of UGTs, with a single dose of 400 mg sotagliflozin resulted in a decrease of 60% for $AUC_{0\text{-}inf}$ and 40% for C_{max} of sotagliflozin. This decrease in exposure to sotagliflozin may decrease efficacy. If an inducer of UGT1A9 is required to be coadministered with sotagliflozin frequent monitoring of glucose levels is recommended *(See NDA210934 original Clinical Pharmacology review, DARRTS 2/20/2019).*

Lithium

On January 4th, 2022, a consult request was sent from Division of Diabetes, Lipid Disorders, and Obesity (DDLO) and Division of Pharmacovigilance (DPV) to evaluate the potential drug-drug interaction (DDI) between sodium-glucose co-transporter 2 (SGLT2)-inhibitors and Lithium. Particularly, whether the concurrent use of SGLT2 inhibitor can affect systemic exposures of lithium. The clinical pharmacology review on potential drug-drug interaction between SGLT2 inhibitors and Lithium *(DARRTS, May 23rd, 2022, Reference ID: 4987369)* recommended SGLT2 inhibitor class labeling change indicating that concomitant use of SGLT2 inhibitor may decrease serum lithium concentrations and recommended more frequent serum lithium concentration monitoring during SGLT2 inhibitor initiation and subsequent dose changes. In accordance with the labels for the other SGLT2 inhibitors, class labeling for the drug-drug interaction of sotagliflozin with lithium was added.

Hydrochlorothiazide (HCTZ)

HCTZ did not have a clinically relevant effect on sotagliflozin exposure compared with sotagliflozin alone. Co-administration of sotagliflozin reduced HCTZ C_{max} and AUC_{tau} by 36% and

25%, respectively, with treatment ratios (sotagliflozin + HCTZ / HCTZ) and associated 90% CIs of 0.64 (0.57 to 0.72) and 0.75 (0.69 to 0.81), respectively. The decrease in PK exposure is within the PK variability of HCTZ and within the recommended dose increments for HCTZ (1.5 to 2-fold) (*Study INT14905*).

Ramipril

Sotagliflozin and ramipril were well tolerated when given alone or in co-administration. Following co-administration of multiple dose sotagliflozin with multiple dose ramipril, there was no change in sotagliflozin mean AUC_{tau} (treatment ratio: 1.00), while mean Cmax decreased by 13% (treatment ratio: 0.87). Ramipril mean AUC_{tau} and C_{max} were 88% and 32% higher, respectively. Ramipril is almost completely metabolized to ramiprilat, which has about 6 times the ACE inhibitory activity of ramipril. Administration of multiple dose ramipril with multiple dose sotagliflozin versus alone, did not result in a clinically relevant change in exposure of ramiprilat, with treatment ratios of 1.19 and 1.09 for ramiprilat mean AUC_{tau} and C_{max} (*Study INT14935*).

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

Material attributes and manufacturing process parameters changes have been made between the proposed 200 mg and 400 mg to-be-marketed tablet formulation and the 200 mg tablet formulation used in the clinical studies. The sponsor conducted a randomized, open-label, 2-treatment, 4-period, 2-sequence, replicated crossover design, bioequivalence study (*BEQ14993*) to demonstrate PK bridge between the to-be-marketed formulation (Test – 400 mg tablet) and the clinical study formulation (Reference – 2 x 200 mg tablet) in healthy subjects (n=66) under fasted condition. The 90% CIs for the Test/Reference geometric mean C_{max} and $AUC_{0\text{-}inf}$ ratios are within the 80 – 125% bioequivalence range (**Table 3**). The mean terminal $t_{1/2}$ (25.9 h ± 14.5h for Test vs 24.7 ± 13 h for Reference) and median Tmax are similar (4.19 h for Test vs 4.83 h for Reference) for both the formulations. Both formulations of sotagliflozin were well tolerated. A relative BA study between the 200 mg to-be-marketed formulation and the 200 mg formulation used the clinical studies is not needed because it was concluded that adequate *in vitro* data were provided to support bridging of the 200 mg and 400 mg formulations (*NDA 216203, Integrated Quality review, Reference ID: 5117120, Jan 27, 2023*).

Table 3: Statistical summary of PK parameters of relative bioavailability of sotagliflozin to-be-marketed (Test) and Phase 3 clinical trial (Reference) tablets

Comparison	Parameter	Estimate	90% CI
Treatment T vs. Treatment R	C_{max}	0.94	(0.86 to 1.04)
	$AUC_{0\text{-}72h}$	0.92	(0.83 to 1.03)

Treatment R (reference) = 200 mg dry granulation tablet (2 x 200mg)
Treatment T (test) = 400 mg dry granulation tablet (1x 400mg)

Source: Table 16 CSR BEQ1499

4. APPENDICES

4.1. Summary of studies reviewed

NDA 216203 consists of 33 *in-vitro* studies (all were previously reviewed under NDA 210934, 02/20/2019) and 36 *in-vivo* clinical and clinical pharmacology studies (24 studies were previously reviewed under NDA 210934, 02/20/2019). In addition, 5 population pharmacokinetics and exposure-response analysis reports were submitted.

Table 4.1.1. Summary of previously reviewed clinical studies under NDA 216203 (*Clinical Pharmacology Review, 02/20/2019*)

Study ID	Study Description	Formulation	Study population
Phase 1 studies			
101	Single- and multiple-ascending dose safety, tolerability, food effect, PK, and PD study	Oral solution and capsule	Healthy subjects
102	Bioavailability of oral formulations evaluating PK, PD, safety, and tolerability	Oral solution and tablets	T2DM
103	DDI study with metformin	Oral tablets	Healthy subjects
104	PD of sotagliflozin relative to meals	Oral tablets	Healthy subjects
106	Single ascending dose safety, tolerability, and PK study	Oral tablets	Healthy subjects
108	Single dose absorption, metabolism, and excretion study of [^{14}C]-sotagliflozin	Oral solution	Healthy subjects
109	Thorough QT study	Oral tablets	Healthy subjects
110	Multiple dose safety, tolerability, and PK study	Oral tablets	Healthy subjects
111	PD study of sotagliflozin and canagliflozin	Oral tablets	Healthy subjects
114	DDI study with digoxin	Oral tablets	Healthy subjects
115	DDI study with rosuvastatin	Oral tablets	Healthy subjects
116	Single dose PK study in subjects with hepatic impairment compared to normal hepatic function	Oral tablets	Subjects with hepatic impairment or normal hepatic function
117	Bioequivalence of oral formulations evaluating PK,	Oral tablets	Healthy subjects

	PD, safety, and tolerability		
120	DDI study with Ortho-Cyclen	Oral tablets	Healthy women
121	Single dose PK study in subjects with varying degrees of renal function and normal renal function	Oral tablets	Subjects with renal impairment or normal renal function
INT14936	DDI study with rifampicin	Oral tablets	Healthy subjects
INT14937	DDI study with mefenamic acid	Oral tablets	Healthy subjects
INT14972	DDI study with a substrate cocktail of midazolam and metoprolol	Oral tablets	Healthy subjects
PKM15047	Food effect on tablet formulation and relative bioavailability of tablet formulation compared to oral solution	Oral solution and tablets	Healthy subjects
BEQ15271	Bioequivalence of two 200-mg tablet formulations	Oral tablets	Healthy subjects
Phase 2 studies			
201	Multiple-dose proof of concept study	Oral solution	T2DM
Pharmacometrics studies			
Study number	Study objectives	Clinical studies included	
POH0532	Population PK of sotagliflozin to simulate the impact of varying degrees of renal impairment on the PK profile of sotagliflozin	LX4211.110, LX4211.107, LX4211.121	
LX4211-N101	Population PK of sotagliflozin to determine the effects of covariates on the PK of sotagliflozin	LX4211.101, LX4211.110, LX4211.117, LX4211.203, LX4211.204, LX4211.206, LX4211.309, LX4211.310	
LX4211-N103	Population exposure response model to characterize the relationship of sotagliflozin exposure with body weight and PPG; and to describe the probability of occurrence of positively adjudicated severe hypoglycemia and positively adjudicated DKA events as a function of sotagliflozin exposure	LX4211.204, LX4211.206, LX4211.309, LX4211.310	

Table 4.1.2. Summary of clinical studies reviewed under NDA 216203

Study ID	Study Description	Formulation	Study population
Phase 1 studies			
PKM15402	▪ To determine the absolute bioavailability of sotagliflozin ▪ Phase 1, single-center, open-label, two-period, one-sequence, single dose study	Oral tablets	Healthy volunteers
BEQ14993	To determine the bioequivalence of a single dose of one 400 mg tablet of sotagliflozin (test) compared to two 200 mg tablets of sotagliflozin	Oral tablets	Healthy volunteers
BDR14994	To assess the relative bioavailability of sotagliflozin following a single dose of 400 mg sotagliflozin prototype tablets p1, p2, and p3 versus reference 2 x 200-mg tablets in fasted conditions in healthy subjects. Phase 1, single-center, open-label, single-dose, 4-period, 4 sequence crossover study	Oral tablets	Healthy volunteers
TDR15349 (1 center in China)	To assess the safety and tolerability of sotagliflozin after a multiple oral dose administration in Chinese healthy subjects. Phase 1, randomized, double-blind, placebo-controlled, ascending multiple-dose study	Oral tablets	Healthy volunteers
LX4211.107 DM	• PK and PD in renally impaired T2DM patients • Phase 1, parallel-group, multiple-dose PK and PD study	Oral tablets	T2DM
INT14905	To assess the effects of multiple-dose hydrochlorothiazide (HCTZ; 25 mg once daily) on the steady-state PK of sotagliflozin (400 mg once daily) - Open-label, crossover, single-sequence, 2-period	Oral tablets	Healthy volunteers
INT14935	To evaluate the effects of multiple dose ramipril on the steady state pharmacokinetic (PK) parameters of sotagliflozin and its main metabolite (M19) - Open-label, crossover, single-sequence, 2-period	Oral tablets	Healthy volunteers
LX4211.105 DM	PD when administered concurrently with JANUVIA® (sitagliptin), Safety, Tolerability	Oral tablets	T2DM

Phase 2 studies			
PDY15079	To assess safety and tolerability of sotagliflozin, added to the standard of care treatment, in hemodynamically stable patients with worsening of heart failure, compared to placebo. A coprimary objective of this trial is the estimation of the effect of sotagliflozin, when added to the standard of care treatment, on changes in plasma volume, as assessed by direct (indicator dilution) and/or indirect (hem concentration) methods, in hemodynamically stable patients with worsening of heart failure, compared to placebo Phase 2, randomized, double-blind, placebo-controlled, parallel arm trial in 3 cohorts	Oral tablets	Heart failure, Patients with WHF requiring administration of IV diuretics
PDY15010	To compare the metabolic and gastrointestinal PD effects of an 8-week treatment with 400 mg sotagliflozin once daily to an 8-week treatment to 25 mg empagliflozin once daily Single-center, randomized, double-blind, double-dummy, active-control, parallel-group multiple dosing study	Oral tablets	T2DM
Phase 3 studies			
SOLOIST (EFC15156)	A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Effects of Sotagliflozin on Clinical Outcomes in Hemodynamically Stable Patients Post Worsening Heart Failure	Oral tablets	Hemodynamically stable patients post worsening heart failure
SCORED (EFC14875)	Effects of Sotagliflozin on Cardiovascular and Renal Events in patients with type 2 Diabetes, cardiovascular risk factors and moderately impaired renal function) that support the efficacy of sotagliflozin in patients with T2DM at high risk for CV and renal events.	Oral tablets	T2DM at high risk for CV and renal even

4.2. Summary of Bioanalytical Method Validation and Performance

The bioanalytical methods used in clinical studies for measurement of sotagliflozin and sotagliflozin-3-O- glucuronide (M19) in human plasma and urine are summarized in **Table 4.2.1** and the key descriptive parameters for each assay are summarized in **Tables 4.2.1—4.2.6**. In general, all the bioanalytical methods were fully validated and found to be sensitive and accurate for the determination of sotagliflozin and sotagliflozin-3-O-glucuronide in human plasma and urine.

Table 4.2.1. Summary of bioanalytical validation studies and associated clinical studies

Method[a]	Matrix	Analyte	Calibration curve[b]	LLOQ (ng/mL)	Accuracy (%)	Within-run precision (%)	Between-run precision (%)	Clinical studies	Study report location
LX4HPP (7648-309)	K_2EDTA Plasma	sotagliflozin	0.200 to 200 ng/mL r^2 = 0.9970	0.200	85.0 to 115.0% 80.0 to 120% at LLOQ	≤15.0% (≤20.0% at the LLOQ)	≤15.0% (≤20.0% at the LLOQ)	LX4211.101, LX4211.102 LX4211.103, LX4211.106 LX4211.107, LX4211.108 LX4211.109, LX4211.110 LX4211.201, LX4211.202 LX4211.203	NDA 210934, Sequence 0001, Module 5.3.1.4
L42HPP (8288062)	K_2EDTA Plasma	sotagliflozin-3-O-glucuronide	4.00 to 4000 ng/mL r^2 = 0.9957	4.00	±15.0% bias (±20.0% at the LLOQ)	≤15.0% (≤20.0% at the LLOQ)	≤15.0% (≤20.0% at the LLOQ)	LX4211.109 LX4211.110	NDA 210934, Sequence 0001, Module 5.3.1.4
LLGHPP (8292042)	K_2EDTA Plasma	sotagliflozin	2.00 to 2000 ng/mL r^2 = 0.9983	2.00	±15.0% bias (±20.0% at the LLOQ)	≤15.0% (≤20.0% at the LLOQ)	≤15.0% (≤20.0% at the LLOQ)	LX4211.116, LX4211.120, LX4211.121 LX4211.204, LX4211.206 LX4211.309, LX4211.310 INT14972, INT14936 INT14937, PKM15047	NDA 210934, Sequence 0001, Module 5.3.1.4
		sotagliflozin-3-O-glucuronide	10.00 to 10 000 ng/mL r^2 = 0.9922	10.00	±15.0% bias (±20.0% at the LLOQ)	≤15.0% (≤20.0% at the LLOQ)	≤15.0% (≤20.0% at the LLOQ)		
DOH1487 (8361031)	K_2EDTA Plasma	sotagliflozin	2.00 to 2000 ng/mL r^2 = 0.9979	2.00	±15.0% bias (±20.0% at the LLOQ)	≤15.0% (≤20.0% at the LLOQ)	≤15.0% (≤20.0% at the LLOQ)		NDA 210934, Sequence 0001, Module 5.3.1.4
		sotagliflozin-3-O-glucuronide	10.00 to 10 000 ng/mL r^2 = 0.9981	10.00	±15.0% bias (±20.0% at the LLOQ)	≤15.0% (≤20.0% at the LLOQ)	≤15.0% (≤20.0% at the LLOQ)		
DME0590 (8361617)	Human Urine	sotagliflozin	2.00 to 2000 ng/mL r^2 = 0.9943	2.00	±20.0% bias (±25.0% at the LLOQ)	≤20.0% (≤25.0% at the LLOQ)	≤20.0% (≤25.0% at the LLOQ)	INT14936 INT14937	NDA 210934, Sequence 0001, Module 5.3.1.4
		sotagliflozin-3-O-glucuronide	10.00 to 10 000 ng/mL r^2 = 0.9969	10.00	±20.0% bias (±25.0% at the LLOQ)	≤20.0% (≤25.0% at the LLOQ)	≤20.0% (≤25.0% at the LLOQ)		

Source: individual bioanalytical method reports
K_2EDTA = dipotassium ethylenediaminetetraacetic acid; LLOQ = lower limit of quantitation
a Previous method number provided in parentheses as reference
b Weighted ($1/x^2$) linear regression

(*Source*: *Table 25 of Summary of biopharmaceutic studies and associated analytical methods)*

Table 4.2.2. Summary of Bioanalytical Method Validation *(Method LX4HPP, Report 7648-309)*

Analyte	LX4211 (sotagliflozin, SAR439954)
Analytical matrix	K2EDTA Plasma
Analytical technique / method of detection	Supported-liquid extraction / LC-MS/MS
Internal standard	LX4211-d5
Validated range	0.200 (LLOQ) to 200 ng/mL
QC levels	0.600 ng/mL, 25 ng/mL, 150 ng/mL, 1500 ng/mL
Calibration model	Linear regression ($1/x^2$)
Storage conditions	-60 to -80°C
Accuracy	Within 85-115% (80-120% for LLOQ)

Stability	Autosampler stability: 88 hours Bench-top stability: 24 hours Processed-sample stability: 91 hours Free-thaw stability: five cycles Long term stability: 436 days Stock solution stability: 42 days
Precision (Within-run and between-run)	≤15% (≤20% for LLOQ)

(Source: Summarized from Bioanalytical Method Validation report LX4HPP and addendums)

Table 4.2.3. Summary of Bioanalytical Method Validation *(Method L42HPP, Report 8288062)*

Analyte	LX4211-3-O-Glucuronide
Species	Human
Analytical matrix	K_2EDTA Plasma
Internal standard (ISTD)	D5-LX4211-3-O-Glucuronide
Validated method	L42HPP
Validated range	4.00 to 4000 ng/mL
Quality Control (QC) levels	4.00 ng/mL, 12.0 ng/mL, 300 ng/mL, 3000 ng/mL, 20000 ng/mL, 100000 ng/mL
Analytical technique/method of detection	Protein precipitation / LC-MS/MS
Sample Volume	0.0500 mL
Calibration model:	Linear regression
Weighting factor:	$1/x^2$
Precision and accuracy:	Requirements fulfilled
Stability of standard stock solutions:	LX4211-3-O-Glucuronide: 6 hours at room temperature LX4211-3-O-Glucuronide: 1 day at 2 to 8°C
Stability of intermediate solutions:	LX4211-3-O-Glucuronide: 6 hours at room temperature LX4211-3-O-Glucuronide: 15 days at 2 to 8°C
Processed-sample stability	LX4211-3-O-Glucuronide: 99 hours at 2 to 8°C
Processed-sample viability	LX4211-3-O-Glucuronide: 105 hours at 2 to 8°C
Sample collection stability	LX4211-3-O-Glucuronide: 2 hours at room temperature LX4211-3-O-Glucuronide: 2 hours on wet ice
Freeze-thaw matrix stability	LX4211-3-O-Glucuronide: 5 cycles at -10 to -30°C LX4211-3-O-Glucuronide: 5 cycles at -60 to -80°C
Room Temperature Matrix Stability	LX4211-3-O-Glucuronide: 25 hours at room temperature
Long term frozen matrix stability	LX4211-3-O-Glucuronide: 191 days at -10 to -30°C LX4211-3-O-Glucuronide: 191 days at -60 to -80°C
Maximum validated analytical run size	96 injections

*Long term frozen matric stability was demonstrated up to 560 days.
(Source: Summarized from Bioanalytical Method Validation report L42HPP and addendums)

Analytes	LX4211 LX4211-3-O-Glucuronide
Species	Human
Analytical matrix	K_2EDTA Plasma
Internal standard (ISTD)	D_5-LX4211 D_5-LX4211-3-O-Glucuronide
Validated method	LLGHPP
Validated range	LX4211: 2.00 to 2000 ng/mL LX4211-3-O-Glucuronide: 10.0 to 10000 ng/mL
Quality Control (QC) levels	LX4211: 2.00 ng/mL, 6.00 ng/mL, 100 ng/mL, 1500 ng/mL, 10000 ng/mL LX4211-3-O-Glucuronide: 10.0 ng/mL, 30.0 ng/mL, 500 ng/mL, 7500 ng/mL, 50000 ng/mL
Analytical technique/method of detection	Protein precipitation / LC-MS/MS
Sample Volume	50.0 µL
Calibration model	Linear regression
Weighting factor	$1/x^2$
Precision and accuracy	Requirements fulfilled
Stability of primary standard solutions	LX4211:455 days at 2 to 8°C LX4211-3-O-Glucuronide: 304 days at 2 to 8°C
Stability of intermediate solutions	LX4211: 123 days at 2 to 8°C* LX4211-3-O-Glucuronide: 15 days at 2 to 8°C** *Established under (b) (4) 7648309 **Established under (b) (4) 3288062
Processed-sample stability	LX4211: 100 hours at 2 to 8°C LX4211-3-O-Glucuronide: 100 hours at 2 to 8°C
Processed-sample viability	LX4211: 160 hours at 2 to 8°C LX4211-3-O-Glucuronide: 160 hours at 2 to 8°C
Sample collection stability	LX4211: 2 hours at room temperature LX4211-3-O-Glucuronide: 2 hours at room temperature LX4211: 2 hours on wet ice LX4211-3-O-Glucuronide: 2 hours on wet ice

*Long term frozen matric stability was demonstrated up to 560 days.
(Source: Summarized from Bioanalytical Method Validation report L42HPP and addendums)

Table 4.2.4. Summary of Bioanalytical Method Validation (Method LLGHPP, Report 8292042)

Freeze-thaw matrix stability	LX4211: 5 cycles at -10 to -30°C LX4211-3-O-Glucuronide: 5 cycles at -10 to -30°C LX4211: 5 cycles at -60 to -80°C* LX4211-3-O-Glucuronide: 5 cycles at -60 to -80°C
Room Temperature Matrix Stability	LX4211: 24 hours at room temperature LX4211-3-O-Glucuronide: 24 hours at room temperature
Long-term Frozen Matrix Stability	LX4211: 309 days at -10 to -30°C LX4211-3-O-Glucuronide: 309 days at -10 to -30°C LX4211: 309 days at -60 to -80°C LX4211-3-O-Glucuronide: 309 days at -60 to -80°C
Maximum validated analytical run size	124 injections

*Long term frozen matric stability was demonstrated up to 874 days for both LX4211 and LX4211-3-O- Glucuronide.
(Source: Summarized from Bioanalytical Method Validation report LLGHPP and addendums)

Table 4.2.5. Summary of Bioanalytical Method Validation *(Method SA3GHPP, Report DOH1487)*

Analytes	SAR439954	SAR439954-3-O-glucuronide
Species	Human	
Analytical Matrix	K_2EDTA Plasma	
Internal Standards (ISTD)	SAR439954-D_5	D_5-SAR439954-3-O-glucuronide
Validated Method	SA3GHPP	
Validated Range	2.00 to 2000 ng/mL	10.0 to 10000 ng/mL
Quality Control (QC) levels	2.00, 6.00, 20.0, 80.0, 1000, 1500, and 10000 ng/mL	10.0, 30.0, 100, 400, 5000, 7500, and 50000 ng/mL
Analytical technique/method of detection	Protein precipitation / LC-MS/MS	
Sample Volume	50.0 µL	
Calibration Model	Linear regression	
Weighting Factor	$1/x^2$	
Accuracy and Precision (including maximum run size and internal standard response	Requirements fulfilled	
ISTD Response Average % RSD	4.2%	4.6%
Maximum Run Size	96 injections	
Dilution	10000 ng/mL at 10X	50000 ng/mL at 10X
Run Blanks and Interference of Analyte on other Analytes or Internal standard	Passes acceptance criteria	
Carryover	Passes acceptance criteria	
Matrix Selectivity and Matrix Effect	Passes acceptance criteria, See Section 5.1	
Matrix Factor (MF)	Passes acceptance criteria	
Extraction Recovery	Passes acceptance criteria	
Hemolysis	Passes acceptance criteria	
Hyperlipidemia	Passes acceptance criteria, See Section 5.2	
Solution Stability – Stored	Primary standard solutions* 455 days at 2 to 8°C	304 days at 2 to 8°C
	Intermediate solutions** HIT: 58 days at 2 to 8°C	
Solution Stability – Bench Top	Primary standard solutions 6 hours at room temperature Intermediate solutions 6 hours at room temperature (250000 ng/mL) ISTD working solution 6 hours at room temperature	
Matrix Bench-Top Stability*	24 hours at room temperature	
Matrix Freeze-Thaw Stability*	5 cycles at -10 to -30°C and -60 to -80°C	
Matrix Frozen Stability*	874 days at -10 to -30°C 874 days at -60 to -80°C	309 days at -10 to -30°C 874 days at -60 to -80°C
Processed Sample Stability *	100 hours at 2 to 8°C	
Processed Sample Viability*	160 hours at 2 to 8°C	
Stability in Blood*	2 hours at room temperature 2 hours on wet ice	
Hamilton Star Automation	Passes acceptance criteria	
Cross Validation	Passes acceptance criteria	

*Established and Reported under (b) (4) 8292042.
**Established and Reported under (b) (4) 8293214.

(LX4211= sotagliflozin, SAR439954)

(Source: page 10 of Study DOH1487 report)

Table 4.2.6. Summary of Bioanalytical Method Validation *(Method STGFHUP, Study DME0590 report)*

Analytes	SAR439954	SAR439954-3-O-glucuronide
Species	Human	
Analytical Matrix	Urine Treated with Triton X-100 to approximately 0.1% solution	
Internal Standards (ISTD)	SAR439954-D_5	D_5-SAR439954-3-O-glucuronide
Qualified Method	STGFHUP	
Qualified Range	2.00 to 2000 ng/mL	10.0 to 10000 ng/mL
Quality Control (QC) levels	2.00, 6.00, 100, and 1500 ng/mL	10.0, 30.0, 500, 7500, and 125000 ng/mL
Analytical technique/method of detection	Liquid-liquid extraction / LC-MS/MS	
Sample Volume	100 µL	
Calibration Model	Linear regression	
Weighting Factor	$1/x^2$	
Accuracy and Precision	Requirements fulfilled	
Dilution	1500 ng/mL at 50X Dilution factor confirmed	125000 ng/mL at 100X and 7500 ng/mL at 50X Dilution factor confirmed
Carryover	Passes acceptance criteria	
Matrix Effect	Passes acceptance criteria	
Matrix Selectivity	Passes acceptance criteria	
Matrix Bench-Top Stability	30 hours at room temperature	
Matrix Freeze-Thaw Stability	6 cycles at -60 to -80°C	
Matrix Frozen Stability	39 days at -10 to -30°C 120 days at -60 to -80°C	
Processed Sample Stability	66 hours at 2 to 8°C	
Variability of Triton X-100	Passes acceptance criteria	
API5500 Platform Qualification	Passes acceptance criteria	

(Source: page 9 of Study DME0590 report)

4.3 Individual Study Reviews

4.3.1. Study BEQ14993 — Relative bioavailability of sotagliflozin in Healthy Volunteers (HV)

Title: A bioequivalence study testing two formulations of sotagliflozin in healthy male and female subjects under fasted conditions.

Objectives

• Primary: to determine bioequivalence of a single dose of one 400 mg tablet of sotagliflozin (test) compared to two 200 mg tablets of sotagliflozin (reference)

• Secondary:

- Safety and tolerability of single doses sotagliflozin.
- To assess the single-dose PK of sotagliflozin.

Study population: healthy male and female subjects (n=66)

Drug product:

Sotagliflozin was administered as a 400 mg dose single dose in both treatment sequences:

- **Treatment R (reference)** = 2 x 200 mg sotagliflozin (b) (4) tablet
- **Treatment T (test) =** 1 x 400 mg sotagliflozin (b) (4) tablet

Breakfast was to be omitted on Day 1 of dosing to allow for 10 hours of fasting before IMP administration, with lunch to take place 4 hours after IMP administration.

- Duration: Four periods of 7 days, including 1 day of treatment plus PK sampling, and 6 days of PK sampling only:
  - **Period 1**: 7 days, from D1 to D7,
  - **Period 2**: 7 days, from D1 to D7,
  - **Period 3**: 7 days, from D1 to D7,
  - **Period 4**: 7 days, from D1 to D7.

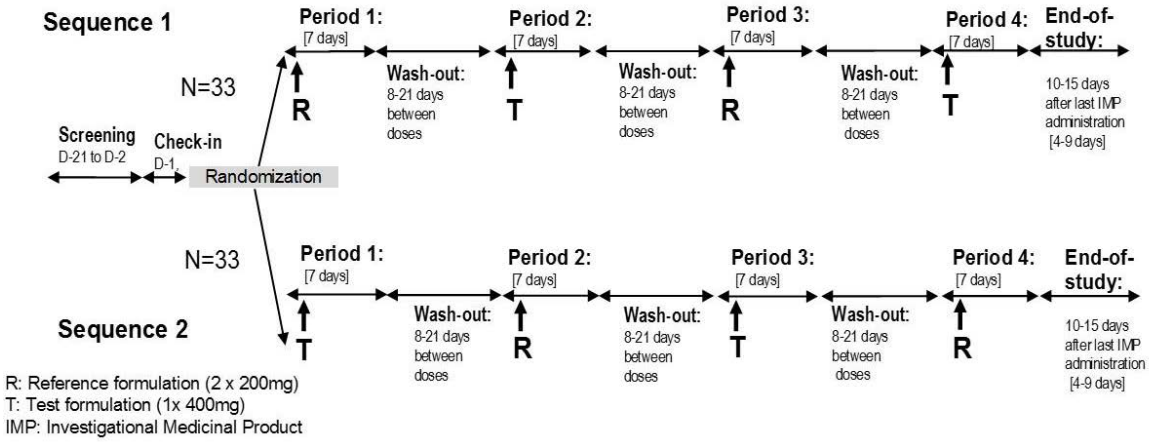

Figure 4.3.1.1: Study design *(Source: Figure 1 of Study BEQ14993 CSR)*

PK sampling: Sotagliflozin PK blood samples are collected at 0 and at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120 and 144 post-dose for all periods.

Results: PK results are shown as below.

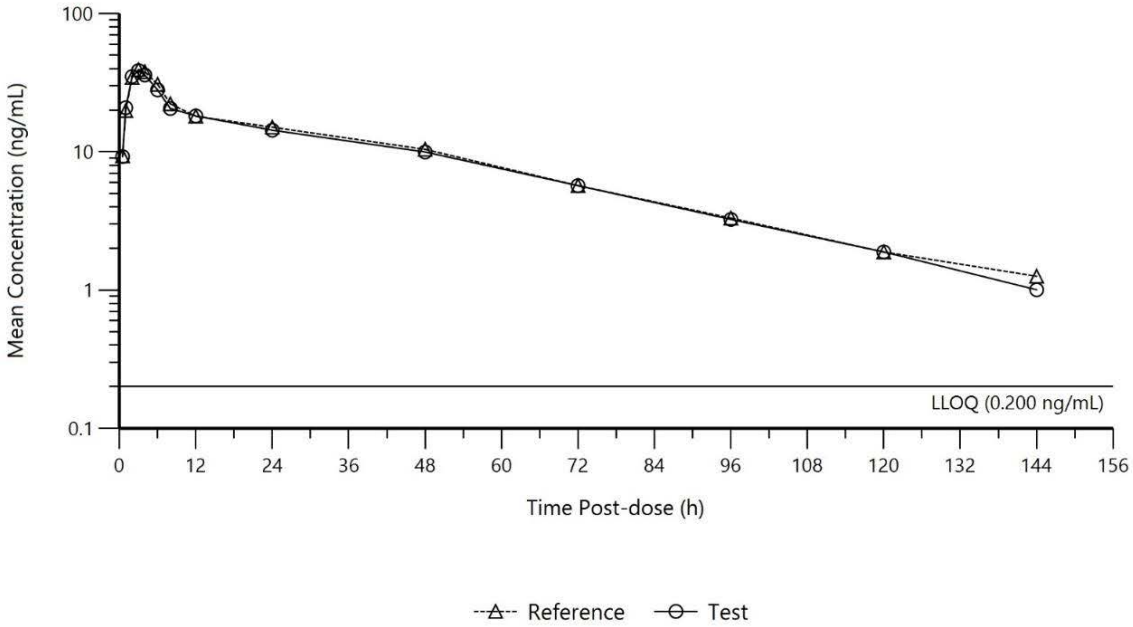

Figure 4.3.1.2. Mean (+SD) plasma concentration-time profiles of sotagliflozin following single oral dose administration of Treatment T and Treatment R to healthy subjects (semi-logarithmic scales) *(Source: Figure 2 of Study BEQ14993 CSR)*

Table 4.3.1.1. Pharmacokinetic parameters of sotagliflozin following single dose administration of sotagliflozin as a single 400 mg tablet (Treatment T) ***(****Source: Table 14 of Study BEQ14993 CSR)*

	Treatment T						
	C_{max} (ng/mL)	t_{max} (h)	t_{last} (h)	AUC_{last} (ng.h/mL)	AUC (ng.h/mL)	AUC_{0-72h} (ng.h/mL)	$t_{1/2z}$ (h)
N	127	127	126	126	119	127	123
Mean	48.8	4.19	128.12	1180	1220	985	25.9
SD	36.9	4.96	23.19	707	766	529	14.5
SE	3.27	0.44	2.07	62.9	70.2	46.9	1.31
Min	1.06	1.00	12.00	7.76	9.10	9.10	3.33
Median	36.7	3.00	144.00	1030	1040	896	21.5
Max	229	48.00	144.63	4170	4230	3340	99.7
CV%	76	118	18	60	63	54	56
Geometric Mean	38.3	3.20	124.75	991	1010	851	23.1

TP4 data for Subject (b) (6) were excluded from statistics due to the incidence of vomiting in TP4 that occurred within 2x median t_{max} and within 6 hours post-dose.

AUC_{last} and t_{last} for Subject (b) (6) in TP2 were excluded from statistics as they were likely truncated due to no reportable concentration result at 144 hours post-dose.

Refer to Table 12 for AUC values that were excluded from statistics due to extrapolation of AUC >20%.

Refer to Table 13 for $t_{1/2z}$ and AUC values that were not calculable due to poor fit of regression for extrapolation (R squared adjusted <0.7) or there were <3 quantifiable concentrations occurring after C_{max} in the PK profile.

Table 4.3.1.2. Pharmacokinetic parameters of sotagliflozin following single dose administration of sotagliflozin as two 200 mg tablets (Treatment R) ***(****Source: Table 15 of Study BEQ14993 CSR)*

	Treatment R						
	C_{max} (ng/mL)	t_{max} (h)	t_{last} (h)	AUC_{last} (ng.h/mL)	AUC (ng.h/mL)	AUC_{0-72h} (ng.h/mL)	$t_{1/2z}$ (h)
N	129	129	129	129	120	129	124
Mean	50.8	4.83	129.31	1220	1230	1010	24.7
SD	43.8	7.39	21.70	731	765	542	13.0
SE	3.85	0.65	1.91	64.4	69.8	47.7	1.16
Min	8.07	0.50	48.00	316	326	295	7.98
Median	37.1	3.00	144.00	1070	1070	909	21.5
Max	367	48.00	144.80	3760	4140	3010	86.0
CV%	86	153	17	60	62	53	52
Geometric Mean	39.8	3.29	127.03	1040	1050	894	22.1

Refer to Table 12 for AUC values that were excluded from statistics due to extrapolation of AUC >20%.
Refer to Table 13 for $t_{1/2z}$ and AUC values that were not calculable due to poor fit of regression for extrapolation (R squared adjusted <0.7) or there were <3 quantifiable concentrations occurring after C_{max} in the PK profile.

Table 4.3.1.3. Statistical summary of PK parameters of relative bioavailability of sotagliflozin Test and Reference tablets *(Source: Table 16 of Study BEQ14993 CSR)*

Comparison	Parameter	Estimate	90% CI
Treatment T vs. Treatment R	C_{max}	0.94	(0.86 to 1.04)
	AUC_{0-72h}	0.92	(0.83 to 1.03)

Treatment R (reference) = 200 mg (b) (4) tablet (2 x 200mg)
Treatment T (test) = 400 mg (b) (4) tablet (1x 400mg)
Subject (b) (6) period 4 (Test) PK parameters were excluded from analysis due to the incidence of vomiting in period 4 which occurred within 2x median t_{max} and within 6 hours post-dose.

Conclusions:

- The point estimates and associated 90% CIs for the Test/Reference ratios for C_{max} and AUC_{0-72h} of sotagliflozin were 0.94 (0.86 to 1.04) and 0.92 (0.83 to 1.03), respectively, and were within the 0.80 to 1.25 bioequivalence range.
- The 1 ×400 mg sotagliflozin (b) (4) tablet (Treatment T) was bioequivalent to 2 ×200 mg sotagliflozin (b) (4) tablet (Treatment R) in healthy male and female subjects under fasting conditions.
- Both formulations of sotagliflozin were well tolerated.

4.3.2. Study BDR14994 — Relative bioavailability of sotagliflozin in HV

Title: An open-label, randomized, single-dose, 4-period, 4-sequence, crossover relative bioavailability study comparing sotagliflozin prototypes tablets with reference tablet in healthy subjects

Objectives

• Primary: to assess the relative bioavailability of sotagliflozin following a single dose of 400 mg sotagliflozin prototype tablets p1, p2, and p3 versus reference 2 x 200-mg tablets in fasted conditions in healthy subjects.

• Secondary:

- To assess the clinical and laboratory safety of a single oral dose of sotagliflozin.
- To assess the single-dose PK of sotagliflozin/ sotagliflozin 3-O-glucuronide.

Study population: healthy male and female subjects (n=12)

Drug product:

Sotagliflozin was administered in a dosage of 400 mg in all treatment sequences:

- **Reference formulation:** 400 mg sotagliflozin (2 x 200-mg tablets)
- **Prototype 1 (p1):** 400 mg sotagliflozin (1 x 400-mg tablet)
- **Prototype 2 (p2):** 400 mg sotagliflozin (1 x 400-mg tablet)
- **Prototype 3 (p3):** 400 mg sotagliflozin (1 x 400-mg tablet)

Each formulation was administered in the fasting condition with 240 mL of water on Day 1 of the appropriate therapy plan, according to the randomization schedule.

- Treatment periods: Four periods of 7 days, including 1 day of treatment plus PK sampling, and 6 days of PK sampling only:
  - **Period 1**: 7 days, from D1 to D7,
  - **Period 2**: 7 days, from D1 to D7,
  - **Period 3**: 7 days, from D1 to D7,
  - **Period 4**: 7 days, from D1 to D7.

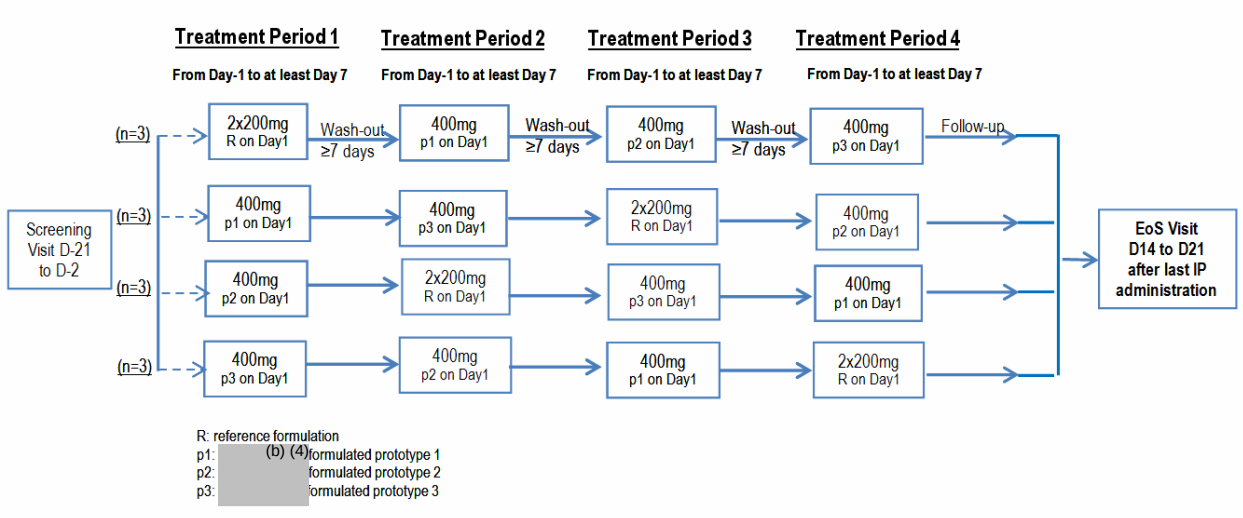

Figure 4.3.2.1: Study design *(Source: Figure 1 of Study BDR14994 CSR)*

PK sampling: Sotagliflozin PK blood samples are collected at 0 and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120 and 144 post-dose for all periods.
Results: PK results are shown as below.

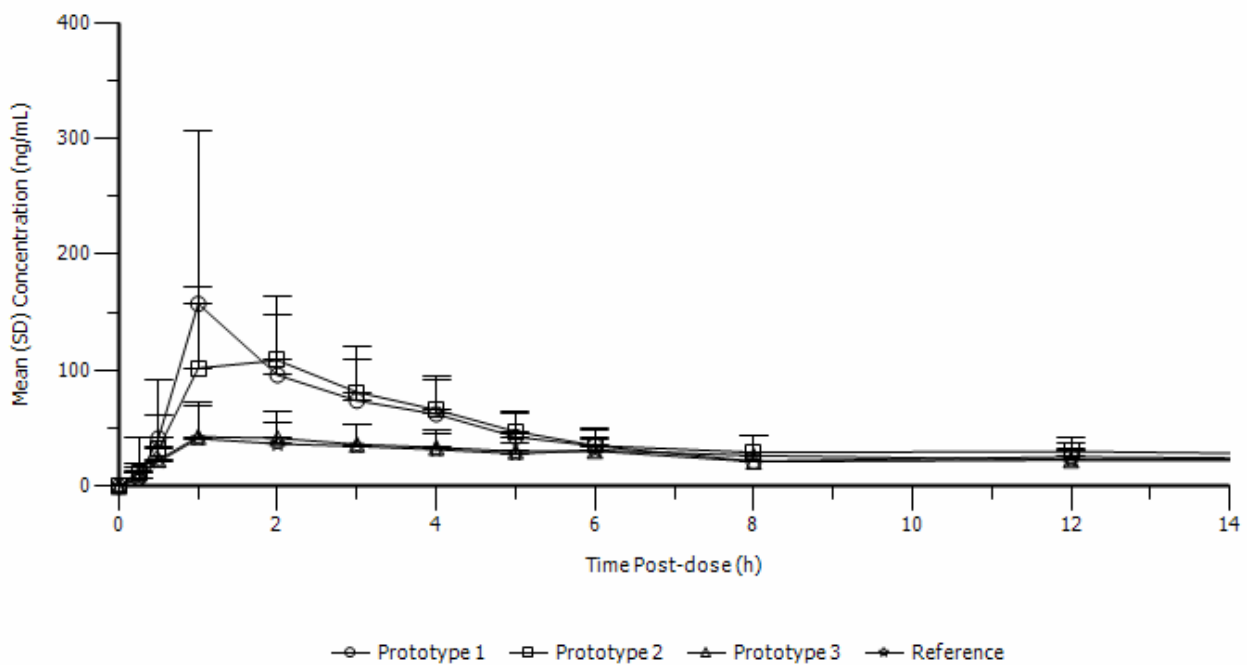

Figure 4.3.2.2. Mean (+SD) plasma concentrations of sotagliflozin following single dose administration of sotagliflozin as reference, p1, p2, and p3 formulations *(Source: Figure 2 of Study BDR14994 CSR)*

Table 4.3.2.1. Formulation effect on C_{max}, AUC_{last}, and AUC for sotagliflozin: Point estimates of formulation ratios with 90% confidence intervals *(Source: Table 19 of Study BDR14994 CSR)*

Comparison	Parameter	Estimate	90% CI
Prototype 1 versus Reference	C_{max}	3.020	(2.437 to 3.743)
	AUC_{last}	1.112	(1.015 to 1.217)
	AUC	1.203	(1.006 to 1.438)
Prototype 2 versus Reference	C_{max}	2.422	(1.828 to 3.209)
	AUC_{last}	1.224	(1.092 to 1.372)
	AUC	1.289	(1.002 to 1.658)
Prototype 3 versus Reference	C_{max}	1.010	(0.869 to 1.174)
	AUC_{last}	0.973	(0.863 to 1.096)
	AUC	1.032	(0.805 to 1.324)

Conclusions:

- Systemic exposure to sotagliflozin was similar between the homothetic formulation (p3) and reference formulation, with formulation ratio point estimates (90% CIs) of 1.010 (0.869 to 1.174), 0.973 (0.863 to 1.096), and 1.032 (0.805 to 1.324) for C_{max}, AUC_{last}, and AUC, respectively.
- The point estimates for the treatment ratios for the (b) (4) formulations p1 or p2 for C_{max} were substantially increased relative to reference. However, AUC and AUC_{last} were only slightly increased for p1 or p2 relative to reference. The (b) (4) homothetic formulation p3 was comparable to reference in terms of C_{max}, AUC_{last}, and AUC.
- All formulations of sotagliflozin were safe and well tolerated.

4.3.3. Study INT14905 —DDI study with hydrochlorothiazide (HCTZ) in HV

Title: A phase 1, single-center, open-label, two-period, single-sequence, multiple-dosing drug-drug interaction study of sotagliflozin and hydrochlorothiazide in healthy male and female subjects

Applicant's rationale: Pharmacokinetic (PK)-based drug-drug interaction (DDI) between sotagliflozin and HCTZ were not anticipated; however, since these two drugs can be widely used concurrently in the target patient populations, this Phase 1 DDI study in healthy subjects aimed to provide more definitive assessment of clinical DDI potential between sotagliflozin and HCTZ**.**

Objectives

• Primary: DDI between sotagliflozin and hydrochlorothiazide

• Secondary:

- safety and tolerability of multiple-dose sotagliflozin with and without co-administration of multiple-dose HCTZ.
- To assess the effects of multiple-dose sotagliflozin on the steady-state PK of HCTZ.

Study population: healthy male and female subjects (n=16)

Drug product:

- **Sotagliflozin (Sotagliflozin - SAR439954)**: 400 mg (2 x 200-mg tablet, Sanofi), 10 days of QD dosing (5 days given alone in Treatment Period 1, 5 days under co-administration with HCTZ in Treatment Period 2).
- **Hydrochlorothiazide**: 25-mg tablet (commercial formulation), 9 days of QD dosing (Treatment Period 2 only; 4 days given alone, 5 days under co-administration with sotagliflozin).

Each investigational medical product (IMP) was administered prior to the breakfast meal (breakfast was provided within 10 minutes after dosing) with 240 mL of non-carbonated water. The 2 study drugs were administered in the following doses:

• Period 1: 400 mg sotagliflozin (2 x 200-mg tablet QD x 5 days) on Days 1 to 5.

• Period 2: 25 mg HCTZ (1 x 25-mg tablets QD x 9 days) on Days 1 to 9, 400 mg sotagliflozin (2 x 200-mg tablet QD x 5 days) co-administered on Days 5 to 9.

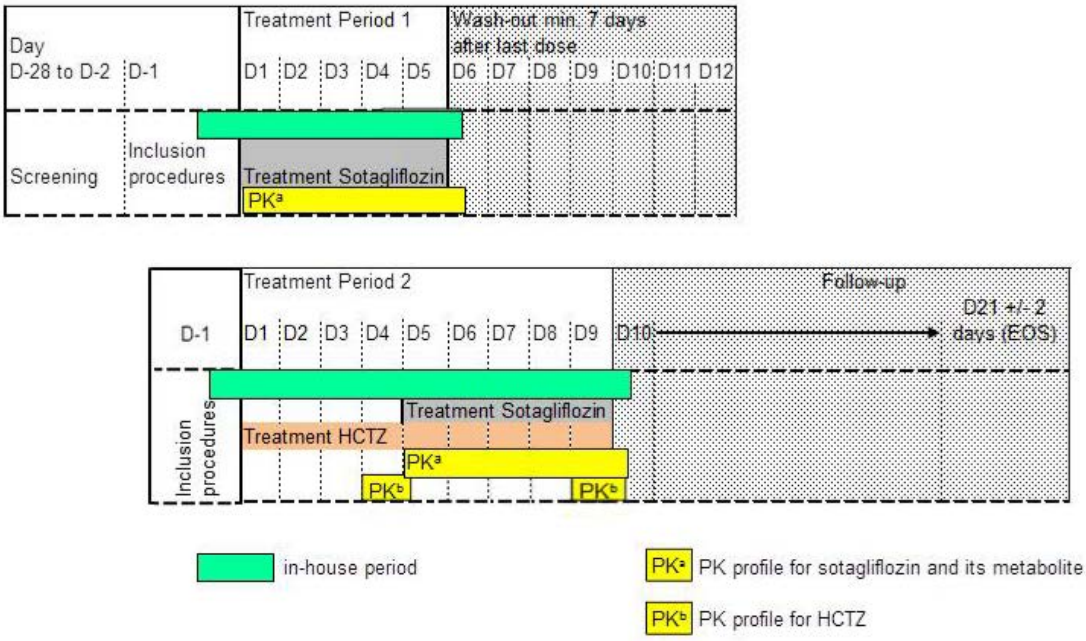

Figure 4.3.3.1. Study design *(Source: Figure 1 of Study INT14905 CSR)*

PK sampling: Sotagliflozin PK blood samples collected at 0 and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12 and 24 hours post-dose (Period 1, day 5; Period 2, day 9). HCTZ PK blood samples collected at 0 and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose (Period 2, day 9).
Results: PK results are shown as below.

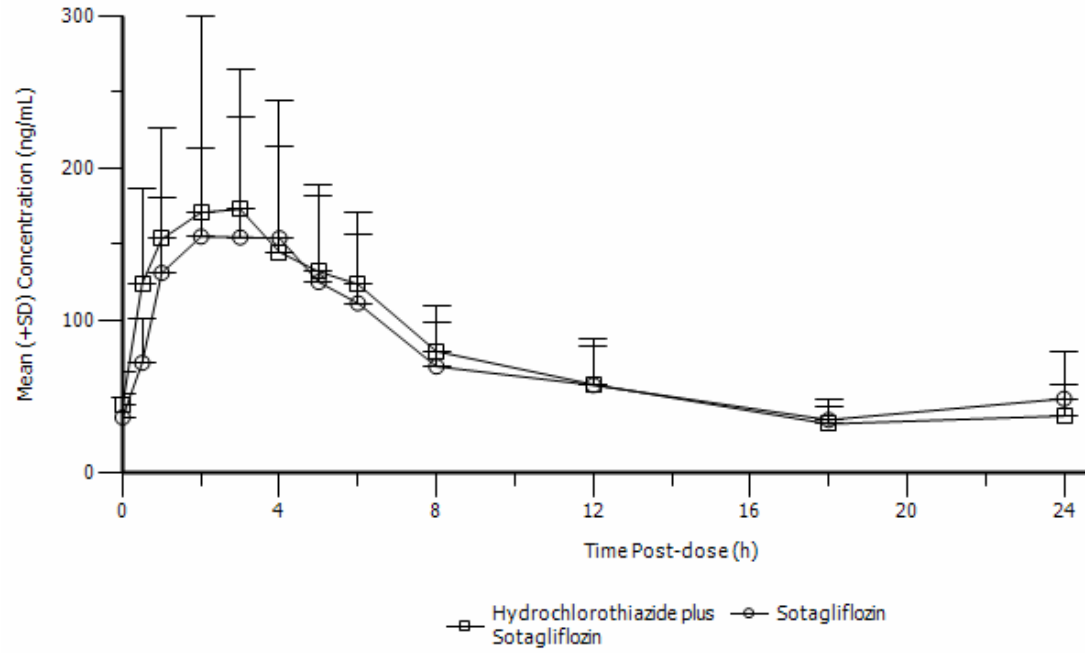

Figure 4.3.3.2. Mean (+SD) plasma concentrations of sotagliflozin following multiple-dose administration of sotagliflozin alone and following co-administration with multiple-dose hydrochlorothiazide *(Source: Figure 2 of Study INT14905 CSR)*

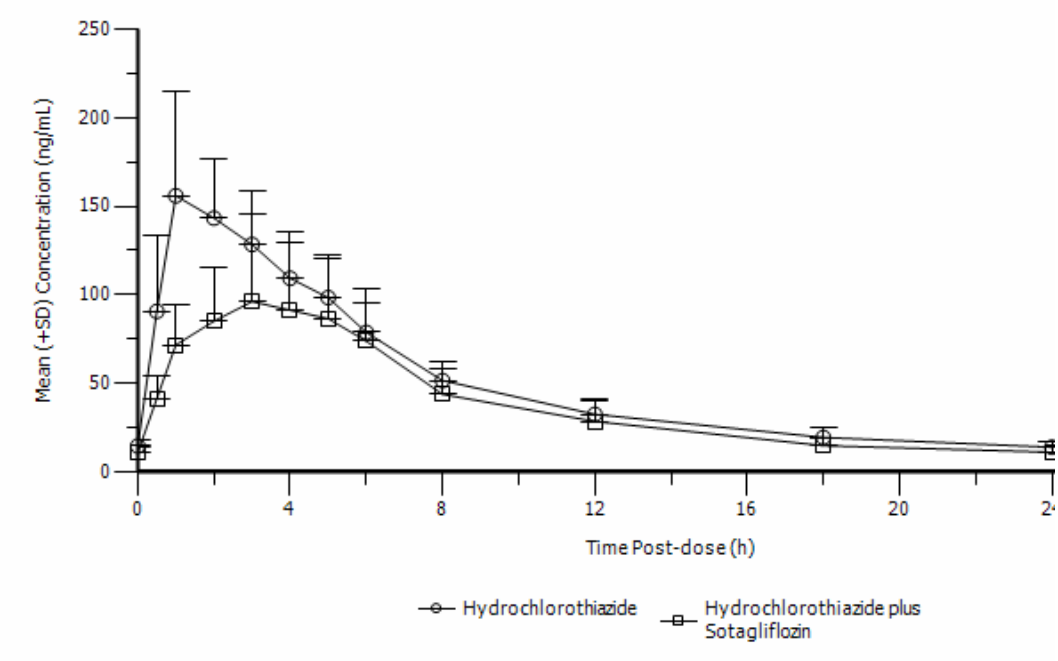

Figure 4.3.3.3. Mean (+SD) plasma concentrations of hydrochlorothiazide following multiple-dose administration of hydrochlorothiazide alone and following co-administration with multiple-dose sotagliflozin *(Source: Figure 6 of Study INT14905 CSR)*

Table 4.3.3.1. Effect of Hydrochlorothiazide on the PK of sotagliflozin *(Source: Table 19 of Study INT14905 CSR)*

Comparison	Parameter	Estimate	90% CI
SAR439954 + HCTZ versus SAR439954 alone	C_{max}	1.06	(0.89 to 1.25)
	AUC_{tau}	1.04	(0.91 to 1.19)

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Table 4.3.3.2. Effect of sotagliflozin on hydrochlorothiazide PK *(Source: Table 19 of Study INT14905 CSR)*

Comparison	Parameter	Estimate	90% CI
SAR439954 + HCTZ versus HCTZ alone	C_{max}	0.64	(0.57 to 0.72)
	AUC_{tau}	0.75	(0.69 to 0.81)

Conclusions:

- HCTZ did not have a clinically relevant effect on sotagliflozin exposure compared with sotagliflozin alone.
- Co-administration of sotagliflozin reduced HCTZ C_{max} and AUC_{tau} by 36% and 25%, respectively, with treatment ratios (sotagliflozin + HCTZ / HCTZ) and associated 90% CIs of 0.64 (0.57 to 0.72) and 0.75 (0.69 to 0.81), respectively.

The decrease in PK exposure is within the PK variability of HCTZ and within the recommended dose increments for HCTZ (1.5 to 2-fold).

4.3.4. Study INT14935 —DDI study with ramipril in HV

Title: An open label, 2-treatment, 2-period, single sequence study to evaluate pharmacokinetic drug-drug interaction between ramipril and sotagliflozin at steady state in healthy subjects

Sponsor's rationale: Carboxylesterase 1 is mainly responsible for activation of ramipril into its active metabolite, ramiprilat, in the liver. Ramiprilat is mainly excreted renally. While no relevant PK interaction is expected, common co-medication of the target population for an investigational product in clinical development will provide more definitive assessment of clinical drug-drug interaction potential.

Objectives

• Primary: DDI between sotagliflozin and ramipril

• Secondary:

- safety and tolerability of multiple-dose sotagliflozin with and without co-administration of multiple-dose ramipril.
- To assess the effects of multiple-dose sotagliflozin on the steady-state PK of ramipril.

Study population: healthy male and female subjects (n=16)

Drug product:

- **Sotagliflozin (Sotagliflozin - SAR439954)**: 400 mg (2 x 200-mg tablet, Sanofi), 10 days of QD dosing (5 days given alone in Treatment Period 1, 5 days under co-administration with ramipril in Treatment Period 2).
- **Ramipril**: 2.5-mg tablet (commercial formulation), 10 days of QD dosing (Treatment Period 2 only; 5 days given alone, 5 days under co-administration with sotagliflozin).

Each IMP was administered prior to the breakfast meal (breakfast was provided within 10 minutes after dosing).

This study was conducted as a single-center, open-label, 2-period, single-sequence, drug-drug interaction study. The 2 study drugs were administered in the following doses:

- Period 1: 400 mg sotagliflozin (2 x 200-mg tablet QD x 5 days) on Days 1 to 5. under fasted conditions (10-hours overnight fast).
- Period 2: subjects began a 10-day ramipril regimen with a single morning oral dose of 2.5 mg ramipril on Day 1 followed by QD morning oral dose of 5 mg ramipril (2 x 2.5-mg tablets) from Days 2 to 5 under fasted conditions (10-hour overnight fast). From Days 6 to 10, subjects received QD single morning oral intake of 5 mg ramipril (2 x 2.5-mg tablets) concomitantly with QD single morning oral dose of 400 mg sotagliflozin [2 x 200-mg tablets]) under fasted conditions (10-hour overnight fast).

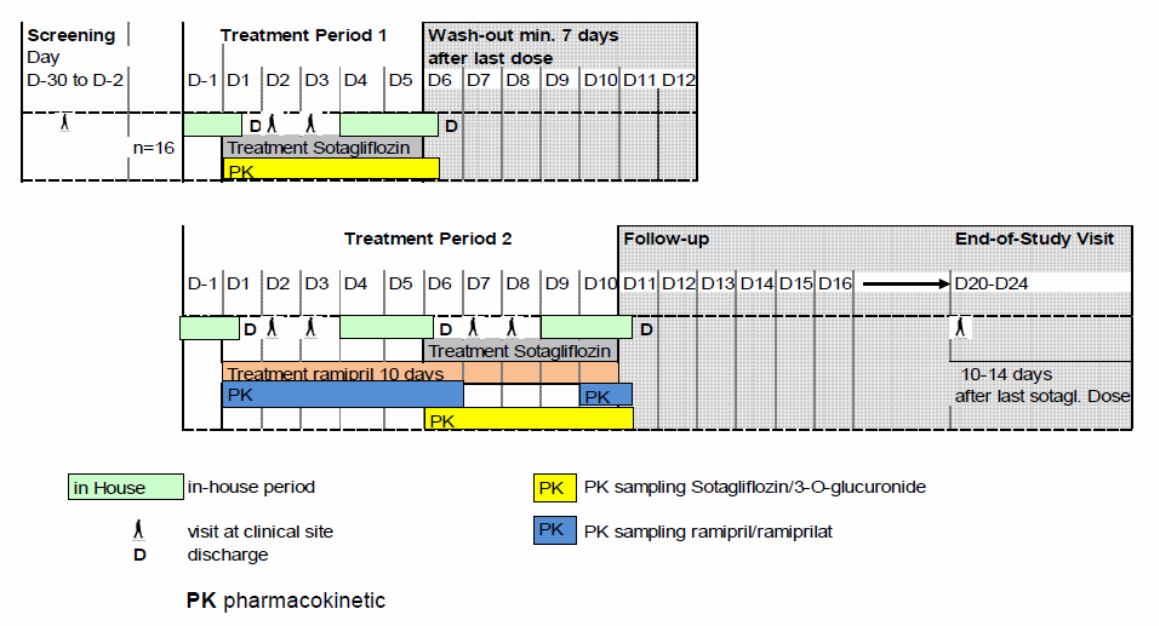

Figure 4.3.4.1: Study design *(Source: Figure 1 of Study INT14935 CSR)*

PK sampling: Sotagliflozin PK blood samples collected at 0 and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 18 and 24 hours postdose (Period 1, days 5; Period 2, day 10). Ramipril PK blood samples collected at 0 and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16 and 18 hours post-dose (Period 2, day 5) and 0 and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 18 and 24 hours post-dose (Period 2, day 10).

Results: PK results are shown as below.

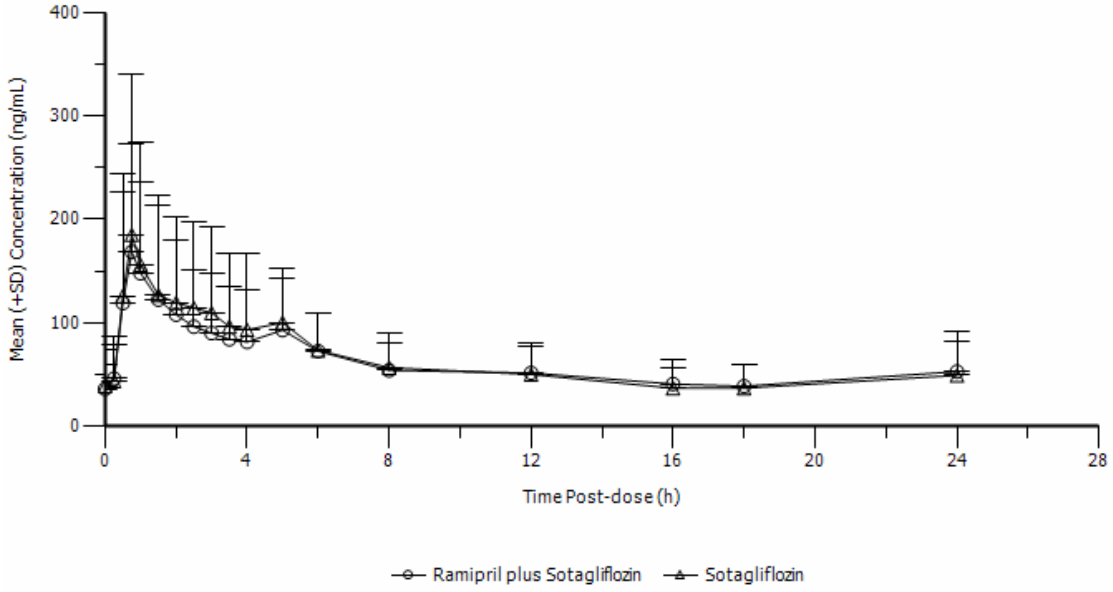

Figure 4.4.3.2. Mean (+SD) plasma concentrations of sotagliflozin following multiple-dose administration of sotagliflozin alone and following co-administration with multiple-dose ramipril *(Source: Figure 2 of Study INT14935 CSR)*

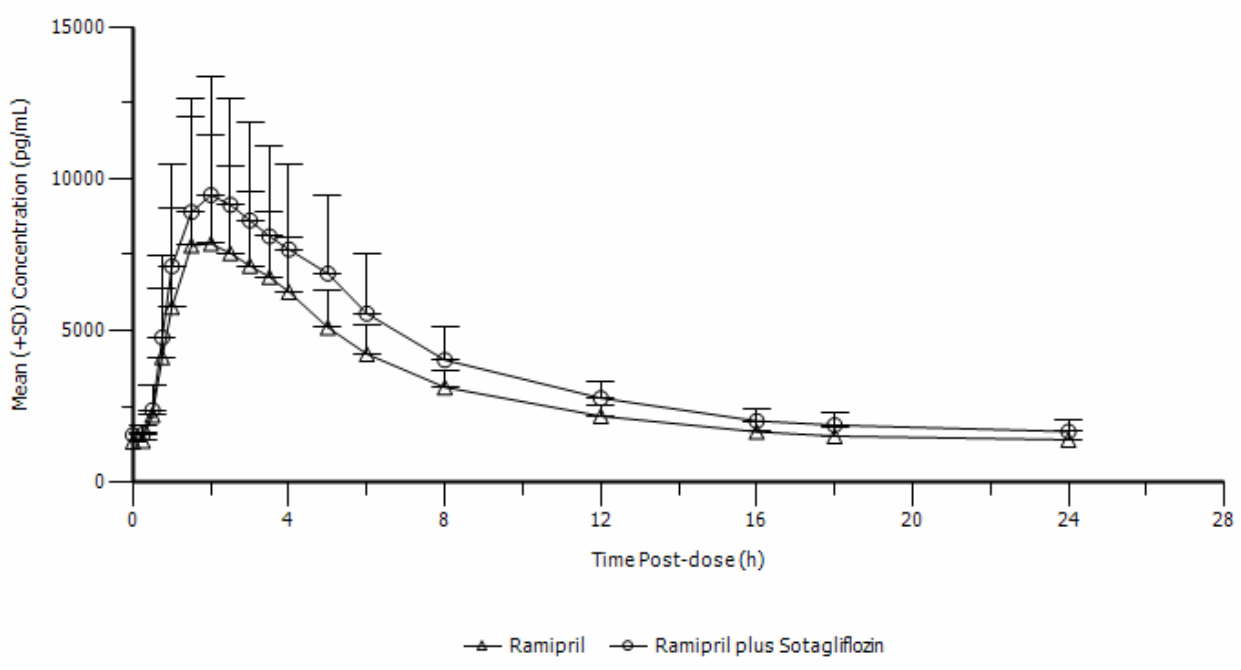

Figure 4.3.4.3. Mean (+SD) plasma concentrations of ramiprilat following multiple-dose administration of ramipril alone and following co-administration with multiple-dose sotagliflozin *(Source: Figure 10 of Study INT14935 CSR)*

Table 4.3.4.1. Treatment effect on sotagliflozin C_{max} and AUC_{tau}: Point estimates of treatment ratios with 90% confidence intervals *(Source: Table 21 of Study INT14935 CSR)*

Comparison	Parameter	Estimate	90% CI
Sotagliflozin + Ramipril vs Sotagliflozin alone	C_{max}	0.87	(0.73 to 1.03)
	AUC_{0-24}	1.00	(0.91 to 1.11)

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Table 4.3.4.2. Treatment effect on ramipril C_{max} and AUC_{tau}: Point estimates of treatment ratios with 90% confidence intervals *(Source: Table 31 of Study INT14935 CSR)*

Comparison	Parameter	Estimate	90% CI
Sotagliflozin + Ramipril vs Ramipril alone	C_{max}	1.32	(0.98 to 1.78)
	AUC_{0-24}	1.88	(1.46 to 2.43)

Conclusions:

- Sotagliflozin and ramipril were well tolerated when given alone or in co-administration.
- Co-administration of multiple dose sotagliflozin with multiple dose ramipril, there was no change in sotagliflozin mean AUC_{tau} (treatment ratio: 1.00), while mean C_{max} decreased by 13% (treatment ratio: 0.87).
- For metabolite sotagliflozin-3-O-glucuronde, AUC_{tau} and C_{max} were similar when multiple dose sotagliflozin was administered alone or with multiple dose ramipril, with treatment ratios of 1.06 and 1.01, respectively.
- Ramipril mean AUC_{tau} and C_{max} were 88% and 32% higher, respectively, when multiple dose ramipril was co-administered with multiple dose sotagliflozin versus alone.
- Administration of multiple dose ramipril with multiple dose sotagliflozin versus alone, did not result in a clinically relevant change in exposure of ramiprilat, with treatment ratios of 1.19 and 1.09 for ramiprilat mean AUC_{tau} and C_{max}, respectively. Ramipril is almost completely metabolized to ramiprilat, which has about 6 times the ACE inhibitory activity of ramipril. The observed increase in ramipril exposure with no significant increase in ramiprilat exposure, does not necessitate a dose adjustment.

4.3.5. Study PKM15402 — Absolute bioavailability of sotagliflozin in HV

Title: A Phase 1, single-center, open-label, two-period, one-sequence, single dose study to determine the absolute bioavailability of sotagliflozin in healthy male and female subjects

Objectives

• Primary: to assess the absolute bioavailability of sotagliflozin

• Secondary:

- Safety and tolerability of single doses sotagliflozin.
- To assess the PK of sotagliflozin and its main metabolite M19 after a single oral dose of 400 mg sotagliflozin.

Study population: healthy male and female subjects (n=6)

Drug product:

- **Treatment A:** Sotagliflozin (Sotagliflozin - SAR439954) 400 mg (2 x 200-mg tablet, Sanofi), and IV ^{14}C-sotagliflozin microtracer.
- **Treatment B:** Sotagliflozin (Sotagliflozin - SAR439954) 400 mg (2 x 200-mg tablet, Sanofi), and IV ^{14}C-sotagliflozin microtracer + oral charcoal.

Each IMP was administered prior to the breakfast meal (breakfast was provided within 10 minutes after dosing). Subjects were to be under fasting conditions for at least 10 hours before the oral IMP administration during which only water was permitted.

The treatment sequences were as follows:

- Treatment Period (TP) 1: Treatment A.
- Treatment Period (TP) 2: Treatment B.

For each subject, the total duration of study participation was up to 55 days and included:

- Screening: 2 to 28 days prior to study drug administration.
- Treatment Periods (TP1 and TP2): 9 days (from Day -1 morning to Day 8 morning) including 1 treatment day on Day 1 (single oral dose of sotagliflozin + IV microdose of ^{14}C-sotagliflozin, with or without co-administration of oral charcoal).
- Washout Period: at least 10 days between sotagliflozin dosing days.
- End-of-study (EOS): 11 to 15 days after last dose of sotagliflozin in TP2 (Days 12 to 16).

Figure 1 - Study design

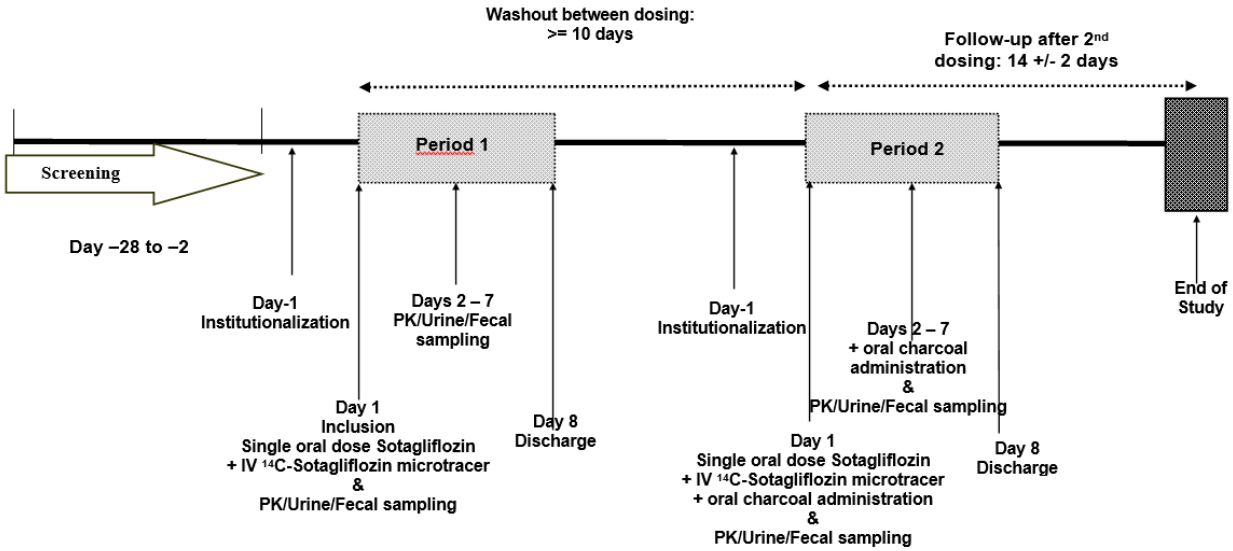


Figure 4.3.5.1: Study design *(Source: Figure 1 of Study PKM15402 CSR)*

PK sampling: Sotagliflozin/ sotagliflozin-3 O glucuronide (cold) PK blood samples are collected at 0 and at 1, 2, 4, 6, 7, 8, 10, 12, 16, 24, 28, 32, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144 and 156 hours postdose. Sotagliflozin/ sotagliflozin-3 O glucuronide (AMS/total radioactivity) PK blood samples are collected at 5 hr 45 min, 5 hr 50 min, 5 hr 55 min, 6 hr, 6 hr 5 min, 6 hr 10 min, 6 hr 15 min, 6 hr 20 min, 6 hr 25 min, 6 hr 30 min, 6 hr 45 min, 7 hr, 7 hr 15 min, 7 hr 30 min, 7 hr 45 min, 8 hr, 8 hr 30 min, 9 hr, 9 hr 30 min, 10 hr, 10 hr 30 min, 11 hr, 11 hr 30 min, 12, 13, 14, 16, 24, 28, 32, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144 and 156 hours postdose.
Results: PK results are shown as below.

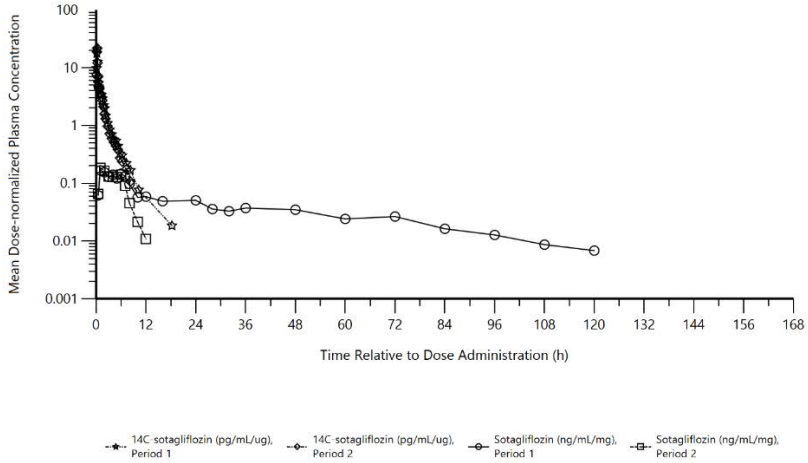


Figure 4.3.5.2. Mean sotagliflozin and ^{14}C-sotagliflozin plasma concentration-time profiles (dose normalized) following oral administration of sotagliflozin tablets and IV infusion of ^{14}C-

sotagliflozin microtracer, with (TP2) and without (TP1) charcoal co-administration (semi-logarithmic scale) *(Source: Figure 2 of Study PKM15402 CSR)*

Table 4.3.5.1. Mean ±SD (geometric mean) [CV%] plasma pharmacokinetic parameters of sotagliflozin and ^{14}C-sotagliflozin following oral administration of sotagliflozin tablets and IV infusion of ^{14}C-sotagliflozin microtracer, with and without charcoal co-administration
(Source: Table 15 of Study PKM15402 CSR)

A: Sotagliflozin (after 400 mg oral tablets)			B: ^{14}C-sotagliflozin (after 100 µg IV, "microtracer")		
PK Parameters	**Without Charcoal (TP1)**	**With Charcoal (TP2)**	**PK Parameters**	**Without Charcoal (TP1)**	**With Charcoal (TP2)**
N	6	6	N	6	6
C_{max} (ng/mL)	89.3 ± 39.3 (81.6) [44]	101 ± 52.0 (89.6) [51]	C_{max} (pg/mL)[d]	2090 ± 843 (1950) [40]	2170 ± 731 (2050) [34]
t_{max} [a] (h)	1.50 (1.00-7.20)	2.00 (1.00-6.02)	t_{max} [a] (h)	0.25 (0.17-0.33)	0.25 (0.18-0.25)
AUC_{last} (ng·h/mL)	1680 ± 945 (1450) [56]	439 ± 226 (395) [52]	AUC_{last} (pg·h/mL)[d]	1460 ± 266 (1440) [18]	1360 ± 302 (1340) [22]
AUC (ng·h/mL)	1970 ± 1000[b] (1740) [51]	449 ± 233 (405) [52]	AUC (pg·h/mL)[d]	1500 ± 301[c] (1470) [20]	1400 ± 302 (1380) [22]
t_{last} [a] (h)	120.00 (84.00-156.05)	12.00 (12.00-12.00)	t_{last} [a] (h)	9.15 (7.28-18.25)	8.24 (7.25-8.25)
$t_{1/2z}$ (h)	34.5 ± 4.17[b] (34.3) [12]	1.72 ± 0.240 (1.71) [14]	$t_{1/2z}$ (h)	2.29 ± 0.767[c] (2.18) [34]	1.92 ± 0.454 (1.87) [24]
CL/F (L/h)	263 ± 157[b] (230) [60]	1090 ± 502 (988) [46]	CL (L/h)	69.0 ± 13.8[c] (67.9) [20]	73.8 ± 14.4 (72.6) [19]
V_z/F (L)	13200 ± 8390[b] (11400) [63]	2770 ± 1490 (2430) [54]	V_z (L)	221 ± 63.5[c] (214) [29]	205 ± 70.5 (196) [34]
V_{dss}/F (L)	12300 ± 6770[b] (11100) [55]	5050 ± 2600 (4480) [52]	V_{dss} (L)	126 ± 46.4[c] (119) [37]	119 ± 54.1 (110) [46]

NA = Not Applicable
[a] Median (Min, Max)
[b] N=5; R^2 adjusted <0.7 for sotagliflozin profile for Subject (b) (6) in TP1
[c] N=5; R^2 adjusted <0.7 for ^{14}C-sotagliflozin profile for Subject (b) (6) in TP1
[d] Note different units for AUC, AUClast, and Cmax compared to oral administration of 400 mg sotagliflozin

Table 4.3.5.2. Treatment effect on dose normalized AUC_{last} and AUC for sotagliflozin-3-O-glucuronide: point estimates of treatments ratio (oral with charcoal versus oral without charcoal) with 90% confidence interval *(Source: Table 20 of Study PKM15402 CSR)*

Comparison	Parameter	Estimate	90% CI
Oral with charcoal vs Oral without charcoal	Dose Normalized AUC_{last}	0.29	(0.22 to 0.37)
	Dose Normalized AUC	0.28	(0.21 to 0.36)

6 subjects did not receive 14C-IV sotagliflozin and had no PK parameters calculated
For sotagliflozin 400 mg oral, dose normalized AUClast = AUClast/400 and dose normalized AUC = AUC/400
For sotagliflozin 100 ug IV, dose normalized AUClast = AUClast/0.1 and dose normalized AUC = AUC/0.1
PGM=PRODOPS/SAR439954/PKM15402/CSR/REPORT/PGM/pk_pkm15402_intext.sas
OUT=REPORT/OUTPUT/pk_sota_glu_oral_k_t_2_i.rtf (10SEP2019 - 17:06)

Conclusions:

- The absolute bioavailability of oral sotagliflozin tablets was approximately 25% (90% CI: 16% to 39%) for AUC_{last}.
- Charcoal co-administration rapidly caused plasma sotagliflozin concentrations to drop below the limit of quantification and profoundly decreased sotagliflozin systemic exposure. Consistent with changes in the plasma PK profiles, charcoal co-administration also reduced total urinary excretion of sotagliflozin and sotagliflozin-3-O-glucuronide and reduced urinary recoveries at later collection intervals.
- A pronounced first pass effect was observed based on metabolic ratios of oral versus IV administration. Sotagliflozin-3-O-glucuronide was confirmed to be the major circulating metabolite based on comparison of total radioactivity and sotagliflozin-3-O-glucuronide plasma concentration-time profiles.

4.3.6. Study TDR15349 — Pharmacokinetics in Chinese HVs

Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Ascending Multiple-dose Study to Determine the Safety, Tolerability, Pharmacodynamics and Pharmacokinetics of Orally Administered Sotagliflozin in Healthy Chinese Subjects

Objectives

• Primary: to assess the safety and tolerability of sotagliflozin after a multiple oral dose administration in Chinese healthy subjects

• Secondary:

- To assess the pharmacokinetic (PK) parameters of sotagliflozin after a multiple oral dose administration in Chinese healthy subjects.
- To assess the pharmacodynamics (PD) parameters of absolute urinary glucose excretion after a multiple oral dose administration in Chinese healthy subjects.

Study population: healthy Chinese subjects (male and female ≥18 to ≤45 years of age) with body weight between 50.0 and 95.0 kg (n=24)

Drug product:

- **Test product:** Sotagliflozin 200 mg as 1 x 200-mg sotagliflozin oral tablets & Sotagliflozin 400 mg as 2 x 200-mg sotagliflozin oral tablets.
- **Reference therapy:** Placebo tablets (identical to sotagliflozin in appearance).

A total of 24 subjects were randomized to: placebo (N=6), sotagliflozin 200 mg (N=9), and sotagliflozin 400 mg (N=9). All 24 subjects were treated with study drug. At Baseline subjects in the placebo group were slightly younger than sotagliflozin group; subjects in the sotagliflozin 400 mg group were older. Mean ages were 27.0, 31.9, and 36.3 years for subjects in the placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg groups, respectively. All subjects in the placebo group were male while both sotagliflozin groups were 77.8% male. All subjects were Asian and not Hispanic or Latino. All subjects (100%) in all 3 treatment groups completed the study.

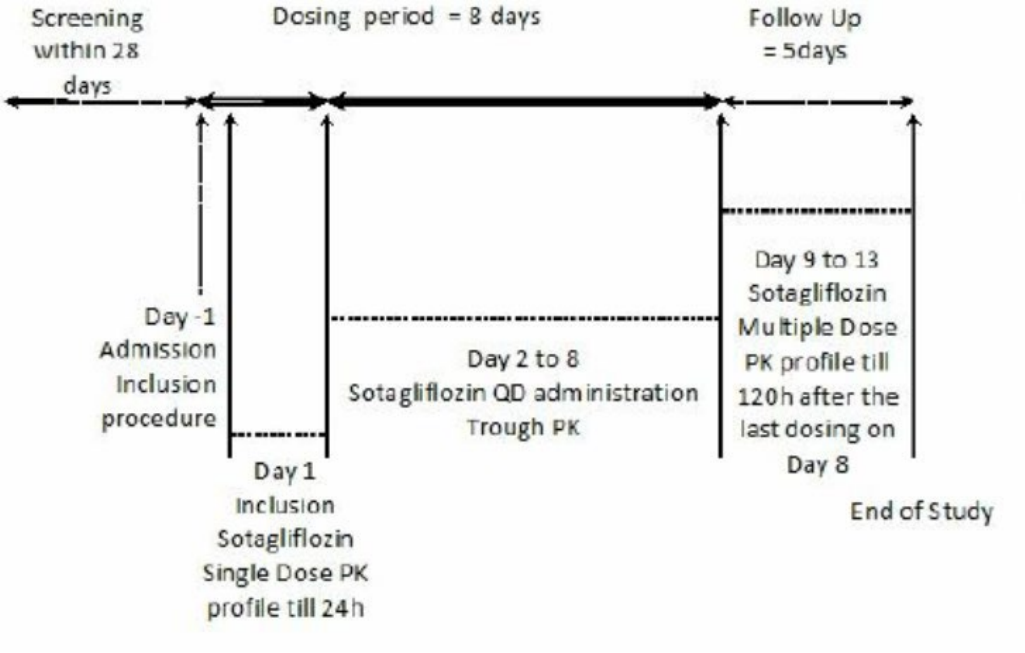
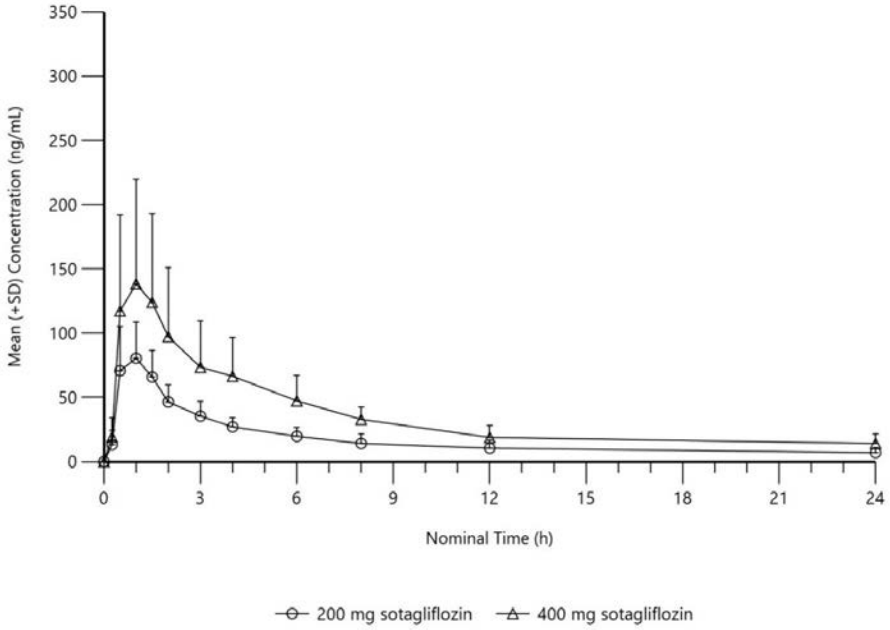
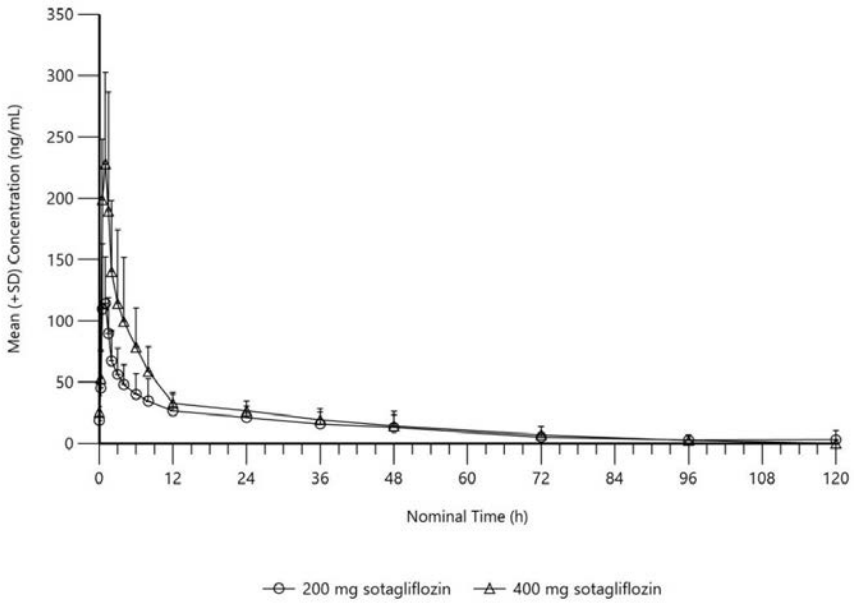


Figure 4.3.6.1: Study design *(Source: Page 9 of Study TDR15349 CSR)*
PK sampling: PK blood samples are collected at 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12 and 24 hours on day 1 along with pre-dose sample on days 2, 3, 4, 5, 6 and 7.

Results: PK results are shown as below.



(A) Day 1



(B) Day 8

Figure 4.3.6.2. Mean (SD) sotagliflozin plasma concentration-time profiles following (A) single dose (Day 1) and (B) multiple qd dose (Day 8) of 200 mg and 400 mg of sotagliflozin *(Source: Page 11 of Study TDR15349 CSR)*

Table 4.3.6.1. Mean ±SD (geometric mean) [CV%] of LX4211-GLU pharmacokinetic parameters following single and multiple dose administration of 200 mg and 400 mg sotagliflozin
(Source: Page 14 of Study TDR15349 CSR)

	200 mg		400 mg	
PK Parameters	**Day 1**	**Day 8**	**Day 1**	**Day 8**
N	9	9	9	9
C_{max} (ng/mL)	4300 ± 1420 (4030) [33]	5210 ± 1560 (4940) [30]	8250 ± 2750 (7920) [33]	12500 ± 4750 (11900) [38]
C_{trough} (ng/mL)	NA	1890 ± 726 (1750) [39]	NA	3150 ± 1150 (2970) [37]
t_{max} [a] (h)	1.50 (1.00-1.50)	1.00 (1.00-2.00)	1.50 (1.00-4.00)	1.50 (1.00-1.50)
AUC_{tau} (ng·h/mL)	32000 ± 12600 (28600) [39]	55800 ± 17900 (52200) [32]	61700 ± 11600 (60800) [19]	103000 ± 37900 (98400) [37]
AUC_{last} (ng·h/mL)	NA	125000 ± 51900 (114000) [42]	NA	198000 ± 64400 (189000) [32]
AUC (ng·h/mL)	NA	120000 ± 44200[b] (111000) [37]	NA	191000 ± 60400[c] (182000) [32]
$t_{1/2z}$ (h)	NA	24.8 ± 11.2[b] (22.7) [45]	NA	22.0 ± 15.6 (18.3) [71]
R_{ac}	NA	1.85 ± 0.362 (1.83) [20]	NA	1.65 ± 0.375 (1.62) [23]
$R_{ac"Cmax"}$	NA	1.23 ± 0.139 (1.23) [11]	NA	1.52 ± 0.222 (1.50) [15]

NA = Not Applicable
a Median (Min-Max)
b N = 8, since a regression analysis could not be applied for LX4211-GLU for 1 subject
c N = 8, since 1 subject was excluded due to AUC_{extrap} >20% for LX4211-GLU

Conclusions:

- Following single and multiple qd administration, sotagliflozin was rapidly absorbed at both 200 and 400 mg dose levels with a median t_{max} of 1.00 h postdose (individual t_{max} range: 0.50-1.50 h).
- On Day 8, sotagliflozin mean terminal half-lives ($t_{1/2z}$) (20.5 h for 200 mg dose and 22.4 h for 400 mg dose) and CL/F (267 L/h for 200 mg dose and 307 L/h for 400 mg dose) were similar between the 2 dose levels.
- Mean accumulation ratios (R_{ac} and $R_{ac"Cmax"}$) ranged from 1.45 to 2.05, indicating a moderate degree of accumulation of sotagliflozin following multiple dosing. The pooled accumulation ratio of sotagliflozin 200 mg and 400 mg after 8 days of qd administration were 1.57 (90% CI: 1.38 to 1.78) for C_{max} and 1.84 (90% CI: 1.69 to 2.01) for AUC_{tau}, respectively.
- Systemic exposure of sotagliflozin increased in an approximately dose proportional manner. For a 2-fold increase between doses on Day 8, the estimated increases for C_{max} and AUC_{tau} were 1.89-fold (90% CI: 1.47 to 2.43) and 1.70-fold (90% CI: 1.27 to 2.29), respectively. Over the same dose range, the estimated increases in C_{max} and AUC_{tau} on Day 1 were similar (1.56-fold [90% CI: 1.07 to 2.26] and 2.02-fold [90% CI: 1.50 to 2.73], respectively).
- Within-subject variability were approximately 22% [90% CI: 17.0%, to 30.8%] for C_{max} and 15% [90% CI: 11.4% to 20.6%] for AUC_{tau} and between subject variability in exposure (based on C_{max} and AUC_{tau}) was moderate to high for both dose levels and on both days with CV% estimates ranging from 31% to 57%.
- Following single and multiple dose administration of sotagliflozin, LX4211-GLU appeared rapidly in the system circulation at both dose levels with a median t_{max} of between 1.00 and 1.50 h postdose (individual subject range 1.00-4.00 hours). On Day 8, LX4211-GLU mean terminal half-lives ($t_{1/2z}$) were 24.8 h and 22.0 h for 200 and 400 mg dose levels, respectively.
- Based on mean C_{trough} time profiles, steady state plasma concentrations of LX4211-GLU appeared to have been achieved by Day 6 (data not shown). There was evidence of some accumulation of LX4211-GLU at both the 200 mg and 400 mg dose levels with mean R_{ac} and $R_{ac"Cmax"}$ ranging from 1.23 to 1.85.
- Systemic exposure of LX4211-GLU showed a dose-dependent increase with mean AUC_{tau} and C_{max} approximately 1.85- and 2.40-fold higher at the 400 mg dose level compared to the 200 mg dose level on Day 8.
- UGE was elevated relative to the placebo group in the 200 mg and 400 mg groups over both Day 1 and Day 8 and increased slightly between Day 1 and Day 8 in both groups.
- An increased frequency of TEAEs was observed with sotagliflozin 200 mg and 400 mg as compared to placebo; all TEAEs were of mild intensity, did not require corrective treatment (except for topical iodophor for folliculitis), and resolved without sequelae.

- Following single and multiple qd administration, sotagliflozin was rapidly absorbed at both 200 and 400 mg dose levels.
- Systemic exposure of sotagliflozin increased in an approximately dose proportional manner.
- UGE was increased in both sotagliflozin groups relative to placebo over day 1 and Day 8.

Reviewer comment: Analyses of clinical safety data from this study demonstrated that sotagliflozin 200 mg and 400 mg were well-tolerated, and no significant safety findings were identified in healthy male and female Chinese subjects when given orally qd for 8 days.

4.3.7. Study PDY15010— Cardiovascular Effects Sotagliflozin vs Empagliflozin in T2DM with hypertension Patients (Phase IIa)

Title: A Randomized, Double-blind, Parallel-group, 2-treatment, Multiple Dose Study to Assess the Intestinal, Metabolic, and Cardiovascular Effects of an 8 Week Treatment with Sotagliflozin qd as Compared with Empagliflozin qd in T2DM Patients with Mild to Moderate Hypertension.

Objectives

• Primary: To compare the metabolic and gastrointestinal pharmacodynamic (PD) effects of an 8-week treatment with 400 mg sotagliflozin once daily (QD) to an 8-week treatment with 25 mg empagliflozin QD in mild or moderate hypertensive T2DM patients on a stable treatment regimen with metformin and an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) under standardized diet conditions.

• Secondary:

- To compare the renal and cardiovascular PD effects of an 8-week treatment with 400 mg sotagliflozin QD to an 8-week treatment with 25 mg empagliflozin QD in mild or moderate hypertensive T2DM patients on a stable treatment regimen with metformin and an ACE inhibitor or ARB.
- To evaluate the safety and tolerability of an 8-week QD treatment with 400 mg sotagliflozin or 25 mg empagliflozin in mild to moderate hypertensive T2DM patients on a stable treatment with metformin and an ACE inhibitor or ARB.
- To evaluate the PK profile of sotagliflozin in steady-state conditions.

Study population: Male or female patients with T2DM (diagnosed at least 1 year before screening visit), between 18 and 74 years of age, with body weight between 50.0 and 130 kg if male, and between 40.0 and 110 kg if female, and body mass index between 18.0 and 38.0 kg/m2, inclusive, with hypertension grades 1 or 2 as defined by the European Society of Hypertension/European Society of Cardiology at screening; glycosylated hemoglobin A1c at screening was to be between 6.5% and 11%; on a stable treatment with metformin (i.e., with no change in dose regimen or in dose levels in the last 3 months prior to screening and until randomization); on a stable treatment with an ACE inhibitor or an ARB (i.e., no change in dose regimen or in dose levels in the last 4 weeks prior to screening and until randomization); on a stable treatment with an ACE inhibitor or an ARB after switching from beta-blockers and/or thiazides for eligible patients after screening (i.e., no change in dose regimen and in dose levels in the last 4 weeks prior to run-in phase and until randomization); estimated glomerular filtration rate at screening was to be 60 mL/min/1.73 m2 or higher. (n=41)

Drug product:

- **Treatment (A):** Sotagliflozin 400 mg and placebo were each administered as 2 × 200-mg tablets QD prior to the first meal of the day for 56 days (Days 1 to 56).

- **Treatment (B):** Empagliflozin and placebo were each administered as 1 × 25-mg capsule QD prior to the first meal of the day for 56 days (Days 1 to 56).

This was a Phase 2a, single-center, randomized, double-blind, double-dummy, active-control, parallel-group multiple dosing study. A total of 41 T2DM patients with mild or moderate hypertension were enrolled into the study. After an initial in-house period of 5 days (Day -5 to Day 1 in the morning) to evaluate PD baseline parameters under standardized conditions, patients were randomized 1:1 to an 8-week (56 days) multiple dosing treatment of 400 mg sotagliflozin QD or empagliflozin 25 mg QD.
Patients returned for a second in-house period to the unit in the last 5 days (Day 52 to Day 57 in the morning) of treatment for re-analyses of all PD assessments on treatment under the same standardized conditions.
For the 5-day baseline PD assessment period the patients were admitted to the unit on Day -5. They received standardized meals 3 times a day plus a standardized snack at bedtime during these days. The ambulatory blood pressure monitoring (ABPM) was set up for the time of the in-house stay. On specific days, the cardiovascular baseline assessment was performed, i.e., pulse wave velocity (Day -2) and echocardiography (Day -3 ± 1 day) as described in the flowchart. On Day -1, the further PD baseline assessments were performed with fractioned 24-hour urine collection, blood sampling for postprandial glucose and insulin/glucagon profiles. Feces collection was performed over 48 hours (Days -2 and -1). In the morning of Day 1 the collection period ended, and the first dose of investigational medicinal product (IMP) was given prior to breakfast. Thereafter the patients were released from the unit. They continued dosing QD for 56 days (Days 1 through 56) with at least 3 outpatient visits, one between Days 3 to 10, one between Days 11 to 28, and one between Days 29 and 49, at least 7 days apart.
On Day 52, the on-treatment PD in-house assessment period started with admission to the unit and the same schedule of standardized meals as at baseline. On specific days, echocardiography (Day 54 ±1 day) was assessed again. On Day 56, the on-treatment PD assessments were performed with identical schedule as at baseline on Day -1. On the morning of Day 57, the collection period ended, and the patients were to be discharged after breakfast.
For each patient, the total duration of the study was a maximum of approximately 105 days for patients without a drug washout/switch period or 175 days for patients with a drug washout/switch period:

- Screening: 2 to 29 days (Day -35 to Day -7)
- Drug washout/switch period, only for patients who were on beta-blockers and/or thiazides and had to switch to ACE inhibitor or ARB prior to the run-in period: up to 10 weeks
- Run-in period: 5 days (Days -5 to -1)
- Treatment period: 56 days (Days 1 to 56)
- Follow-up: 7 to 14 days (Day 63 to Day 70)

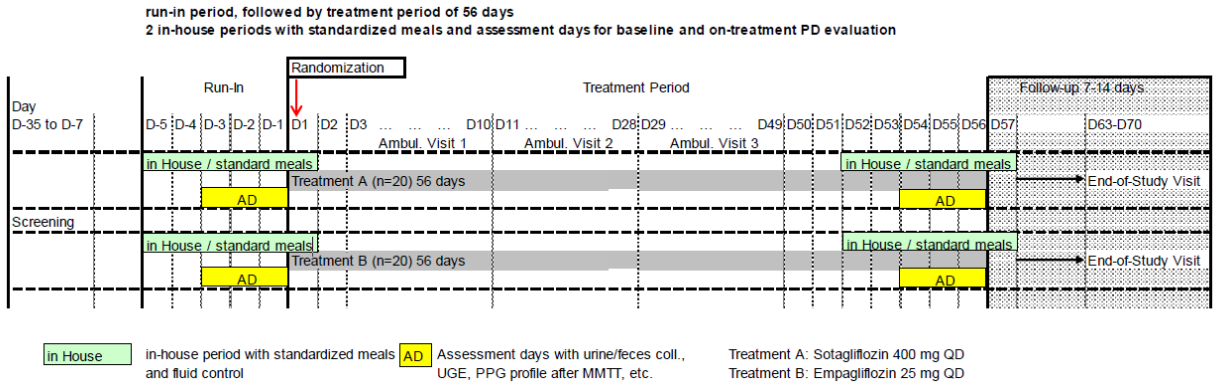


Figure 4.3.7.1: Study design *(Source: Figure 1 in Study PDY15010 CSR)*

PK sampling: One PK profile will be taken from each patient at end of treatment on Day 56 in a blinded manner. Sotagliflozin/ sotagliflozin-3 O glucuronide (M19) PK blood samples are collected at 0, 1, 2, 3, 5, 7, 10 and 24 hours on day 56 along with pre-dose sample on days 2, 3, 4, 5, 6 and 7.

Results:

Pharmacodynamics evaluation:

The mean (±SEM) 24-hour UGE at baseline was 28.714 (±11.2070) mmol, increasing to 155.044 (±10.3794) mmol at Week 8 in the sotagliflozin 400 mg group, and 15.218 (±6.2795) mmol at baseline, increasing to 175.645 (±14.9254) mmol at Week 8 in the empagliflozin 25 mg group **(Figure 4.3.7.2).**

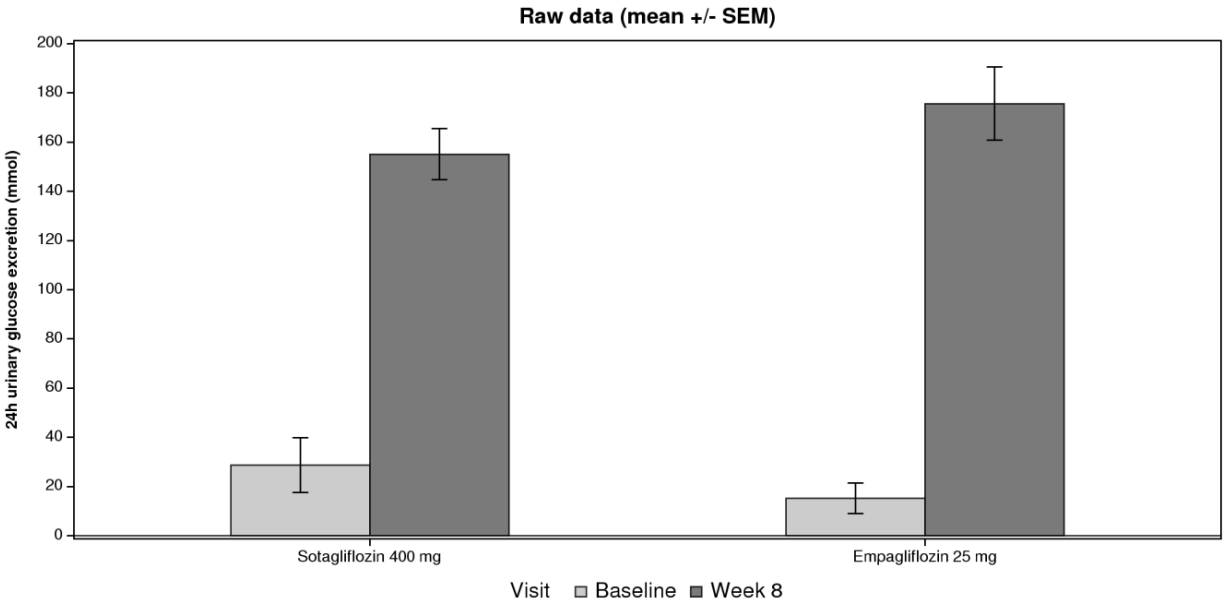


Figure 4.3.7.2. Graph of (mean ± SEM) on raw data at baseline and Week 8 for 24h urinary glucose excretion (mmol) - PD population *(Source: Figure 3 in Study PDY15010 CSR)*

The 14-hour plasma glucose profiles of the sotagliflozin 400 mg and empagliflozin 25 mg groups at baseline and Week 8 showed overall similarity **(Figure 4.3.7.3).**

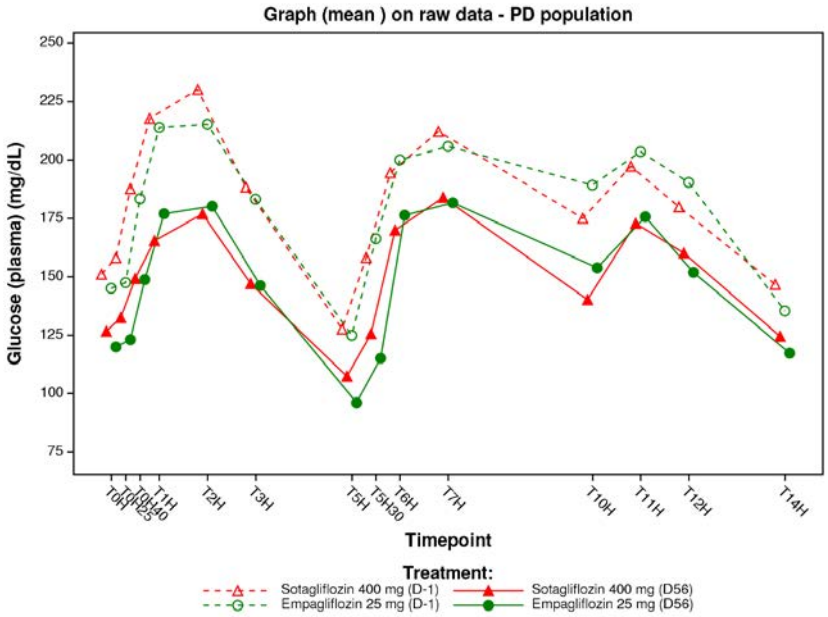


Figure 4.3.7.3. Graph of (mean) on raw data for 14-hour plasma glucose profile - PD population *(Source: Figure 10 in Study PDY15010 CSR)*

The 14-hour plasma insulin profiles of the sotagliflozin 400 mg and empagliflozin 25 mg groups at baseline and Week 8 showed overall similarity with less postprandial insulin peaks after 8 weeks of treatment **(Figure 4.3.7.4).**

Figure 4.3.7.4. Graph of (mean ± SEM) on raw data at baseline and Week 8 for plasma insulin incremental $AUC_{0:00\text{-}5:00h}$ - PD population *(Source: Figure 12 in Study PDY15010 CSR)*

There were no LS mean differences that reached the level of statistical significance for sotagliflozin versus empagliflozin for any of the 24-hour AMBP for SBP or DBP. There were no LS mean differences that reached the level of statistical significance for sotagliflozin versus empagliflozin for seated diurnal SBP and DBP. The mean (SEM) change from baseline for VTI over LVOT was numerically smaller in patients treated with sotagliflozin 400 mg compared to patients treated with empagliflozin 25 mg. The mean (SEM) decrease from baseline for LVEDD was similar in the sotagliflozin 400 mg group (-0.9 [0.61]) compared to the empagliflozin 25 mg group (-0.9 [0.82]). The mean (SEM) change from baseline for LVEF was numerically larger in the sotagliflozin 400 mg group (5.1 [1.87]) compared to the empagliflozin 25 mg group (3.0 [2.51]). The mean (SEM) change from baseline for the E/e' ratio was numerically larger in the sotagliflozin 400 mg group (0.394 [0.5925]) compared to the empagliflozin 25 mg group (-0.373 [0.4258]). The mean (SEM) change from baseline for the E/A ratio was numerically larger in the sotagliflozin 400 mg group (0.012 [0.0487]) compared to the empagliflozin 25 mg group (-0.005 [0.0335]).

Adverse events evaluation:
Overall, TEAEs were experienced by 16 of the 20 patients (80.0%) in the sotagliflozin 400 mg group and 13 of the 21 patients (61.9%) in the empagliflozin 25 mg group. There were no deaths, no SAEs, no TEAEs that led to permanent treatment discontinuation, and no severe TEAEs (≥Grade 3) during the study. There were no AESIs; however, TEAEs defined as EOSIs were experienced by 3 patients in the sotagliflozin 400 mg group. **(Table 4.3.7.1).**

n (%)	Sotagliflozin 400 mg (N=20)	Empagliflozin 25 mg (N=21)
Patients with any TEAE	16 (80.0%)	13 (61.9%)
Patient with any grade ≥ 3 TEAE	0	0
Patient with any grade 3-4 TEAE	0	0
Patient with any grade 5 TEAE	0	0
Patients with any treatment emergent SAE	0	0
Patients with any treatment emergent AE of special interest (AESI)	0	0
Patients with any treatment emergent AE defined as event of special interest (EOSI)	4 (20.0%)	1 (4.8%)
Patients with any TEAE leading to permanent treatment discontinuation	0	0

TEAE: Treatment emergent adverse event, SAE: Serious adverse event
n (%) = number and percentage of patients with at least one TEAE
Note: An adverse event is considered as treatment emergent if it occurred from the time of the first investigational medicinal product (IMP) administration up to 10 days (1 day for Hypoglycemia) after the last IMP administration (included).
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Table 4.3.7.1. Overview of adverse event profile: TEAEs - Safety population
(Source: Table 14 in Study PDY15010 CSR)

Pharmacokinetics evaluation:

Descriptive statistics of the steady-state PK parameters of sotagliflozin and sotagliflozin-3-O-glucuronide on Day 56 (Week 8) following administration of sotagliflozin 400 mg QD (Treatment A) on Days 1 to 56 are presented in **Tables 4.3.7.2** and **4.3.7.3** respectively.

	Treatment A (2 x 200 mg sotagliflozin tablets QD on Days 1 to 56)						
	C_{max} (ng/mL)	t_{max} (h)	C_{trough} (ng/mL)	AUC_{tau} (ng.h/mL)	CL_{ss}/F (L/h)	V_{ss}/F (L)	MRT_{tau} (h)
N	19	19	19	19	19	19	19
Mean	210	1.68	34.1	1540	312	2640	8.33
SD	133	1.51	19.6	669	143	1440	1.46
SE	30.5	0.35	4.50	154	32.7	330	0.336
Min	64.0	0.83	14.9	671	123	1060	4.69
Median	178	1.00	23.9	1440	277	2100	8.60
Max	597	5.17	88.2	3250	596	6090	10.5
CV%	63	90	57	43	46	55	18
Geometric Mean	177	1.33	29.8	1410	284	2320	8.19

Table 4.3.7.2. Steady-state pharmacokinetic parameters of sotagliflozin on Day 56 following administration of 400 mg sotagliflozin QD on Days 1 to 56 (Treatment A)
(Source: Table 22 in Study PDY15010 CSR)

	Treatment A (2 x 200 mg sotagliflozin tablets QD on Days 1 to 56)					
	C_{max} (ng/mL)	t_{max} (h)	C_{trough} (ng/mL)	AUC_{tau} (ng.h/mL)	$R_{met"AUCtau"}$	$R_{met"Cmax"}$
N	19	19	19	19	19	19
Mean	25500	2.14	6170	234000	158	159
SD	10400	1.52	5170	158000	77.2	90.0
SE	2390	0.35	1180	36200	17.7	20.6
Min	6680	0.83	1340	65400	31.1	13.8
Median	25100	2.00	5630	223000	162	156
Max	41000	6.98	26000	657000	305	365
CV%	41	71	84	67	49	57
Geometric Mean	22800	1.80	5050	192000	137	129

Table 4.3.7.3. Steady-state pharmacokinetic parameters of sotagliflozin-3-O-glucuronide on Day 56 following administration of 400 mg sotagliflozin QD on Days 1 to 56 (Treatment A)
(Source: Table 23 in Study PDY15010 CSR)

Conclusions:
Following administration of 2 × 200 mg sotagliflozin QD (Treatment A) for 56 days, sotagliflozin was readily absorbed with a median (range) t_{max} of 1.00 (0.83-5.17) hour; its metabolite sotagliflozin-3-O glucuronide readily appeared in plasma with a median (range) t_{max} of 2.00 (0.83-6.98) hours. After reaching C_{max}, plasma concentrations of sotagliflozin and sotagliflozin-3-O-glucuronide declined over the dosing interval. Sotagliflozin and sotagliflozin-3-O-glucuronide mean C_{trough} values represented 16% and 24% of their respective mean C_{max} values. Mean $R_{met\text{“}AUCtau\text{”}}$ and $R_{met\text{“}Cmax\text{”}}$ values were 158 and 159, respectively.

Reviewer comment: Sotagliflozin 400 mg and empagliflozin 25 mg were generally well tolerated with no observed relevant differences in the overall safety profile between treatments.

4.3.8. Study PDY15079 — Efficacy of Sotagliflozin in Patients (Phase II, Cardiovascular Indications; WHF and Hypertension)

Title: An exploratory, randomized, double-blind, placebo-controlled, parallel arm trial of the safety and pharmacodynamic activity of sotagliflozin in hemodynamically stable patients with worsening heart failure

Objectives

• Primary:

- To assess the safety and tolerability of sotagliflozin, added to the standard of care treatment, in hemodynamically stable patients with worsening of heart failure, compared to placebo.
- To estimate the effect of sotagliflozin, when added to the standard of care treatment, on changes in plasma volume, as assessed by direct (indicator dilution) and indirect (hemoconcentration) methods, in hemodynamically stable patients with worsening of heart failure, compared to placebo.

• Secondary:

- Explore the effect of sotagliflozin, added to standard of care treatment, on erythropoiesis, as assessed by changes in plasma erythropoietin levels, in hemodynamically stable patients with worsening of heart failure, compared to placebo
- Explore the effect of sotagliflozin, added to standard of care treatment, on changes in plasma NT-proBNP levels, in hemodynamically stable patients with worsening of heart failure, compared to placebo.

Study population: Patients (male and female ≥18 years of age) who had been admitted to the hospital or had urgent visit to emergency department or heart failure unit/clinic or infusion center for congestive heart failure (CHF). (n=32)

Drug product:

- **Test product:** Sotagliflozin 200 mg as 1 x 200-mg sotagliflozin oral tablet and Sotagliflozin 400 mg as 2 x 200-mg sotagliflozin oral tablets.
- **Reference therapy:** Placebo tablets (identical to sotagliflozin in appearance).

This was a randomized, double-blind, placebo-controlled, parallel arm trial of the safety, tolerability and pharmacodynamic activity of sotagliflozin in hemodynamically stable patients with worsening heart failure. Study drug was initiated (either in the hospital or outpatient facility) within 7 days following completion of intravenous diuretic therapy and continued in an outpatient setting for a total of 14 days. All patients had a Screening period up to 3 weeks. An initial cohort of patients (Cohort 1) received sotagliflozin 200 mg (n=10) or placebo (n=5) orally for 14 days. Following safety monitoring and review of Cohort 1 by the Data Monitoring Committee (DMC), Cohort 2 received sotagliflozin 400 mg (n=11) or placebo (n=6) orally for 14 days. Following safety monitoring and review of Cohort 2 by the DMC enrollment was halted;

no patients were enrolled into Cohort 3. Following randomization, patients had a 14-day Treatment Period and a 2-week posttreatment Follow-up Period. A total of 32 patients ≥18 years of age were randomly assigned (2:1, sotagliflozin: placebo) amongst the following 3 treatment groups: (1) sotagliflozin 200 mg once daily [Cohort 1] (qd), (2) sotagliflozin 400 mg qd [Cohort 2], or (3) placebo qd [Cohorts 1 and 2].

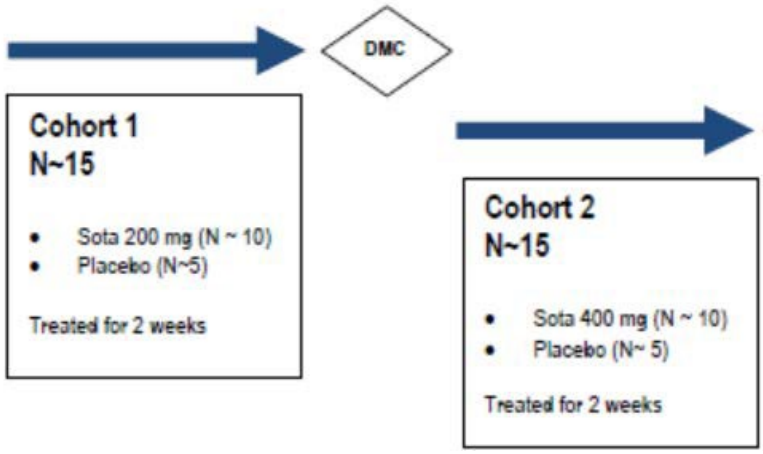


Figure 4.3.8.1: Study design *(Source: Page 9 in Study PDY15079 CSR)*

Results: Safety results

Number of Patients With	Placebo (N=10)	Sotagliflozin 200 mg (N=10)	Sotagliflozin 400 mg (N=11)
Any TEAE	4 (40.0%)	3 (30.0%)	5 (45.5%)
Any Treatment-Emergent SAE	1 (10.0%)	0	0
Any Severe TEAE (CTCAE >= Grade 3)	1 (10.0%)	0	1 (9.1%)
Any TEAE Related to Study Drug	0	0	2 (18.2%)
Any Treatment-Emergent AESI	0	0	0
Any TEAE Leading to Death	0	0	0
Any TEAE Leading to Permanent Treatment Discontinuation	0	0	1 (9.1%)

Note: TEAE = Treatment-emergent adverse event; SAE = Serious adverse event; AESI = Adverse Event of Special Interest.

Table 4.3.8.1. Overall Summary treatment-emergent adverse event - Safety population *(Source: Table 2 in Study PDY15079 CSR)*

Conclusions:

- The percentages of patients with any treatment-emergent adverse event (TEAE), serious TEAE, or severe TEAE were comparable across treatment groups.
- The incidence of treatment related TEAEs in the sotagliflozin 400 mg group was higher than either the sotagliflozin 200 mg or the placebo groups.
- The only patient with a TEAE leading to treatment discontinuation was in the sotagliflozin 400 mg group; the reported PT was Dermatitis allergic.
- There were no deaths due to TEAEs or treatment-related SAEs in any of the treatment groups.
- There were no reports of AESI (pregnancy, symptomatic overdose, or ALT ≥3X ULN) in this study, and no patient experienced liver function test results that were deemed to be a PCSA.
- Any EOSI that occurred (MACE or diarrhea) were reported as AEs. Myocardial infarction was reported by 1 patient in the sotagliflozin 400 mg group and diarrhea was reported in all 3 treatment groups: placebo (n=2, 20.0%), sotagliflozin 200 mg (n=1, 10.0%) and sotagliflozin 400 mg (n=1, 9.1%).
- There was only 1 AE of hypoglycemia, which was nonserious, in the sotagliflozin 400 mg group. The event was of mild intensity, started on Day 18 (resolved on Day 34), and was deemed unrelated to either IMP or NIMP.

Reviewer comment: Clinical safety data from this study demonstrated that doses of 200 mg and 400 mg sotagliflozin were well-tolerated.

4.3.9. Study LX4211.105 DM— PD of Sotagliflozin in T2DM Patients (Phase I, DM Indication; NDA 210934)

Title: A Phase 1, Open-label, 3-period, 3-treatment, Single- dose Crossover Study to Evaluate the Pharmacodynamic Effects of LX4211 when Administered Concurrently with JANUVIA® (sitagliptin) in Subjects with Type 2 Diabetes Mellitus

Objectives

• Primary:

- Evaluate the effect of single doses of LX4211 and sitagliptin, on glucagon-like peptide-1 (GLP-1) (total and active), when administered alone and concurrently in subjects with T2DM.

• Secondary:

- Evaluate the pharmacodynamic (PD) effects of single doses of LX4211 and sitagliptin when administered alone and concurrently in subjects with T2DM utilizing:
  - Fasting plasma glucose (FPG)
  - Postprandial glucose (PPG)
  - Insulin
  - Peptide YY (PYY)
  - Urinary glucose excretion (UGE)
- Evaluate the safety and tolerability of LX4211 and sitagliptin when administered alone and concurrently in subjects with T2DM

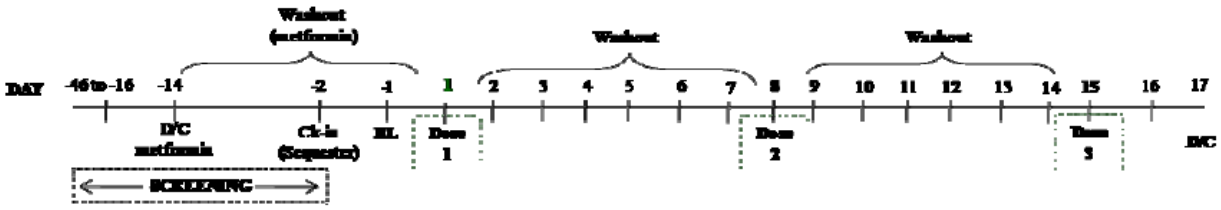
Study population: Patients (male and female adults, ≥18 to ≤65 years of age) with history of T2DM for at least 3 months prior to Screening with the following laboratory values; hemoglobin A1c (HbA1c) value of ≥6.5 to ≤10.5%, C-peptide ≥1.0 ng/mL and Body mass index (BMI) ≤45 kg/m^2 at Screening and planned Day -2 (n=18)

Drug product:

- **Treatment (A):** 400 mg of LX4211 given in a solid, oral dosage form (as 2 × 200 mg tablets)
- **Treatment (B):** 100 mg of sitagliptin given in a solid, oral dosage form (as 1 × 100 mg JANUVIA® [sitagliptin] tablet)
- **Treatment (C):** 400 mg of LX4211 + 100 mg of sitagliptin

This was a single-center, randomized, open-label, 3-period, 3-treatment, crossover study to assess the effects of LX4211 and sitagliptin on GLP-1 (total and active). Subjects with T2DM were recruited for participation in this study. In addition, the PD, safety, and tolerability of LX4211 and sitagliptin, when administered alone and concurrently in subjects with T2DM, were evaluated. Eighteen subjects were randomly assigned among 3 blocks of 6 treatment sequences. Each treatment sequence within a subject consisted of the previously stated 3 treatments, A, B and C.

The study consisted of a Screening period (including an initial 14-day washout period for subjects taking metformin and an initial 2-day run-in period for diet stabilization and baseline testing), 3 successive, single-dose periods (separated by 7-day washout periods), and a 2-day follow-up period. During their visit to the clinic on Day -14, all subjects received a glucometer and paper diary, along with instructions on how to use the glucometer, when to perform their daily finger sticks, and how to complete the paper diary. Subjects were instructed to return to the clinic should their fasting blood glucose values (via finger stick) exceed 280 mg/dL and were given dietary guidelines and restrictions to follow during the initial washout. Eligible subjects taking metformin began a 14-day washout period on Day -14. Any subject who was unable to complete the initial washout period or who was instructed to resume their prior diabetic therapy was considered a screen failure. All subjects checked into the clinic on Day -2 for verification of eligibility criteria, diet stabilization, and sequestration. At Baseline (Day -1), qualified subjects were randomly assigned to 1 of 6 treatment sequences (n=3 for each sequence). All qualified subjects also underwent baseline testing on Day -1 of the study. On Day 1, subjects received their first assigned study drug (LX4211, sitagliptin, or LX4211 + sitagliptin) as a single oral dose, following an overnight fast, 1 hour prior (±5 minutes) to starting to eat the morning meal. Subjects received single oral doses of LX4211, sitagliptin, or LX4211 + sitagliptin, in 3 successive treatment periods (on Days 1, 8, and 15, respectively) separated by a minimum 7-day washout. Main PD endpoints were GLP-1 (total and active), FPG, PPG, Insulin, PYY and UGE.



Note: On Day -14, metformin was to be discontinued (D/C). On Day -2, subjects were to be checked-in (Ck-in) to clinic and remain sequestered until discharge. Baseline (BL) evaluations were to be performed on Day -1. On Day 17, subjects were to be discharged (D/C) from the study.

Figure 4.3.9.1: Study design *(Source: Figure 9.1-1. in Study LX4211.105-DM CSR, NDA 210934)*

Results:

Safety results:

Overall, a total of 4 subjects (4/18, 22.2%) reported at least 1 TEAE. Constipation was the most prevalent TEAE observed (3/18, 16.7%); 2 of the 3 subjects experiencing constipation were receiving Treatment C (LX4211 + sitagliptin) and 1 subject was receiving Treatment B (sitagliptin alone). There were no deaths, SAEs, or AEs leading to discontinuation in the study.

	Number (%) of Subjects			
Parameter	Treatment A LX4211 (N=18)	Treatment B Sitagliptin (N=18)	Treatment C LX4211 + Sitagliptin (N=18)	Overall (N=18)
Subjects with at least 1 TEAEs	1 (5.6)	2 (11.1)	4 (22.2)	4 (22.2)
Subjects with at least 1 SAE	0	0	0	0
Subjects with discontinuation due to AE	0	0	0	0
Subjects with death due to AE	0	0	0	0

Source: Table 14.3.1.1
Note: AE = adverse event; N = number of subjects, SAE = serious adverse event TEAE = treatment-emergent adverse event Note: If a subject experienced more than 1 event within the same preferred term for a treatment, only 1 occurrence was included in the incidence for that treatment.

Table 4.3.9.1. Overall Summary of Treatment-emergent Adverse Events by Treatment (Safety Population)
(Source: Table 12.2.1-1. in Study LX4211.105-DM CSR, NDA 210934)

Conclusions & Reviewer comments:

- There were no safety or tolerability concerns with the administration of 400 mg LX4211 alone or in combination with 100 mg sitagliptin in these study subjects with T2DM.
- Pharmacodynamic Conclusions are irrelevant for the current proposed indication under NDA 216203, hence Pharmacodynamic analyses were not reviewed.

4.3.10. Study LX4211.107 DM— PK/PD of Sotagliflozin in T2DM with moderate to severe renal impairment Patients (Phase I, DM Indication; NDA 210934)

Title: A Phase 1, Randomized, Double-blind, Placebo-controlled Parallel-group Study to Evaluate the Pharmacodynamic and Pharmacokinetic Effects of LX4211 in Subjects with Type 2 Diabetes Mellitus and Moderate to Severe Renal Impairment

Objectives

• Primary:

- To evaluate the effect of LX4211 on postprandial glucose (PPG), measured as the change from Baseline to Day 7, in patients with type 2 diabetes mellitus (T2DM) and moderate to severe renal impairment.

• Secondary:

- The safety and tolerability of LX4211 in patients with T2DM and moderate to severe renal impairment.
- The PD effects of LX4211 on FPG and GLP-1 (total and active), measured as the change from Baseline to Day 7, in patients with T2DM and moderate to severe renal impairment
- The single-dose and multiple-dose PK effects of LX4211 in patients with T2DM and moderate to severe renal impairment.

Study population: Patients (male and female adults, ≥18 to ≤80 years of age) with history of T2DM for at least 6 months prior to Screening with the following laboratory values; Fasting serum glucose ≤270 mg/dL, hemoglobin A1c (HbA1c) value of ≥6.5 to ≤10.5%, C-peptide ≥1.0 ng/mL and Body mass index (BMI) ≤45 kg/m^2 and with moderate to severe renal impairment with an eGFR of 15 to 59 mL/min/1.73 m^2 (inclusive) at Screening, based on the MDRD equation. (**n=30**; n=15 for 2 × 200-mg tablets of LX4211 once daily for 7 days and n=15 for 2 × matching placebo tablets once daily for 7 days)

Drug product:

- **Test product:** Sotagliflozin 200 mg as 1 x 200-mg sotagliflozin oral tablet and Sotagliflozin 400 mg as 2 x 200-mg sotagliflozin oral tablets.
- **Reference therapy:** Placebo tablets (matching and identical to sotagliflozin in appearance).

Pharmacokinetic variables were to include the AUC from time 0 to the last measurable concentration ($AUC_{(0\text{-}last)}$), AUC from time 0 extrapolated to infinity ($AUC_{(0\text{-}inf)}$), AUC from time 0 to 24 hours ($AUC_{(0\text{-}24)}$) maximum observed plasma concentration (C_{max}), time at which Cmax occurred (t_{max}), apparent terminal elimination rate constant in plasma (λ_z), accumulation ratio AUC (R_{AUC}), accumulation ratio for C_{max} (RC_{max}), and apparent terminal elimination half-life in plasma ($t_{1/2}$). Pharmacokinetic variables were to be derived from plasma concentrations using the actual sampling.

Assessments for safety included ECGs, physical examination (including vital signs), clinical laboratories (chemistry, hematology, lipid profile, and urinalysis), and FPG. Monitoring of AEs was also considered to be a safety assessment.

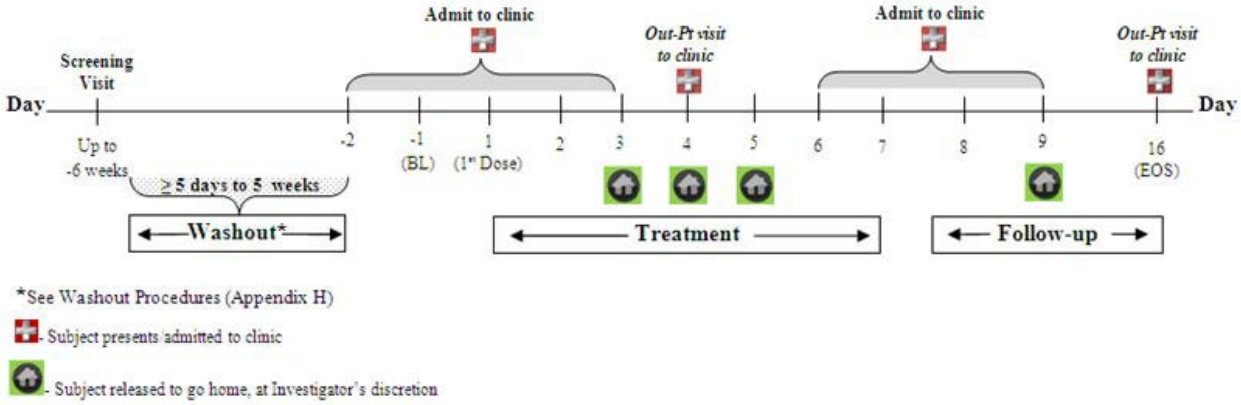


Figure 4.3.10.1: Study design *(Source: Figure 9.1-1. in Study LX4211.107-DM CSR, NDA 210934)*

PK sampling: PK samples were to be collected at the following time points ± 3 minutes on Days 1 and 7: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 hours postdose.

Results: *Pharmacokinetics results* **(Tables 4.3.10.1, 4.3.10.2 & 4.3.10.3)**

Parameter (unit) Statistics	Renal Impairment: Baseline eGFR ≥45 mL/min/1.73 m²		Renal Impairment: Baseline eGFR <45 mL/min/1.73 m²		Overall	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
C_{max} (ng/mL)						
Mean [N] SD	113 [10] (53.9)	274 [9] (165)	94.7 [6] (34.4)	180 [6] (58.3)	106 [16] (47.2)	236 [15] (138)
Geometric Mean (CV%)	101 (47.5)	238 (60.2)	87.7 (36.3)	169 (32.5)	95.6 (44.3)	208 (58.4)
t_{max} (h)						
Median [N] (Min-Max)	1.48 [10] (0.98-6.02)	1.02 [9] (0.97-5.97)	3.49 [6] (1.50-6.05)	1.98 [6] (1.00-2.07)	2.27 [16] (0.98-6.05)	1.52 [15] (0.97-5.97)
$AUC_{(0\text{-last})}$ (ng•h/mL)						

Mean [N] SD	1070 [9] (410)	4239 [9] (2870)	1048 [5] (442)	3356 [6] (1630)	1062 [14] (404)	3885 [15] (2420)
Geometric Mean (CV%)	986 (38.3)	3643 (67.7)	953 (42.1)	3024 (48.6)	974 (38.1)	3382 (62.3)
$AUC_{(0\text{-}inf)}$ (ng•h/mL)						
Mean [N] SD	1670 [1] (ND)	NA	1815 [1] (ND)	NA	1742 [2] (103)	NA
Geometric Mean (CV%)	1670 (ND)	NA	1815 (ND)	NA	1741 (5.9)	NA
$AUC_{(0\text{-}24)}$ (ng•h/mL)						
Mean [N] SD	1070 [9] (410)	2879 [9] (1752)	1048 [5] (442)	2213 [6] (1126)	1062 [14] (404)	2613 [15] (1524)
Geometric Mean (CV%)	987 (38.3)	2523 (60.9)	953 (42.1)	1979 (50.9)	974 (38.1)	2290 (58.3)
$t_{1/2}$ (h)						
Mean [N] (SD)	7.86 [1] (ND)	18.1 [3] (2.36)	7.23 [1] (ND)	16.6 [2] (1.26)	7.54 [2] (0.448)	17.5 [5] (1.98)
RAUC						
Mean [N] SD	NA	2.74 [9] (1.09)	NA	2.18 [5] (0.902)	NA	2.54 [14] (1.03)
RC_{max}						
Mean [N] (SD)	NA	2.43 [9] (1.21)	NA	1.97 [6] (0.421)	NA	2.25 [15] (0.979)

Source: Table 14.2.2.3, Table 14.2.2.5
ND: Not determinable; NA: Not applicable
Note: Moderate renal impairment was Baseline eGFR value ≥45 mL/min/1.73 m^2.
Note: Severe renal impairment was Baseline eGFR <45 mL/min/1.73 m^2.
Note: $AUC_{(0\text{-}last)}$ was calculated as AUC from 0 to 24 hours on Day 1 and AUC from 0 to 48 hours on Day 7.
Note: $AUC_{(0\text{-}inf)}$ and $t_{1/2}$ were not calculated if less than 3 data points in the terminal phase, and were excluded if R2 for λ_z estimation was less than 0.8 or the interval for λ_z estimation was less than 2 times the corresponding $t_{1/2}$.

Table 4.3.10.1. Summary of LX4211 Pharmacokinetic Parameters (PK Population)
(Source: Table 11.4.2.2-1. in Study LX4211.107-DM CSR, NDA 210934)

Parameter (unit)	Day	N	Geometric Mean	Day 7/Day 1 Geometric Mean Ratio (%) (90% CI) [a]
C_{max} (ng/mL)	1	16	95.55	210.78 (175.34, 253.38)
	7	15	201.40	
$AUC_{(0\text{-}24)}$ (ng•h/mL)	1	14	970.28	235.97 (196.16, 283.87)
	7	15	2289.62	

Source: Table 14.2.2.4
a. The results are based on an analysis of variance model with a fixed effect for day and a random effect for patient. The dependent variable is the natural logarithm of the PK parameters.

Table 4.3.10.2. Statistical Analysis of LX4211 Pharmacokinetic Parameters to Assess Drug Accumulation (PK Population)
(Source: Table 11.4.2.3-1. in Study LX4211.107-DM CSR, NDA 210934)

Day	Parameter	Renal Impairment Baseline eGFR (mL/min/1.73 m^2)	N	Geometric Mean	Baseline eGFR values ≥45 / <45 mL/min/1.73 m^2 Geometric Mean Ratio (%) (90% Confidence Interval) [a]
1	C_{max} (ng/mL)	≥45	10	100.57	114.63 (71.74, 183.19)
		<45	6	87.73	
	$AUC_{(0-24)}$ (ng•h/mL)	≥45	9	986.55	103.51 (63.87, 167.74)
		<45	5	953.14	
	$AUC_{(0-last)}$ (ng•h/mL)	≥45	9	986.48	103.50 (63.87, 167.72)
		<45	5	953.14	
7	C_{max} (ng/mL)	≥45	9	238.36	140.95 (89.09, 223.00)
		<45	6	169.11	
	$AUC_{(0-24)}$ (ng•h/mL)	≥45	9	2523.23	127.49 (78.44, 207.21)
		<45	6	1979.13	
	$AUC_{(0-last)}$ (ng•h/mL)	≥45	9	3643.42	120.48 (73.36, 197.85)
		<45	6	3024.13	

Source: Table 14.2.2.5

[a] The results are based on an analysis of variance model with a fixed effect for renal impairment status. The dependent variable is the natural logarithm of the PK parameters.

Table 4.3.10.3. Statistical Analysis of LX4211 Pharmacokinetic Parameters to Assess Renal Impairment Impact (PK Population)
(Source: Table 11.4.2.4-1. in Study LX4211.107-DM CSR, NDA 210934)

Safety and adverse effects results **(Tables 4.3.10.4 & 4.3.10.5)**

	LX4211 N = 16	Placebo N = 15
Number of patients (%) with at least 1 TEAE	7 (43.8%)	5 (33.3%)
Number of patients (%) with at least 1 drug-related TEAE	1 (6.3%)	3 (20.0%)
Number of patients (%) with at least 1 SAE	0	0
Number of patients (%) with discontinuation due to TEAE	0	0
Number of patients (%) with death due to AE	0	0

Source: Table 14.3.1.1.
Note: TEAE = Treatment-emergent adverse event. SAE = serious adverse event.

Note: Drug-related TEAEs include those TEAEs that were possibly, probably, or definitely related to LX4211 or placebo.

Note: For the summary of number (%) of patients, if a patient experienced more than 1 event within the same preferred term for a treatment, only 1 occurrence was included in the incidence for that treatment. For the summary of number of events, all events were counted.

Table 4.3.10.4. Overall Summary of Treatment-Emergent Adverse Events by Treatment Group (Safety Population)
(Source: Table 12.2.1-1. in Study LX4211.107-DM CSR, NDA 210934)

System Organ Class Preferred Term	Number (%) of Patients	
	LX4211 N = 16	Placebo N = 15
Gastrointestinal disorders	**1 (6.3)**	**3 (20.0)**
Diarrhea	1 (6.3)	2 (13.3)
Vomiting	1 (6.3)	1 (6.7)
Constipation	0	1 (6.7)
General disorders and administration site conditions	**0**	**1 (6.7)**
Edema peripheral	0	1 (6.7)
Infections and infestations	**3 (18.8)**	**0**
Chest wall abscess	1 (6.3)	0
Gastroenteritis bacterial	1 (6.3)	0
Sinusitis	1 (6.3)	0
Injury, poisoning and procedural complications	**2 (12.5)**	**0**
Laceration	2 (12.5)	0
Joint injury	1 (6.3)	0
Investigations	**1 (6.3)**	**0**
Blood creatinine increased	1 (6.3)	0
Metabolism and nutrition disorders	**1 (6.3)**	**3 (20.0)**
Hypoglycemia	1 (6.3)	2 (13.3)
Hypercalcemia	0	1 (6.7)
Skin and subcutaneous tissue disorders	**0**	**1 (6.7)**
Papule	0	1 (6.7)

Source: Table 14.3.1.2.
Note: If a patient experienced more than 1 event within the same SOC or PT for a treatment, only 1 occurrence was included in the incidence for that treatment.

Table 4.3.10.5. Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group (Safety Population)
(Source: Table 12.2.2-1. in Study LX4211.107-DM CSR, NDA 210934)

Conclusions:

- Following single or multiple doses of LX4211 400 mg qd to patients with T2DM and moderate to severe renal impairment, individual t_{max} ranged from 1 to 6 hours. Half-life after multiple doses was approximately 17 hours.
- On average, accumulation of LX4211 C_{max} and AUC following 7 days of LX4211 400 mg qd doses was approximately 2.1- and 2.4-fold, respectively.
- The PK profile of LX4211 was, in general, similar for patients in either Baseline eGFR subgroup of renal impairment (Baseline eGFR ≥45 mL/min/1.73 m^2, Baseline eGFR <45 mL/min/1.73 m^2).
- There were no safety or tolerability concerns with the administration of 200 and 400 mg LX4211 in patients with T2DM and moderate to severe renal impairment. The frequency of AEs was similar between patients taking LX4211 and those taking placebo.
- Pharmacodynamic Conclusions are irrelevant for the current proposed indication under NDA 216203, hence Pharmacodynamic analyses were not reviewed.

Reviewer comment:

- The PK profile of LX4211 was, in general, similar for patients in eGFR subgroup of renal impairment (Baseline eGFR ≥45 mL/min/1.73 m^2, Baseline eGFR <45 mL/min/1.73 m^2).
- The impact of renal impairment on the exposure parameters was not concluded statistically. The slight difference in the mean exposure following the last dose was likely related to the small sample size (n = 6 for patients with Baseline eGFR values <45 mL/min/1.73 m^2), and 2 patients in the Baseline eGFR values ≥45 mL/min/1.73 m^2 subgroup with substantially higher concentration on Day 7 compared to other patients.
- LX4211 was safe and well tolerated in patients with T2DM and moderate to severe renal impairment. The frequency of AEs was similar between patients taking LX4211 and those taking placebo.
- Pharmacodynamic Conclusions are irrelevant for the current proposed indication under NDA 216203, hence Pharmacodynamic analyses were not reviewed.

4.4 Pharmacometrics review

4.4.1 Summary of findings

4.4.1.1 Key review questions

4.4.1.1.1 Is the proposed dosing regimen acceptable for the patients with renal impairment [redacted](b) (4)?

Yes, the proposed dosing regimen is acceptable.

The sotagliflozin exposures increase following the increase in renal impairment severity (see **section 3.3.3.1**). Our evaluation focused on whether the increased exposure may lead to additional safety concern and change in the dose titration pattern.

Per communication with the medical team, the common safety events are diarrhea, hypoglycemia, and volume depletion. The exposure-response model developed using patients with type 2 diabetes mellitus (T2DM) predicted an approximate 5% incidence of diarrhea in placebo group, compared to a 5% to 12% incidence in patients with sotagliflozin 400 mg once daily (**Figure 4.4.2.4**). However, the dose can be downtitrated if patients are intolerant. No E-R relationships between sotagliflozin exposure and the occurrence of hypoglycemia or volume depletion were identified after the inclusion of covariate effects.

Reviewer performed independent analyses to explore whether the dose titration pattern changes in patients with different renal function using data from SOCRED and SOLOIST trials. Per the trial design, patients may up- and down-titrate dosing based on tolerability. There appeared a trend of increasing fraction of patients down-titrated due to AE following the worsening of the renal function in SCORED (**Figure 4.4.3.2.8)**. However, this was not observed in SOLOIST (**Figure 4.4.3.2.8**). Considering the small number of patients experiencing dose reduction and the limited number of patients with mild and severe renal impairment in SCORED, the trend was not considered clinically relevant. Overall, no apparent trends were observed between RI vs. anytime up-titrated **(Figure 4.4.3.2.5**), down-titrated following up-titration (**Figure 4.4.3.2.6**), and dose at the study end (**Figure 4.4.3.2.7**) in both trials.

4.4.1.1.2 Did the 400 mg QD show superior efficacy compared to 200 mg QD based on data from SCORED and SOLOIST?

There is no sufficient evidence to suggest that 400 mg QD dose is superior to 200 mg QD dosing. Reviewer performed independent analyses to correlate the efficacy endpoint, event rate (per 100 patient-years) of combined investigator-reported cardiovascular (CV) death, hospitalization for heart failure (HHF), and urgent visit for heart failure (UVHF), and the RI to inform the potential exposure-response for efficacy. In SCORED, the event rate increased following the increase in renal impairment severity, which was observed in both treatment group

and placebo group, suggesting the efficacy was driven by renal function rather than sotagliflozin exposure. No clear trend was observed in SOLOIST.

4.4.1.2 Label Statements

12.3 Pharmacokinetics

Elimination

Excretion

The median population PK model predicted CL/F in type 2 diabetes mellitus patients with normal renal function was (b) (4) L/hr.

Specific Population

Effects of Age, Sex, Race, and Body Weight on Pharmacokinetics

Based on population PK analysis, age, body weight, sex, and race (non-white versus primarily whites) do not have a clinically meaningful effect on PK of sotagliflozin.

4.4.2 Results of sponsor's analysis

Because of the early termination of the two pivotal trials, there were no plasma samples collected from SCORED, while a few sparse plasma samples were available from the month 12 timepoint in the SOLOIST (approximately 120 samples from sotagliflozin arm). As a result, the population PK (PPK) model and exposure-response (ER) model for safety were developed using data from patients with type-2 diabetes mellitus (T2DM). No ER analysis was conducted for efficacy.

PPK analysis

Data for this population PK analysis were obtained from subjects enrolled in 4 Phase 1, 2 Phase 2, and 7 Phase 3 studies of sotagliflozin. The analysis dataset contained 17,645 observations from 2354 subjects. After all necessary data exclusions, the final analysis dataset consisted of 16,186 sotagliflozin concentrations from 2258 subjects. Most of the subjects were white (83%), male (56.3%), and had normal renal function (33.1%). The largest baseline disease status group was T2DM (92.9%). The median baseline body weight (range) was 87 kg (44 to 216 kg). The median age (range) was 63 years (20-89 years). **Table 4.4.2.1** shows the summary statistics of subject demographics.

Table 4.4.2.1. Overall Summary Statistics of Subject Demographics

Variable		Overall (n= 2258)
Age	Mean (SD)	61.2 (12.2)
	Median	63
	Min, Max	20, 89
Baseline alanine aminotransferase (U/L)	Mean (SD)	25.2 (15.6)
	Median	21
	Min, Max	2, 162
Baseline aspartate aminotransferase (U/L)	Mean (SD)	22.2 (11.4)
	Median	19
	Min, Max	7, 156
Body mass index (kg/m^2)	Mean (SD)	31.8 (5.63)
	Median	31
	Min, Max	17.9, 68.3
Baseline eGFR (mL/min/1.73m^2)	Mean (SD)	74.2 (29.9)
	Median	76.9
	Min, Max	14, 230
Baseline bilirubin, total (mg/dL)	Mean (SD)	0.47 (0.261)
	Median	0.409
	Min, Max	0.0877, 2.87
Baseline weight (kg)	Mean (SD)	89.2 (18.8)
	Median	87
	Min, Max	44, 216
Baseline disease status, N (%)	Healthy Volunteer	140 (6.2)
	Type 2 Diabetes	2097 (92.9)
	Heart Failure	21 (0.93)
Ethnicity, N (%)	Not Hispanic or Latino	1545 (68.4)
	Hispanic or Latino	699 (31)
	Not Reported	14 (0.62)
Fed, N (%)	No	2201 (97.5)
	Yes	57 (2.52)
Formulation, N (%)	Tablet	2177 (96.4)
	Solution	81 (3.59)
Phase of Study, N (%)	1	156 (6.91)
	2	45 (1.99)
	3	2057 (91.1)
Race, N (%)	Caucasian	1875 (83)
	African American	183 (8.1)
	Asian	84 (3.72)
	Pacific Islander	6 (0.266)
	American Indian or Alaska Native	73 (3.23)
	Other	37 (1.64)
Baseline renal function category, N (%)	Normal	747 (33.1)
	Mild	718 (31.8)
	Moderate	632 (28)
	Severe	160 (7.09)
	End Stage	1 (0.0443)
Gender, N (%)	Male	1272 (56.3)
	Female	986 (43.7)

Inline table. Abbreviations: eGFR, estimated glomerular filtration rate; Max, maximum; Min, minimum; n, number of individuals; SD, standard deviation.
KIWI Version 4 202105 - File ID: 2223961 - Summary Statistics Table Profile: 3657.

(Source: lx4211-n106-pop-pk-rpt, Table 4)

Results from previous modeling efforts (which included pooled data from 3 Phase 1 studies and 1 Phase 2 study) were used as a starting point for the base PK model in this analysis. The previous model was a 2-compartment model with sigmoid absorption and linear clearance, including formulation effects on first-order absorption rate constant (ka) and apparent central volume of distribution (Vc/F), and food effects on zero-order input duration (D1), Vc/F, and bioavailability fraction (F1). Initial application and re-estimation of this 2-compartment model using the current pooled dataset provided acceptable model predictions. Interindividual variability was included on D1, ka, apparent clearance (CL/F), Vc/F, apparent intercompartmental clearance (Q/F), and apparent peripheral volume of distribution (Vp/F). The final model parameter estimates are shown in **table 4.4.2.2**.

Table 4.4.2.2. Final Population Pharmacokinetic Model Parameter Estimates

Parameter		Final Parameter Estimate		Magnitude of Variability	
		Population Mean	%RSE[b]	Final Estimate	%RSE[b]
D1	Duration of Zero-Order Input (mg/h)	0.626	6.59	69.5 %CV	19.2
	Prop. Shift in D1 for Fed Administration for Solution	-0.505	17.7		
KA	First-order Absorption Rate Constant (1/h)	3.58[a]	20.7	98.0 %CV	12.7
	Prop. Shift in Ka for Tablet	-0.722[a]	8.30		
CL/F	Apparent Central Clearance (L/h)	231	1.36	50.5 %CV	3.30
	Exponent of (EGFRMDRT/77.2) for CL/F	0.416	4.57		
	Exponent of (WTKG/87) for CL/F	0.815	6.32		
	Proportional Shift in CL/F for HF patients	-0.518	9.86		
	Exponent of (AGE/63) for CL/F	-0.600	9.56		
Vc/F	Apparent Central Volume of Distribution (L)	1380	18.1	88.0 %CV	8.29
	Prop. Shift in Vc/F for Fed Administration of Tablet	2.28	40.2		
	Prop. Shift in Vc/F for Fed Administration of Solution	0.932	36.2		
	Prop. Shift in Vc/F for Fasted Administration for Tablet	5.30	21.5		
	Exponent of (WTKG/87) for Vc/F	1.25	10.7		
	Proportional Shift in Vc/F for T2DM patients	-0.450	14.8		
	Proportional Shift in Vc/F for HF patients	-0.711	10.9		
Q/F	Apparent Intercompartmental Clearance (L/h)	470	6.29	84.0 %CV	14.3
	Exponent of (AGE/63) for Q/F	-1.31	12.3		
Vp/F	Apparent Peripheral Volume of Distribution (L)	5630	3.91	55.4 %CV	16.0
F1	Solution - Bioavailability of Fed Relative to Fasted	0.948	4.98	NE	NA
RV for Phase 1 and 2 Studies		0.144	0.964	38.0 %CV	NA
RV for Phase 3 Studies		0.185	1.71	43.0 %CV	NA

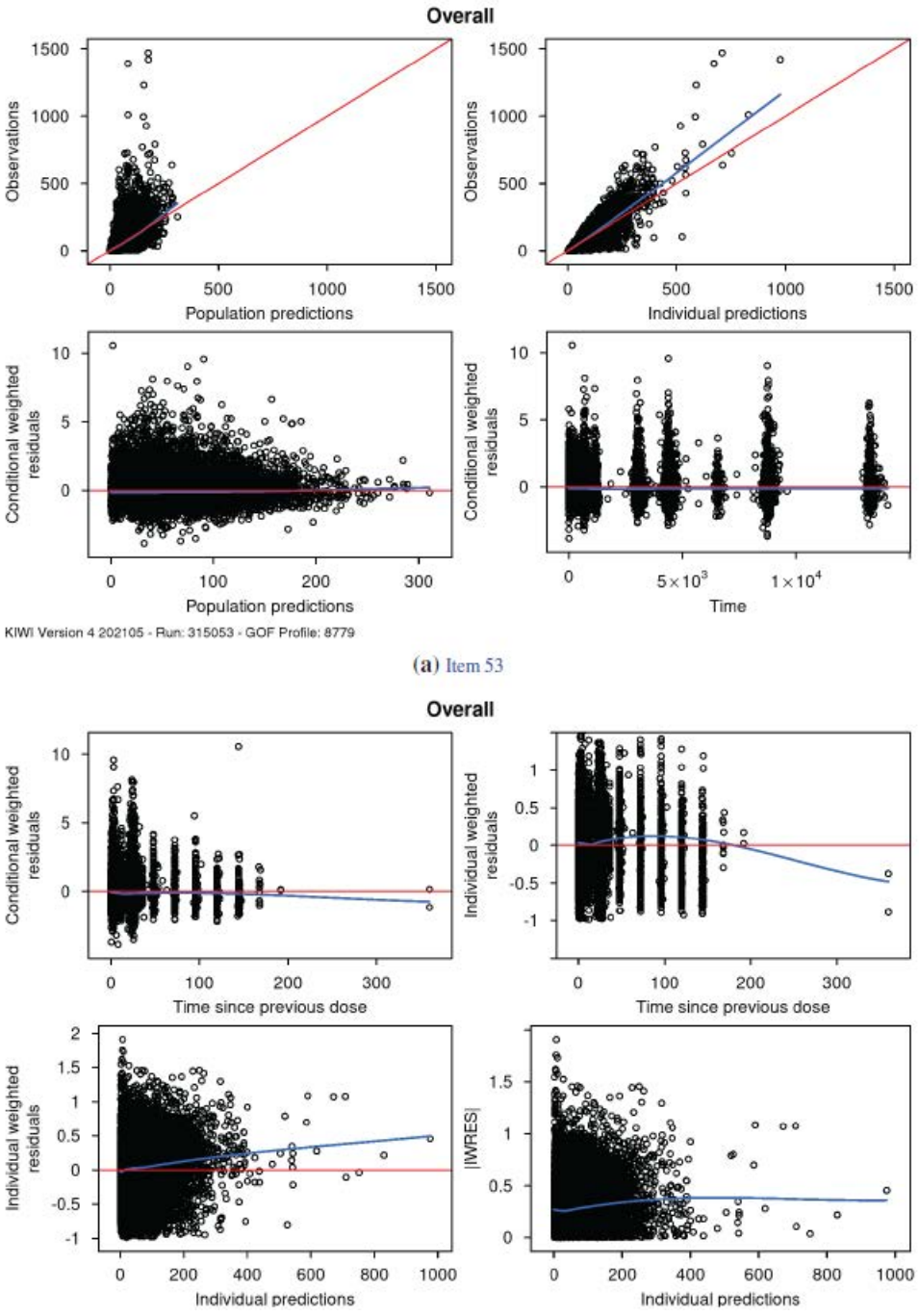
Inline table. Abbreviations: AGE, baseline age; %CV, coefficient of variation expressed as a percent; EGFRMDRT, time-varying estimated glomerular filtration rate; IIV, interindividual variability; NA, not applicable; NE, not estimated; %RSE, relative standard error expressed as a percent; RV, residual variability; T2DM, type 2 diabetes mellitus; HF, heart failure; WTKG, baseline body weight.
[a] The following parameter estimates were found to be highly correlated ($r^2 \geq 0.81$): KA: Prop. Shift in Ka for Tablet, KA: First-order Absorption Rate Constant (1/h).
[b] MATRIX = S
Shrinkage estimates: 28.3% for IIV in D1, 30.9% for IIV in KA, 5.8% for IIV in CL/F, 39.7% for IIV in Vc/F, 19.0% for IIV in Q/F, and 15.9% for IIV in Vp/F.
KIWI Run 315053.

(Source: lx4211-n106-pop-pk-rpt, Table 10)

The final population PK model goodness-of-fit plots are shown in **figure 4.4.2.1**. The under-prediction at higher observed sotagliflozin concentrations was noted in the final PK model. This could be due to sparse sampling during absorption phase. Prediction-Corrected Visual Predictive Check (pcVPC) plots showed acceptable predictive capability of the final model (**Figure 4.4.2.2)**.

The covariate effects included in the final PK model describe a 50.5% reduction in typical D1 for fed status relative to fasted status for the solution formulation. Typical ka is predicted to decrease by 72.2% for tablet formulation as compared to solution. With power term estimates of 0.815 and 1.25 for the effect of baseline body weight on CL/F and Vc/F, respectively, the typical CL/F is predicted to increase (less than proportionally), and typical Vc/F is predicted to increase (more than proportionally) with increasing baseline body weight. Apparent clearance is also predicted to increase less than proportionally with increasing eGFR (as described by the estimated power term of 0.416). A decrease in typical CL/F and Q/F is predicted with increasing age (with power term estimates of -0.6 and -1.31, respectively). Diagnosis was a significant predictor of CL/F and Vc/F, with heart failure patients having a lower CL/F (51.8% reduction relative to healthy subjects), and both T2DM and heart failure patients having a lower Vc/F (45.0% and 71.1% reduction, respectively, relative to healthy subjects). However, it is important to note that heart failure patients comprised only 1% of the total analysis dataset.

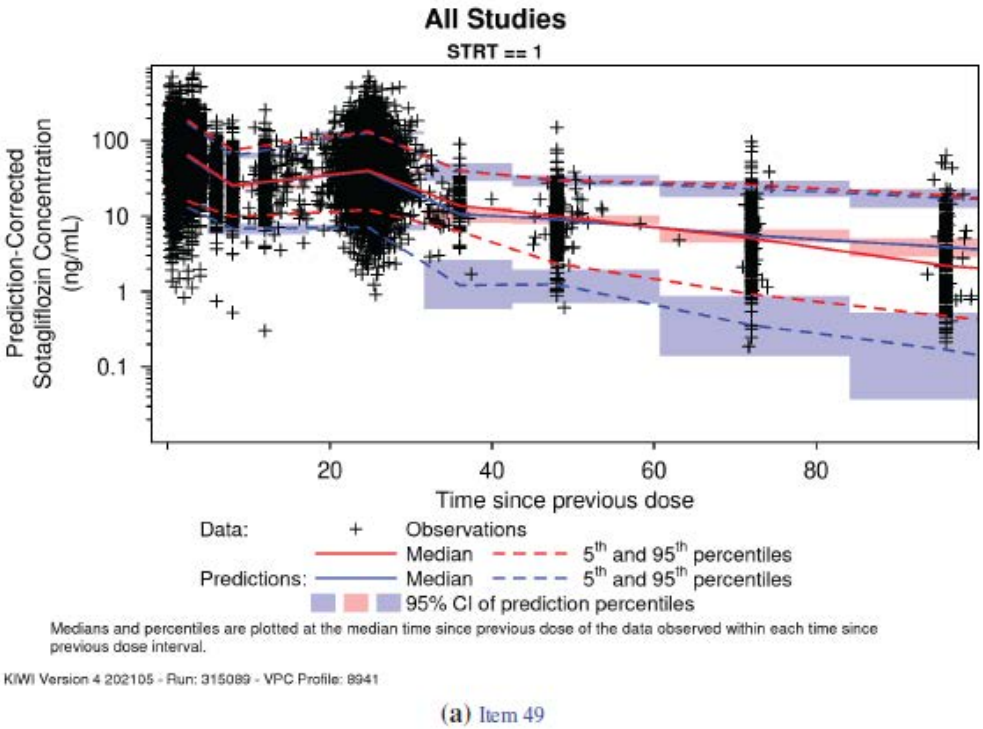
Figure 4.4.2.1. Overall Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model



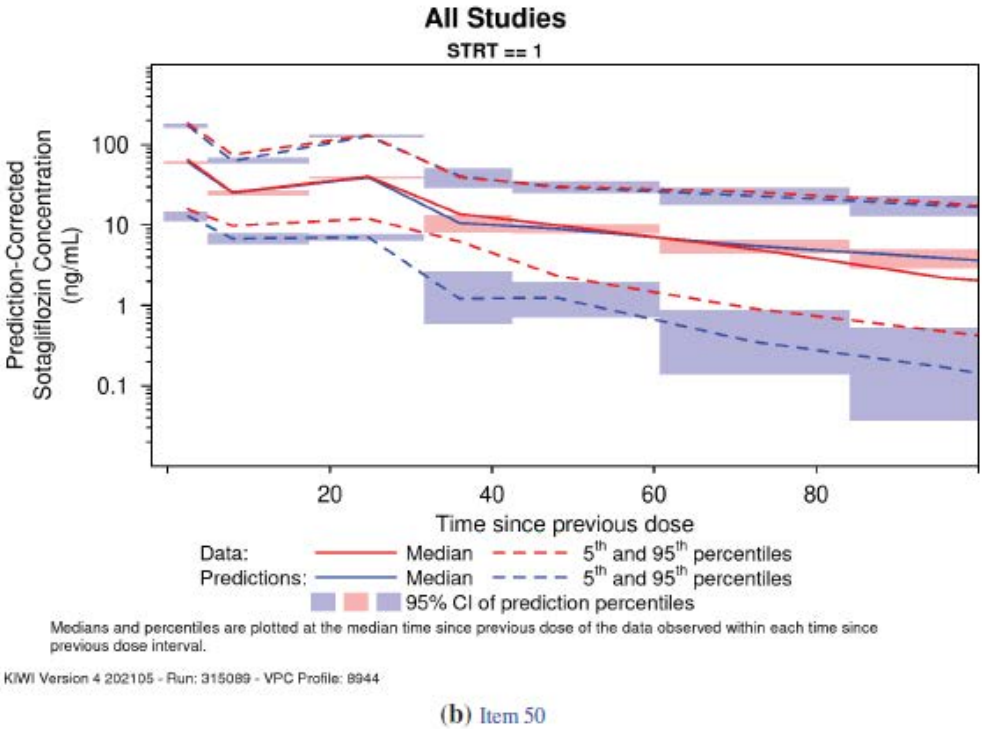
(a) Item 53

(Source: lx4211-n106-pop-pk-rpt, Figure 13)

Figure 4.4.2.2. Prediction-Corrected Visual Predictive Check for the Final Population Pharmacokinetic Model



(a) Item 49



(b) Item 50

Abbreviations: CI, confidence interval.

(Source: lx4211-n106-pop-pk-rpt, Figure 11)

Individual empiric PK parameter estimates from the final population PK model were used to simulate steady state sotagliflozin exposures for each patient with T2DM in the analysis population that received the 400 mg dose. Summary statistics of these exposures are presented in **table 4.4.2.3**. The geometric mean (%CV) values for $AUC_{0\text{-}24,ss}$, $C_{avg,ss}$, $C_{max,ss}$, and $C_{min,ss}$ were 1690.7 ng x h/mL (54.229%), 70.594 ng/mL (54.229%), 110.65 ng/mL (44.413%), and 46.529 ng/mL (75.114%), respectively.

Table 4.4.2.3. Summary Statistics of Steady-State Exposures for T2DM Patients Receiving the 400 mg Dose

Parameter	n	Mean	SD	GeoMean	GeoCV	Median	Min	Max
AUCss (ng x h/mL)	1510	1931.6	1105.4	1690.7	54.229	1652.7	369.98	12365
Cavgss (ng/mL)	1510	80.652	46.153	70.594	54.229	69.005	15.448	516.28
Cmaxss (ng/mL)	1510	121.59	58.446	110.65	44.413	107.05	37.35	611.66
Cminss (ng/mL)	1510	57.956	41.959	46.529	75.114	46.504	4.0481	455.36

Item 6. Abbreviations: AUCss, steady-state area under the concentration-time curve from 0-24 hours; Cavgss, steady-state average concentration; Cmaxss, steady-state maximum concentration; Cminss, steady-state minimum concentration; GeoMean, geometric mean; GeoCV, geometric coefficient of variation; Min, minimum; Max, maximum; n, number of patients; SD, standard deviation; T2DM, type 2 diabetes mellitus.

(Source: lx4211-n106-pop-pk-rpt, Table 11)

ER analysis for safety

Safety data for E-R analyses were obtained from 7 Phase 3 studies (EFC14833, EFC14834, EFC14835, EFC14837, EFC14867, EFC14868, and EFC15166), as described in **table 4.4.2.4**. All participants were male and female adults with T2DM. Patients received sotagliflozin either 200 or 400 mg QD. Among the 3370 patients, 1520 patients (45.1%) were female, and 1850 patients (54.9%) were male. The population was primarily white (82.9%); 7.0% of patients were black or African American, 4.9% were Asian, 3.4% were American Indian or Alaska native, 1.5% were categorized as “other” race, and 0.2% were Native Hawaiian or other Pacific Islander. The age of the patients ranged from 18 to 89 years, with a median age of 64 years. The median body weight at baseline was 87.5 kg, with a range of 42.4 to 162.5 kg. The summary of statistics of subject demographics is shown in **table 4.4.2.5**.

The pharmacodynamic (PD) endpoints for safety modeling included AEs of diarrhea, hypoglycemia, and volume depletion, which were agreed by Agency in pre-NDA meeting. Individual PK metrics ($AUC_{0\text{-}24h}$, C_{max}, and C_{avg}) were estimated from final PPK model. The summary of statistics of event rates is shown in **table 4.4.2.6**.

Table 4.4.2.4. Studies Included in the Exposure-Response Safety Analysis of Sotagliflozin

Study Number	Study Title	Dosing Regimens	Duration of Dosing
Phase 3			
EFC14833 (SOTA-MONO)	A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of sotagliflozin as monotherapy in patients with type 2 diabetes mellitus who have inadequate glycemic control	Placebo qd (n = 133) Sotagliflozin 200 mg qd (n = 133) Sotagliflozin 400 mg qd (n = 133)	26 weeks
EFC14834 (SOTA-MET)	A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of sotagliflozin added to metformin in patients with type 2 diabetes mellitus who have inadequate glycemic control on metformin	Placebo qd + metformin (n = 259) Sotagliflozin 400 mg qd + metformin (n = 259)	79 weeks
EFC14835 (SOTA-SU)	A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of sotagliflozin added to a sulfonylurea alone or in combination with metformin in patients with type 2 diabetes who have inadequate glycemic control on a sulfonylurea alone or with metformin	Placebo qd + sulfonylurea + metformin (n = 253) Sotagliflozin 400 mg qd + sulfonylurea + metformin (n = 254)	79 weeks
EFC14837 (CKD3)	A randomized, double-blind, placebo-controlled, 3-arm, parallel-group, 52-week multicenter study to evaluate the efficacy and safety of sotagliflozin in patients with type 2 diabetes mellitus and moderate renal impairment who have inadequate glycemic control	Placebo qd (n = 260) Sotagliflozin 200 mg qd (n = 267) Sotagliflozin 400 mg qd (n = 260)	52 weeks
EFC14867 (SOTA-EMPA)	A 26-week randomized, double-blind, controlled, parallel-group, multicenter study to evaluate the efficacy and safety of sotagliflozin compared to empagliflozin, and placebo in patients with type 2 diabetes who have inadequate glycemic control on dipeptidyl peptidase 4 inhibitor (DPP4(i)) with or without metformin	Placebo qd (n = 154) Empagliflozin 25 mg qd (n = 309)[a] Sotagliflozin 400 mg qd (n = 307)	26 weeks
EFC14868 (SOTA-INS)	A randomized, double-blind, placebo-controlled, parallel-group, 52-week multicenter study to evaluate the efficacy and safety of sotagliflozin in patients with type 2 diabetes who have inadequate glycemic control on basal insulin alone or in addition to oral antidiabetes drugs (OADs)	Placebo qd + Lantus® (n = 144) Sotagliflozin 200 mg qd + Lantus® (n = 141) Sotagliflozin 400 mg qd + Lantus® (n = 285)	52 weeks
EFC15166 (CKD4)	A randomized, double-blind, placebo-controlled, 3-arm, parallel-group, 52-week multicenter study to evaluate the efficacy and safety of sotagliflozin in patients with type 2 diabetes mellitus and severe renal impairment who have inadequate glycemic control	Placebo qd (n = 93) Sotagliflozin 200 mg qd (n = 94) Sotagliflozin 400 mg qd (n = 90)	52 weeks

Abbreviations: n, number of patients; OADs, oral antidiabetes drugs; qd, once daily.
[a] Patients who were randomized to treatment with empagliflozin were not included in the exposure-response safety analyses.

(Source: lx4211-n108-e-r-safety-analysis-rpt, Table 1)

Table 4.4.2.5. Summary Statistics of Demographic Characteristics for the Exposure-Response Safety Analysis of Adverse Events, by Treatment and Overall

Patient Characteristic	Statistic	Treatment			Overall
		Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	
Baseline Age (y)	Mean (SD)	62.6 (10.4)	64.5 (11.0)	62.3 (10.2)	62.8 (10.5)
	Median	63.0	66.0	63.0	64.0
	Min, Max	18, 89	25, 88	24, 89	18, 89
	n	1313	566	1491	3370
Baseline Body Weight (kg)	Mean (SD)	88.9 (17.8)	88.8 (18.2)	90.0 (18.8)	89.4 (18.4)
	Median	87.3	86.4	88.0	87.5
	Min, Max	42.4, 153.9	47.8, 150.3	44.0, 162.5	42.4, 162.5
	n	1313	566	1491	3370
Baseline Body Mass Index (kg/m^2)	Mean (SD)	32.0 (5.3)	32.1 (5.5)	32.1 (5.6)	32.1 (5.4)
	Median	31.5	31.6	31.3	31.4
	Min, Max	19.7, 46.5	18.0, 53.6	18.1, 49.6	18.0, 53.6
	n	1313	566	1491	3370
Race, n (%)	American Indian or Alaska native	45 (3.4)	20 (3.5)	50 (3.4)	115 (3.4)
	Asian	81 (6.2)	16 (2.8)	67 (4.5)	164 (4.9)
	Black or African American	98 (7.5)	39 (6.9)	100 (6.7)	237 (7.0)
	Native Hawaiian or other Pacific Islander	2 (0.2)	2 (0.4)	4 (0.3)	8 (0.2)
	White	1069 (81.4)	478 (84.5)	1247 (83.6)	2794 (82.9)
	Other	18 (1.4)	11 (1.9)	23 (1.5)	52 (1.5)
Sex, n (%)	Male	710 (54.1)	300 (53.0)	840 (56.3)	1850 (54.9)
	Female	603 (45.9)	266 (47.0)	651 (43.7)	1520 (45.1)
Baseline Disease Status, n (%)	Type 2 diabetes	1313 (100.0)	566 (100.0)	1491 (100.0)	3370 (100.0)

(Source: lx4211-n108-e-r-safety-analysis-rpt, Table 4)

Table 4.4.2.6. Summary Statistics of Adverse Event Occurrence Rates, by Adverse Events of Interest

Adverse Event	Occurrence		
	No	Yes	Total
All Patients, n (%)			
Diarrhea	3162 (93.83)	208 (6.17)	3370
Hypoglycemia	2450 (72.70)	920 (27.30)	3370
Volume Depletion	3312 (98.28)	58 (1.72)	3370
Total	8924	1186	10110
Sotagliflozin-Treated Patients, n (%)			
Diarrhea	1912 (92.95)	145 (7.05)	2057
Hypoglycemia	1463 (71.12)	594 (28.88)	2057
Volume Depletion	2015 (97.96)	42 (2.04)	2057
Total	5390	781	6171
Placebo-Treated Patients, n (%)			
Diarrhea	1250 (95.20)	63 (4.80)	1313
Hypoglycemia	987 (75.17)	326 (24.83)	1313
Volume Depletion	1297 (98.78)	16 (1.22)	1313
Total	3534	405	3939

Source: d1er-saf\tables\rtf\freq-resp-pde.rtf.

(Source: lx4211-n108-e-r-safety-analysis-rpt, Table 5)

Diarrhea

Overall, a total of 208 patients (6.2%) had at least 1 occurrence of diarrhea during the treatment period, with 63 patients administered placebo (4.8% of the patients receiving placebo) and 145 patients administered sotagliflozin (7.1% of the patients receiving active treatment) (**Table 4.4.2.6**). **Table 4.4.2.7** provides the summary statistics of patient characteristics, stratified by the occurrence of diarrhea. The PK exposures stratified by occurrence of diarrhea is shown in **table 4.4.2.8**. Although mean and median exposure values were slightly higher in patients who experienced diarrhea compared to patients who did not, the range of exposures overlapped between these two groups.

Table 4.4.2.7. Summary Statistics of Demographic Characteristics, by the Occurrence of Diarrhea

Patient Characteristic	Statistic	Occurrence of Diarrhea		Overall
		No	Yes	
Baseline Age (y)	Mean (SD)	62.7 (10.4)	65.0 (10.9)	62.8 (10.5)
	Median	63.0	67.0	64.0
	Min, Max	18, 89	24, 88	18, 89
	n	3162	208	3370
Baseline Body Weight (kg)	Mean (SD)	89.3 (18.3)	90.4 (18.7)	89.4 (18.4)
	Median	87.5	87.1	87.5
	Min, Max	42.4, 162.5	47.6, 144.0	42.4, 162.5
	n	3162	208	3370
Baseline Body Mass Index (kg/m^2)	Mean (SD)	32.0 (5.4)	32.4 (5.7)	32.1 (5.4)
	Median	31.4	32.0	31.4
	Min, Max	18.0, 53.6	21.3, 46.4	18.0, 53.6
	n	3162	208	3370
Race, n (%)	American Indian or Alaska native	105 (3.3)	10 (4.8)	115 (3.4)
	Asian	153 (4.8)	11 (5.3)	164 (4.9)
	Black or African American	219 (6.9)	18 (8.7)	237 (7.0)
	Native Hawaiian or other Pacific Islander	8 (0.3)	0 (0.0)	8 (0.2)
	White	2627 (83.1)	167 (80.3)	2794 (82.9)
	Others	50 (1.6)	2 (1.0)	52 (1.5)
Sex, n (%)	Male	1744 (55.2)	106 (51.0)	1850 (54.9)
	Female	1418 (44.8)	102 (49.0)	1520 (45.1)
Baseline Disease Status, n (%)	Type 2 diabetes	3162 (100.0)	208 (100.0)	3370 (100.0)

Abbreviations: Max, maximum; Min, minimum; n, number of patients; SD, standard deviation.

(Source: lx4211-n108-e-r-safety-analysis-rpt, Table 6)

Table 4.4.2.8. Summary Statistics of Sotagliflozin Exposure Measures, by the Occurrence of Diarrhea

Exposure Measure	Statistic	Occurrence of Diarrhea		Overall
		No	Yes	
Sotagliflozin Average AUC_{0-24} (ng × h/mL)	Mean (SD)	1595.336 (1231.357)	1675.716 (1206.769)	1601.002 (1229.523)
	Median	1300.299	1421.348	1316.283
	Min, Max	51.66, 19642.12	222.67, 9864.76	51.66, 19642.12
	n	1912	145	2057
Sotagliflozin Average C_{avg} (ng/mL)	Mean (SD)	66.611 (51.414)	69.967 (50.387)	66.848 (51.337)
	Median	54.292	59.346	54.960
	Min, Max	2.16, 820.13	9.30, 411.89	2.16, 820.13
	n	1912	145	2057
Sotagliflozin Average C_{max} (ng/mL)	Mean (SD)	98.022 (64.423)	110.222 (64.944)	98.882 (64.519)
	Median	85.389	97.186	86.196
	Min, Max	3.85, 923.12	25.08, 510.43	3.85, 923.12
	n	1912	145	2057
Sotagliflozin Steady-State AUC_{0-24} (ng × h/mL)	Mean (SD)	1718.599 (1056.534)	1814.427 (1078.424)	1725.354 (1058.110)
	Median	1466.312	1640.787	1474.947
	Min, Max	194.67, 12364.87	228.37, 8326.53	194.67, 12364.87
	n	1912	145	2057
Sotagliflozin Steady-State C_{avg} (ng/mL)	Mean (SD)	71.758 (44.114)	75.759 (45.028)	72.040 (44.180)
	Median	61.224	68.509	61.584
	Min, Max	8.13, 516.28	9.54, 347.66	8.13, 516.28
	n	1912	145	2057
Sotagliflozin Steady-State C_{max} (ng/mL)	Mean (SD)	106.749 (56.919)	115.977 (60.637)	107.399 (57.222)
	Median	94.842	104.842	95.642
	Min, Max	13.57, 611.66	25.39, 441.46	13.57, 611.66
	n	1912	145	2057

Abbreviations: AUC_{0-24}, area under the concentration-time curve from 0 to 24 hours; C_{avg}, average concentration; C_{max}, maximum concentration; Max, maximum; Min, minimum; n, number of patients; SD, standard deviation.

(Source: lx4211-n108-e-r-safety-analysis-rpt, Table 10)

The effect of steady-state and average sotagliflozin exposures (AUC_{0-24}, C_{avg}, and C_{max}) on the probability of the first occurrence of diarrhea was evaluated using linear and nonlinear models. Linear functional forms of average C_{max}, steady-state C_{max}, steady-state AUC_{0-24}, and steady-state C_{avg} were tested. Both exponential and maximum pharmacologic effect (E_{max}) functions of average C_{avg} and average AUC_{0-24} were tested for the probability of diarrhea. A comparison of E-R models for the probability of diarrhea is shown in **table 4.4.2.9**. All exposure measures and functional forms were significant predictors of the probability of diarrhea. The model with the most significant decrease in VOF (-10.721) was the linear function of sotagliflozin average C_{max}. However, the linear sotagliflozin $C_{max,ss}$ model had a similarly significant decrease (-10.081).

Since all sotagliflozin exposure measures were highly correlated and sotagliflozin $C_{max,ss}$ was significant for all AEs, the linear function of sotagliflozin $C_{max,ss}$ was selected for inclusion in the base E-R model for the probability of diarrhea. Age was the only significant covariate incorporated into the ER model (α=0.01). The final model estimates are shown in **table 4.4.2.10**. VPC plot showed acceptable predictive capability of the ER model (**Figure 4.4.2.3**).

Table 4.4.2.9. Summary of Evaluation of Sotagliflozin Exposure Measures for the Occurrence of Diarrhea

Parameter Affected	Covariate Added	Functional Form	Ver	Change in VOF[a]	df	*P* value[b]
Reference Model Filename: diar-int-only.ctl (VOF = 1561.504)						
Exposure Measure	Sotagliflozin Average C_{max} (ng/mL)	Linear	01	-10.721	1	1.060E-03
	Sotagliflozin Steady-State C_{max} (ng/mL)	Linear	01	-10.081	1	1.499E-03
	Sotagliflozin Average AUC_{0-24} (ng × h/mL)	E_{max}	01	-10.502	2	5.243E-03
	Sotagliflozin Average C_{avg} (ng/mL)	E_{max}	01	-10.502	2	5.243E-03
	Sotagliflozin Steady-State AUC_{0-24} (ng × h/mL)	Linear	01	-6.56	1	1.043E-02
	Sotagliflozin Steady-State C_{avg} (ng/mL)	Linear	01	-6.56	1	1.043E-02
	Sotagliflozin Average C_{avg} (ng/mL)	Exponential	01	-5.45	1	1.957E-02
	Sotagliflozin Average AUC_{0-24} (ng × h/mL)	Exponential	01	-5.449	1	1.958E-02

Abbreviations: AUC_{0-24}, area under the concentration-time curve from 0 to 24 hours; C_{avg}, average concentration; C_{max}, maximum concentration; df, number of degrees of freedom associated with this addition to the model; E_{max}, maximum pharmacologic effect; IIV, interindividual variability; *P*, probability; Ver, version number of the control stream; VOF, value of the objective function.
[a] Change in the value of the objective function relative to the reference model.
[b] Statistical significance (α = 0.05).
[c] Change in the magnitude of IIV on the indicated parameter expressed as a percentage relative to the reference model.
Source: d1er-saf\nm\base\summary-l2116-main_analysis-2-diarrhea_exposure evaluation-1.docx.

(Source: lx4211-n108-e-r-safety-analysis-rpt, Table 11)

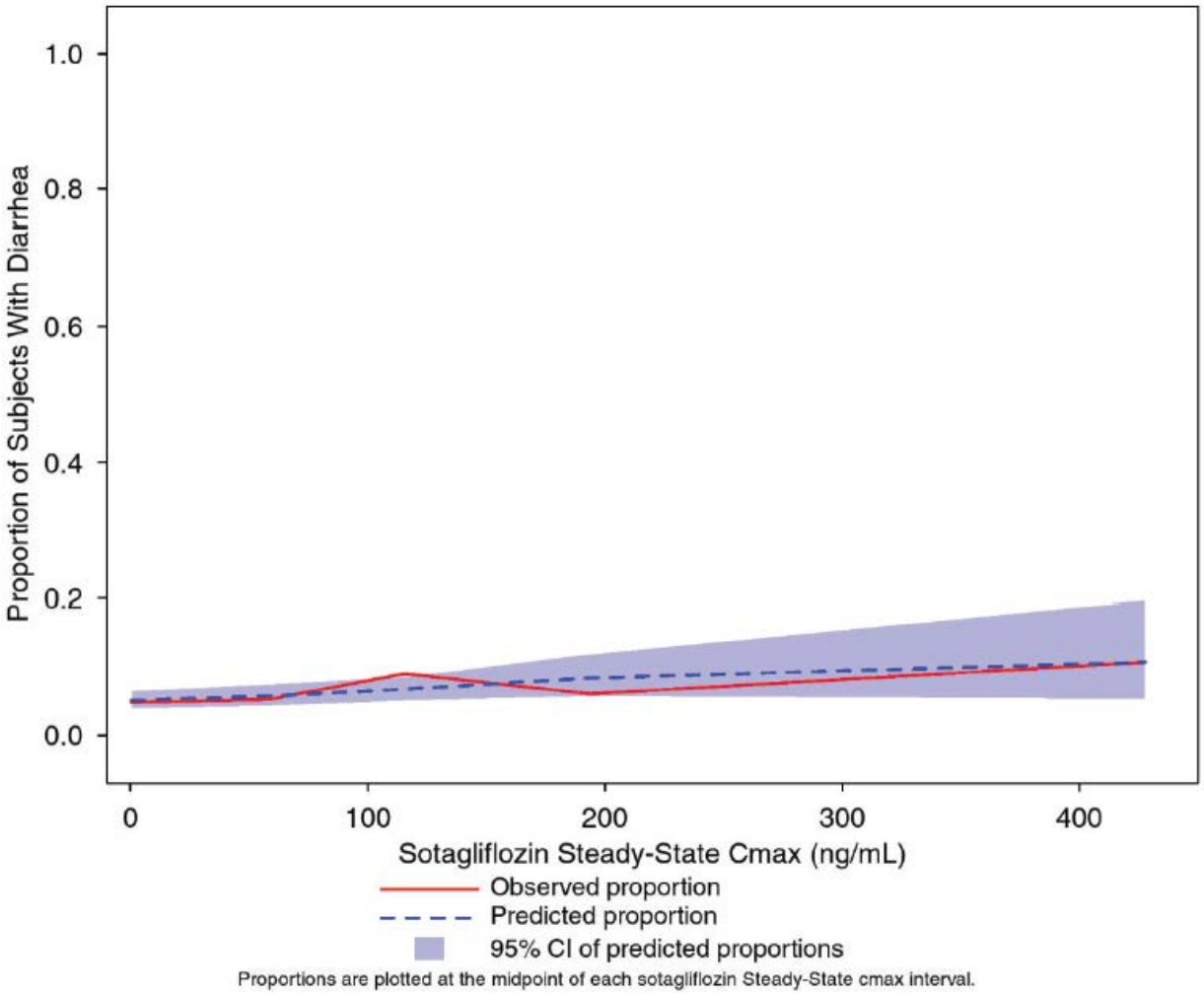
Table 4.4.2.10. Parameter Estimates and Standard Errors from the Final Exposure-Response Model for the Occurrence of Diarrhea

Parameter	Estimate	Standard Error	%RSE	*P* value	Odds Ratio	95% CI for Odds Ratio Lower Bound	95% CI for Odds Ratio Upper Bound
Intercept	-4.1174	0.4717	11.4569	< 0.0001	NA	NA	NA
Sotagliflozin Steady-State C_{max} (ng/mL)	0.0025	0.0009	37.2354	0.007	1.003	1.001	1.004
Baseline Age (y)	0.0190	0.0073	38.5669	0.01	1.019	1.005	1.034

Abbreviations: CI, confidence interval; C_{max}, maximum concentration; NA, not applicable; *P*, probability; %RSE, relative standard error expressed as a percent.

(Source: lx4211-n108-e-r-safety-analysis-rpt, Table 14)

Figure 4.4.2.3. Visual Predictive Check Plot for the Final Exposure-Response Model for the Occurrence of Diarrhea Versus Sotagliflozin Steady-State C_{max}

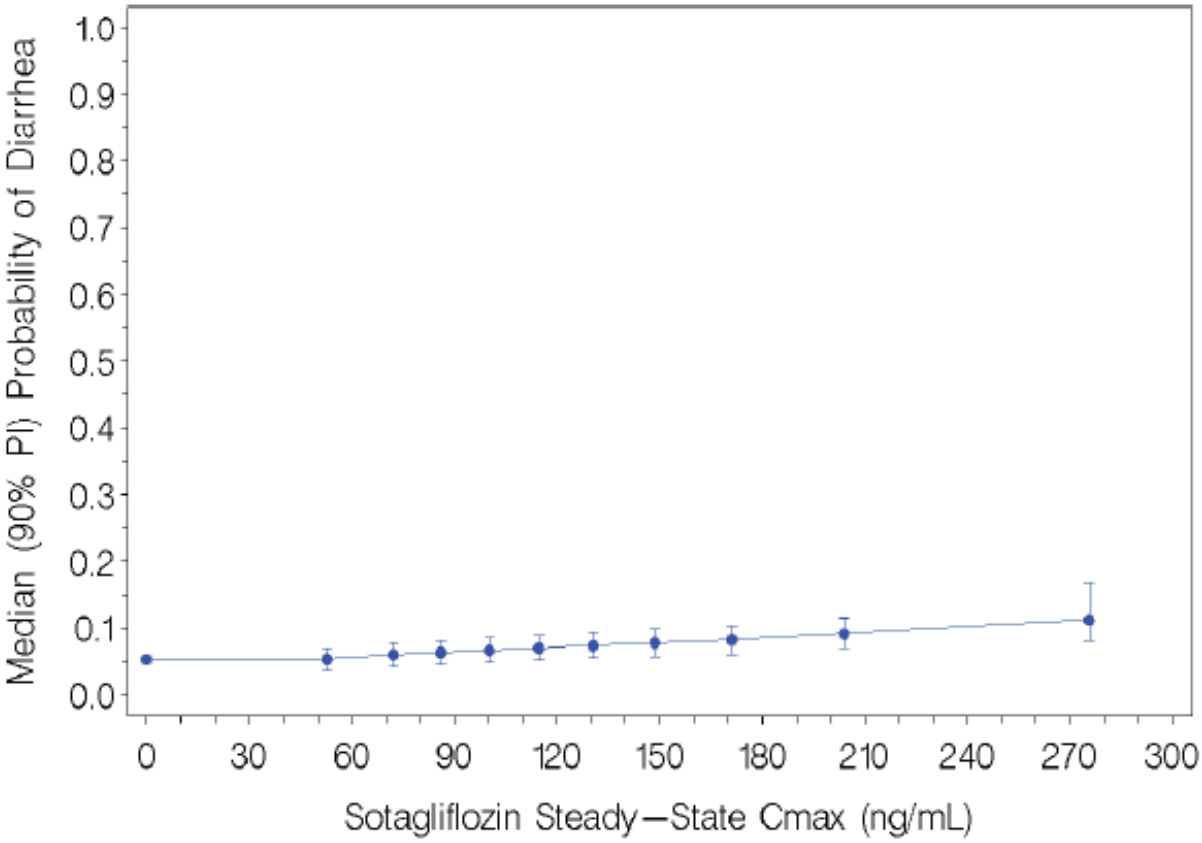


Abbreviations: CI, confidence interval; C_{max}, maximum concentration.

(Source: lx4211-n108-e-r-safety-analysis-rpt, Figure 5)

Simulations were performed to predict the range of expected safety outcomes of 10,000 virtual patients receiving 200 mg of sotagliflozin for 2 weeks, followed by 400 mg for 50 weeks for an additional 2 weeks. The final population PK model was used to obtain simulated sotagliflozin $C_{max,ss}$ values for each virtual patient to predict the probability of safety responses using the E-R diarrhea model. The median (90% PI) predicted probability of diarrhea versus sotagliflozin $C_{max,ss}$ is provided in **Figure 4.4.2.4**. The model-predicted probability of diarrhea increased with increasing sotagliflozin $C_{max,ss}$. Placebo patients were predicted to have an approximate 5% incidence of diarrhea, compared to a 5% to 12% incidence with sotagliflozin 400 mg once daily.

Figure 4.4.2.4. Simulated Median (90% Prediction Interval) Probability of Diarrhea Versus Sotagliflozin Steady-State C_{max} in Virtual Patients Using the Final Exposure-Response Model



The symbols and bars represent the median and 90% prediction interval, respectively, graphed at the median of the range of values within each decile of sotagliflozin steady—state Cmax.

Abbreviations: C_{max}, maximum concentration; PI, prediction interval.

(Source: lx4211-n108-e-r-safety-analysis-rpt, Figure 8)

Hypoglycemia and depletion

The PK metrics were not significantly correlated with the probability of hypoglycemia and depletion after accounting for all the covariates.

Reviewer's comment: The applicant's PPK and ER analysis for safety appears to be acceptable. The results can be used to support the labeling statement. See additional analysis from Reviewer in **section 4.4.3**.

4.4.3 Reviewer's analysis

4.4.3.1 Introduction

SCORED was to compare the effect of sotagliflozin to placebo on total occurrences of CV death, HHF, and UVHF in patients with T2DM, moderate-to-severe renal impairment, and other CV risk factors. The primary objective of SOLOIST was to compare the effect of sotagliflozin to placebo on the total occurrences of CV death, HHF, and UVHF in hemodynamically stable patients after admission for post-worsening heart failure (WHF). Due to the early termination of the two pivotal trials, no information of exposure-response relationship for neither safety nor efficacy could be investigated in target patient population. On the other hand, both pivotal trials enrolled patients with varying degrees of renal impairment and the sotagliflozin exposures increased following the increase in renal impairment severity (see **section 3.3.3.1**).

For both trials, patients in treatment arm received 200 mg QD sotagliflozin from Day 1 and titrated up to 400 mg QD without safety concern. At any time during the study, dose reduction from 400 mg QD to 200 mg QD was allowed if any tolerability issue occurred. Once reduced, the dose of 200 mg QD was to be maintained for the duration of the remaining double-blind study treatment period. The dose modification information could inform safety.

In this analysis, the reviewer explored the correlation between renal impairment severity and dose modification as well as the efficacy endpoint, event rate of combined investigator-reported CV death, HHF, and UVHF.

4.4.3.2 Results

Dose modification vs. RI

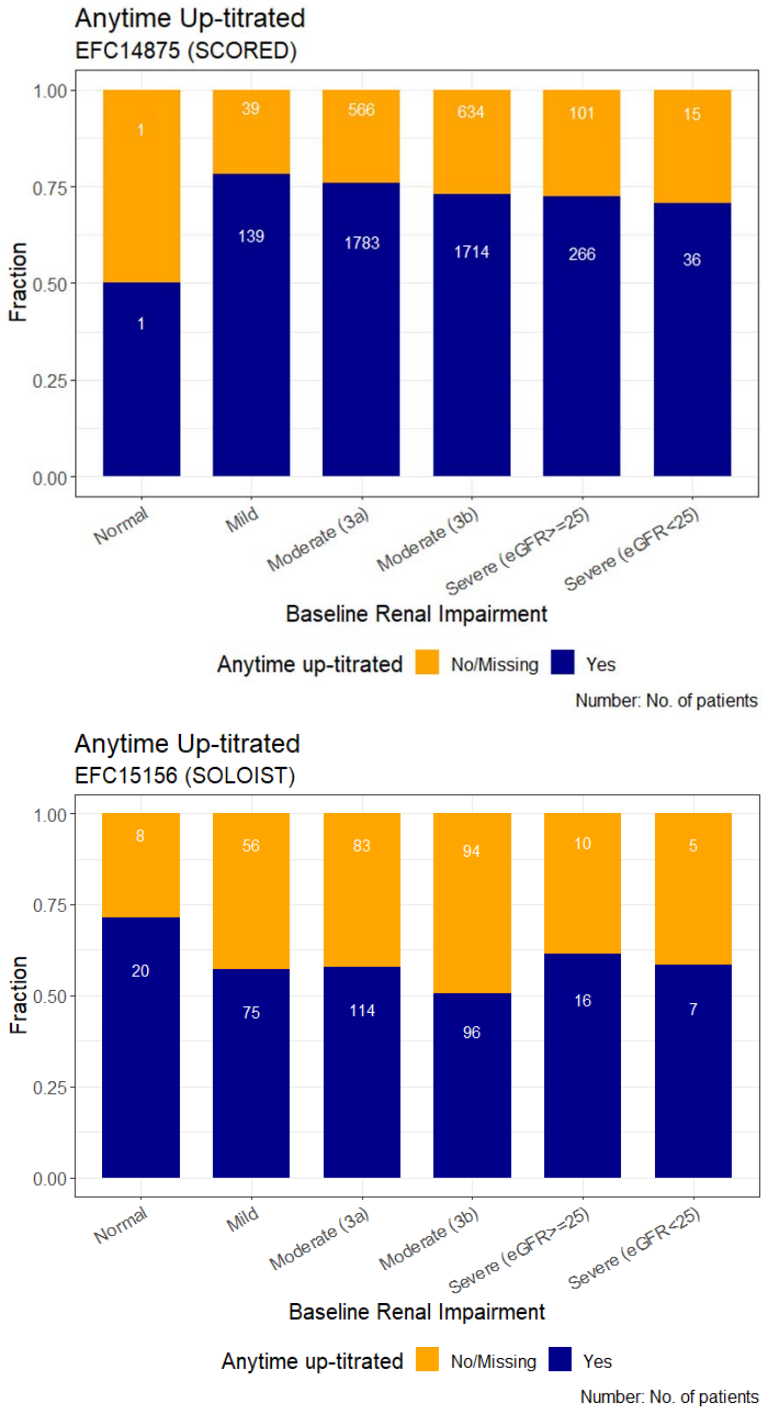
The dose modification (anytime up-titrated, down-titrated following up-titration, dose at the study end, and reason for down-titration) were plotted against varying degrees of renal impairment for SCORED and SOLOIST. The renal impairment categories were divided based on:

- Normal: eGFR >= 90 mL/min/1.73m^2
- Mild: eGFR >= 60 to <90 mL/min/1.73m^2
- Moderate (3a): eGFR >= 45 to < 60 mL/min/1.73m^2
- Moderate (3b): eGFR >= 30 to < 45 mL/min/1.73m^2
- Severe: eGFR >= 15 to < 30 mL/min/1.73m^2

No apparent trends were observed between RI vs. anytime up-titrated (**Figure 4.4.3.2.5**), down-titrated following up-titration (**Figure 4.4.3.2.6**), and dose at the study end (**Figure 4.4.3.2.7**) for both trials. There appeared a trend of increasing fraction of patients down-titrated due to AE following the worsening of the renal function in SCORED (**Figure 4.4.3.2.8**). However, this was not observed in SOLOIST (**Figure 4.4.3.2.8**). Considering the small number of patients

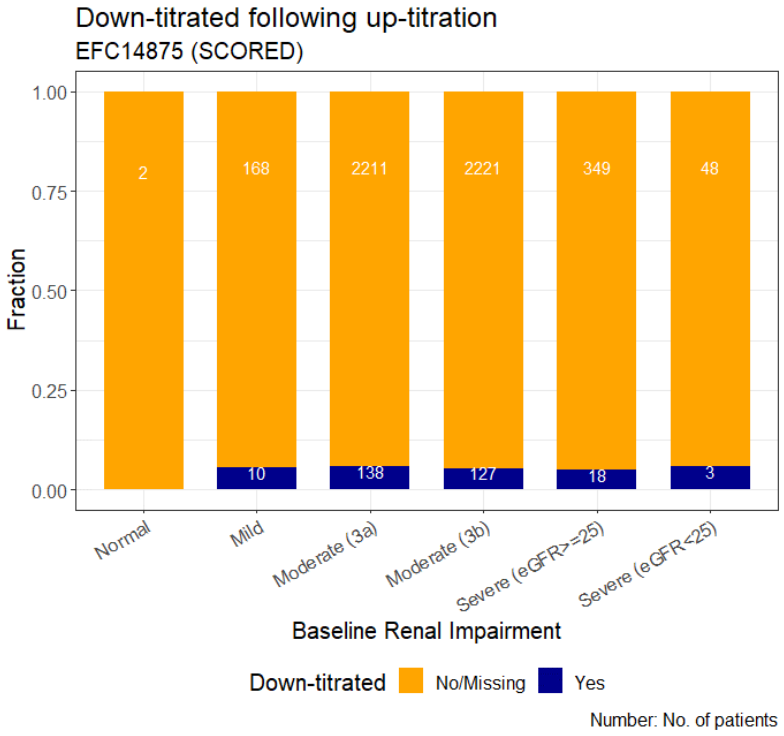
experiencing dose reduction and the limited number of patients with mild and severe renal impairment in SCORED, the trend was not considered clinically relevant.

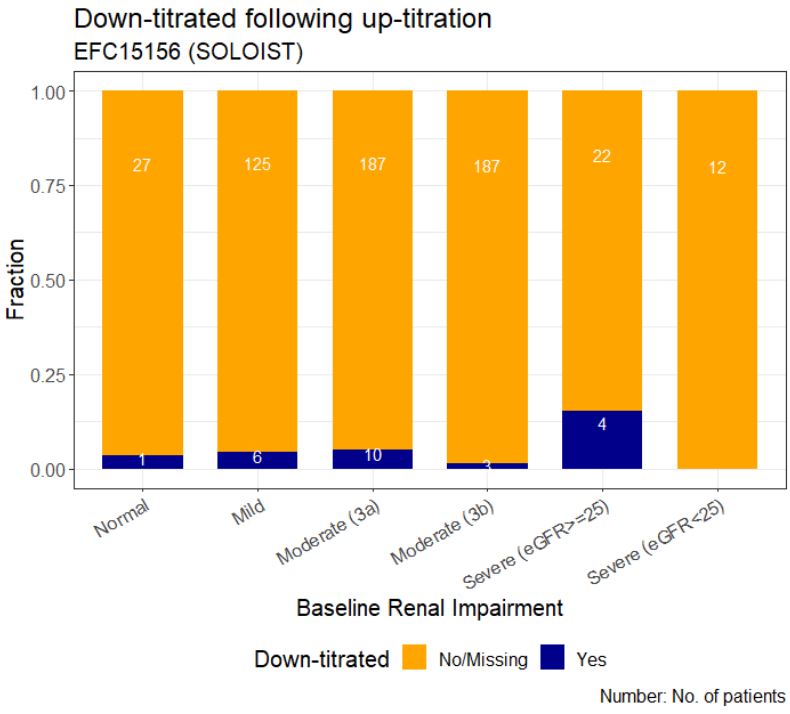
Figure 4.4.3.2.5. Fraction of Patients Up titrated at any time in SCORED (top) and SOLOIST (bottom) stratified by renal impairment categories



(Source: Reviewer's analysis)

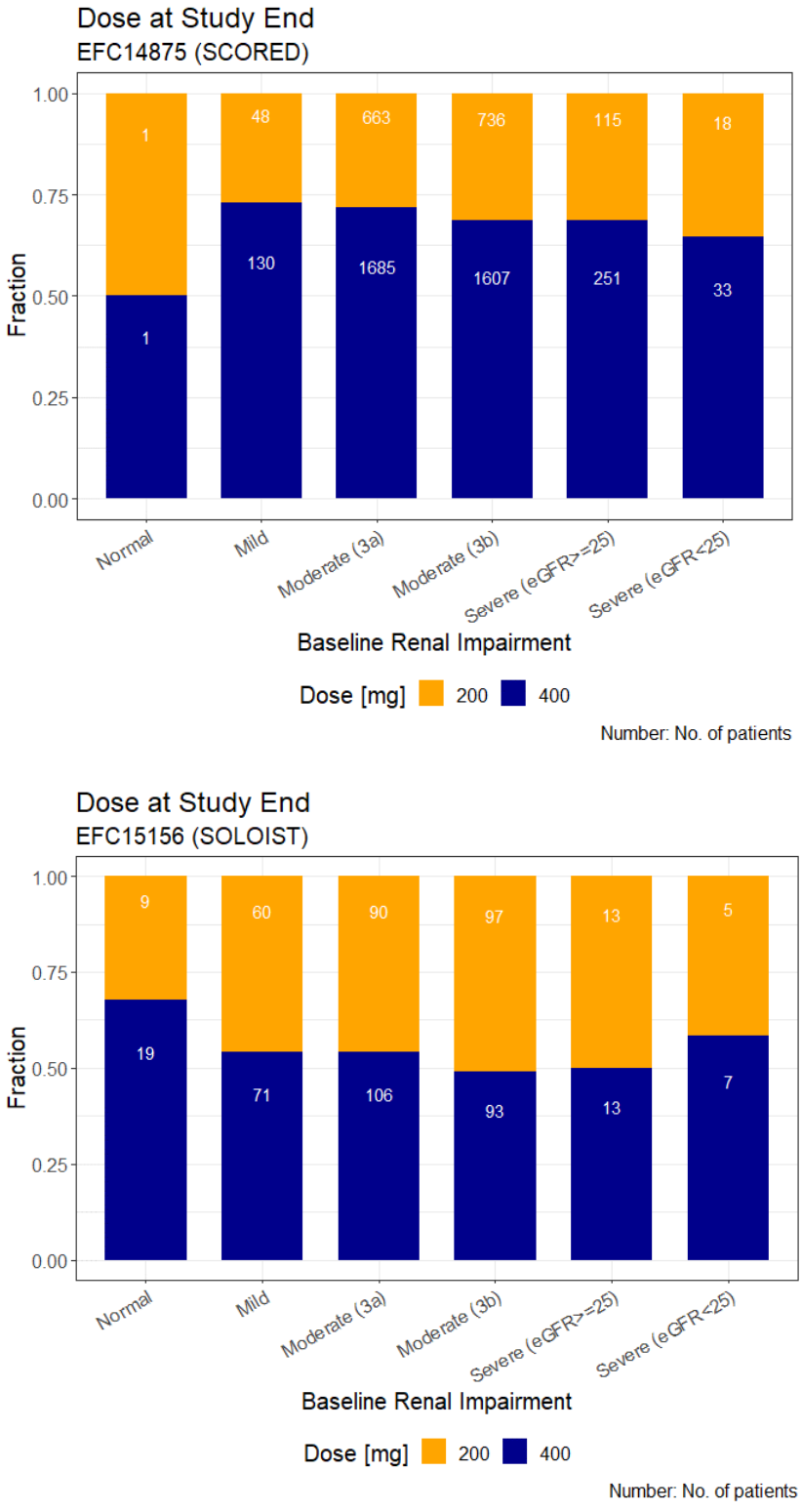
Figure 4.4.3.2.6. Fraction of Patients Down-titrated Following Up-titration in SCORED (top) and SOLOIST (bottom) stratified by renal impairment categories





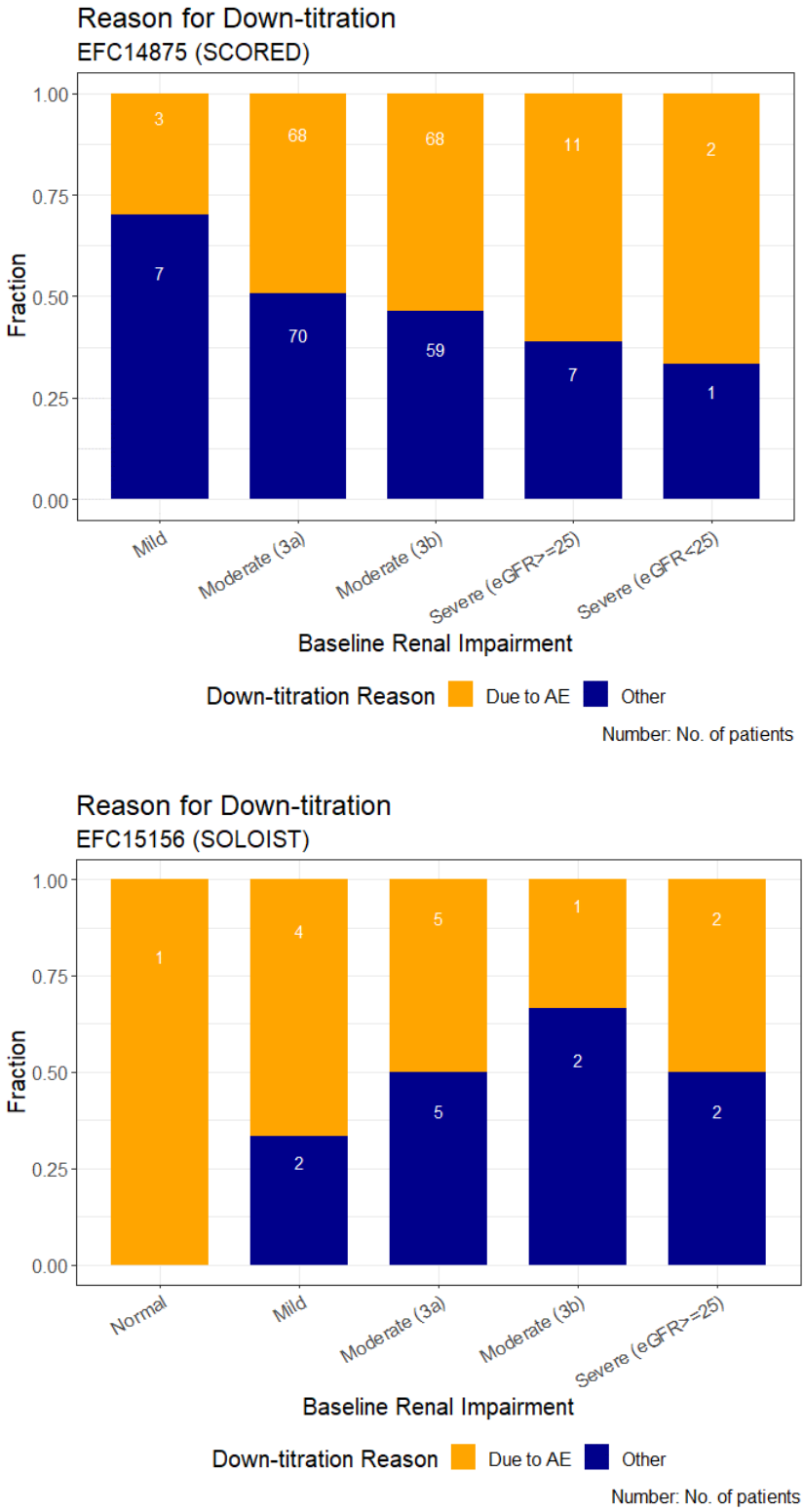
(Source: Reviewer's analysis)

Figure 4.4.3.2.7. Dose at Study End in SCORED (top) and SOLOIST (bottom) stratified by renal impairment categories



(Source: Reviewer's analysis)

Figure 4.4.3.2.8. Reason for Down-titration in SCORED (top) and SOLOIST (bottom) stratified by renal impairment categories

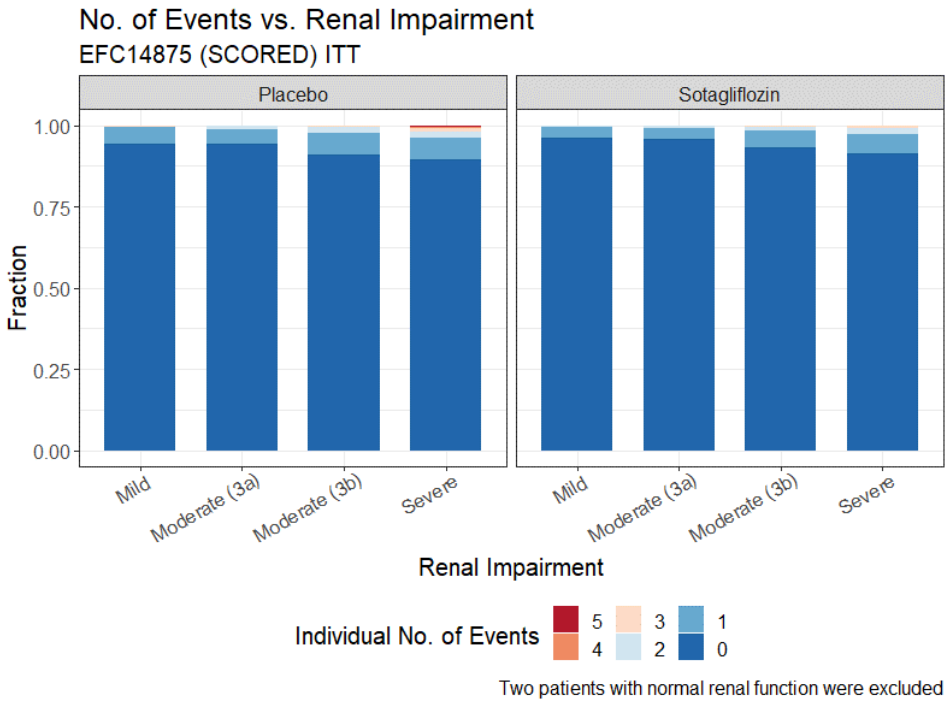


(Source: Reviewer's analysis)

Efficacy vs. RI

The number of events for SCORED was shown in **figure 4.4.3.2.9** and **table 4.4.3.2.11**. There appeared a trend that the event rate increased following the severity of the renal function, which was observed in both placebo arm and treatment arm (**Figure 4.4.3.2.10**). As a result, the efficacy was mainly driven by renal function, not the PK exposures.

Figure 4.4.3.2.9. Number of Events in SCORED Stratified by Renal Impairment Categories and Treatment Arm



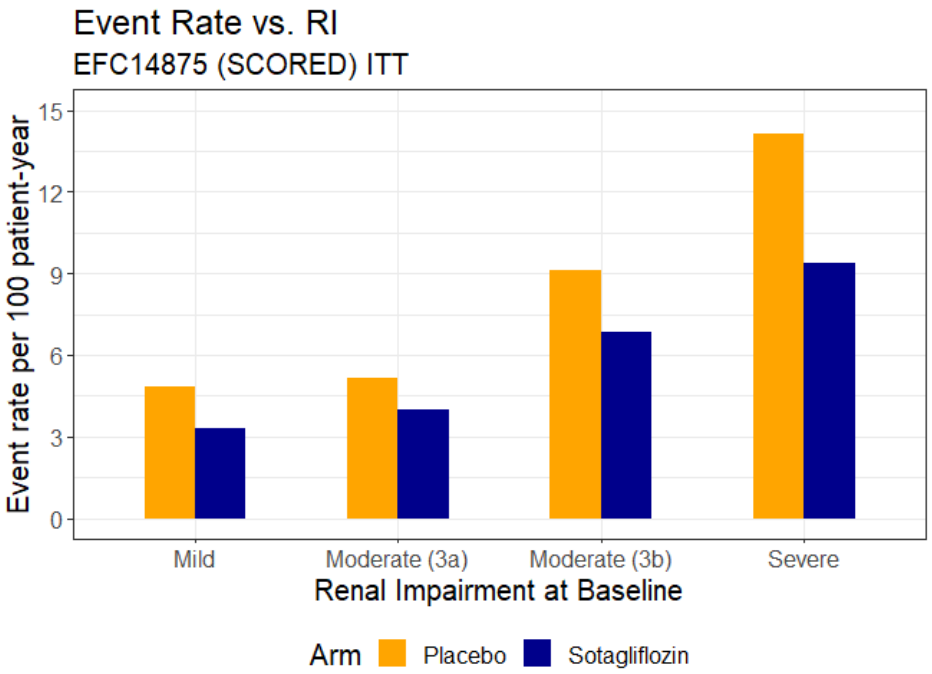
(Source: Reviewer's analysis)

Table 4.4.3.2.11. Summary of Statistics of Events in SCORED Stratified by Renal Impairment Categories and Treatment Arm

RI		Mild	Moderate (3a)	Moderate (3b)	Severe
eGFR [mL/min/1.73m^2]		≥60, <90	≥45, <60	≥30, <45	≥15, <30
No. Event (duration at risk in years) [N]	Placebo	12 (248.3) [180]	167 (3233.2) [2410]	280 (3076.2) [2308]	71 (502.5) [393]
	Sotagliflozin	8 (240.6) [178]	127 (3186.3) [2346]	214 (3121.6) [2347]	51 (544.1) [418]

(Source: Reviewer's analysis)

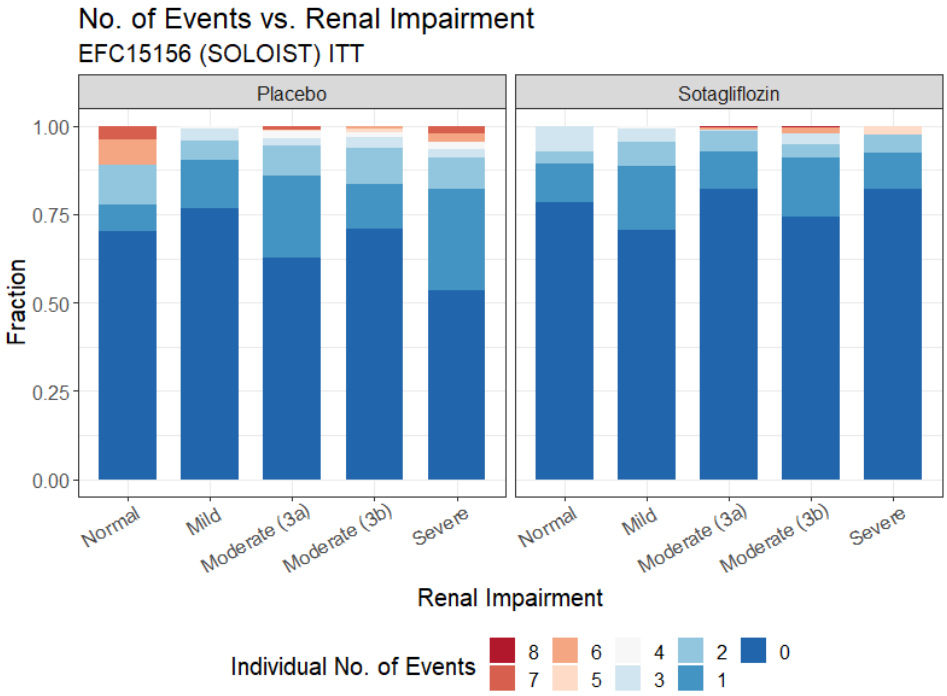
Figure 4.4.3.2.10. Correlation between Event Rate and Renal Impairment Categories in SCORED Stratified by Treatment Arm



(Source: Reviewer's analysis)

The number of events for SOLOIST was shown in **figure 4.4.3.2.11** and **table 4.4.3.2.12**. No apparent trend was observed between efficacy and renal impairment categories (**Figure 4.4.3.2.12**).

Figure 4.4.3.2.11. Number of Events in SOLOIST Stratified by Renal Impairment Categories and Treatment Arm



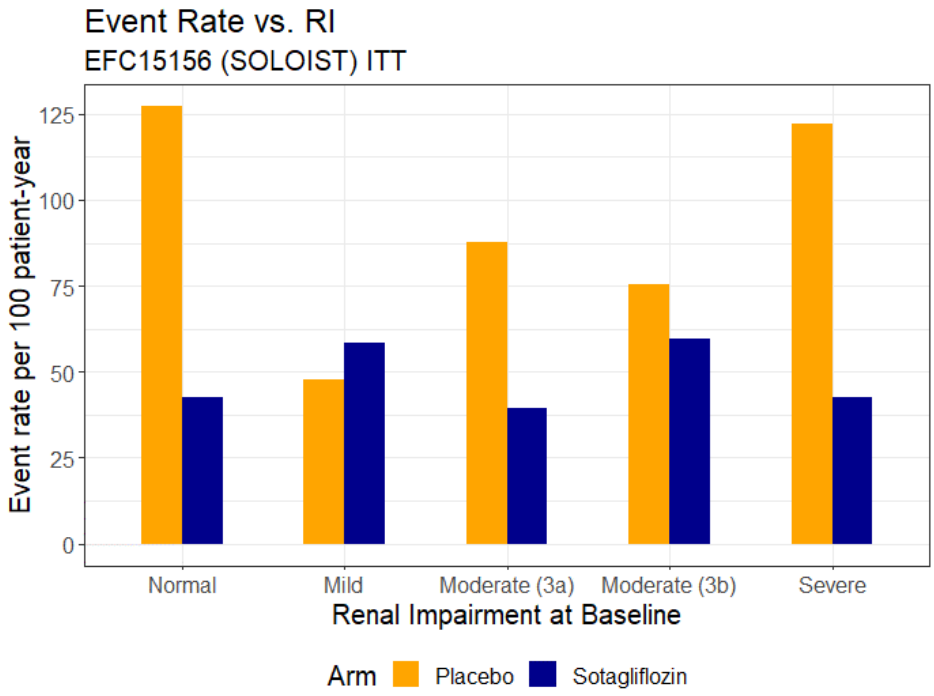
(Source: Reviewer's analysis)

Table 4.4.3.2.12. Summary of Statistics of Events in SOLOIST Stratified by Renal Impairment Categories and Treatment Arm

RI		Normal	Mild	Moderate (3a)	Moderate (3b)	Severe
eGFR [mL/min/1.73m^2]		≥90	≥60, <90	≥45, <60	≥30, <45	≥15, <30
No. Event (duration at risk in years) [N]	Placebo	27 (21.24) [27]	63 (132.04) [167]	124 (141.09) [193]	94 (124.87) [165]	41 (33.51) [45]
	Sotagliflozin	11 (25.86) [28]	61 (104.74) [132]	60 (152.16) [197]	90 (151.32) [190]	13 (30.48) [39]

(Source: Reviewer's analysis)

Figure 4.4.3.2.12. Correlation between Event Rate and Renal Impairment Categories in SOLOIST Stratified by Treatment Arm

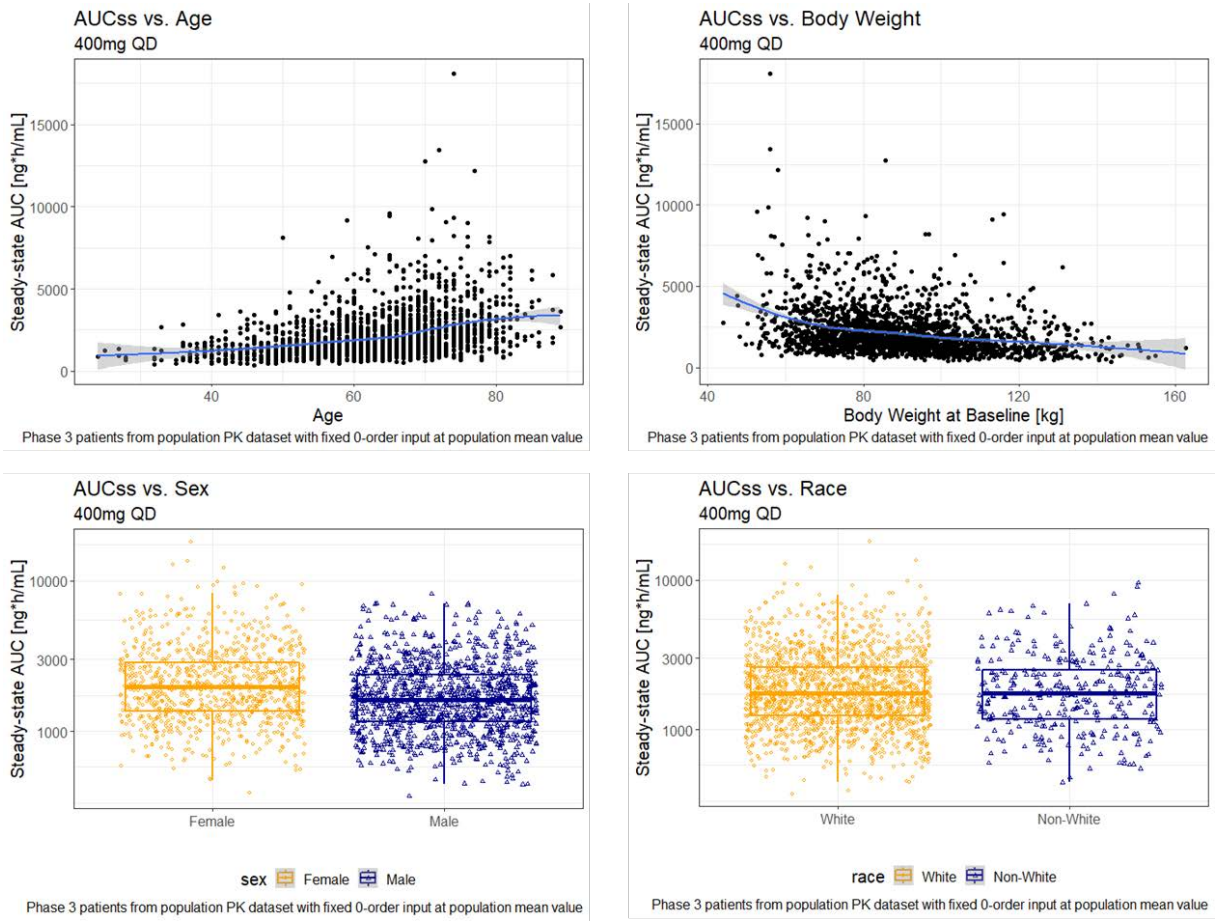


(Source: Reviewer's analysis)

Age, body weight, sex, and race on PK

To explore the effect of age, body weight, sex, and race on PK, PPK simulation was performed using the final PPK model estimated individual PK parameters for the phase 3 patients with T2DM. The steady-state AUC vs. covariates were plotted in **figure 4.4.3.2.13**. The steady-state AUC appeared to be increased following the increase in age and decrease in body weight. Considering no apparent exposure-response relationship for safety was identified, the observed trends were not considered clinically relevant. There were substantial overlaps in steady-state AUC between females and males as well as between White and non-White.

Figure 4.4.3.2.13. Simulated Steady-state AUC in Patients with T2DM vs. Age, Body Weight, Sex, and Race



(Source: Reviewer's analysis)

4.4.3.3. Summary

No clinically meaningful correlation was observed between renal impairment severity and dose modification or efficacy. The relevant labeling statement is acceptable.

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/s/

MOHAMED NOUNOU
03/15/2023 01:59:17 PM

YE YUAN
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HAO ZHU
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03/16/2023 09:45:15 AM

Memorandum

Division of Pharmacology/Toxicology
Office of Cardiology, Hematology, Endocrinology, & Nephrology
Center for Drug Evaluation and Research

Date:	December 12, 2022
NDA #	216203
Applicant:	LEXICON PHARMACEUTICALS INC
Drug:	(b) (4) (sotagliflozin)
Primary Reviewer:	Baichun Yang, PhD
Secondary Reviewer:	Xuan Chi, PhD
Subject:	Secondary P/T review of Sotagliflozin application with an emphasis on EPC, Section 8.1 (Pregnancy), and Section 12.1 (Mechanism of Action) labeling

Background:

Lexicon Pharmaceuticals Inc is seeking market approval for sotagliflozin, proposed trade name (b) (4) to treat adult heart failure patients. The study drug was also submitted under NDA-210934 indicated as an adjunct therapy to insulin for the treatment of Type 1 diabetes. The nonclinical program of NDA-210934 was considered supportive of approval of sotagliflozin (see primary review by Dr. Brundage dated 11/28/2018 and secondary review by Dr. Bourcier dated 2/22/2022 in DARRTS). A Complete Response letter was issued for NDA-210934 on 3/22/2019 due to an unfavorable clinical benefit-risk assessment resulted from an increased risk of diabetic ketoacidosis in the sotagliflozin dose groups.

For the current NDA indicated for heart failure, the primary nonclinical reviewer, Dr. Baichun Yang, concludes that the pharmacology and toxicology data support approval of sotagliflozin (see primary review by Dr. Yang dated 10/28/2022 in DARRTS). *I concur with Dr. Yang's assessment.*

This secondary review is focused on three labeling review issues regarding the EPC, Section 8.1 (Pregnancy) and Section 12.1 (Mechanism of Action), that came up during the review.

Established Pharmacologic Class (EPC) Assignment

EPC Proposed by the Applicant and the Basis

(b) (4) Several SGLT2 inhibitors (e.g., dapagliflozin, empagliflozin) are currently marketed for treatment of heart failure and are labeled with the EPC of a sodium-glucose cotransporter 2 (SGLT2) inhibitor. There are currently no SGLT1 or SGLT1/2 inhibitors approved for the heart failure indication.

(b) (4)

In vitro studies demonstrate that sotagliflozin inhibits human SGLT2 with similar potency (IC50) as does other SGLT2 inhibitors (e.g., dapagliflozin, canagliflozin, and empagliflozin). However, unlike these approved drugs, sotagliflozin inhibits SGLT1 with higher potency (see Table 1) and achieves functional inhibition of SGLT1 at the proposed clinical dose, most readily apparent as gastrointestinal adverse effects observed clinically and nonclinically.

Table 1. In vitro SGLT1 and SGLT2 selectivity (Table from primary review of NDA-210934 by Dr. Patricia Brundage)

Compound	IC50 (nM) at SGLT2	n	IC50 (nM) at SGLT1	n	Selectivity Ratio (SGLT1/SGLT2)
Sotagliflozin	1.8	8	36.3	9	20
Dapagliflozin	2.0	8	287.4	7	144
Canagliflozin	3.2	8	422.2	8	132
Empagliflozin	2.4	5	1371	4	571

(b) (4)

. As described by Pitt, et al.[2], SGLT1 inhibition may add benefit to SGLT2 inhibition for cardiac and cardiorenal outcomes, at least in patients with T2D. However, this conclusion was not based on a direct comparison with the SGLT2 inhibitors, but extrapolated from a meta-analysis data with SGLT2 inhibitors, which failed to show a reduction of stroke and only a modest reduction in the incidence of MI. The mechanism of this added benefit remains undetermined but was proposed to be related to increased GLP-1 as a result of SGLT1 inhibition in the intestines.

Division Conclusion and Recommendation

The EPC of sotagliflozin proposed by the Division is SGLT2 inhibitor. This is based on the following considerations:

- Based on the guidance 'Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information', the EPC should be clinically meaningful and should be relevant and specific to a drug product's indication. Overall, there is inadequate data to conclude that SGLT1 inhibition contributes to the mechanism of

[1] Seidelmann SB, Feofanova E, Yu B, Franceschini N, Claggett B, Kuokkanen M, Puolijoki H, Ebeling T, Perola M, Salomaa V, Shah A, Coresh J, Selvin E, MacRae CA, Cheng S, Boerwinkle E, Solomon SD. Genetic Variants in SGLT1, Glucose Tolerance, and Cardiometabolic Risk. J Am Coll Cardiol. 2018 Oct 9;72(15):1763-1773.
[2] Pitt, B., Steg, G., Leiter, L.A. et al. The Role of Combined SGLT1/SGLT2 Inhibition in Reducing the Incidence of Stroke and Myocardial Infarction in Patients with Type 2 Diabetes Mellitus. Cardiovasc Drugs Ther 36, 561–567 (2022). (It is noted that the Dr. Pitt and other co-authors on this paper served as the chair or was a member of SOLOIST and/or SCORED trial and received consulting fees from Lexicon, the applicant of this NDA.)

efficacy of sotagliflozin beyond inhibition of SGLT2 (b) (4) Describing SGLT1 inhibition by sotagliflozin in section 12.1 of the label would be more appropriate in the context of adverse gastrointestinal-related signs as observed in the treatment groups in both clinical and nonclinical studies.

- None of the nonclinical pharmacology studies submitted by the applicant clearly discerned the individual contributory role of SGLT1 and SGLT2 inhibition regarding sotagliflozin's pharmacodynamic activity in vivo. The in vivo pharmacology study using a rat model of heart failure with preserved ejection fraction (HFpEF) showed significant improvement in surrogate markers of cardiac function following treatment with sotagliflozin for 6 weeks. However, a concurrent control with a SGLT2 inhibitor was not included in the study and the contribution by SGLT2 vs. SGLT1 inhibition cannot be distinguished. No pharmacology studies have been conducted in SGLT2 KO mice treated with sotagliflozin, which would have provided more definitive evidence whether a pharmacodynamic effect of sotagliflozin still exists in the absence of SGLT2, and to what extent.
- The contribution of SGLT2 inhibition to efficacy of sotagliflozin is not in doubt, as several selective SGLT2 inhibitors are currently approved for the heart failure indication. There is currently no definitive data indicative of additional cardiac benefit of sotagliflozin compared with these selective SGLT2 inhibitors.

Pregnancy Labeling

During the labeling review of NDA-sotagliflozin, DPMH asked the PT team to comment on the restricted use of SGLT2i in the second and third trimester of pregnancy and during lactation, based on the nonclinical findings.

(b) (4) (b) (4) (b) (4) The renal macroscopic change (i.e., dilated renal pelvis and dilated ureter) in the F1 pups exposed at ≥30 mg/kg is considered treatment related. In the juvenile animal study dosed with sotagliflozin from PND 21 to PND 90, dose-related increased kidney weights were observed for males given ≥10 mg/kg/day and females given ≥30 mg/kg/day and was correlated with renal tubular dilation for animals given ≥30 mg/kg/day. These findings are also consistent with similar effects observed in the PPND and/or juvenile studies with other SGLT2 inhibitors (e.g., dapagliflozin, canagliflozin, empagliflozin and ertugliflozin). They are also consistent with renal findings in adult rat administered with sotagliflozin, albeit at higher dose levels and appears to be reversible after a 4-week recovery. These renal effects are considered secondary to the pharmacodynamic activity of this class of drugs and the increased sensitivity in juvenile animals is likely attributed to the reduced ability of the developing kidney to handle the increased urine volumes associated with SGLT2i induced osmotic diuresis.

Given that sotagliflozin is distributed to most fetal tissues including the kidney when administered to dams during gestation and the species differences in the timing of kidney structural maturation between rats and human, the treatment-related renal effects in the juvenile rats are considered relevant to the assessment of gestational clinical risk, instead of a pediatric risk of nephrotoxicity.

The structural renal development in the juvenile rat corresponds to renal development in humans during the late second and third trimester of pregnancy[3,4]. At recovery necropsy of the juvenile study with sotagliflozin, there was partial reversibility of the renal effects. For other drugs in this class, the reversibility of the renal effects in PPND or juvenile studies ranges from partial to complete. The long-term functional consequence of a human fetus exposed to sotagliflozin is unclear. As these are undesired effects with inconsistent data on reversibility, and likely clinically relevant, it is recommended that the risk summary and animal data sections for section 8.1 disclose the renal pelvic dilatation and other renal changes in rats from the post-natal developmental and juvenile toxicology studies with sotagliflozin, which are considered relevant to fetal renal development during the second and third trimesters of pregnancy. This recommendation has been communicated to the DPMH team.

The suggested language relevant to reproductive toxicities in Section 8.1 of the drug label is included below:

8.1 Pregnancy

Risk Summary

In rats, renal changes were observed when sotagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Exposure approximately 5 times the clinical exposure at the maximum recommended human dose (MRHD) of 400 mg QD caused increased kidney weights and renal pelvis and tubule dilatations that were partially reversible. *[see Data]*.

Data

Animal Data

In embryo-fetal development studies in rats and rabbits, sotagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans.

Sotagliflozin was not teratogenic when administered at doses up to 100 mg/kg/day in pregnant rats during embryonic organogenesis (40 times the human exposure at the MRHD). Higher exposures (350mg/kg or 161 times the human exposure at the MRHD) resulted in embryo-lethality, effects on fetal growth, and cardiovascular and skeletal fetal abnormalities commensurate with maternal toxicity.

Sotagliflozin was not teratogenic when administered at doses up to 200 mg/kg/day in pregnant rabbits (9 times the human exposure at the MRHD).

In a prenatal and postnatal development study in pregnant and lactating rats, sotagliflozin was administered at oral doses up to 100 mg/kg/day from gestation Day 6 through to lactation Day 20 (weaning). An increased incidence of dilated kidneys with discoloration and dilated ureters was observed at doses ≥30 mg/kg (≥4 times the human exposure at the MRHD). Sotagliflozin did not adversely affect developmental landmarks, sexual maturation, or reproductive performance of the offspring at doses up to 40 times the human exposure at the MRHD.

Sotagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 3, 10, 30, and 75 mg/kg/day caused dose-related increased kidney weights for males given ≥ 10 mg/kg/day and females given ≥ 30 mg/kg/day and was correlated with renal tubular and

[3] Frazier KS. Species Differences in Renal Development and Associated Developmental Nephrotoxicity. Birth Defects Res. 2017 Oct 2;109(16):1243-1256

[4] Frazier KS. The Impact of Functional and Structural Maturation of the Kidney on Susceptibility to Drug and Chemical Toxicity in Neonatal Rodents. Toxicologic Pathology 2021, Vol. 49(8) 1377-1388

pelvis dilation for animals given ≥ 30 mg/kg/day. These findings were fully or partially reversed after a 29-day recovery period. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimesters of human development."

Mechanism of Action Labeling

In keeping with the approved label of SGLT2 inhibitors (e.g., dapagliflozin, canagliflozin, empagliflozin) indicated for heart failure and the unclear nature of the contribution of SGLT1 inhibition to the cardiac benefit (as discussed in detail in the EPC portion of this memo), the suggested language for Section 12.1 of the sotagliflozin label is included below:

12.1 Mechanism of Action

(b) (4)

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/s/

XUAN CHI
02/09/2023 08:41:54 AM

TODD M BOURCIER
02/10/2023 10:48:05 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	216203
Supporting document/s:	2, 20
Applicant's letter date:	12/30/2021, 05/20/2022
CDER stamp date:	12/30/2021, 05/27/2022
Product:	Inpefa or (b) (4) ™ (Sotagliflozin, LX4211, SAR439954)
Indication:	Heart Failure
Applicant:	Lexicon Pharmaceuticals, Inc
Clinical Review Division:	Division of Cardiology and Nephrology (DCN)
Pharm/Tox Division	Division of Pharm/Tox for Cardiology, Hematology, Endocrinology, and Nephrology (DPT-CHEN)
Reviewer:	Baichun Yang
Supervisor/Team Leader:	Xuan Chi
Clinical Division Director:	Norman Stockbridge
Project Manager:	KANE, BRIDGET E.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 216203 are owned by Lexicon Pharmaceuticals, Inc or are data for which Lexicon Pharmaceuticals, Inc has obtained a written right of reference. Any information or data necessary for approval of NDA 216203 that Lexicon Pharmaceuticals, Inc does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 216203.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction (and Clinical Rationale)

Sotagliflozin (LX4211) is an orally administered small molecule, dual sodium-glucose cotransporter 1 (SGLT1) and sodium-glucose cotransporter 2 (SGLT2) inhibitor, seeking marketing approval to reduce the risk of major adverse cardiovascular events in adults with heart failure or with type 2 diabetes mellitus (T2DM), chronic kidney disease and other cardiovascular risk factors. SGLT1 inhibition in the intestines may improve glucose control. SGLT2 inhibition blocks glucose reabsorption in the renal proximal tubules resulting in increased urinary glucose excretion (UGE), which leads to caloric loss and diuresis. Sotagliflozin also reduces sodium reabsorption in the proximal tubules and increases the delivery of sodium to the distal tubules of the kidney. This may influence several physiological functions including, but not restricted to, lowering both pre- and afterload of the heart and downregulation of sympathetic activity, and decreased intraglomerular pressure. All these effects may contribute to the improvement in cardiovascular (CV) and renal outcomes observed with SGLT2/SGLT1 inhibitors in adults with T2DM.

1.2 Brief Discussion of Nonclinical Findings

Sotagliflozin is a potent dual inhibitor of human SGLT2 (IC_{50} 1.8 nM) and SGLT1 (IC_{50} 36.3 nM). SGLT2 inhibition blocks glucose reabsorption in the renal proximal tubules resulting in increased urinary glucose excretion (UGE). SGLT1 inhibition in the intestines may improve glucose control by reducing or delaying postprandial glucose absorption delivering more glucose distally and increasing the release of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) levels into the portal circulation, which in turn increase insulin secretion. Oral administration of sotagliflozin caused consistently significant UGE in mice, rats, dogs, and monkeys in a dose-dependent fashion, with ED_{50} values of ~1.8, 0.75, and 0.2 mg/kg respectively. In various animal models of diabetes mellitus (both T2DM and T1DM) or obesity, sotagliflozin inhibited SGLT1 and SGLT2, resulting in improved glycemic control and lower HbA1c levels. Chronic treatment with sotagliflozin in a ZSF-1 rat model of systemic arterial hypertension with diabetes mellitus and obesity [a metabolic rat model of heart failure with preserved ejection fraction (HFpEF)] showed significant improvement in in vivo surrogate markers of diastolic dysfunction including left ventricular end-diastolic pressure, left atrial remodeling, and isovolumetric relaxation time, and resulted in recovery of heart rate and increased cardiac output.

Sotagliflozin also reduces sodium reabsorption in the proximal tubules and increases the delivery of sodium to the distal tubules of the kidney[1,2,3]. This may influence several physiological functions including, but not restricted to, lowering both pre- and afterload of the heart and downregulation of sympathetic activity, and decreased intraglomerular pressure.

Sotagliflozin may improve metabolic adaptation of the cardiomyocyte to the in vivo conditions related to cardiac adverse remodeling in diabetic cardiomyopathy. All these effects may be beneficial to adults with T2DM regarding cardiovascular (CV) and renal outcomes.

Safety pharmacology studies assessing the cardiovascular, neurological, respiratory, renal, and gastrointestinal effects of sotagliflozin did not identify any acute safety concerns at clinical exposure levels (NOAELs 100 mg/kg in dogs or rats, ≥24X MHRD).

The pharmacokinetics (PK) of sotagliflozin has been assessed in mice, rats, dogs, and monkeys after both intravenous (IV) and oral dosing. Sotagliflozin is rapidly absorbed across species after oral dosing with a bioavailability in rats and dogs (50-71%) that is comparable to that in the human (63%). Sotagliflozin is extensively distributed throughout the body in the rat, although levels in brain, spinal cord, eye, bone, and bone marrow are relatively low. Plasma protein binding of sotagliflozin is high across species including humans (>91%).

Sotagliflozin is extensively metabolized in the mouse, rat, monkey, and human, but shows little apparent metabolism in the dog. In humans, direct glucuronidation is the predominant route of metabolism; while in the rat and mouse, there is more oxidative metabolism in addition to glucuronidation. The sotagliflozin glucuronide conjugate, sotagliflozin-3-O-glucuronide, accounts for 94% of total radioactivity in human plasma and is higher than in the rat and the mouse. As sotagliflozin-3-O-glucuronide has minimal pharmacological activity at SGLT1 and SGLT2 and is not an acyl glucuronide of sotagliflozin, there is no toxicological concern at clinical exposure. UGT1A9 and, to a lesser extent, CYP3A4 are responsible enzymes for the metabolism of sotagliflozin in humans.

In rats, excretion of an orally administered dose was primarily recovered in the feces (82%) with 13% excreted in the urine. Whereas, in humans, the main route of elimination was through the urine (57%) with 37% excreted in the feces.

The toxicity profile of sotagliflozin was evaluated by a nonclinical development program conducted in accordance with international guidances appropriate for a novel, small

[1] Lapuerta P et al., Development of sotagliflozin, a dual sodium-dependent glucose transporter 1/2 inhibitor. Diabetes and Vascular Disease Research. 2015;12: 101-10.
[2] Tsimihodimosa V et al., SGLT2 inhibitors and the kidney: Effects and mechanisms. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2018; 12: 1117–1123.
[3] Sen T et al., A kidney perspective on the mechanism of action of sodium glucose co-transporter 2 inhibitors. Cell Metabolism 2021; 33: 732-739

molecule therapeutic intended for chronic use. This includes a single-dose rat study, a battery of definitive repeat-dose general toxicity studies in rats (up to 26 weeks) and dogs (up to 39 weeks), a full battery of genetic toxicity studies, mouse and rat carcinogenicity studies, and a battery of exploratory and definitive reproductive and developmental toxicity studies in rats and rabbits. Other toxicity studies were performed as needed.

In general toxicity studies, the rat was the more sensitive one of the two species used. Target organs include the kidney (cortical tubule dilation and inflammation/hyperplasia), bladder (inflammation/hyperplasia), prostate (inflammation), bone (increased trabecular bone), and stomach (nonglandular hyperplasia/hyperkeratosis and ulcers), most of which were identifiable after 4 weeks of dosing in the rat. Adverse effects in the dog were generally limited to gastrointestinal-related clinical signs and an increase in heart rate. Thyroid (follicular cell hyperplasia/adenoma/carcinoma) was an additional target organ identified in the 2-year carcinogenicity study in rats.

Renal tubule dilation was observed at doses ≥30 mg/kg/day in the 6-month rat study [males, AUC_{0-24} 15077 ng·h/ml, 8X maximal human recommended dose (MHRD)] and at doses ≥10 mg/kg/day in the 2-year study in males (AUC_{0-24} 5440 ng·h/ml, 3X MHRD) and females (AUC_{0-24} 9540 ng·h/ml, 5X MHRD). The reversible tubule dilation, which was associated with an increase in kidney weight but no biomarker changes indicating renal injury, is considered an adaptive change to the polyuria and is consistent with the findings of other SGLT2 inhibitors. Urinary tract inflammatory changes and hyperplasia/hypertrophy affecting the renal pelvis, urinary bladder, and/or urethra in the 6-month study were largely limited to the high dose females (300 mg/kg/day, AUC_{0-24} 267278 ng·h/ml, 138X MHRD); however, in the 2-year rat study, inflammatory changes and infection affecting the kidney and bladder occurred across all dose groups (≥10 mg/kg/day) in males (AUC_{0-24} 5440 ng·h/ml, 3X MHRD). These dose-related increases in urinary tract inflammation/infection, which were considered secondary to pharmacodynamically mediated glucosuria and/or calculi formation, were not associated with any neoplastic changes in the urinary tract in the 2-year study at exposures up to 15X MHRD in males (AUC_{0-24} 28500 ng·h/ml) and 45X MHRD in females (AUC_{0-24} 87800 ng·h/ml). Renal changes in dogs were limited to reversible increases in kidney weight.

The no-effect dose of sotagliflozin for prostate inflammation was 30 mg/kg/day in the 6-month rat study and falls below the lowest doses evaluated in the 2-year rat studies (<10mg/kg/day). Prostate inflammation was observed in all pivotal toxicology studies in rats including the juvenile animal study. Moderate to marked prostate inflammation was observed at the mid and high doses (17-54X MHRD) in the 6-month rat study with no apparent reversibility after the 4-week recovery. In the 2-year rat study, sotagliflozin caused moderate to severe prostate inflammation across all dose groups (≥10 mg/kg/day, 3X MHRD). The mechanism of prostate inflammation is unknown. While some cases appear to be related to urinary tract inflammation/infection, there was a general absence of bladder or other urinary tract inflammation/infection associated with the prostate inflammation in the 6-month study. The possible involvement of SGLT1,

which is expressed in the prostate, cannot be excluded. No inflammation was observed in the mouse or the dog.

In the 6-month rat study, there was a dose-related increase in trabecular bone of the sternum (minimal to moderate) and decrease in the calciotropic hormones 1,25-dihydroxyvitamin D and parathyroid hormone (PTH) in all dose groups (≥30 mg/kg/day, 8X MHRD) that are likely due to changes in calcium homeostasis as a result of intestinal SGLT1 inhibition. Only reduction in 1,25-dihydroxyvitamin D levels occurred in the 9-month dog study at the mid and high dose. Gastrointestinal (GI)-related clinical signs including vomiting, watery feces, and diarrhea are common in dogs, which may minimize the intestinal SGLT1 inhibition-induced changes in calcium homeostasis, lead to less clinical manifestations in bones.

Higher incidences of glandular stomach acute erosions/ulcers, non-glandular stomach hyperplasia/hyperkeratosis were observed in the 4-week, 26-week, and 2-year rat studies at doses ≥30 mg/kg/day (8X MHRD). These findings may be related to SGLT1 inhibition. However, there were no similar findings in dogs dosed up to 9 months or clinical reports indicative of gastrointestinal injury.

There were higher incidences of thyroid follicular cell hyperplasia, adenoma, and carcinoma in all sotagliflozin dose levels in both males and females in the 2-year rat study. The thyroid follicular cell hyperplasia, adenoma, and carcinoma are continuous histological changes of pathological cellular growth. However, independent FDA statistical analysis did not find the thyroid follicular cell carcinoma at the high dose to be statistically significant in pairwise analysis, and the Executive Carcinogenicity Assessment Committee (ECAC) concurred that there were no treatment-related increases in neoplasms in rats at doses up to 75 mg/kg (18-54X MHRD). Without the end point of neoplasm, the significance of continuous pathological cellular growth in thyroid in rats is limited.

Reproductive and developmental toxicity were assessed in fertility and early embryonic development, embryofetal development, and pre- and post-natal development animal studies. Sotagliflozin had no effects on reproductive performance or fertility indices in male and female rats at exposures up to 55-138X the MHRD despite mortality/ moribundity in females and significant reductions in weight gain in males at 19-25X the MHRD. Sotagliflozin was not teratogenic in the rat at 100 mg/kg (40X MHRD) or in the rabbit at 200 mg/kg (9X MHRD). In rats, a higher dose (350 mg/kg; 161X MHRD) caused both maternal and fetal toxicity including significant reduction in maternal weight gain, embryo-lethality, reduced fetal weights, altered sex ratio, and cardiovascular and skeletal malformations. The 200 mg/kg dose in rabbits caused significant reductions in maternal weight gain, but had no effect on fetal survival or growth, or caused any malformations.

In the post-natal development study in the rat, sotagliflozin had no effect on developmental landmarks, sexual maturation, neural behavior development, or reproductive performance of the F1 generation (up to 19-25X MRHD). However,

sotagliflozin caused dilation of the renal pelvis in F1 pups exposed at ≥30 mg/kg (4-7X MHRD) in utero and during lactation, resulting in a NOAEL of 10 mg/kg/day (1.3-2.5X MHRD for the F1 generation.

The kidney was also identified as a target organ in male and female juvenile rats with renal tubular and pelvis dilatation at 5-11X MHRD in the juvenile animal study. Increases in kidney weights and renal mineralization (males only) across all dose groups (~1X MHRD) were observed as well. All treatment-related renal changes demonstrated full or partial reversibility following the 4-week recovery period.

The renal changes in rats in the post-natal development and juvenile animal studies are considered secondary to the pharmacodynamic activity of the drug and are consistent with the effects of other SGLT2 inhibitors. Given that sotagliflozin is distributed to most fetal tissues including the kidney when administered to dams during gestation and the differences in the timing of kidney development/maturation between rats and humans, the treatment-related renal effects in the juvenile rats are considered relevant to the assessment of reproductive and developmental risk. The morphological and functional renal development in the juvenile rat corresponds to renal development in humans during the late second and third trimester through approximately 2 years of age. Lactational exposure may also pose a risk to the developing human kidney as sotagliflozin was excreted in maternal milk (1.3-fold higher than plasma; on AUC basis) in rats.

Sotagliflozin was not mutagenic or clastogenic in a standard battery of two in vitro and one in vivo GLP genetic toxicology studies.

The potential of sotagliflozin to induce tumors was assessed in the 6-month transgenic RasH2 mouse study and the 2-year rat carcinogenicity study. There were no statistically significant increases in neoplasms considered treatment related in transgenic RasH2 mice dosed up to 100 mg/kg. Nor were there any treatment-related neoplasms in male (up to 15X MHRD) and female (up to 45X MHRD) rats. This negative carcinogenetic outcome for sotagliflozin differs from other SGLT2 inhibitors which are typified by neoplasms of the adrenals, testes, and renal tubules. The absence of renal and adrenal tumors is particularly noteworthy for this SGLT1/2 inhibitor because the tumorigenic MOA for these tumors is reportedly carbohydrate malabsorption secondary to intestinal SLGT1 inhibition. The absence of these tumors with sotagliflozin is likely due to less carbohydrate malabsorption than observed with other class members at the doses evaluated in these studies.

In conclusion, potential safety issues identified from the nonclinical program derive from intended pharmacological action of sotagliflozin on SGLT1 and SGLT2, rather than from compound-specific toxicity.

1.3 Recommendations

1.3.1 Approvability

The nonclinical data support market approval of sotagliflozin.

1.3.2 Additional Non-Clinical Recommendations

Adaptive changes to renal structures and increased susceptibility to urinary tract inflammation and infection were derived from glucosuria and osmotic diuresis secondary to renal SGLT2 inhibition. These events are expected to occur clinically with long-term use of sotagliflozin as with other marketed SGLT2 inhibitors.

A definitive cause for prostate inflammation observed in rats is not established; it is plausible that both SGLT1 inhibition and urinary tract infection or inflammation are contributory events. A functional consequence of prostate inflammation was not identified in the nonclinical program which is reassuring that an adverse clinical outcome is unlikely with prolonged administration. However, as SGLT1 inhibition represents a novel pharmacological target, the long-term clinical outcome for prostate health is uncertain and could only be further addressed by subsequent post-market experience.

Also related to SGLT1 being a novel pharmacological target, the long-term clinical outcome of increased glucose/water residence time in the gastrointestinal tract must also await post-market experience. The nonclinical program identified pathological changes to the gastrointestinal tract and to bone (secondary to altered calcium homeostasis) at exposures higher than the therapeutic dose. The degree of effect in clinical trials thus far has resulted in diarrhea, but no other gastrointestinal or bone-related adverse events as observed in the nonclinical program.

1.3.3 Labeling

(b) (4) in Risk Summary under section 8.1 Pregnancy. Under section 13.1 Carcinogenesis, the interpretation for (b) (4) in the rat carcinogenicity study is “a (b) (4) from FDA analysis of (b) (4) (b) (4) Revised wording (additions in **bold**; deletions in strikeout) are recommended in the following boxes:

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number 1018899-04-1

Generic Name Sotagliflozin

Code Name SAR439954, LX4211, LX-4211, LP-802034

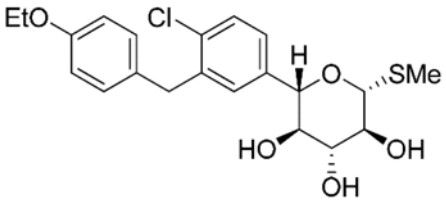
Chemical Name

Chemical Abstract Services (CAS)	β-L-Xylopyranoside, methyl 5-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-1-thio-, (5S)-
International Union of Pure and Applied	Methyl (5S)-5-[4-chloro-3-(4-ethoxybenzyl)phenyl]-1-thio- β-L-xylopyranoside

Other chemical name (WHO)	Methyl (5S)-5-C-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-1-thio-β-L-xylopyranoside
Other chemical name	(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)- 6- (methylthio)tetrahydro-2H-

Molecular Formula/Molecular Weight $C_{21}H_{25}ClO_5S$ / 424.94

Structure



Pharmacologic Class

Sodium-dependent glucose co-transporter (SGLT) 1 and 2 inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

Nonclinical submission was cross-referenced to following NDA and INDs:
NDA 210934, Zynquista (sotagliflozin) for treatment type 1 diabetes mellitus;
IND 102191, (b) (4)
IND 135095, Sotagliflozin for treatment of heart failure and (b) (4)

2.3 Drug Formulation

Sotagliflozin is available as an immediate release tablet at 200 mg strength. The composition of sotagliflozin 200 mg film-coated tablets is provided below along with function of excipients and reference to Pharmacopoeia standards.

Components	Unit quantity (mg/tablet)	Percentage (w/w)	Function	Reference to standards[a]
Sotagliflozin	200.000	(b) (4)	Active substance	In-house monograph
(b) (4)			(b) (4)	Ph. Eur.-NF
Microcrystalline cellulose (b) (4)				Ph. Eur.-NF
Croscarmellose sodium				Ph. Eur.-NF
(b) (4)				Ph. Eur.-NF
Talc				Ph. Eur.-USP
Magnesium stearate[c]				Ph. Eur.-NF
Core tablet mass	(b) (4)	**100.00**		
Film-coating				
(b) (4)			(b) (4)	In-house monograph
				Ph. Eur.-USP
Black ink[f]				In-house monograph
Film-coated tablet mass	**384.533**			

a When reference is made to a Pharmacopoeia, this means that the current edition of this Pharmacopoeia is applied.

b Also referred to as Colloidal silicon dioxide NF common standard.

c (b) (4)

d (b) (4) polyvinyl alcohol partly hydrolyzed (Ph. Eur.-USP), (b) (4) titanium dioxide (b) (4) (Ph. Eur.-USP), (b) (4) talc (Ph. Eur.-USP) and (b) (4) indigo carmine aluminum lake (b) (4) - (b) (4)

e (b) (4)

f shellac (b) (4) (Ph. Eur.-USP/NF), (b) (4) isopropyl alcohol (Ph. Eur.-USP), (b) (4) - black iron oxide (b) (4) (NF), (b) (4) N-butyl alcohol (NF), (b) (4) propylene glycol (Ph. Eur.-USP), (b) (4) ammonium hydroxide at (b) (4) (Ph. Eur.-NF).

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Population - Adults with heart failure [redacted] acute or worsening heart failure; and Adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.

Dosing Regimen - The recommended starting dose of sotagliflozin is 200 mg once daily (QD) before the first meal of the day. Sotagliflozin should be increased to 400 mg QD in patients tolerating the 200 mg dosage. For patients with [redacted] decompensated heart failure, dosing may begin [redacted] hemodynamically stable, including [redacted] or immediately upon discharge.

2.7 Regulatory Background

Summary of Key Relevant Regulatory Information

Application #	Submission/FDA Correspondence	Date
IND 135095	Agreed Initial Pediatric Plan -Agreement (Full Waiver Agreed)	03-Nov-2021
NDA 210934	Complete Response - not favorable Risk/benefit assessment	22-Mar-2019
	Pharm/Tox review - Approvable	28-Nov-2018

3 Studies Submitted and Reviewed

SED00079	Role of combined SGLT1 and SGLT2 inhibition (sotagliflozin) in diabetic cardiomyopathy
LX4211-n107	In Silico Analysis of Impurities of Sotagliflozin

3a Previously Reviewed Information

Dr. Patricia Brundage of DPT-CHEN reviewed the nonclinical information submitted under NDA 210934 (sotagliflozin for treatment type 1 diabetes mellitus). The review was checked into DARRTS on 11/28/2018. It was concluded that “The nonclinical data support market approval of sotagliflozin”. Nonclinical information in the current review for NDA 216203 is mostly excerpted from or based on Dr. Patricia Brundage’s review dated on 11/20/2018 (see the appendix).

4 Pharmacology

4.1 Primary Pharmacology

Sotagliflozin is a potent dual inhibitor of human SGLT2 (IC_{50} 1.8 nM) and SGLT1 (IC_{50} 36.3 nM). Through its activity at SGLT2, sotagliflozin caused consistent significant urinary glucose excretion in mice, rats, dogs, and monkeys in a dose-dependent fashion during the first 24 hours following oral administration. The ED_{50} for sotagliflozin is ~1.8,

0.75, and 0.2 mg/kg in mice, rats, and dogs, respectively. In various animal models of diabetes mellitus [both type 2 diabetes mellitus (T2DM) and type 1 diabetes mellitus (T1DM)] or obesity, sotagliflozin inhibited SGLT1 and SGLT2, resulting in improved glycemic control and lower hemoglobin A1c (HbA1c) levels.

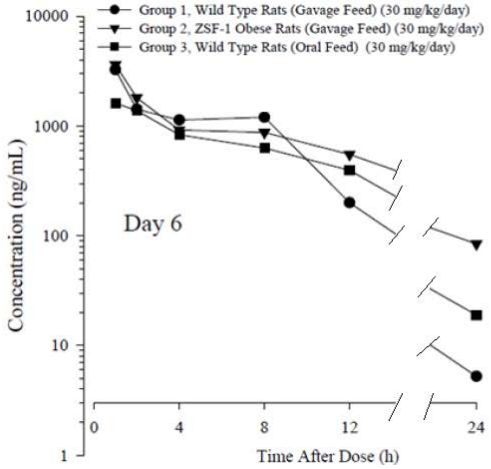
SED00079 Role of combined SGLT1 and SGLT2 inhibition (sotagliflozin) in diabetic cardiomyopathy

This study was done in [redacted] (b) (4) and reported in 2020. A ZSF-1 rat model of systemic arterial hypertension with diabetes mellitus and obesity, characterized by left ventricular diastolic dysfunction and congestion, and mimics several key features of metabolic syndrome with heart failure with HFpEF (heart failure with preserved ejection fraction), was used. The following hypotheses were assessed:

- Chronic treatment with sotagliflozin improves cardiac function and myocardial remodeling in a model of diabetic cardiomyopathy on both cell and organ levels.
- Chronic treatment with sotagliflozin reduces Na^+ uptake into cardiomyocytes and improves cardiomyocytes Ca^{2+} handling in diabetic hearts.
- Chronic treatment with sotagliflozin reduces myocardial glucose uptake *in vivo* as well as accumulation of advanced glycation end products in diabetic hearts.
- Chronic treatment with sotagliflozin reduces myocardial fibrosis and improves myocardial remodeling in diabetic hearts.

For pharmacokinetics (PK) and dose validation, 6 male WKY (wild type) rats and 6 male obese ZSF-1, 16 weeks of age, the same age as the beginning of the treatment in the main part of the study, were administered sotagliflozin at 30 mg/kg/day by oral gavage as well as by oral feeding for 6 days. LX4211 (sotagliflozin) plasma concentrations on day 6 are shown in Figure 1. Plasma LX4211 PK parameters are shown in Table 1.

Figure 1. Mean plasma sotagliflozin concentrations



Analyte	Dose Level (mg/kg/day)	Animal Type	Dose Group	Parameter	Time after Dose (h) 1	2	4	8	12	24
LX4211	30	Wild Type Rats (Gavage Feed)	1	Mean	3260	1420	1130	1200	200	5.23
				CV%	23	21	18	21	30	200
		ZSF-1 Obese Rats (Gavage Feed)	2	Mean	3600	1810	919	874	551	84.5
				CV%	19	24	13	44	48	73
		Wild Type Rats (Oral Feed)	3	Mean	1620	1380	831	630	394	19.0
				CV%	44	4	25	24	25	110
LX4211-3-O-Glucuronide	30	Wild Type Rats (Gavage Feed)	1	Mean	67.0	22.7	25.8	29.3	1.46	0.00
				CV%	59	51	32	64	125	NA
		ZSF-1 Obese Rats (Gavage Feed)	2	Mean	53.6	28.1	14.5	12.5	5.64	0.610
				CV%	23	22	18	45	72	200
		Wild Type Rats (Oral Feed)	3	Mean	22.6	25.9	8.94	7.19	2.01	0.00
				CV%	78	28	38	24	91	NA

CV% - Coefficient of variation.
NA – Not applicable.
Note: Values are rounded to three significant figures (whole number for CV%).

Table 1. Summary of plasma sotagliflozin PK parameters

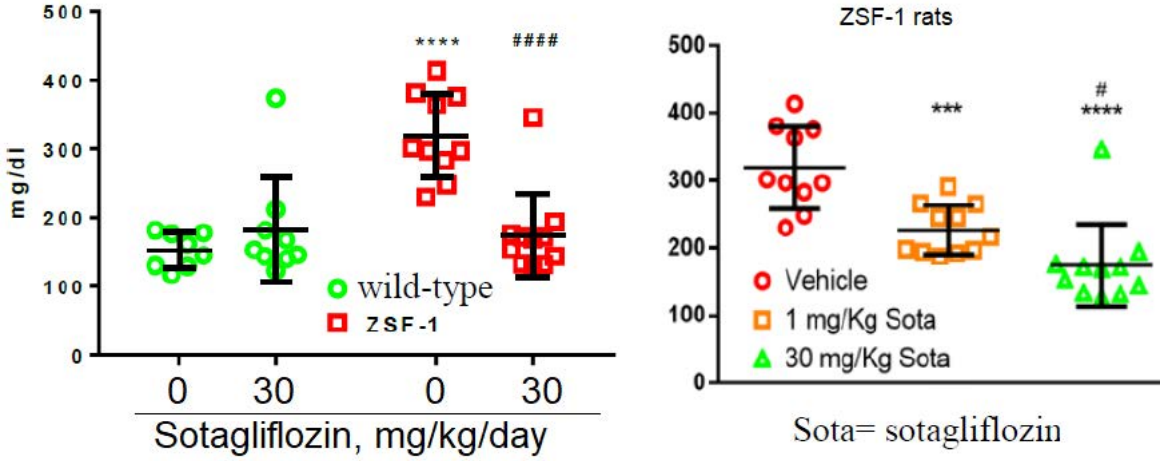
Analyte	Interval (Day)	Dose Level (mg/kg/day)	Animal Type	Dose Group	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{0-24} (ng·h/mL)	AUC_{2-24} (ng·h/mL)
LX4211	6	30	Wild Type Rats (Gavage Feed)	1	3260	1.0	15200	15200	11300
			ZSF-1 Obese Rats (Gavage Feed)	2	3600	1.0	17500	17500	13000
			Wild Type Rats (Oral Feed)	3	1620	1.6	11600	11600	9660
LX4211-3-O-Glucuronide	6	30	Wild Type Rats (Gavage Feed)	1	67.0	1.0	298	307	229
			ZSF-1 Obese Rats (Gavage Feed)	2	53.6	1.0	238	238	170
			Wild Type Rats (Oral Feed)	3	25.9	2.0	113	125	97.5

Notes Values are rounded to three significant figures (one decimal place for t_{max}).

With exception of 1 hour post dose, the coefficient of variation of the sotagliflozin plasma levels in the oral feeding group was not bigger than the gavage groups, suggesting that oral feeding is not inferior to the gavage feeding technique. Thus, a dose of 30 mg/kg/day of sotagliflozin given by oral gavage in WKY and ZSF-1 obesity as well as by oral feeding in WKY was suitable in the rat model to reach plasma levels previously shown to inhibit SGLT1. Therefore, this dosage was given in the main experiments with 6 weeks chronic treatment. The oral feeding technique was used through the main part of the study.

Wild-type (WT) rats and ZSF-1 rats were orally administered either vehicle or sotagliflozin at 1 or 30 mg/kg/day from age Week 17 to Week 23. In this model, fasting serum glucose levels were significantly elevated in the diseased animals at Week 23 when compared with the wild type animals. A dose-dependent reduction of serum glucose was observed following administration of 1 and 30 mg/kg sotagliflozin. Chronic treatment with 30 mg/kg/day sotagliflozin normalized serum glucose in the diseased animals (Figure 2). However, sotagliflozin at either concentration had no effect on body weight in WKY or ZSF-1.

Figure 2. Fasting serum glucose in week 23 in rats (*p value vs. WT Vehicle, # p vs. ZSF-1 Vehicle; modified from the submission)



The effects of 6-week daily treatment with sotagliflozin in rats on cardiovascular function and morphology were assessed. At baseline (week 16 prior to the treatment) when compared to WT group, ZSF-1 group had higher blood pressure (BP) and stroke volumes, lower heart rates, and similar ejection fraction and cardiac output (Figure 3, Figure 4). Treatment with sotagliflozin did not affect any of BP parameters in ZSF-1 group, but showed lower systolic BP (137 vs 158 mmHg in vehicle; $p<0.001$), mean BP (105 vs 122 mmHg in vehicle; $p<0.001$, Figure 3) and diastolic BP (89 vs 104 mmHg in vehicle; $p < 0.01$) in WT group. Treatment with 30 mg/kg/day sotagliflozin for 6 weeks led to a recovery of heart rate in ZSF-1 animals (Figure 4). This resulted in increased cardiac output in sotagliflozin-treated ZSF-1 rats when compared to untreated ZSF-1 rats and the wild-type controls (Figure 4).

Figure 3. Mean blood pressure in rats (Sota 30 = sotagliflozin 30 mg/kg/day, from the submission)

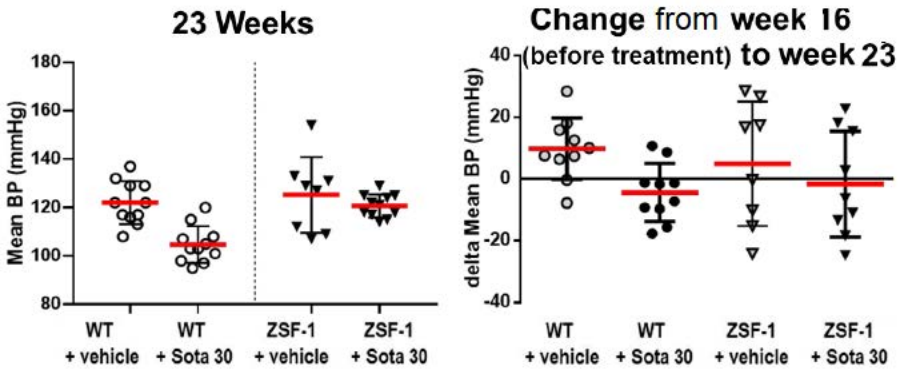
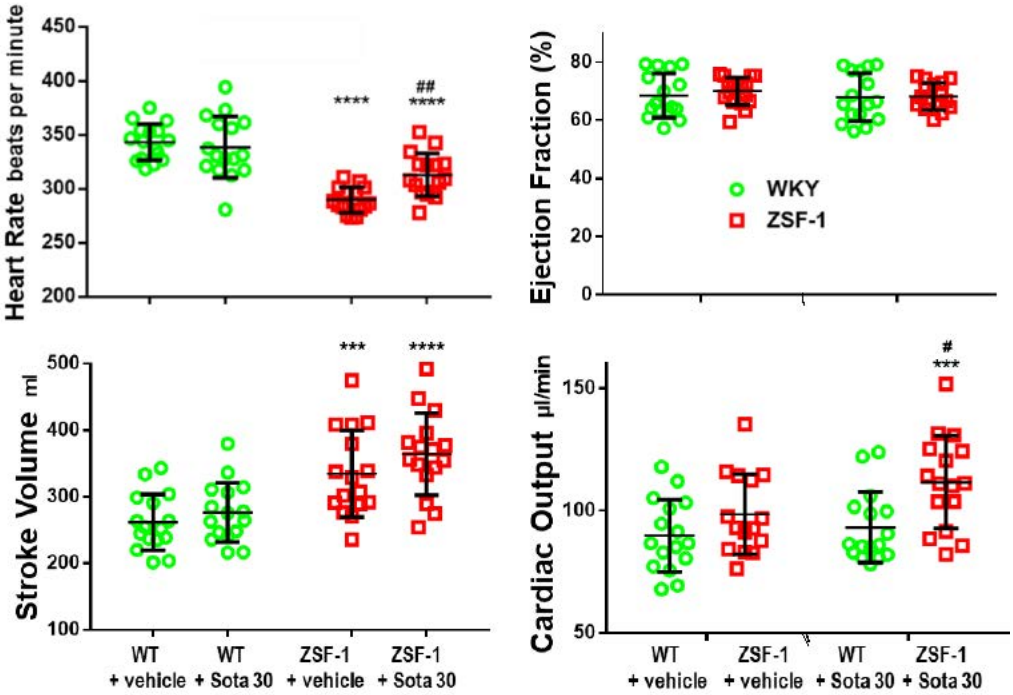
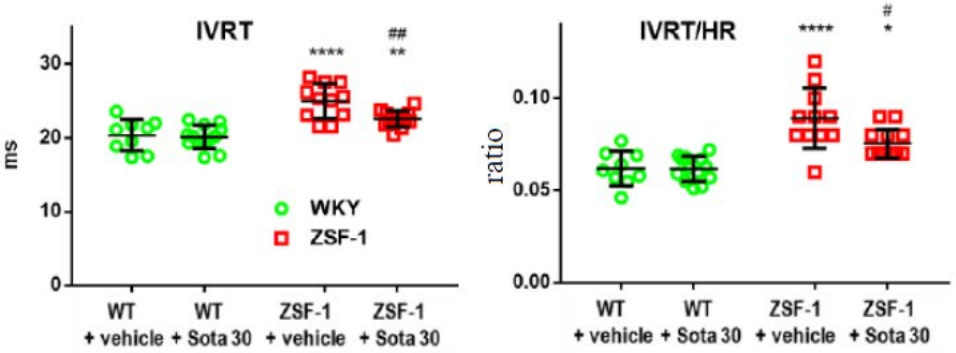


Figure 4. Left ventricular systolic function in rats during week 23 (Sota 30 = sotagliflozin 30 mg/kg/day, *p value vs. WT Vehicle, # p value vs. ZSF-1 Vehicle; from the submission)



Isovolumetric relaxation time (IVRT), an established marker of early relaxation in the left ventricle, was significantly prolonged in ZSF-1 rats. Chronic administration of 30 mg/kg/day sotagliflozin led to a shortening of the isovolumetric relaxation time in ZSF-1 rats (Figure 5), suggesting improved relaxation in the diseased animals treated with sotagliflozin.

Figure 5. Effect of sotagliflozin on isovolumetric relaxation time in rats (from the submission)

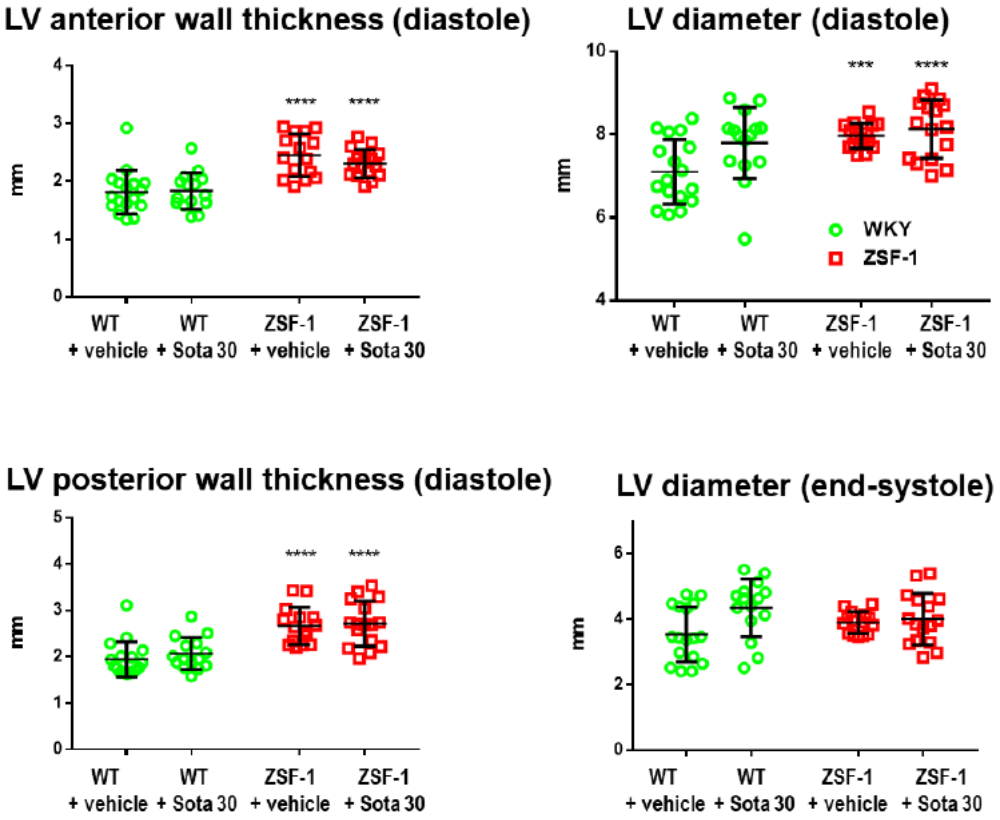


IVRT = isovolumetric relaxation time; IVRT/HR = ratio of isovolumetric relaxation time to heart rate; Sota 30 = 30 mg/kg/day sotagliflozin; WKY = wild type. *p value vs. WT Vehicle, # p value vs. ZSF-1 Vehicle

At week 23, ZSF-1 animals showed LV hypertrophy as reflected by end-diastolic wall thickness. Treatment with Sotagliflozin 1 or 30 mg/kg/day had no impact on LV remodeling in ZSF-1 (Figure 6). Results by this measurement were confirmed by

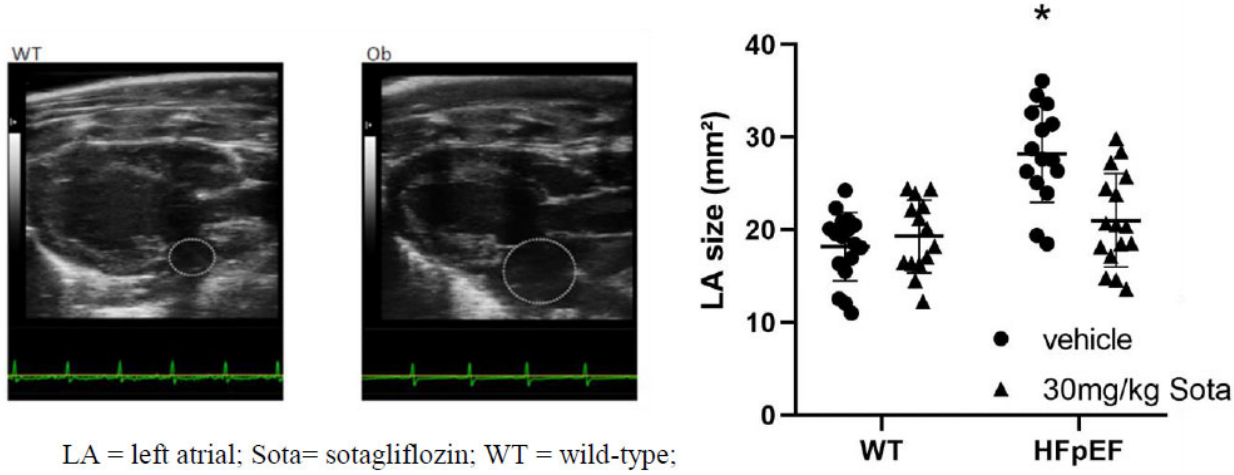
dissected organ weight when normalized to tibia length. Left atrial area measured in parasternal long axis view was increased in ZSF-1 rats likely reflecting chronically elevated left ventricular end-diastolic pressure. Following chronic treatment with 30 mg/kg/day sotagliflozin, left atrial size was numerically lower in treated ZSF-1 vs. untreated ZSF-1 and not significantly different from WT (Figure 7).

Figure 6. End-diastolic wall thickness in rats (from the submission)



Sota 30 = 30 mg/kg/day sotagliflozin; WKY = wild type. *p value vs. WT Vehicle, # p value vs. ZSF-1 Vehicle

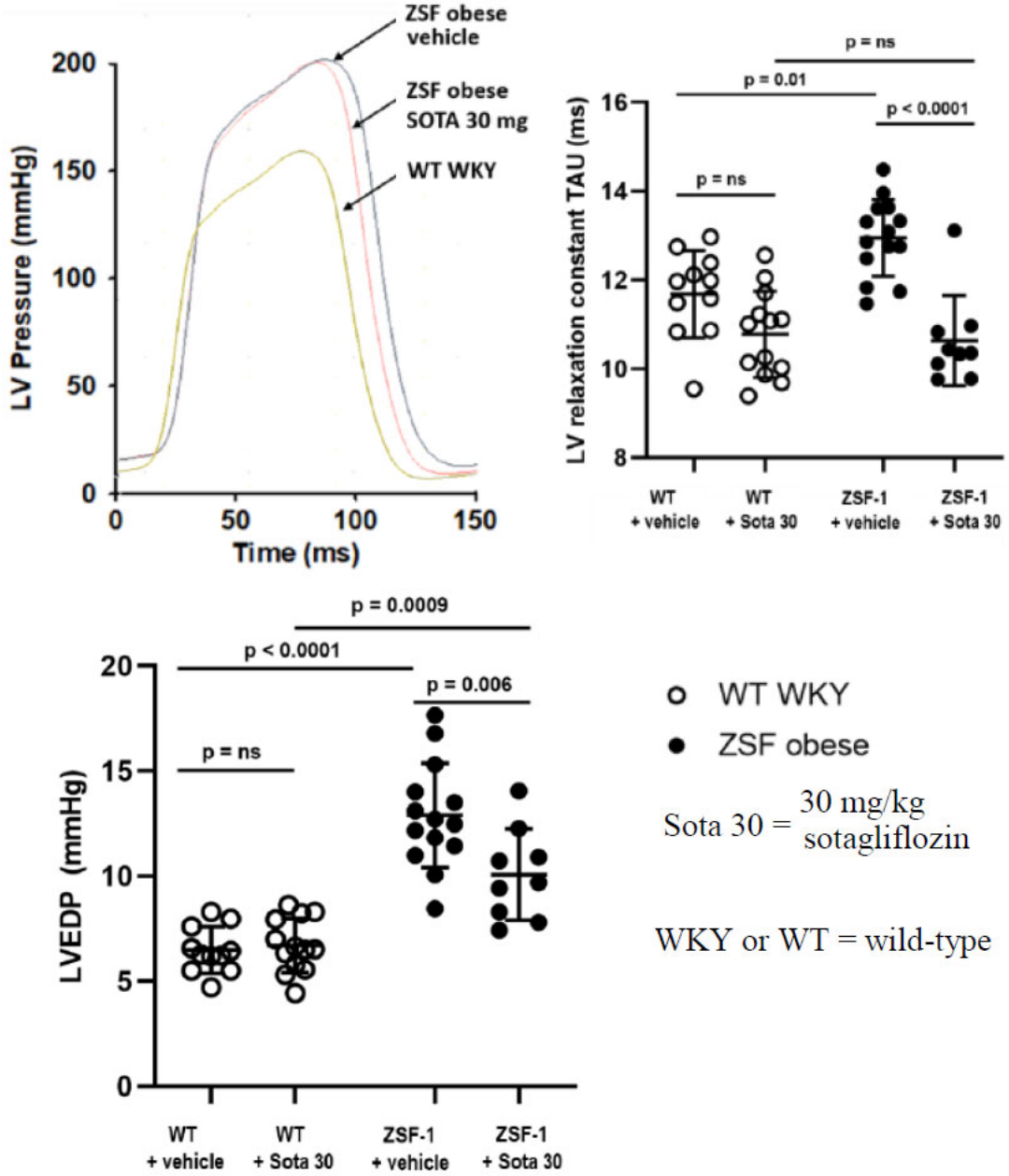
Figure 7. Left atrial size in rats during week 23 (from the submission)



LA = left atrial; Sota= sotagliflozin; WT = wild-type;

Invasive hemodynamics was performed pre-sacrifice in all groups at Week 23. ZSF-1 animals had elevated left ventricular peak pressure and sotagliflozin did have an effect on this parameter. The relaxation constant of left ventricular pressure was significantly slower in ZSF-1 animals, and this was normalized by chronic treatment with sotagliflozin. In addition, left ventricular end-diastolic pressure, a key indicator of congestion in HFpEF, was increased in ZSF-1 animals, and this increase was partially and significantly attenuated by chronic treatment with sotagliflozin (Figure 8).

Figure 8. Effect of sotagliflozin on invasive hemodynamic parameters in wild-type and ZSF-1 rats (From the submission)



In week 23, determined by positron emission tomography (PET), glucose uptake in myocardium was significantly attenuated in ZSF-1 vs. WT rats. Sotagliflozin had no effect on the glucose uptake in WT or ZSF-1 rats.

Urine volume was significantly higher in ZSF-1 than in WT rats. Sotagliflozin had a trend of increase in urine volume in both ZSF-1 and WT rats.

For ex vivo assessments, left and right ventricular cardiomyocytes were isolated after the in vivo measurements at week 23. When compared to cardiomyocytes from WT rats, cells from ZSF-1 rats had longer sarcomere length, lower diastolic cytosolic $[Ca^{2+}]i$, accelerated kinetics of Ca^{2+} release and contraction (time to peak) as well as the kinetics of cytosolic Ca^{2+} decay and sarcomere relengthening, much more prone to chaotic irregular activity. Sotagliflozin treatment had no effects on these parameters of cardiomyocytes from ZSF-1 rats.

Following 6-week treatment with sotagliflozin, no difference in overall fibrosis were found between all groups. Sotagliflozin-treatment generally did not affect myocardial glucose transporter GLUT1 and GLUT4 levels. Other ex vivo determinations in cardiomyocytes suggested compensatory changes in excitation-contraction coupling and metabolic signaling, and sotagliflozin-treatment generally did not affect these changes.

In conclusion, chronic treatment with sotagliflozin in a metabolic rat model of HFpEF improved strong in vivo surrogate markers of diastolic dysfunction including left ventricular end-diastolic pressure, left atrial remodeling, and isovolumetric relaxation time. Sotagliflozin treatment also resulted in recovery of heart rate and increased cardiac output in the diseased animals. Sotagliflozin may improve metabolic adaptation of the cardiomyocyte to the in vivo conditions related to cardiac adverse remodeling in diabetic cardiomyopathy but had no effect on intrinsic cardiomyocyte contractility or Ca^{2+} signaling.

4.2 Secondary Pharmacology

Sotagliflozin (10 µM; 4249 ng/mL) did not demonstrate clinically relevant cross-reactivity in a panel of 75 receptors, enzymes, and ion channels (percent inhibition of control specific binding <50%).

Sotagliflozin showed cross-reactivity with two other members of the SGLT family: human SGLT5 (IC_{50} = 54.1 nM; 23 ng/mL) and human SGLT6 (IC_{50} = 27.3 nM; 12 ng/mL). Human SGLT5 is mainly localized in the kidney cortex with an expression pattern resembling that of SGLT2. It primarily functions to reabsorb mannose and fructose in a sodium-dependent manner. SGLT6 [also known as sodium myo-inosital cotransporter 2 (SMIT2)], which co-transports myo-inositol (over glucose) in a sodium-dependent manner, is expressed in the brain and spinal cord, as well as in the kidney and intestine. Distribution of sotagliflozin to the brain was very low in rats with concentrations well below that found in circulating blood and showed no evidence of

accumulation. There was also no evidence of central nervous system (CNS) activity in the pivotal toxicology studies in the rat and dog, or in the clinical studies. There was little cross reactivity with human SGLT3 (IC_{50} >10 μM), human SGLT4 (IC_{50} = 6.19 μM), and human sodium myo-inositol cotransporter 1 (IC_{50} = 4.35 μM).

4.3 Safety Pharmacology

Safety pharmacology studies assessing the cardiovascular, neurological, respiratory, renal, and gastrointestinal effects of sotagliflozin did not identify any acute safety concerns at clinical exposure levels[4].

- hERG assay - IC_{50} >23.5 μM
- Cardiovascular telemetry study in Beagle dogs - no effect on QT or QTc interval at dose levels up to 500 mg/kg; significantly higher heart rates (51% higher than controls) at 500 mg/kg, No Observed Adverse Effect level (NOAEL) was 100 mg/kg
- No adverse effects on the central nervous, respiratory, and gastric intestinal systems in rats at doses ≤100 mg/kg
- Pharmacologic effects on the renal system which are expected based on the mechanism of action and were considered non-adverse at doses ≤100 mg/kg in rats
- In vitro binding assay for 79 receptors/ion channels did not show any significant effect (<50% stimulation or inhibition)

5 Pharmacokinetics/ADME

The pharmacokinetics (PK) of sotagliflozin has been assessed in mice, rats, dogs, and monkeys after both intravenous (IV) and oral dosing.

- Plasma protein binding of sotagliflozin in vitro was 97.7, 97.7, 98.5, 91.7, and 93.8% in mice, rats, dogs, monkeys, and humans, respectively.
- Following oral administration, sotagliflozin was rapidly absorbed across species; sotagliflozin systemic exposure in all species tested was dose-dependent; oral bioavailability of sotagliflozin was ~98, 56, 50-70, and 5% in mice, rats, dogs, and monkeys, respectively.
- Mean volume of distribution at steady state was 2.1, 1.4, 1.4, and 2.2 L/kg in mice, rats, dogs, and monkeys, respectively.
- In rats, sotagliflozin was extensively distributed into tissues and organs (although levels in CNS, eye, bone, and bone marrow were relatively low), moderately into fetal tissues, excreted in the milk (mean milk:plasma concentration ratios were greater than one at 8 and 24 hours postdose), no accumulation in any tissue.

[4] Human steady-state exposure of sotagliflozin at 400 mg QD: mean AUC_{24} 1932 ng·h/ml, max AUC_{24} 12365 ng·h/ml, mean C_{max} 121.6 ng.ml (286 nM), max C_{max} 611.7 ng/ml (1439 nM), mean $C_{average}$ 80.7 ng/ml, max $C_{average}$ 516.3 ng/ml (from Study LX4211-N106, Table S4)

- Sotagliflozin-3-Oglucuronide, other positional glucuronides, and sulfoxide metabolites were observed in both the mouse and rat. The major sotagliflozin-derived metabolites found in human plasma were also found in rat plasma, albeit at lower levels. A major detoxification route in humans is via direct glucuronidation of sotagliflozin. Glucuronide conjugates of sotagliflozin showed little to no pharmacologic activity against SGLT1 and SGLT2.
- UGT1A9 and, to a lesser extent, CYP3A4 were the enzymes responsible for the metabolism of sotagliflozin *in vitro*
- The major route of excretion in the rat is via the feces.

6 General Toxicology

Seven oral GLP toxicology studies have been completed: a single-dose study in the rat, 4-week repeat dose studies (with 2 weeks recovery) in the rat and the dog, 13-week repeat dose studies (with 4 weeks recovery) in the rat and the dog, 26-week repeat dose study (with 4 weeks recovery) in the rat, and 39-week repeat dose study (with 4 weeks recovery) in the dog. Summaries of these toxicology studies with sotagliflozin are in Table 2. The rat was the more sensitive one of the two species.

In rat repeat-dose toxicology studies, sotagliflozin-related clinical signs included decreased body weight gain and body weight change along with increased food consumption. These changes were likely related to the expected sotagliflozin-related pharmacologic effect of decreased gastrointestinal (GI) glucose absorption and renal glucose reabsorption, with a resultant increase in urinary glucose excretion accompanied with osmotic diuresis. Regardless of the specific mechanism, the sotagliflozin-related changes did not result in consequential untoward findings and were not considered adverse. Glucosuria was a predisposing factor for infection and inflammation of the urogenital system. Sotagliflozin administration also resulted in increased urinary calcium and phosphorous excretion. Adverse findings including renal cortical tubule dilation and inflammation/hyperplasia, inflammation/hyperplasia in bladder, inflammation in prostate, increased trabecular bone, and stomach nonglandular hyperplasia/hyperkeratosis and glandular ulcers are summarized in Table 2. Target organs in rats include the kidney, bladder, prostate, bone, and stomach, most of which were identifiable after 4 weeks of dosing.

In dog repeat-dose toxicology studies, adverse effects were generally limited to GI-related clinical signs and an increase in heart rate (Table 2). Hepatocellular cytoplasmic rarefaction (lesser cytoplasmic density than normal) was observed in the 39-week study. This finding was considered a physiologic response to sotagliflozin-induced glucosuria; therefore, the decrease in hepatocellular glycogen was a secondary and not a direct effect. Glycogen depletion had fully reversed by the end of the recovery phase. Because cytoplasmic rarefaction in liver is a normal physiologic response to sotagliflozin-related pharmacologic effect, this finding was not considered adverse.

Based on the study results, the low-observed-adverse level (LOAEL) for male rats and No-observed adverse level (NOAEL) for female rats in 26-week oral sotagliflozin were 30 and 30 mg/kg/day, respectively; the NOAEL in 39-week oral sotagliflozin for male and female beagle dogs was 20 mg/kg/day (Table 2).

Table 2. Summary of general toxicity studies

Study, Species	Dose, mg/kg/day	Main compound-related adverse findings	LOAEL	NOAEL
			mg/kg/day	
Single-dose with 14-day observation, rats	0, 10, 100, 1000, or 2000	At ≥1000 mg/kg, reversible ↓serum chloride, & ↑serum urea nitrogen. At 2000 mg/kg, transient alterations in stool character.	1000	100
4-week repeat dose toxicity study, rats	0, 10, 30, 100, or 1000/500 mg/kg/day	↑absolute kidney weights at ≥30 mg/kg/day & relative kidney weights at all doses; reversible diffuse kidney tubular dilatation & glandular stomach acute erosions/ulcers at ≥30 mg/kg/day; ↑femur subphyseal bone that did not completely reverse at 1000/500 mg/kg/day. Mortality at 1000/500 mg/kg/day	30	10
13-week repeat dose toxicity study, rats	0, 3, 10, 30, or 100	↓total serum protein & albumin at ≥10 mg/kg/day; ↑kidney & liver weights at ≥3 mg/kg/day; reversible kidney tubular dilatation at ≥3 mg/kg/day. (Most changes reversed at ≤ 30 mg/kg/day)	30	10
26-week repeat dose toxicity study, rats	0, 30, 75, or 300	One female at 300 mg/kg/day dead on Day 90 due to hepatocellular necrosis, which may be secondary to sepsis or endotoxemia following drug-related inflammation/infection of the urinary tract; ↑urine Ca^{2+} & P^{3+} excretion, serum urea nitrogen & alkaline phosphatase (ALT) activity at ≥30 mg/kg/day, ↑serum gamma glutamyl transferase (GGT) activity at 300 mg/kg/day; Reversible ↓1,25-dihydroxyvitamin D & parathyroid hormone (PTH) at ≥75 mg/kg/day, ↓calcitonin at≥75 mg/kg/day (M); Reversible ↑kidney weight at ≥30 mg/kg/day and adrenal weight at ≥75 (M) and 300 (F) mg/kg/day; Reversible dilatation of kidney cortical tubules & ↑trabecular bone adjacent to the growth plate (sternum) at ≥30 (M) and ≥75 (F) mg/kg/day; non-glandular stomach hyperplasia/hyperkeratosis at ≥30 mg/kg/day (M, still present by the end of recovery period at ≥75 mg/kg/day); ↑severity of prostatic inflammation at ≥75 mg/kg/day (M); transitional cell hyperplasia/ hyperkeratosis within the renal pelvis & hyperplasia/ hypertrophy in the urinary bladder at 300 mg/kg/day (F). Exposure at LOAEL doses: Cmax 2360 & 13,333 ng/mL for M & F, respectively; AUC_{0-24} 15,077 & 84,145 ng•hr/mL for M & F, respectively.	Males: 30; Females: 75	Males: Not established Females: 30
4-week repeat dose toxicity study, dogs	0, 30, 100, or 500	↓BW and thymus weight at 500 mg/kg/day; thymic cortex lymphoid depletion at ≥30 mg/kg/day. Clinical GI signs at ≥100 mg/kg	100	30
13-week repeat dose toxicity study, dogs	0, 30, 100, or 300	Ocular discharge at ≥100 mg/kg/day; changes in stool character at 300 mg/kg/day; reversible ↑heart rate, MCV and MCH at 300 mg/kg/day; reversible ↑liver & gallbladder weights at ≥100 mg/kg/day & kidney weight at 300 mg/kg/day (M); reversible ↓hepatocyte vacuoles at ≥30 mg/kg/day, reversible ↑gallbladder epithelial vacuolization at ≥100 mg/kg/day (M).	100	30
39-week repeat dose toxicity study, dogs	0, 20, 60, or 200	↑Urine Ca^{2+} & P^{3+} excretion at ≥20 mg/kg/day; reversible ↑kidney weights at ≥20 mg/kg/day. ↓1,25-dihydroxyvitamin D at ≥60 mg/kg Exposure at 200 mg/kg/day: Cmax 21.9 & 20.9 ug/mLfor M & F, respectively; AUC_{0-24} 158 & 144 ug•hr/mL for M & F, respectively.	60	20

Exposure to the major human metabolite sotagliflozin-3-O-glucuronide, which was identified later in clinical development, was evaluated only in a 1-month dose range finding study in the mouse. Moreover, measured exposure to sotagliflozin-3-O-glucuronide in the 2-year rat and 6-month transgenic mouse carcinogenicity studies was minimal. There was also little to no metabolism of sotagliflozin in the dog. However, the toxicological concern of sotagliflozin-3-Oglucuronide is minimal as the metabolite demonstrated minimal pharmacological activity at SGLT1 and SGLT2 and it is not an acyl glucuronide. Additional evaluation was not considered necessary.

A 4-week dose range finding study in wild-type CByB6F1 mice was also conducted in support of the 6-month transgenic RasH2 mouse carcinogenicity study. In this dose range finding study with oral sotagliflozin at 30, 100, 300, and 600 mg/kg/day in mice, sotagliflozin caused general debilitation and mortality at ≥300 mg/kg/day. Mice dosed at ≥300 mg/kg/day also had degeneration of olfactory epithelium of the nasal turbinates, which was consistent with gastric reflux following gavage. The NOAEL was 100 mg/kg/day.

7 Genetic Toxicology

A standard battery of GLP genetic toxicology studies including an in vitro bacterial reverse mutation (Ames) assay, an in vitro chromosomal aberration test in CHO cells, and an in vivo rat bone marrow micronucleus assay were completed with sotagliflozin. Sotagliflozin was neither mutagenic nor clastogenic in the three valid assays.

8 Carcinogenicity (excerpted from Dr. Patricia Brundage's review with minimal edits)

The carcinogenic potential of sotagliflozin was evaluated in a 26-week transgenic RasH2 mouse carcinogenicity study and a 2-year rat carcinogenicity study. The Executive Carcinogenicity Committee (ECAC) concluded that both studies adequately addressed the carcinogenicity of sotagliflozin, noting prior concurrence with the dose selection and protocols for both studies. Sotagliflozin did not cause any treatment-related, statistically significant neoplasms in transgenic RasH2 (Tg.RasH2) mice or the rat in either sex. This differs from other SGLT2 inhibitors which are typified by neoplasms of the adrenals, testes, and renal tubules.

26-Week Oral Gavage Carcinogenicity Study in RasH2 Mice

Tg.RasH2 mice were administered doses of 0 (vehicle), 10, 30, or 100 mg/kg/day sotagliflozin by oral gavage for 26 weeks. A positive control group of Tg.RasH2 mice were administered a single intraperitoneal dose of N-methyl-N-nitrosourea (MNU) on Day 1. The study also included wild type RasH2 mice dosed with sotagliflozin through Week 26 for toxicokinetic assessments of sotagliflozin and sotagliflozin-3-O-glucuronide (major human metabolite).

The maximal tolerated dose (MTD) of 100 mg/kg/day was used as the primary endpoint for dose selection for the 26-week study based on treatment-related mortality at doses of ≥300 mg/kg in the 4-week study in wild type mice dosed at 30, 100, 300, and 600 mg/kg. The mid and low doses were based on exposure ratios.

Evaluation of Tumor Findings

The Tg.rasH2 mouse carcinogenicity study was considered by the ECAC to be an adequate tumor assessment, noting prior agreement with the dose selection and protocol (16 September 2015). There were no statistically significant, treatment-related increases in tumor incidence in Tg.RasH2 mice at doses up to 100 mg/kg in either sex.

Non-neoplastic Findings and Metabolite Exposure

The non-neoplastic finding of renal tubular dilatation (minimal) across all doses in both males and females is attributed to sotagliflozin's pharmacodynamic activity. Although exposure to the major human metabolite sotagliflozin-3-O-glucuronide in mice was less than in humans, there is no safety concern as sotagliflozin-3-O-glucuronide does not demonstrate significant pharmacological activity and it is not an acyl glucuronide.

Transgenic Mouse Toxicokinetic Parameters: Week 26

	Dose (mg/kg)	Sex	AUC (ng*h/mL)	Safety Margin*
Sotagliflozin	10	M	6270	3X
		F	14800	8X
	30	M	27500	8X
		F	53100	27X
	100	M	87400	44X
		F	207000	105X
Sotagliflozin-3-O-glucuronide	10	M	90	<1X
		F	557	<1X
	30	M	330	<1X
		F	1470	<1X
	100	M	1330	<1X
		F	6990	<1X

*Safety margin calculations for sotagliflozin-3-O-glucuronide are based on sotagliflozin-3-O-glucuronide AUC exposure of 133423 ng*h/mL at 400 mg/day on Day 10 (Study LX4211.110) and safety margin calculations for sotagliflozin are based on sotagliflozin AUC exposure of 1932 ng*h/mL at 400 mg/day (Study LX4211-N106).

104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Sotagliflozin

Sprague Dawley rats were dosed daily with 0 (vehicle), 10, 30, or 75 mg/kg sotagliflozin by oral gavage for 90 weeks (females) or 95 weeks (males). In concurrence with the recommendation received from the ECAC, all groups were sacrificed as survival reached 20 animals in the male and female control groups (21 female controls were surviving at the time of sacrifice). A satellite groups of rats were dosed for toxicokinetic assessments of sotagliflozin and sotagliflozin-3-O- glucuronide (major human metabolite) on Day 1 and Week 26.

The high dose was based on the MTD from the 6-month study in Sprague Dawley rats, which showed lower relative body weight in males and mortality due to urinary tract toxicity in females at 300 mg/kg.

Evaluation of Tumor Findings

The 2-year rat carcinogenicity study was considered by the ECAC to be an adequate tumor assessment, noting prior agreement with the dose selection and protocol (12 June 2013). Sotagliflozin had no significant effect on overall survival.

There was an increase in the incidence of thyroid follicular cell carcinoma accompanied by follicular cell hyperplasia in sotagliflozin-treated males. The sponsor's analysis identified a statically significant increase in the incidence of thyroid follicular cell carcinoma at the high dose (75 mg/kg); however, an independent FDA statistical analysis did not find the thyroid follicular cell carcinoma at the high dose to be statistically significant in pairwise analysis. In females, there was a numerical increase in the incidence of follicular cell hyperplasia at 10 and 30 mg/kg and thyroid follicular cell adenoma at 75 mg/kg. The incidence of follicular cell adenoma and combined follicular adenomas/carcinomas at the high dose in females was statistically significant by trend, but not by pairwise comparison. Historical control data for follicular cell adenomas in female Sprague Dawley rats in 2-year carcinogenicity studies conducted at (b) (4) (b) (4) (median of 0%; mean of 0.4715%) supports the classification of the tumors as rare (≤1%). The ECAC concurred that there were no treatment-related increases in neoplasms in rats at doses up to 75 mg/kg [18-54X the maximal human recommended dose (MHRD)] that were considered statistically significant by trend and pairwise comparisons, whether by the sponsor's analysis (Peto) or the FDA's analysis (polyK).

The absence of neoplastic findings differs from other SGLT2 inhibitors, which are typified by neoplasms of the adrenals, testes, and/or renal tubules. The lack of renal and adrenal tumors is particularly noteworthy for this mixed inhibitor of SGLT1 and SGLT2 because the tumorigenic mechanism of action (MOA) for these tumors is considered to be carbohydrate malabsorption secondary to intestinal SLGT1 inhibition[5,6]. SGLT1 inhibition increases the intestinal sugar content that undergoes fermentation causing local acidosis. This increases the solubility and intestinal absorption of calcium causing transient hypercalcemia. This is evidenced by the increase in trabecular bone, tissue mineralization, increased urinary calcium excretion, and reductions in vitamin D and parathyroid hormone levels. It seems likely that less carbohydrate malabsorption and lower drug exposure may explain the absence of these tumors in the 2-year carcinogenicity study. This would also account for the relatively lower incidence of tissue mineralization and increased trabecular bone caused by sotagliflozin in comparison to SGLT2 inhibitors.

[5] Mamidi RNVS, et al. (2014) Carbohydrate malabsorption mechanism for tumor formation in rats treated with the SGLT2 inhibitor canagliflozin. Chemico-Biol Inter 221; 109-118.

[6] Ways K, et al. (2015) Successful integration of nonclinical and clinical findings in interpreting the clinical relevance of rodent neoplasia with a new chemical entity. Toxicol Path 43; 48-56.

Summary of Thyroid Tumors & Associated Hyperplasia									
Tissue/Tumor	Sex	Incidence				Statistics (p-value)			
		Sotagliflozin Dose Groups (n=65)				Sponsor[1]		FDA Biostatician[2]	
		0	10	30	75	Trend	Pairwise (High Dose)	Trend	Pairwise (High Dose)
Exposure Multiples[3]	M		3X	8X	15X				
	F		5X	21X	45X				
Hyperplasia, Follicular Cell	M	0	3	3	3	--	--	--	--
	F	0	1	2	0	--	--	--	--
Thyroid/Follicular Cell Adenoma	M	4	5	4	3	NC	NC	0.6699	0.4829
	F	0	0	0	3	0.0142	0.1199	0.0168	0.1383
Thyroid/Follicular Cell Carcinoma	M	0	3	3	4	0.0660	0.0415	0.0656	0.0568
	F	0	0	1	0	0.2847	NC	0.5000	NC
Thyroid/Follicular Cell Carcinoma & Adenoma	M	4	8	7	7	0.2656	0.2060	0.2825	0.2559
	F	0	0	1	3	0.0199	0.1199	0.0211	0.1383

[1] The statistical method used by the sponsor is Peto method, which is the asymptotic fixed interval-based prevalence test.
[2] The statistical method used by FDA is Poly-3, which adjusts for differences in mortality among treatment groups by defining a new number of animals at risk for each treatment group.
[3] Exposure multiples based on clinical exposure at 400 mg LX4211 (1932 ng•h/mL [$AUC_{0\text{-}tau}$]).
Blue highlights - Statistically significant differences NC- not calculated

Non-Neoplastic Findings and Metabolite Exposure

Sotagliflozin caused multiple non-neoplastic findings in the kidney, bladder, prostate/seminal vesicles, stomach, and bone in the 2-year rat study. Treatment-related urinary tract inflammation affecting both the kidney and the bladder occurred mainly in males. Treatment-related increases in transitional cell hyperplasia, dilation, inflammation, and necrosis in the renal pelvis/medulla, as well as a general increase in the incidence and severity of transitional cell hyperplasia, chronic-active inflammation, dilatation, ulcer/necrosis, and hemorrhage in the bladder occurred in males across all dose groups (≥10 mg/kg). Several of the males with bacteria in the kidney also had bacteria in the urinary bladder and prostate suggestive of a urinary tract infection. Calculi were also identified in the bladder of several males. The findings were consistent with those observed in the chronic toxicology studies in rats, although the severity of the findings increased in some tissues. The major human metabolite sotagliflozin-3-O-glucuronide was present, although it was significantly less than in humans.

Rat Toxicokinetic Parameters: Week 26				
	Dose (mg/kg)	Sex	AUC (ng*h/mL))	Safety Margin*
Sotagliflozin	10	M	5440	3X
		F	9540	5X
	30	M	14800	8X
		F	40300	21X
	75	M	28500	15X
		F	87800	45X
Sotagliflozin-3-O-glucuronide	10	M	256	<1X
		F	148	<1X
	30	M	537	<1X
		F	517	<1X
	75	M	660	<1X
		F	1220	<1X

*Safety margin calculations for sotagliflozin-3-O-glucuronide are based on sotagliflozin-3-O-glucuronide AUC exposure of 133423 ng*h/mL at 400 mg/day on Day 10 (Study LX4211.110) and safety margin calculations for sotagliflozin are based on sotagliflozin AUC exposure of 1932 ng*h/mL at 400 mg/day (Study LX4211-N106).

9 Reproductive and Developmental Toxicology (excerpted from Dr. Patricia Brundage's review with minimal edits)

The fertility and early embryonic development, fertility and embryo-fetal development, pre- and post-natal development, and juvenile toxicity with sotagliflozin were evaluated in Sprague-Dawley rats. Embryo-fetal development with sotagliflozin was also evaluated in New Zealand White rabbits.

9.1 Fertility and Early Embryonic Development

Oral (Gavage) Study of Fertility and Early Embryonic Development in the Rat

The effects of sotagliflozin on fertility and early embryonic development were evaluated in male and female Sprague-Dawley rats administered 0, 30, 100, or 300 mg/kg/day sotagliflozin via oral gavage. Males were dosed for 4 weeks prior to pairing, during the pairing period, and until the day prior to necropsy for a total of more than 9 weeks prior to termination. Females were dosed for 2 weeks prior to pairing, during the pairing period, and until Gestation Day (GD) 6 with termination on GD 13. The NOAEL for general toxicity in was 100 mg/kg (19-25X MHRD[7]) based on mortality/moribundity in females and significant reductions in weight gain in males (~50% ↓) dosed at 300 mg/kg. Although the cause of death of the female administered 300 mg/kg was not determined, the contribution of sotagliflozin could not be excluded. There were no treatment-related changes in pre-coital time, pregnancy rate, mating index, fertility and nudity indices, and pre- and post-implantation loss, or in semiology parameters. Thus,

[7] Safety margin calculation based on Week 4 $AUC_{0\text{-}24h}$ values in females (47906 ng*h/mL) and males (35770 ng*h/mL) dosed at 100 mg/kg in the 4-week rat toxicology study (Study LX4211-N07); no PK data for fertility and early embryonic development study, and sotagliflozin AUC exposure of 1932 ng*h/mL at maximal human recommend dose (MHRD) of 400 mg/day (Study LX4211-N106).

the NOEL for reproductive performance, fertility, and embryo/fetal viability was 300 mg/kg (55-138X MHRD[8]).

9.2 Embryonic and Fetal Development

Oral Gavage Study for Effects on Embryo-Fetal Development and Toxicokinetics with LX4211 in Rats

Time-mated Sprague Dawley female rats orally administered 0, 30, 100, or 350 mg/kg sotagliflozin from GD 6 to GD 17 to evaluate maternal and embryo-fetal toxicity of sotagliflozin during the period of organogenesis. The doses for the pivotal study were selected based on the results of a range-finding study in rats showing decreased embryo-fetal viability at ≥500 mg/kg. The NOAEL for maternal and fetal toxicity was 100 mg/kg (40X MHRD). The dose of 350 mg/kg (161X MHRD) caused significant reductions in maternal body weight gain (55% ↓), as well as embryo-lethality (increased post-implantation loss), decreased fetal weights, altered sex ratio favoring males, and cardiovascular and skeletal malformations including an absent aortic arch, interrupted aortic arch, retroesophageal aortic arch, hemivertebrae, and fused centrum. Although cardiovascular (absent innominate artery) and skeletal (14th rudimentary ribs and 27 presacral vertebrae) variations were observed at 100 mg/kg, there were no malformations associated with this dose.

Oral Gavage Study for Effects on Embryo-Fetal Development and Toxicokinetics with Sotagliflozin in Rabbits

Time-mated female New Zealand White rabbits were dosed with 0, 50, 100, or 200 mg/kg sotagliflozin from GD 7 to GD 20. A dose-range finding study determined that higher doses caused excessive toxicity, including mortality, at doses ≥300 mg/kg in pregnant rabbits. The maternal NOAEL was 100 mg/kg (1X MHRD) and the fetal NOEL was 200 mg/kg (9X MHRD). Sotagliflozin caused significant reduction in maternal weight gain (77% ↓) at 200 mg/kg. However, there were no effects on embryo-fetal survival, fetal growth, or fetal malformations or variations at exposures up to 9X the MHRD.

9.3 Prenatal and Postnatal Development (PPND)

Oral Gavage Study for Effects on Pre- and Post-natal Development, including Maternal Function, with Sotagliflozin in Rats

The effects of sotagliflozin on pregnant and lactating females and the development of the offspring were evaluated in time-mated Sprague-Dawley rats orally administered 0, 10, 30, or 100 mg/kg sotagliflozin from GD 6 through Lactation Day (LD) 20. The

[8] Safety margin calculation based on Day 178 $AUC_{0\text{-}24h}$ values in females (267278 ng*h/mL) and males (106991 ng*h/mL) dosed at 300 mg/kg in the 26-week rat toxicology study (Study LX4211-N36); no PK data for fertility and early embryonic development study, and sotagliflozin AUC exposure of 1932 ng*h/mL at maximal human recommend dose (MHRD) of 400 mg/day (Study LX4211-N106).

offspring (F1) were examined prior to weaning (LD 0 to LD 21) and during an 8-week maturation/growth phase that began on approximately postnatal day (PND) 28. Parameters evaluated included an assessment of maternal toxicity and pre- and post-natal development of the offspring. Mortality, clinical signs, body weight, food consumption, natural delivery and litter data, and necropsy results in F0 females were evaluated, and mortality, clinical signs body weight, food consumption, developmental landmark and behavioral assessments, reproductive performance, cesarean section data (GD 13), and necropsy results in F1 generation were evaluated.

Although there was a slightly higher incidence of unscheduled deaths in dams (F0) dosed at ≥30 mg/kg, which were associated with adverse clinical signs and macroscopic findings in the kidney and stomach, the deaths were not clearly attributable to treatment. No other effects on natural delivery, litter parameters, pup survival, or necropsy findings were observed. The NOAEL for maternal toxicity was considered to be 100 mg/kg (40X MHRD[9]).

Sotagliflozin treatment had no effect on sexual maturation, neural behavior development, or reproductive performance of the F1 generation at doses up to 100 mg/kg (19-25X MHRD[10]). There were, however, treatment-related renal/ureter macroscopic changes (dilated renal pelvis, discolored kidney, and dilated ureter; absolute number and percentage), likely related to the pharmacodynamic activity of the drug, in the F1 pups exposed at ≥30 mg/kg (4-7X MHRD[11]) in utero and during lactation. The NOAEL for the F1 generation was 10 mg/kg (1.3-2.5X MHRD[12]).

A slight, non-dose-related, but statistically significant delay in incisor eruption (0.8-1 day) compared to vehicle control in F1 pups across all dose groups was within the range of the historical control data and not considered to be test article related or adverse. No treatment-related effects on developmental landmarks were observed.

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[9] Safety margin calculation based on GD 17 $AUC_{0\text{-}24h}$ values in females (78012 ng*h/mL) dosed at 100 mg/kg in the EFD rat study (Study LX4211-N28); no PK data for the PPND study.

[10] Safety margin calculation based on Week 4 $AUC_{0\text{-}24h}$ values in females (47906 ng*h/mL) and males (35770 ng*h/mL) dosed at 100 mg/kg in the 4-week rat toxicology study (Study LX4211-N07); no PK data for the PPND study.

[11] Safety margin calculation based on Week 4 $AUC_{0\text{-}24h}$ values in females (13716 ng*h/mL) and males (8703 ng*h/mL) dosed at 30 mg/kg in the 4-week rat toxicology study (Study LX4211-N07); no PK data for the PPND study.

[12] Safety margin calculation based on Week 4 $AUC_{0\text{-}24h}$ values in females (4814 ng*h/mL) and males (2435 ng*h/mL) dosed at 10 mg/kg in the 4-week rat toxicology study (Study LX4211-N07); no PK data for the PPND study.

F1 Generation Necropsy – Lactation Phase

Dose		0 mg/kg	10 mg/kg	30 mg/kg	100 mg/kg
Pups (Litters)		95 (18)	122 (22)	119 (22)	109 (23)
Kidney dilatation	Pups			4 (3%)	15 (5%)
	Litters			2* (9%)	2** (9%)
Kidney discoloration	Pups			1 (2%)	10 (7%)
	Litter			1*(5%)	2** (9%)
Ureter dilatation	Pups	1		4 (3%)	11 (5%)
	Litters	1		2* (9%)	3** (13%)

9.4 Juvenile Animal Studies

Oral Gavage juvenile Toxicity Study with LX4211 in Rats (with a 4-Week Recovery Period)

Juvenile rats were administered 0, 3, 10, 30, or 75 mg/kg sotagliflozin by oral gavage from PND 21 to PND 90 once daily to evaluate the effects of sotagliflozin in juvenile animals. The study included a 4-week recovery period. In addition to the standard parameters evaluated, urinary biomarker for kidney injury [N-acetyl-β-D-glucosaminidase (NAG) and kidney injury molecule 1 (KIM-1)], age of sexual maturation, bone length, and serum hormone and bone turnover markers [1,25-dihydroxyvitamin D, procollagen type I N-terminal propeptide (P1NP), collagen type I C-telopeptide (CTx), and parathyroid hormone (PTH)] were measured.

Sotagliflozin caused an increase in urinary glucose excretion across all dose levels demonstrating that the drug is pharmacodynamically active in juveniles. There were also increases in urinary volume, and urinary excretion of calcium, phosphorus, and sodium across all dose groups that are attributable to SGLT1/2 inhibition.

The kidney was identified as a target organ in both male and female juvenile rats with renal tubular and pelvis dilatation at ≥30 mg/kg (5-11X MHRD) that correlated with dose-related increases in kidney weights across all dose groups (≥3 mg/kg; ~1X MHRD). Renal mineralization (minimal) was also observed in males at ≥3 mg/kg. All kidney changes demonstrated full or partial reversibility following the 4-week drug-free recovery period. A reversible increase (~2X ↑) in the urinary NAG:creatinine ratio across all sotagliflozin dose groups that was not clearly dose-related may be associated with the renal tubular and pelvis dilation at ≥30 mg/kg. There were, however, no changes in the urinary KIM:creatinine ratio, another biomarker of renal tubule damage. The treatment-related renal changes, which are likely attributable to the pharmacodynamic activity of the drug and are consistent with the SGLT2 inhibitor drug class, are considered relevant to the assessment of reproductive and developmental risk.

Similar to the adult rats, sotagliflozin caused minimal to moderate prostate inflammation in the juvenile males. As only the prostates of the high dose animals (75 mg/kg) were microscopically examined, a NOAEL was not established. There was also a reversible dose-related reduction in prostate weight across all dose groups. The one male with moderate prostate inflammation also had transitional cell hyperplasia and inflammation

in the bladder suggesting a relationship between the prostate and bladder inflammation. Although the inflammation in both organs is considered to be related to treatment, the cause of the inflammation has not been established. No bladder findings were identified in the high dose females.

In the adrenal cortex, an increase in vacuolation (minimal) in males at 75 mg/kg (lower dose groups not examined) correlated to an increase in adrenal weight in males across all dose groups. Adrenal vacuolation has previously been observed with other SGLT2 inhibitors and is likely compensatory response of aldosterone production due to increased sodium excretion.

Unlike other SGLT2 inhibitors, sotagliflozin had no effect on bone length or trabecular bone. Although, there were reversible dose-related decreases in 1,25-dihydroxyvitamin D and PINP in males at ≥10 mg/kg and females at ≥30 mg/kg.

Microscopic Findings in Juvenile Rats - Terminal Sacrifice

		Males					Females				
Dose (mg/kg)		**0**	**3**	**10**	**30**	**75**	**0**	**3**	**10**	**30**	**75**
N		**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**
Kidney											
Mineralization	Minimal		2	1	5	5	1				1
Dilatation, tubule	Minimal		1			6				2	8
	Slight				2	5					1
	Total		1		2	11				2	9
Dilatation, pelvis	Minimal			1	2						
	Slight					3				1	1
	Moderate	1				1					
	Total	1		1	2	4				1	1
Urinary Bladder											
Hyperplasia. transitional cell	Moderate		NE	NE	NE	1		NE	NE	NE	
Inflammation, mixed cell	Minimal		NE	NE	NE	1		NE	NE	NE	
Prostate											
Inflammation	Minimal	1	NE	NE	NE	5	--	--	--	--	--
	Moderate		NE	NE	NE	1	--	--	--	--	--
	Total	1	NE	NE	NE	6	--	--	--	--	--
Adrenal/Cortex											
Vacuolation, increased	Minimal		NE	NE	NE	4		NE	NE	NE	

NE = not examined

A slight, but not statistically significant delay in sexual maturation in males (balano-preputial separation) and females (vaginal patency) at ≥30 mg/kg that was within the laboratory historical control data range. Delays in sexual maturation have been observed with other SGLT2 inhibitors. While the delay in males could possibly be attributed to a decrease in body weight between PND 31 and PND 35 (7-8%, relative to controls), there were no treatment-related reductions in body weight in females. Given that the delay was slight and within the laboratory historical control data range, it is not a significant clinical concern.

Similar to the adults, there was minimal metabolism of sotagliflozin to sotagliflozin-3-Oglucuronide (main human metabolite) in juvenile rats.

10 Special Toxicology Studies

10.1 Phototoxicity

There were no phototoxicity studies conducted given that sotagliflozin does not absorb within the 300 to 800 nm range of the electronic spectrum.

10.2 Immunogenicity

Specific immunotoxicity studies were not considered necessary. No treatment-related effects on myelosuppression, changes in the immune system organ weights or histology, or hematological changes in the repeat dose studies in the rat and dog are indicative of immunotoxicity.

10.3 Abuse Potential

A weight-of-evidence assessment based on available literature data related to SGLT inhibition, animal toxicology data, and clinical data concluded that sotagliflozin's potential risk for abuse is very low.

10.4 Local Tolerance

The irritant or corrosive potential of sotagliflozin was evaluated in male New Zealand White rabbits. Sotagliflozin (0.5 g) applied under occlusion for 4 hours to an area of skin did not cause erythema or edema up to 72 hours after patch removal indicating that sotagliflozin was not a dermal irritant.

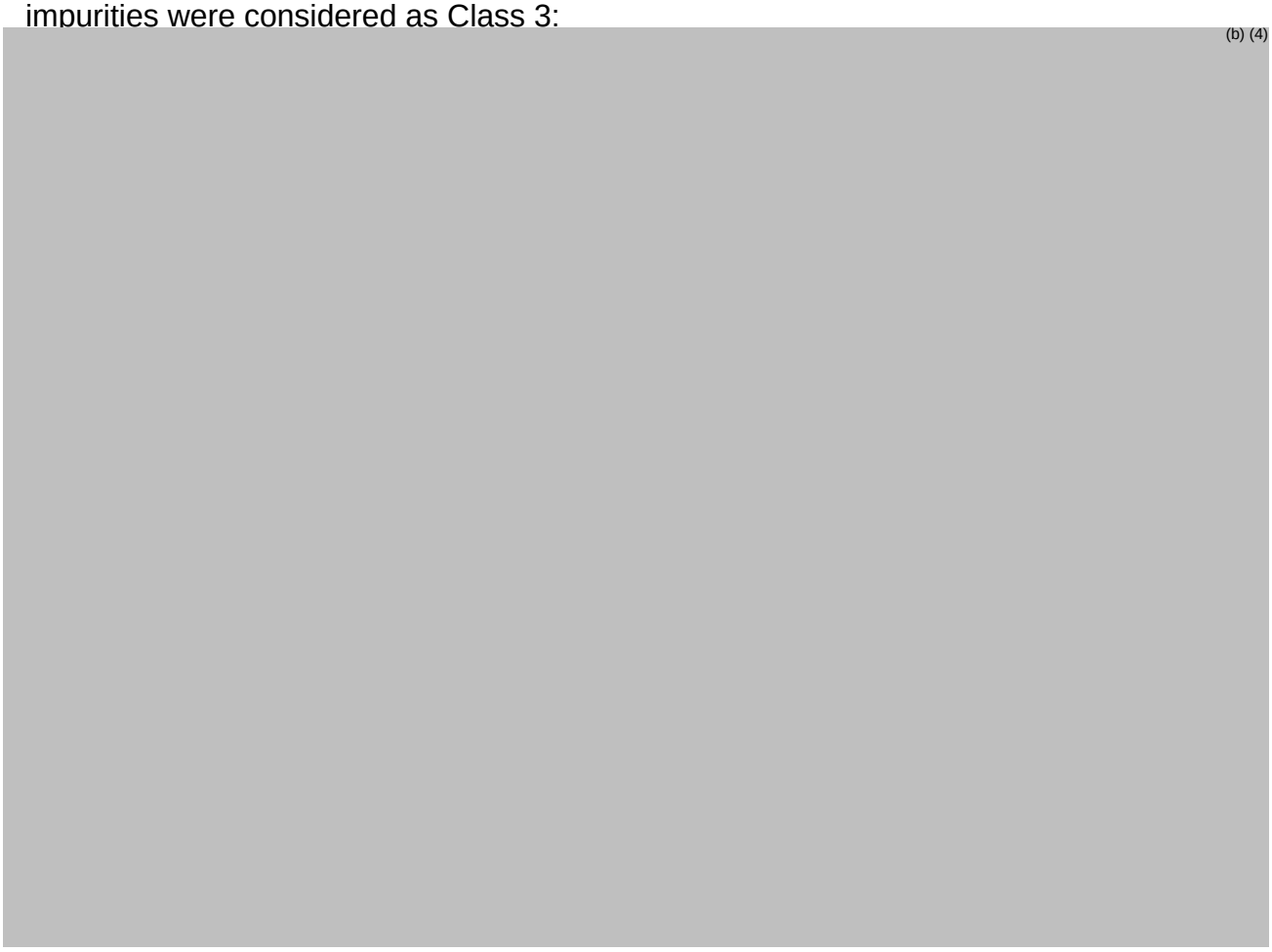
10.5 LX4211-n107 In Silico Analysis of Impurities of Sotagliflozin

A mutagenic risk assessment was performed on actual and potential mutagenic impurities of sotagliflozin. Potential and actual impurities were investigated for structural alerts for mutagenicity using two quantitative structure-activity relationship (QSAR) in silico systems. Expert rule-based methodology and parameters were assessed using Leadscope Genetox Expert Alerts v7 (System: Leadscope Model Applier v3.0.2.4). Statistical-based methodology and parameters were assessed using Leadscope Bacterial Mutation Statistical-Based QSAR model v2.

A total of 50 impurities were assessed. No impurities from the cohorts of concern, Class 1 (i.e., known mutagenic carcinogens), Class 2 (i.e., known mutagen), or Class 4 (i.e., bearing structure alert for mutagenicity, also present in drug substance or compounds related to the drug substance that are known to be non-mutagenic), were identified.

When impurities do not have accompanying carcinogenicity or bacterial mutagenicity data and undergo a Structure-Activity Relationship assessment, a class 3 designation is given when an alerting structure(s) is identified or there are no mutagenicity data. Three impurities were considered as Class 3:

(b) (4)



The acceptable intake for each of these 3 impurities was set as (b) (4) μg/day, as described in CMC section (Module 3 Section S.3.2 – Impurities, subsection 6 Mutagenic Impurities).

The remaining 47 impurities were classified as ICH Class 5 (non-mutagenic) based on the QSAR assessment or the availability of data or information to refute a positive QSAR finding.

11 Integrated Summary and Safety Evaluation

Sotagliflozin (LX4211) is an orally administered small molecule, dual sodium-glucose cotransporter 1 (SGLT1) and sodium-glucose cotransporter 2 (SGLT2) inhibitor. Sotagliflozin is being developed for adults with heart failure (b) (4) acute or worsening heart failure; and adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart

failure. The recommended regimen starts with 200 mg sotagliflozin tablet once daily (QD) before the first meal of the day and is increased to 400 mg sotagliflozin tablet QD in patients tolerating the 200 mg dosage.

Sotagliflozin is a potent dual inhibitor of human SGLT2 (IC_{50} 1.8 nM) and SGLT1 (IC_{50} 36.3 nM). SGLT2 inhibition blocks glucose reabsorption in the renal proximal tubules resulting in increased urinary glucose excretion (UGE). SGLT1 inhibition in the intestines may improve glucose control by reducing or delaying postprandial glucose absorption delivering more glucose distally and increasing the release of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) levels into the portal circulation, which in turn increase insulin secretion. Oral administration of sotagliflozin caused consistently significant urinary glucose excretion in mice, rats, dogs, and monkeys in a dose-dependent fashion, with ED_{50} values of ~1.8, 0.75, and 0.2 mg/kg respectively. In various animal models of diabetes mellitus (both T2DM and T1DM) or obesity, sotagliflozin inhibited SGLT1 and SGLT2, resulting in improved glycemic control and lower HbA1c levels. Chronic treatment with sotagliflozin in a ZSF-1 rat model of systemic arterial hypertension with diabetes mellitus and obesity [a metabolic rat model of heart failure with preserved ejection fraction (HFpEF)] improved *in vivo* surrogate markers of diastolic dysfunction including left ventricular end-diastolic pressure, left atrial remodeling, and isovolumetric relaxation time, resulted in recovery of heart rate and increased cardiac output (Study SED00079).

Sotagliflozin also reduces sodium reabsorption in the proximal tubules and increases the delivery of sodium to the distal tubules of the kidney[1, 2.3]. This may influence several physiological functions including, but not restricted to, lowering both pre- and afterload of the heart and downregulation of sympathetic activity, and decreased intraglomerular pressure.

Sotagliflozin may improve metabolic adaptation of the cardiomyocyte to the in vivo conditions related to cardiac adverse remodeling in diabetic cardiomyopathy. All these effects may be beneficial to adults with type 2 diabetes mellitus regarding cardiovascular (CV) and renal outcomes.

Safety pharmacology studies assessing the cardiovascular, neurological, respiratory, renal, and gastrointestinal effects of sotagliflozin did not identify any acute safety concerns at clinical exposure levels (NOAELs 100 mg/kg in dogs or rats, ≥24X MHRD[13]).

The pharmacokinetics (PK) of sotagliflozin has been assessed in mice, rats, dogs, and monkeys after both intravenous (IV) and oral dosing. Sotagliflozin is rapidly absorbed across species after oral dosing with a bioavailability in rats and dogs (50-71%) that is comparable to that in the human (63%). Sotagliflozin is extensively distributed throughout the body in the rat, although levels in the CNS (brain and spinal cord), eye, bone, and bone marrow are relatively low. Plasma protein binding of sotagliflozin is high

[13] Safety margin calculation based Day 1 AUC_{0-24} value (46254 ng*h/mL) from the 4-week toxicology study in male rats dosed at 100 mg/kg.

across species including humans (>91%).

Sotagliflozin is extensively metabolized in the mouse, rat, monkey, and human, but shows little apparent metabolism in the dog. Although no unique human metabolites were identified, there were significant metabolite differences between species. In humans, direct glucuronidation is the predominant route of metabolism; while in the rat and mouse, there is more oxidative metabolism in addition to glucuronidation. The sotagliflozin glucuronide conjugate, sotagliflozin-3-O-glucuronide, accounts for 94% of total radioactivity in human plasma, whereas sotagliflozin-3-O-glucuronide exposure in the rat and mouse was less than 1X relative to exposure in humans. As sotagliflozin-3-O-glucuronide has minimal pharmacological activity at SGLT1 and SGLT2 and is not an acyl glucuronide of sotagliflozin, there is no toxicological concern at clinical exposure. In vitro phenotyping indicates UGT1A9 and, to a lesser extent, CYP3A4 as enzymes responsible for the metabolism of sotagliflozin in humans.

In rats, excretion of an orally administered dose was primarily recovered in the feces (82%) with 13% excreted in the urine. Whereas, in humans, the main route of elimination was through the urine (57%) with 37% excreted in the feces.

The toxicity profile of sotagliflozin was evaluated in a single-dose rat study, in a battery of definitive repeat-dose general toxicity studies in rats (up to 26 weeks) and dogs (up to 39 weeks), in genetic toxicity studies, in mouse and rat carcinogenicity studies, and in a battery of exploratory and definitive reproductive and developmental toxicity studies in rats and rabbits. Other toxicity studies were performed as needed.

In general toxicity studies, the rat was the more sensitive one of the two species used. Target organs include the kidney (cortical tubule dilation and inflammation/hyperplasia), bladder (inflammation/hyperplasia), prostate (inflammation), bone (increased trabecular bone), and stomach (nonglandular hyperplasia/hyperkeratosis and ulcers), most of which were identifiable after 4 weeks of dosing in the rat. Adverse effects in the dog were generally limited to gastrointestinal-related clinical signs and an increase in heart rate. Thyroid (follicular cell hyperplasia/adenoma/carcinoma) was an additional target organ identified in the 2-year carcinogenicity study in rats.

Renal tubule dilation was observed at doses ≥30 mg/kg/day in the 6-month rat study (males, AUC_{0-24} 15077 ng·h/ml, 8X MHRD) and at doses ≥10 mg/kg/day in the 2-year study in males (AUC_{0-24} 5440 ng·h/ml, 3X MHRD) and females (AUC_{0-24} 9540 ng·h/ml, 5X MHRD). The reversible tubule dilation, which was associated with an increase in kidney weight but no biomarker changes indicating renal injury, is considered an adaptive change to the polyuria and is consistent with the findings of other SGLT2 inhibitors. Urinary tract inflammatory changes and hyperplasia/hypertrophy affecting the renal pelvis, urinary bladder, and/or urethra in the 6-month study were largely limited to the high dose females (300 mg/kg/day, AUC_{0-24} 267278 ng·h/ml, 138X MHRD); however, in the 2-year rat study, inflammatory changes and infection affecting the kidney and bladder occurred across all dose groups (≥10 mg/kg/day) in males (AUC_{0-24} 5440 ng·h/ml, 3X MHRD). These dose-related increases in urinary tract

inflammation/infection, which were considered secondary to pharmacodynamically mediated glucosuria and/or calculi formation, were not associated with any neoplastic changes in the urinary tract in the 2-year study at exposures up to 15X MHRD in males (AUC_{0-24} 28500 ng·h/ml) and 45X MHRD in females (AUC_{0-24} 87800 ng·h/ml). Renal changes in dogs were limited to reversible increases in kidney weight.

The no-effect dose of sotagliflozin for prostate inflammation was 30 mg/kg/day in the 6-month rat study and falls below the lowest doses evaluated in the 2-year rat studies (<10mg/kg/day). Prostate inflammation was observed in all pivotal toxicology studies in rats including the juvenile animal study. Moderate to marked prostate inflammation was observed at the mid and high doses (17-54X MHRD) in the 6-month rat study with no apparent reversibility after the 4-week recovery. In the 2-year rat study, sotagliflozin caused moderate to severe prostate inflammation across all dose groups (≥10 mg/kg/day, 3X MHRD). The mechanism of prostate inflammation is unknown. While some cases appear to be related to urinary tract inflammation/infection, there was a general absence of bladder or other urinary tract inflammation/infection associated with the prostate inflammation in the 6-month study. The possible involvement of SGLT1, which is expressed in the prostate, cannot be excluded. No inflammation was observed in the mouse or the dog.

In the 6-month rat study, there was a dose-related increase in trabecular bone of the sternum (minimal to moderate) and decrease in the calciotropic hormones 1,25-dihydroxyvitamin D and parathyroid hormone (PTH) in all dose groups (≥30 mg/kg/day, 8X MHRD) that are likely due to changes in calcium homeostasis as a result of intestinal SGLT1 inhibition. Only reduction in 1,25-dihydroxyvitamin D levels occurred in the 9-month dog study at the mid and high dose. GI-related clinical signs including vomiting, watery feces, and diarrhea are common in dogs, which may minimize the intestinal SGLT1 inhibition-induced changes in calcium homeostasis, lead to less clinical manifestations in bones.

Higher incidences of glandular stomach acute erosions/ulcers, non-glandular stomach hyperplasia/hyperkeratosis were observed in the 4-week, 26-week, and 2-year rat studies at doses ≥30 mg/kg/day (8X MHRD). These findings may be related to SGLT1 inhibition. However, there were no similar findings in dogs dosed up to 9 months or clinical reports of gastrointestinal injury.

There were higher incidences of thyroid follicular cell hyperplasia, adenoma, and carcinoma in all sotagliflozin dose levels in both males and females in the 2-year rat study. The thyroid follicular cell hyperplasia, adenoma, and carcinoma are continuous histological changes of pathological cellular growth. However, Independent FDA statistical analysis did not find the thyroid follicular cell carcinoma at the high dose to be statistically significant in pairwise analysis, and the ECAC concurred that there were no treatment-related increases in neoplasms in rats at doses up to 75 mg/kg [18-54X the maximal human recommended dose (MHRD)]. Without the end point of neoplasm, the significance of continuous pathological cellular growth in thyroid in rats is limited.

Reproductive and developmental toxicity were assessed in fertility and early embryonic development, embryofetal development, and pre- and post-natal development animal studies. Sotagliflozin had no effects on reproductive performance or fertility indices in male and female rats at exposures up to 55-138X the MHRD despite mortality/ moribundity in females and significant reductions in weight gain in males at 19-25X the MHRD. Sotagliflozin was not teratogenic in the rat at 100 mg/kg (40X MHRD) or in the rabbit at 200 mg/kg (9X MHRD). In rats, a higher dose (350 mg/kg; 161X MHRD) caused both maternal and fetal toxicity including significant reduction in maternal weight gain, embryo-lethality, reduced fetal weights, altered sex ratio, and cardiovascular and skeletal malformations. The 200 mg/kg dose in rabbits caused significant reductions in maternal weight gain, but had no effect on fetal survival or growth, or caused any malformations.

In the post-natal development study in the rat, sotagliflozin had no effect on developmental landmarks, sexual maturation, neural behavior development, or reproductive performance of the F1 generation (up to 19-25X MRHD). However, sotagliflozin caused dilation of the renal pelvis in F1 pups exposed at ≥30 mg/kg (4-7X MHRD) in utero and during lactation, resulting in a NOAEL of 10 mg/kg/day (1.3-2.5X MHRD for the F1 generation.

The kidney was also identified as a target organ in male and female juvenile rats with renal tubular and pelvis dilatation at 5-11X MHRD in the juvenile animal study. Increases in kidney weights and renal mineralization (males only) across all dose groups (~1X MHRD) were observed as well. All treatment-related renal changes demonstrated full or partial reversibility following the 4-week recovery period.

The renal changes in rats in the post-natal development and juvenile animal studies are considered secondary to the pharmacodynamic activity of the drug and are consistent with the effects of other SGLT2 inhibitors. Given that sotagliflozin is distributed to most fetal tissues including the kidney when administered to dams during gestation and the differences in the timing of kidney development/maturation between rats and humans, the treatment-related renal effects in the juvenile rats are considered relevant to the assessment of reproductive and developmental risk. The morphological and functional renal development in the juvenile rat corresponds to renal development in humans during the late second and third trimester through approximately 2 years of age. Lactational exposure may also pose a risk to the developing human kidney as sotagliflozin was excreted in maternal milk (1.3-fold higher than plasma; AUC basis) in rats.

Sotagliflozin was not mutagenic or clastogenic in a standard battery of two in vitro and one in vivo GLP genetic toxicology studies.

The potential of sotagliflozin to induce tumors was assessed in the 6-month transgenic RasH2 mouse study and the 2-year rat carcinogenicity study. There were no statistically significant increases in neoplasms considered treatment related in transgenic RasH2 mice dosed up to 100 mg/kg. Nor were there any treatment-related neoplasms in male

(up to 15X MHRD) and female (up to 45X MHRD) rats. This negative carcinogenetic outcome for sotagliflozin differs from other SGLT2 inhibitors which are typified by neoplasms of the adrenals, testes, and renal tubules. The absence of renal and adrenal tumors is particularly noteworthy for this SGLT1/2 inhibitor because the tumorigenic MOA for these tumors is reportedly carbohydrate malabsorption secondary to intestinal SLGT1 inhibition. The absence of these tumors with sotagliflozin is likely due to less carbohydrate malabsorption than observed with other class members at the doses evaluated in these studies.

In conclusion, potential safety issues identified from the nonclinical program were derived from intended pharmacological action of sotagliflozin on SGLT1 and SGLT2, rather than from compound-specific toxicity.

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