At baseline, median age was 70 years, 34% were female, 93% were White and 4% were Black or African American. Median A1C was 7.1%, median body mass index (BMI) was 31 kg/m^2, and median eGFR was 50 mL/min/1.73 m^2. Median left ventricular ejection fraction (LVEF) was 35% (79% with LVEF < 50%), median N-terminal pro B-type natriuretic peptide (NT-proBNP) was 1806 pg/mL, and the median Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) score was 41.

At baseline, 86% were treated with at least one antihyperglycemic medication, including 52% with a biguanide, 36% with insulin, 19% with a sulfonylurea, 16% with a dipeptidyl peptidase-4 (DPP4) inhibitor, and 3% with a glucagon-like peptide 1 (GLP-1) receptor agonist. At baseline, 91% were treated with inhibitors of the renin-angiotensin-aldosterone system, 92% with a beta blocker, 95% with a loop diuretic, and 10% with another diuretic.

INPEFA was superior to placebo in reducing the risk of the primary composite endpoint (Hazard Ratio [HR] 0.67 [95% confidence interval (CI) 0.53, 0.85]; p = 0.001). (Table 2).

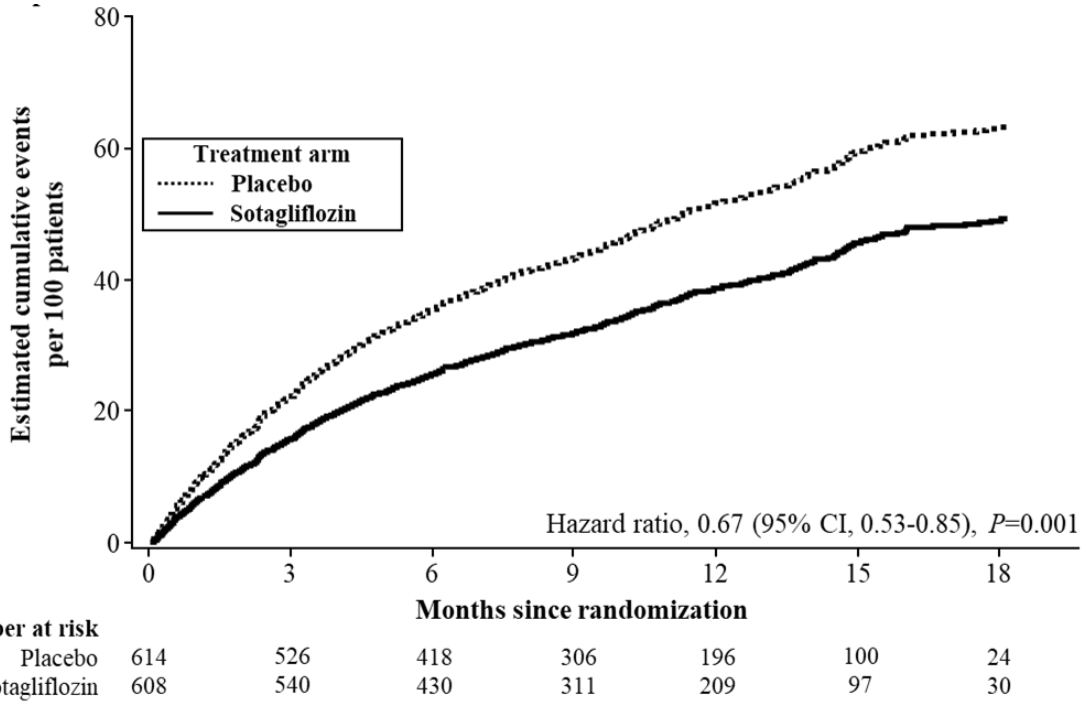
Table 2 Treatment Effect for the Primary Composite, Components and Secondary Endpoint in the SOLOIST Study

	Event Rates per 100 Patient-years		
Primary Endpoint[a]	**INPEFA 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
Primary Endpoint Components			
Cardiovascular death[c,d]	8.4	9.4	0.84 (0.58, 1.23)
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)
Secondary Endpoint[c]			
Hospitalization for heart failure and urgent heart failure visit[c]	40.6	63.9	0.64 (0.50, 0.84) p = 0.0009

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

Figure 3 displays a cumulative events plot of the primary composite endpoint. The INPEFA and placebo event curves diverged early and remained separated over the study period.

Figure 3 **Primary Composite Endpoint (Total Occurrences of Cardiovascular Death, Hospitalization for Heart Failure, and Urgent Heart Failure Visit) Over Time in the SOLOIST Study**



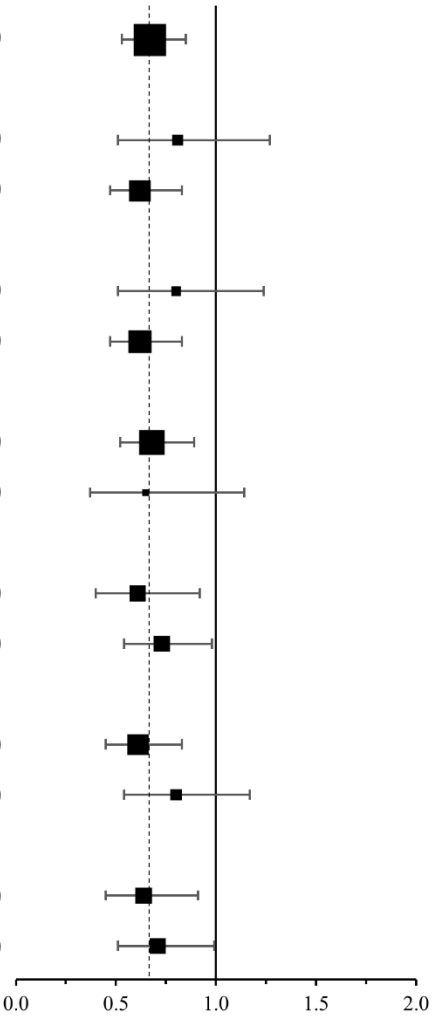
Number at risk							
Placebo	614	526	418	306	196	100	24
Sotagliflozin	608	540	430	311	209	97	30

Primary composite endpoint was based on investigator-reported events in all randomized patients, analyzed according to the treatment group allocated by randomization.

The results of the primary composite endpoint were generally consistent across prespecified subgroups (Figure 4), including screening LVEF < 50 or ≥ 50% and timing of first dose (post-discharge versus prior to discharge).

Figure 4 Treatment Effect for Primary Composite Endpoint (Total Occurrences of Cardiovascular Death, Hospitalization for Heart Failure, and Urgent Heart Failure Visit) Subgroup Analysis (SOLOIST Study)

Subgroup	No. of patients	Events per 100 PY		HR (95% CI)
		Sotagliflozin	Placebo	
Overall	1222	51.3	76.4	0.67 (0.53, 0.85)
Sex				
Female	412	42.0	51.9	0.81 (0.51, 1.27)
Male	810	56.1	89.6	0.62 (0.47, 0.83)
Age (years)				
<65	364	57.4	71.0	0.80 (0.51, 1.24)
≥65	858	48.3	78.6	0.62 (0.47, 0.83)
LVEF at screening (%)				
<50	955	53.7	79.9	0.68 (0.52, 0.89)
≥50	265	43.4	65.7	0.65 (0.37, 1.14)
Baseline NT-proBNP (pg/mL)				
≤ median (1806)	600	34.6	57.4	0.61 (0.40, 0.92)
> median (1806)	600	68.1	94.2	0.73 (0.54, 0.98)
MRA use at baseline				
Yes	788	47.4	76.1	0.61 (0.45, 0.83)
No	434	59.1	76.9	0.80 (0.54, 1.17)
Timing of first dose				
Post-discharge	620	50.3	76.9	0.64 (0.45, 0.91)
Prior to or at discharge	596	52.0	75.9	0.71 (0.51, 0.99)



HF = heart failure; LVEF = left ventricular ejection fraction; MRA-mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro B-type natriuretic peptide; PY = patient-years
Primary composite endpoint was based on investigator-reported events in all randomized patients, analyzed according to the treatment group allocated by randomization.
Discharge may have been from hospital or urgent treatment facility where urgent heart failure visit occurred.
Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

14.2 SCORED Study

The SCORED (Effects of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes Mellitus, Cardiovascular Risk Factors and Moderately Impaired Renal

Function) study (NCT03315143) was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study in patients with type 2 diabetes mellitus (A1C > 7%), chronic kidney disease (eGFR 25 to 60 mL/min/1.73 m^2), and additional cardiovascular risk factors, such as a history of heart failure, obesity, dyslipidemia, hypertension, or elevated cardiac and inflammatory biomarkers, to determine if INPEFA reduces the risk of total occurrence of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit. Of the 10,584 randomized patients, 5,292 were randomized to INPEFA and 5,292 to placebo.

The dose of study drug was to be up-titrated from 200 mg to 400 mg sotagliflozin or matching placebo as soon as 4 weeks or up until 6 months after initiation of treatment. The dose was increased to 400 mg once daily for 3,934 patients (74%) in the INPEFA group and for 3,987 patients (75%) in the placebo group. The median time to up-titration was 29 days. Up-titration was to be performed based on the judgment of the investigator, who considered whether the patient's clinical condition was satisfactory, whether the drug was well tolerated, and whether AEs typical of SGLT2 inhibitors had occurred, such as those associated with volume depletion.

At baseline, median age was 68 years, 45% were female, 82% were White, 3% Black or African American, 6% Asian, and 4% American Indian or Native Alaskan. Median A1C was 8.3%, median BMI was 32 kg/m^2, median eGFR was 45 mL/min/1.73 m^2 (8% with eGFR < 30, 44% with eGFR 30 to < 45, and 48% with eGFR ≥ 45 mL/min/1.73 m^2), and median urinary albumin-to-creatinine ratio (UACR) was 82 mg/g (32% with UACR ≥ 300 mg/g). A history of heart failure was present in 31%, prior myocardial infarction had occurred in 20%, a prior cerebrovascular event had occurred in 9%, and coronary revascularization had been performed in 22% of patients prior to study entry.

At baseline, 97% were treated with at least one antihyperglycemic medication, including 56% with a biguanide, 64% with insulin, 27% with a sulfonylurea, 20% with a DPP4 inhibitor, and 6% with a GLP-1 receptor agonist. At baseline, 88% were treated with inhibitors of the renin-angiotensin-aldosterone system, 14% with a beta blocker, 42% with a calcium channel blocker, 35% with a loop diuretic, and 30% with another diuretic.

INPEFA was superior to placebo in reducing the risk of the primary composite endpoint (HR 0.75 [95% CI 0.63, 0.88]; p < 0.001) (Table 3).

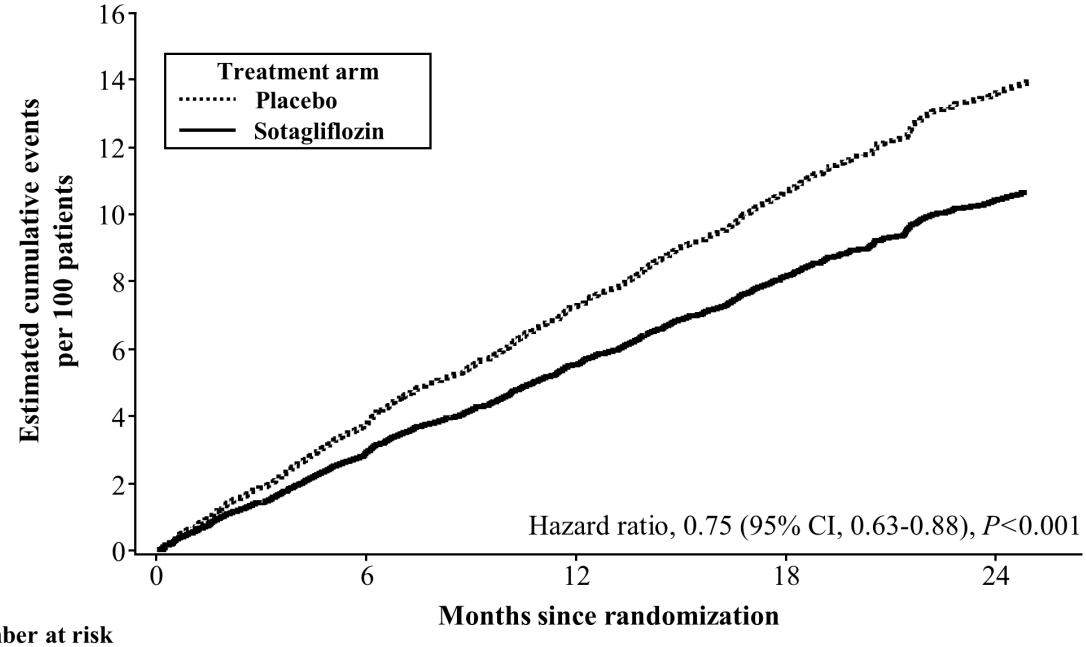
Table 3 Treatment Effect for the Primary Composite, Components and Secondary Endpoint in the SCORED Study

Primary Endpoint[a]	Event Rates (per 100 Patient-years)		Hazard Ratio (95% CI)
	INPEFA 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
Primary Endpoint Components			
Cardiovascular death[c,d]	2.9	3.2	0.90 (0.73, 1.12)
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)
Secondary Endpoint[c]			
Hospitalization for heart failure or urgent heart failure visit[c]	3.5	5.1	0.67 (0.55, 0.82) p = 0.0001

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

Figure 5 displays a cumulative events plot of the primary composite endpoint. The INPEFA and placebo event curves separated early and continued to diverge over the study period following randomization.

Figure 5 **Primary Composite Endpoint (Total Occurrences of Cardiovascular Death, Hospitalization for Heart Failure, and Urgent Heart Failure Visit) Over Time in the SCORED Study**



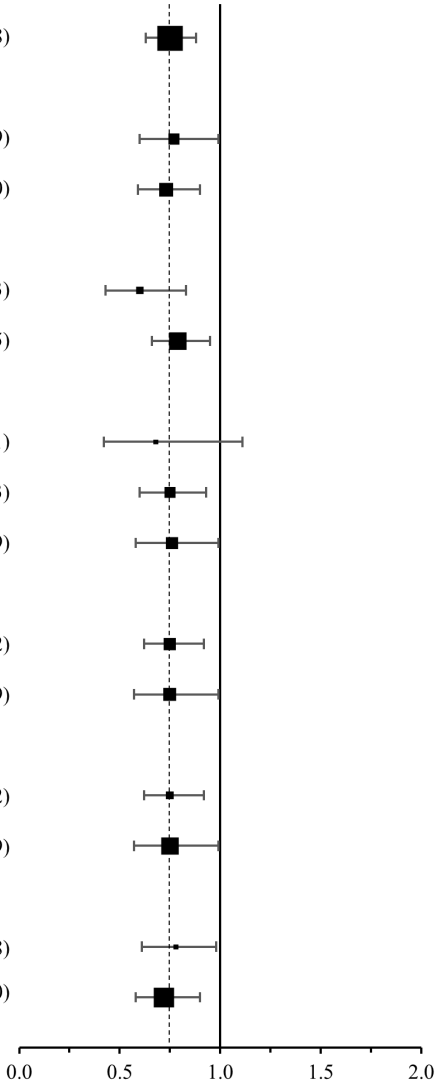
Number at risk					
Placebo	5292	5159	3911	2060	442
Sotagliflozin	5292	5197	3968	2087	445

Primary composite endpoint was based on investigator-reported events in all randomized patients, analyzed according to the treatment group allocated by randomization.

The results of the primary composite endpoint were generally consistent across prespecified subgroups, including history of cardiovascular disease, history of heart failure, and screening LVEF < 50 or ≥ 50% (Figure 6).

Figure 6 Treatment Effect for Primary Composite Endpoint (Total Occurrences of Cardiovascular Death, Hospitalization for Heart Failure, and Urgent Heart Failure Visit) Subgroup Analysis (SCORED Study)

Subgroup	No. of patients	Events per 100 PY		HR (95% CI)
		Sotagliflozin	Placebo	
Overall	10,584	5.6	7.5	0.75 (0.63, 0.88)
Sex				
Female	4754	5.1	6.5	0.77 (0.60, 0.99)
Male	5830	6.1	8.3	0.73 (0.59, 0.90)
Age (years)				
<65	3224	3.8	6.4	0.60 (0.43, 0.83)
≥65	7360	6.4	8.0	0.79 (0.66, 0.95)
Baseline eGFR (mL/min/1.73 m²)				
<30	811	9.4	14.1	0.68 (0.42, 1.11)
≥30 to <45	4655	6.9	9.1	0.75 (0.60, 0.93)
≥45	5116	3.9	5.1	0.76 (0.58, 0.99)
History of CVD				
Yes	5144	7.8	10.6	0.75 (0.62, 0.92)
No	5440	3.6	4.6	0.75 (0.57, 0.99)
History of HF at baseline				
Yes	3283	12.6	16.8	0.75 (0.62, 0.92)
No	7301	2.6	3.4	0.75 (0.57, 0.99)
LVEF at screening (%)				
<50	2160	14.0	18.2	0.78 (0.61, 0.98)
≥50	8405	3.6	4.9	0.72 (0.58, 0.90)



CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; HF = heart failure; PY = patient-years

Primary composite endpoint was based on investigator-reported events in all randomized patients, analyzed according to the treatment group allocated by randomization.
Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

16 HOW SUPPLIED/STORAGE AND HANDLING

INPEFA tablets are oval and film-coated.

Strength (mg)	Color	Printing	Deboss	Bottle/30	Bottle/90
200	Blue	LX200	--	NDC 70183-220-30	NDC 70183-220-90
400	Yellow	--	2457	NDC 70183-240-30	NDC 70183-240-90

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Risk of Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

In patients with type 1 diabetes mellitus, inform them that using INPEFA can increase their risk of life-threatening diabetic ketoacidosis. For all other patients, inform them that INPEFA can cause potentially fatal ketoacidosis and that type 2 diabetes mellitus is a risk factor.

Educate all patients on precipitating factors (such as infection, reduced caloric intake, ketogenic diet, surgery, insulin dose reduction, dehydration, and alcohol abuse) and symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing). Inform patients that blood glucose may be normal even in the presence of ketoacidosis.

Advise patients that they may be asked to monitor ketones. If symptoms of ketoacidosis occur, instruct patients to discontinue INPEFA and seek medical attention immediately *[see Warnings and Precautions (5.1)]*.

Volume Depletion

Inform patients that symptomatic hypotension may occur with INPEFA and advise them to contact their healthcare provider if they experience such symptoms *[see Warnings and Precautions (5.2)]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Serious Urinary Tract Infections

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice promptly if such symptoms occur *[see Warnings and Precautions (5.3)]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Inform patients that the incidence of hypoglycemia is increased when INPEFA is used in combination with insulin and that a lower dose of insulin may be required to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.4)]*.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Inform patients that necrotizing infections of the perineum (Fournier's Gangrene) have occurred with INPEFA in patients with diabetes mellitus. Counsel patients to promptly seek medical attention if they develop pain, tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions (5.5)]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)

Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.6)]*.

Genital Mycotic Infections in Males (e.g., Balanitis)

Inform male patients that yeast infections of the penis (e.g., balanitis or balanoposthitis) may occur, especially in patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.6)]*.

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., urticaria, anaphylactic reactions, and angioedema) have been reported with other SGLT2 inhibitors. Advise patients to immediately report any signs or symptoms suggesting allergic reaction or angioedema and to discontinue the drug until they have consulted their prescribing physician.

Pregnancy

Advise pregnant patients of the potential risk to a fetus with treatment with INPEFA. Instruct patients to immediately inform their healthcare provider if pregnant or planning to become pregnant *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that use of INPEFA is not recommended while breastfeeding *[see Use in Specific Populations (8.2)]*.

Laboratory Tests

Due to its mechanism of action, patients taking INPEFA will test positive for glucose in their urine.

Missed Dose

If a dose of INPEFA is missed by more than 6 hours, take the next dose as prescribed the next day. Advise patients not to take two doses of INPEFA at the same time.

Manufactured for:
Lexicon Pharmaceuticals, Inc. (The Woodlands, TX 77381)