INPHARMD™ **MONOGRAPHS**

# Inpefa™

## (sotagliflozin)

*The latest evidence on drug efficacy & recommendations.*


InpharmD™

**UPDATED** NOVEMBER 2023

# OVERVIEW

## REGIMEN

| | |
|---|---|
| **Generic Name** | sotagliflozin |
| **Trade Name** | Inpefa™ |
| **Manufacturer** | Lexicon Pharmaceuticals, Inc. |
| **FDA Approval** | May 27, 2023 |
| **Dosage** | 200 mg once daily not more than 1 hour before first meal of the day; increase to 400 mg once daily after > 2 weeks; may decrease to 200 mg once daily as necessary based on tolerability |
| **Therapeutic Class** | Dual Sodium-glucose-co-transporter (SGLT)-2 and 1 inhibitor |

### Indications

To 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 (T2DM), chronic kidney disease (CKD), and other cardiovascular risk factors.

## PHARMACOLOGY

Sotagliflozin is an inhibitor of SGLT2 and SGLT1. Inhibiting SGLT2 reduces renal reabsorption of glucose and sodium which may influence several physiological functions such as lowering both pre- and afterload of the heart and downregulating sympathetic activity. 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.

## PHARMACODYNAMICS

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. No increase in QT corrected for heart rate (QTc) was observed with either 800 mg or 2000 mg sotagliflozin.

## PHARMACOKINETICS

**Absorption/Onset**: The absolute bioavailability of oral sotagliflozin 400 mg dose was approximately 25% (90% confidence interval [CI] 16% to 39%) for area under the concentration-time curve from time 0 to last measurable concentration (AUC0-last). The contribution of enterohepatic circulation to the overall exposure is estimated to be approximately 50%. The median time to maximum plasma concentration (Tmax) ranged from 1.25 to 3 hours, over a single-dose range of 200 mg to

2000 mg. Following administration of multiple doses (400 mg and 800 mg), the median Tmax values ranged from 2.5 to 4 hours.

Food Effect: When sotagliflozin tablets were administered with a high-caloric breakfast compared to fasting conditions, plasma exposure to sotagliflozin as measured by Cmax and AUC0-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 a consistent effect of sotagliflozin on urine glucose excretion (UGE), insulin, and postprandial glucose (PPG) across all dose schedules. It is recommended that INPEFA be taken not more than one hour before the first meal of the day.

**Distribution**: Both sotagliflozin and its major human metabolite sotagliflozin 3-O-glucuronide exhibited high binding to human plasma proteins in vitro (> 93% bound), which was not dependent on the concentration of sotagliflozin and sotagliflozin 3-O-glucuronide and was not influenced by the degree of renal or hepatic function.

Following administration of a single 400 mg dose of [14C]-sotagliflozin, the mean blood/plasma ratios for total radioactivity were 0.5 and 0.4 for Cmax and AUC0-last,

respectively, and the mean whole blood to plasma concentration ratio of sotagliflozin ranged from 0.5 to 0.6.

The mean apparent volume of distribution of sotagliflozin following administration of a single 400 mg oral dose of [14C]-sotagliflozin was 9000 L.

**Metabolism**: Substrate of UGT1A9, and to a lesser extent, CYP3A4; metabolized predominantly to sotagliflozin 3-O-glucuronide

**Half-life Elimination**: Parent: mean terminal half-life, 21-35 hours; effective half-life, 5-10 hours

Active metabolite (sotagliflozin 3-O-glucuronide): mean terminal half-life, 19-26 hours

**Duration:** 5 to 10 hours (effective half-life)

**Excretion**: Urine (57%); feces (37%)

# CLINICAL DATA OVERVIEW

*N = 1,222 • Bhatt et al., 2021 • Phase 3, double-blind, randomized, placebo-controlled trial*

## Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

### POPULATION

A total of 1,222 patients underwent randomization: sotagliflozin group (n= 608); placebo group (n= 614)

Median age: 70 years; 33.7% female; 93.2% were White

79.1% had left ventricular ejection fraction (EF) < 50%; median eGFR was 49.7 mL/min/1.73m2; median glycated hemoglobin level 7.1%; median NT-proBNP level 1,799.7 pg/mL

First dose of sotagliflozin or placebo was administered before discharge in 48.8% of patients and after discharge in 51.2%

The vast majority of patients were receiving a RAAS inhibitor, beta-blocker, or loop diuretic; 85.4% of patients were receiving glucose-lowering medication

### METHODS

**Inclusion Criteria:**

18 to 85 years of age

Had been hospitalized because of the presence of signs and symptoms of heart failure and received treatment with intravenous (IV) diuretic therapy

Previous diagnosis of T2DM before index admission or laboratory evidence to support a diagnosis of T2DM during index admission

**Exclusion Criteria:**

End-stage heart failure

Recent acute coronary syndrome, stroke, percutaneous coronary intervention or coronary artery bypass surgery

Estimated glomerular filtration rate (GFR) < 30 mL/min/1.73 m2

**Intervention**: Sotagliflozin vs. placebo

### METHODS

**Primary Endpoint(s):**

Total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure (first and subsequent)

Sotagliflozin: 51% vs. Placebo: 76.3%; hazard ration (HR) 0.67; 95% confidence interval (CI) 0.52 to 0.85; p< 0.001

**Secondary Endpoint(s):**

Total number of hospitalizations and urgent visits for heart failure: 40.4% vs. 63.9%; HR 0.64; 95% CI 0.49 to 0.83; p< 0.001

Incidence of death from cardiovascular causes: 10.6% vs. 12.5%; HR 0.84; 95% CI 0.58 to 1.22

Incidence of death from any cause: 13.5% vs. 16.3%; HR 0.82; 95% CI 0.59 to 1.14

Total number of deaths from cardiovascular causes, hospitalizations for heart failure, nonfatal myocardial infarctions, and nonfatal strokes: 51.4% vs. 71%; HR 0.72; 95% CI 0.56 to 0.92

Total number of deaths from cardiovascular causes, hospitalizations and urgent visits for heart failure, events of heart failure during hospitalization: 54.7% vs. 80.6%; HR 0.68; 95% CI 0.54 to 0.86

### CONCLUSIONS

**Conclusion**: In patients with diabetes and recent worsening heart failure, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure than placebo

**Limitation(s):** Due to change in sponsorship of the trial, enrollment was stopped prior to the initial planned sample size, limiting the trials statistical power to detect a difference in endpoints. The majority of the study population were White, and had fairly well-controlled DM, limited the application of these results to other patient populations and patients with poorly-controlled DM.

**Duration**: Follow-up visits were scheduled at 1, 2, and 4 weeks, at 4 months, and every 4 months thereafter.

Change in score on the Kansas City Cardiomyopathy Questionnaire-12 item (KCCQ-12): Least-squares mean (LSM) change to month 4: 17.7 vs. 13.6; difference 4.1; 95% CI 1.3 to 7

Change in eGFR: LSM change: -0.34 vs. -0.18; difference –0.16; 95% CI –1.3 to 0.98

Safety Outcomes:

- Serious adverse events that led to withdrawal: sotagliflozin 3% vs. placebo 2.8%
- Most common adverse events: hypotension (6% vs. 4.6%), urinary tract infection (4.8% vs. 5.1%), and diarrhea (6.1% vs. 3.4%)
- Acute kidney injury: 4.1% vs. 4.4%; severe hypoglycemia: 1.5% vs. 0.3%

*N = 10,584 • Bhatt et al., 2023 • Phase 3, randomized, double-blind, placebo-controlled trial*

# Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease

## POPULATION

10,584 patients were enrolled (sotagliflozin, n= 5,292; placebo, n= 5,292); baseline characteristics were similar between groups

Median age: 69 years; 44.9% female; 82.7% were White

Median duration of exposure to sotagliflozin was 14.2 months and for placebo was 14.3 months; median duration of follow-up was 16 months in sotagliflozin group and 15.9 months in placebo group

74.5% of patients in sotagliflozin group had dose increased from 200 mg to 400 mg

19.9% had an EF < 40% or less within the past year or hospitalization for

## METHODS

**Inclusion Criteria:**

18 years of age or older

T2DM (glycated hemoglobin level of 7% or higher)

CKD (eGFR 25 to 60 mL/min/1.73m2

Additional cardiovascular risk factors (at least one major risk factor in those 18 years of age or older or at least two minor risk factors in those 55 years of age or older)

**Exclusion Criteria:**

Any plan to start an SGLT2 inhibitor during the trial or any SGLT2 inhibitor < 1 month prior to screening or randomization

History of diabetic ketoacidosis or nonketotic hyperosmolar coma within three months

End-stage heart failure

**Intervention**: Sotagliflozin vs. Placebo

**Duration**: Patients had follow-up visits after randomization at week 4, week 8, week 26, and every 26 weeks thereafter.

## METHODS

**Efficacy:**

- Total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure
- Sotagliflozin: 5.6 events/100 patient-year vs. Placebo: 7.5 events/100 patient-year; HR 0.74; 95% CI 0.63 to 0.88; p< 0.001

**Safety outcomes**:

- Total number of hospitalizations for heart failure and urgent visits for heart failure
    - 3.5 vs. 5.1; HR 0.67; 95% CI 0.55 to 0.82; p< 0.001
- Deaths from cardiovascular causes
    - 2.2 vs. 2.4; HR 0.9; 95% CI 0.73 to 1.12; p= 0.35
- Total number of deaths from cardiovascular causes, hospitalizations for heart failure, nonfatal myocardial infarctions, and nonfatal strokes
    - 7.6 vs. 10.4; HR 0.72; 95% CI 0.63 to 0.83
- Total number of deaths from cardiovascular causes, hospitalizations for heart failure, urgent visits for heart failure, and events of heart failure during hospitalization
    - 6.4 vs. 8.3; HR 0.76; 95% CI 0.65 to 0.89
- First occurrence of the composite of a sustained decrease of at least 50% in the eGFR from

## CONCLUSIONS

**Conclusion**: In patients with diabetes and CKD, with or without albuminuria, sotagliflozin resulted in a lower risk of the composite of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure than placebo, but was associated with adverse events.

**Limitation(s):** The premature cessation of the study due to loss of funding that resulted in the change of endpoints evaluated is a potential limitation as the study may not have been adequately powered for the secondary endpoints evaluat

heart failure in previous two years; median left ventricular ejection fraction was 60%

Median glycated hemoglobin level was 8.3%; median body mass index (BMI) was 31.8 kg/m2; median eGFR was 44.5 mL/min/1.73m2; median urinary albumin-to-creatinine ratio was 71

baseline for at least 30 days, long-term dialysis, renal transplantation, or a sustained eGFR < 15 mL/min/m2 for at least 30 days

  - 0.5 vs. 0.7; HR 0.71; 95% CI 0.46 to 1.08

- Deaths from any cause
  - 3.5 vs. 3.5; HR 0.99; 95% CI 0.83 to 1.18
- Total number of deaths from cardiovascular causes, nonfatal myocardial infarctions, and nonfatal strokes
  - 4.8 vs. 6.3; HR 0.77; 95% CI 0.65 to 0.91
- No significant differences between two groups in percentage of patients with adverse events that occurred or worsened during the treatment period or with events leading to withdrawal of the trial regimen
  - Serious adverse events: 23.4% vs. 25.2%
  - Adverse events that were more common with sotagliflozin: diarrhea (8.5% vs. 6%; p< 0.001), diabetic ketoacidosis (0.6% vs. 0.3%; p= 0.02), genital mycotic infections (2.4% vs. 0.9%; p< 0.001), and volume depletion (5.3% vs. 4%; p= 0.003)
  - No significant differences between groups for bone fractures, urinary tract infections, severe hypoglycemia, acute kidney injury, or amputations
  - Development of hypertension lower with sotagliflozin (2.6% vs. 4.1%); development of hypotension higher with sotagliflozin (2.6% vs. 1.9%; p= 0.009)

*N = 31 • Cherney et al., 2023 • Phase 3, multicenter, randomized, double-blind, placebo-controlled study*

# Efficacy and safety of sotagliflozin in patients with type 2 diabetes and stage 3 chronic kidney disease

## POPULATION

787 patients were randomized (sotagliflozin 200 mg, n= 263; 400 mg, n= 264; placebo, n= 260); baseline characteristics were similar across treatment groups

Mean age: 69 ± 7.9 years; female: 43.6%; White: 84.6% BMI: 32.4 ± 5.4 kg/m2; HBA1c: 8.3% ± 1%; T2DM duration of 17.1 ± 9 years

Mean eGFR was 45 mL/min/1.73m2; 52% had albuminuria (evenly divided between CKD3A and CKD3B

## METHODS

**Inclusion Criteria**:

18 years of age and older

Diagnosed T2DM

Hemoglobin A1c (HbA1c) 7-11%

eGFR 30-60 mL/min/1.73m2

**Exclusion Criteria**:

BMI < 20 kg/m2 or > 45 kg/m2

Systolic blood pressure (SBP) > 180 mmHg or diastolic blood pressure (DBP) > 100 mmHg

History of diabetic ketoacidosis within 12 weeks before screening

Reversible renal failure

Severe hypoglycemia within six months of screening

Use of systemic glucocorticoids > 10 days during 90 days prior to screening

Use of a selective SGLT2 inhibitor within 12 months

## METHODS

**Efficacy:**
Reduction in HBA1c at week 26
LSM change from baseline:

- Placebo: -0.22 ± 0.06
- Sotagliflozin 200 mg: -0.32 ± 0.06

Difference from placebo: -0.1%; 95% CI –0.25 to 0.05); p= 0.2095

- Sotagliflozin 400 mg: -0.46 ± 0.06
- Difference from placebo: -0.24%; 95% CI –0.39 to 0.09; p= 0.0021

**Secondary Endpoint(s):**
Change from baseline to week 26 in FPG and body weight

- FPG (mmol/L, LSM): placebo: -0.4 ± 0.2; sotagliflozin 200 mg: -1 ± 0.2 (difference from placebo –0.6; 95% CI –1.1 to –0.1; p= 0.0144); sotagliflozin 400 mg: -0.9 ± 0.2 (difference from placebo –0.5; 95% CI –0.9 to –0.01; p= 0.0436)

- Body weight (kg, LSM): placebo: -0.4 ± 0.3; sotagliflozin 200 mg: -1.7 ± 0.2 (difference from placebo –1.3; 95% CI –1.9 to –0.6; p< 0.0001); sotagliflozin 400 mg: -1.2 ± 0.3 (difference from placebo –0.8; 95% CI –1.5 to –0.2; p= 0.0155)

Change from baseline to week 12 in SBP (in patients with SBP > 130 mmHg at baseline and all patients)

- SBP >130 mmHg at baseline (mmHg, LSM): placebo: -5.2 ± 1.5; sotagliflozin 200 mg: -7.5 ± 1.6 (difference from placebo –2.3; 95% CI –6.3 to 1.7; p= 0.2627; sotagliflozin 400 mg: -7.7 ± 1.2 (difference from placebo –2.5; 95% CI –6.1 to 1; p= 0.1602)

- All patients (mmHg, LSM): placebo: -3.3 ± 1; sotagliflozin 200 mg and 400 mg: -4.9 ± 1 (difference from placebo –1.6; 95% CI –4.1 to 1; p= 0.2212) for both doses

Urine albumin-creatinine ratio (UACR) in patients with baseline UACR > 3.4 mg/mmol at week 26

## CONCLUSIONS

**Conclusion**: After 26 weeks, HbA1c was significantly reduced with sotagliflozin 400 mg but not 200 mg compared with placebo in this CDK3 cohort. UACR in patients with at least A2 albuminuria was reduced with each of the two doses at 26 weeks but changes were not sustained at week 52.

**Limitation(s):** A majority of the patients were White, thereby limiting the applicability of these results to other patient populations. As there was no active control, it is unknown how sotagliflozin compares to other treatment options (I.e. a selective SGLT2 inhibitor).

- Decrease versus placebo: sotagliflozin 200 mg: 30.7%; 95% CI –44.8% to –13.1%; p= 0.002; sotagliflozin 400 mg: 36.2%; 95% CI –49.9% to –18.7%; p< 0.001

Proportions of patients with an HbA1c <6.5% and <7% at week 26

- HbA1c < 6.5%: Placebo: 4.2%; sotagliflozin 200 mg: 5.7%; sotagliflozin 400 mg: 5.7% (difference from placebo 1.5%; 95% CI –2.2 to 5.2; p= 0.433 for both sotagliflozin groups)

- HbA1c <7%: Placebo: 13.5%; sotagliflozin 200 mg: 19.4% (difference from placebo 6%; 95% CI –0.2 to 12.2; p= 0.614); sotagliflozin 400 mg: 20.8% (difference from placebo: 7.4%; 95% CI 1.1 to 13.7; p= 0.023)

Rescue therapy required:

- 26-week period: 11.2% (placebo); 8.7% (sotagliflozin 200 mg); 6.8% (sotagliflozin 400 mg)

*N = 277 • Cherney et al., 2021 • Phase 3, multicenter, randomized, double-blind, placebo-controlled study*

# Efficacy and safety of sotagliflozin in patients with type 2 diabetes and severe renal impairment

## POPULATION

277 patients were enrolled; baseline characteristics were balanced between treatment groups (placebo, n= 93; sotagliflozin 200 mg, n= 92; sotagliflozin 400 mg n= 92)

Mean HbA1c was 8.1 ± 1.1%; most patients had overt proteinuria, SBP > 130 mmHg, and BMI > 30 kg/m2

## METHODS

**Inclusion Criteria**:

18 years of age and older

Diagnosed T2DM

HbA1c of 7-11%

eGFR 15-30 mL/min/1.73m2

**Exclusion Criteria**:

Use of a selective SGLT2 inhibitor within 12 months

BMI ≤ 20 kg/m2 or > 45 kg/m2

SBP < 120 mmHg or DBP < 60 mmHg while taking hypertensives

History of diabetic ketoacidosis or severe hypoglycemia

Renal disease requiring treatment with immunosuppressive therapy and dialysis within the past 12 months or expectation that dialysis would be needed during the study

Use of systemic glucocorticoids > 10 days during 90 days prior to screening

**Intervention**: Sotagliflozin 200 mg and 400 mg vs. Placebo

## METHODS

**Primary Endpoint(s):** Change from baseline in HbA1c at week 26 (to demonstrate superiority of sotagliflozin 400 mg vs. Placebo)

- LSM –0.1 ± 0.1 (placebo) vs. -0.4 ± 0.1 (sotagliflozin 400 mg); difference –0.3%; 95% CI –0.6 to 0.005; p= 0.096

**Secondary Endpoint(s):** Change from baseline in HbA1c at week 26 with sotagliflozin 200 mg vs. Placebo

- LSM –0.1 ± 0.1 (placebo) vs. -0.07 ± 0.2 (sotagliflozin 200 mg); difference –0.05; 95% CI –0.3 o 0.4; p= 0.812

Change from baseline in HbA1c at week 52 with sotagliflozin 400 mg vs. Placebo

- LSM 0.4 ± 0.2 (placebo) vs. -0.3 ± 0.2 (sotagliflozin 400 mg); difference –0.69; 95% CI –1.15 to –0.23; p= 0.003

Change from baseline in FPG, body weight, and UACR (in patients with baseline UACR ≥ 3.39 mg/mmol) at week 26

- FBG
  - Sotagliflozin 200 mg vs. Placebo: LSM: 0.07 ± 0.5 vs. -0.3 ± 0.5; difference –0.4; 95% CI –1.5 to 0.8; p= 0.5501
  - Sotagliflozin 400mg: -0.6 ± 0.4; difference (vs placebo) -0.7; 95% CI –1.8 to 0.3; p= 0.1779
- Body weight
  - Sotagliflozin 200 mg vs. Placebo: LSM –0.4 ± 0.5 vs. 0.4 ± 0.6; difference –0.8; 95% CI –2.2 to 0.6; p= 0.2432
  - Sotagliflozin 400 mg: -1 ± 0.5; difference (vs placebo) -1.4; 95% CI –2.8 to –0.01; p= 0.0487

## CONCLUSIONS

After 26 weeks, HbA1c reductions with sotagliflozin were not statistically significant vs placebo in adults with T2DM and CKD4.

**Limitation(s):** The use of rescue medication (insulin) may have limited the apparent effect of sotagliflozin compared to placebo. Additionally, the trial was powered for change in HbA1c endpoint, and not for renal parameters which may be important in this patient population.

- UACR (percent change from baseline)
    - Sotagliflozin 200 mg vs. Placebo: -29.8% vs. -11.8%; difference –20.4; 95% CI –44.8 to 14.8; p= 0.222
    - Sotagliflozin 400 mg: -30.5; difference (vs. Placebo) -21.2; 95% CI –45.1 to 13.1; p= 0.197

Change from baseline to week 12 in SPB in all patients and those with SBP ≥ 130 mmHg at baseline

- SBP all patients
    - Sotagliflozin 200 mg vs. Placebo: LSM –5.8 ± 18 vs. -2.5 ± 1.8; difference –3.2; 95% CI –7.4 to 0.9; p= 0.1232
    - Sotagliflozin 400 mg: -7.9 ± 1.8; difference (vs. Placebo) -5.4; 95% CI –9.4 to –1.3; p= 0.0098
- SBP ≥ 130 mmHg at baseline
    - Sotagliflozin 200 mg vs. Placebo: LSM –4.8 ± 1.9 vs. -2.7 ± 1.8; difference –2.1; 95% CI –7.1 to 2.8; p= 0.395
    - Sotagliflozin 400 mg: -7.1 ± 1.8; difference (vs. Placebo) -4.4; 95% CI –9.2 to 0.4; p= 0.072

Proportion of patients with HbA1c < 6.5% and < 7% at week 26

- HbA1c < 6.5%
    - 2.2% (placebo), 5.4% (sotagliflozin 200 mg), 8.7% (sotagliflozin 400 mg)
    - Difference (200 mg vs. Placebo); 3.2%; 95% CI –2.2 to 8.7; p= 0.242; difference (400 mg vs placebo): 6.5%; 95% CI 0.04 to 12.9; p= 0.0513
- HbA1c < 7%
    - 4.3% (placebo), 16.3% (200 mg), 17.4% (400 mg)
    - Difference (200 mg vs. Placebo): 12%; 95% CI 3.5 to 20.6; p= 0.007; difference (400 mg vs. Placebo): 13%; 95% CI 4.3 to 21.8; p= 0.004

Overall incidence of adverse events: 82.8% (placebo) vs. 86.2% (sotagliflozin 200 mg) vs. 81.1% (sotagliflozin 400 mg)
    - Adverse events leading to treatment discontinuation: 12.9% (placebo) vs. 10.6% (200 mg) vs. 13.3% (400 mg)
- Incidence of hypoglycemia: 40.9% vs. 40.4%% vs. 38.9%

*N = 797 • Buse et al., 2018 • Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study*

# Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes

## POPULATION

797 patients were randomized to placebo (n= 268), sotagliflozin 200 mg (n= 263), or sotagliflozin 400 mg; baseline characteristics

59.6% used CSII and 40.4% used MDI

Mean age: 46.1 years; 51.7% female; 92.2% White; mean baseline HbA1c: 7.57%; mean BMI: 29.66 kg/m2

Mean baseline daily total insulin dose: 0.73 IU/kg; mean duration of diabetes: 24.4 years

## METHODS

**Inclusion Criteria:**

At least 18 years old with T1DM

Using either MDI (multiple daily injections) or continuous subcutaneous insulin infusion (CSII) for insulin delivery

HbA1c 7-11%

**Exclusion Criteria:**

Beta-hydroxybutyrate (BHB) levels > 0.6 mmol/L

Use of antidiabetic agent other than insulin or insulin analog

Use of SGLT2 inhibitor within 8 weeks prior to randomization

Chronic systemic corticosteroid use

**Intervention**: Sotagliflozin 200mg or 400 mg vs. Placebo (all in combination with optimized insulin)

## METHODS

**Primary Endpoint(s):** Change in HbA1c from baseline to week 24 (placebo-adjusted LSM)

- Sotagliflozin 200 mg: 0.36%; 95% CI –0.45 to –0.27; p< 0.001
- Sotagliflozin 400 mg: 0.41%; 95% CI –0.5 to –0.32; p< 0.001
- LSM differences remained significant at week 52

**Secondary Endpoint(s):** Composite of proportion of patients with HbA1c < 7%, no episode of severe hypoglycemia, and no episode of diabetic ketoacidosis at week 24

- 21.64% (placebo) vs. 33.46% (200 mg) vs. 43.51% (400 mg)
- Differences compared to placebo were significant and remained significant at 52 weeks
- Differences in proportions of patients who achieved HbA1c < 7% and experienced severe hypoglycemia (≤ 3%) or diabetic ketoacidosis (≤ 1.5%) was not statistically significant

HbA1c < 7%

- Week 24: 22.8% vs. 36.9% vs. 46.9%
- Week 52: 20.9% vs. 30% vs. 35.5%

Total daily insulin dose LSM difference from placebo at week 24

- Sotagliflozin 200 mg: -5.7%; 95% CI –12.82 to 1.42; p= 0.12
- Sotagliflozin 400 mg: -12.67%; 95% CI –19.79 to –5.55; p< 0.001

## CONCLUSIONS

In a 1-year T1DM study, sotagliflozin combined with optimized insulin therapy was associated with sustained HbA1c reduction, weight loos, lower insulin dose, fewer episodes of severe hypoglycemia, improved patient-reported outcomes, and more KDA relative to placebo.

**Limitation(s):** Limitations of the study include that insulin dose was optimized prior to therapy, which may not reflect what occurs in a real-world setting. Additionally, patients with an HbA1c >11 were excluded so results may not be applicable to patients with poorly controlled DM. Patients also had frequent SMBG and ketone testing, which may not always be feasible in clinical practice.

Change in BMI at week 24 (LSM difference from placebo)

- Sotagliflozin 200 mg: -2.35 kg; 95% CI –2.85 to –1.85
- Sotagliflozin 400 mg: -3.45 kg; 95% CI –3.95 to –2.94

Frequency of documented hypoglycemia (events per person-year) over 52 weeks

- 96.1 (placebo) vs. 84.1 (200 mg; relative rate vs placebo 0.88; 95% CI 0.77 to 0.99; p= 0.04) vs. 90 (400 mg; relative rate 0.93; 95% CI 0.82 to 1.06; p= 0.28)

At least one positively adjudicated diabetic ketoacidosis event: 0.4% (placebo), 3.4% (200 mg), 4.2% (400 mg).

Any adverse event: 80.6% (placebo), 81.7% (200 mg), 79.8% (400 mg).

*N = 782 • Danne et al., 2018 • Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study*

# HbA1c and hypoglycemia deductions at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with type 1 diabetes

## POPULATION

782 patients were randomized to: placebo (n= 258), sotagliflozin 200 mg (n= 261), sotagliflozin 400 mg (n= 263); baseline characteristics were similar between groups

74.3% used MDI, 35.7% used CSII

Mean age: 41.2 years; 48.1% female; 96.2% White

Mean diabetes duration: 18.4 years; mean HbA1c: 7.75%; HbA1c < 7% at baseline: 17.9%; mean total daily insulin dose: 0.74 IU/kg

Mean BMI: 27.77 kg/m2

## METHODS

**Inclusion Criteria:**

At least 18 years old with T1DM

Using either MDI or CSII for insulin delivery with no change in insulin delivery within three months of screening

HbA1c 7-11%

**Exclusion Criteria:**

Beta-hydroxybutyrate (BHB) levels > 0.6 mmol/L

Use of antidiabetic agent other than insulin or insulin analog

Any prior exposure to sotagliflozin

Chronic systemic corticosteroid use

Severe hypoglycemic event 1 month prior to screening

**Intervention:** sotagliflozin 200 mg or 400 mg vs. Placebo

## METHODS

**Primary Endpoint(s):**

Change in HbA1c from baseline to 24 weeks (difference from placebo, LSM)

- Sotagliflozin 200 mg: -0.37 ± 0.058; 95% CI –0.48 to –0.25; p< 0.001
- Sotagliflozin 400 mg: -0.35 ± 0.058; 95% CI –0.37 to –0.24; p< 0.001
- Significant differences also seen at week 52

**Secondary Endpoint(s):**

Composite of proportion of patients with HbA1c < 7%, no episode of severe hypoglycemia, and no episode of diabetic ketoacidosis at week 24

- 15.12% (placebo) vs. 31.42% (200 mg) vs. 32.32% (400 mg)
- Differences compared to placebo were significant and remained significant at 52 weeks
- Differences in proportions of patients who achieved HbA1c < 7% and experienced severe hypoglycemia (< 2%) or diabetic ketoacidosis (< 1%) was not statistically significant

HbA1c < 7%

- Week 24: 15.1% vs. 33.3% vs. 33.8%
- Week 52: 15.5% vs. 27.2% vs. 27.8%

Total daily bolus insulin dose LSM difference from placebo at week 24

- Sotagliflozin 200 mg: -12.94%; 95% CI –20.5 to –5.38; p< 0.001

## CONCLUSIONS

**Conclusion**: In a 1-year study, sotagliflozin was associated with significantly significant HbA1c reductions. More episodes of DKA and fewer episodes of documented and severe hypoglycemia were observed in patients using sotagliflozin relative to those receiving placebo.

**Limitation(s):** The study design allowed for more frequent insulin adjustments and glucose monitoring than may be feasible in clinical practice.

- Sotagliflozin 400 mg: -16.37%; 95% CI –23.9 to –8.83; p< 0.001

Total daily basal insulin dose LSM difference from placebo at week 24

- Sotagliflozin 200 mg: -5.82%; p= 0.007
- Sotagliflozin 400 mg: -4.67%; p= 0.03

Change in BMI at week 24 (LSM difference from placebo)

- Sotagliflozin 200 mg: -1.98 kg; 95% CI –2.53 to –1.44; p< 0.001
- Sotagliflozin 400 mg: -2.58 kg; 95% CI –3.12 to –2.04; p< 0.001

Frequency of documented hypoglycemia over 52 weeks (LSM differences in events per patient per day vs placebo)

- Sotagliflozin 200 mg: -0.026; 95% CI –0.048 to –0.005; p= 0.017
- Sotagliflozin 400 mg: -0.03; 95% CI –0.051 to –0.009; p= 0.006

Any adverse event: 61.2% (placebo), 68.2% (200 mg), 68.6% (400 mg)

- Serious adverse events: 6.6% vs. 10% vs. 8%

At least one positively adjudicated diabetic ketoacidosis event: 0 (placebo), 2.3% (200 mg), 3.4% (400 mg)

*N = 1,402 • Garg et al., 2017 • Phase 3, multicenter, randomized, double-blind, placebo-controlled trial*

# Effects of sotagliflozin added to insulin in patients with type 1 diabetes

## POPULATION

1,402 patients were randomized to: sotagliflozin (n= 699) and placebo (n= 703); baseline characteristics were similar between groups

Mean age: 43.3; 42.4 years (sotagliflozin; placebo); female: 48.8%; 51.8%; White: 88.6%; 88.3%

Duration of diabetes: 20.5; 19.6 years; HbA1c: 8.26; 8.21; daily dose of insulin: 0.69; 0.71 IU/kg

BMI: 28.29; 28.01 kg/m2

Subcutaneous injections: 60.7%; 60.2%; pump: 39.2%; 39.8%

## METHODS

**Inclusion Criteria:**

18 years of age or older

T1DM for at least 1 year

Treatment with insulin at a stable basal dose for at least two weeks prior to screening

HbA1c 7-11%

BMI ≥ 18.5 kg/m2

**Exclusion Criteria:**

Severe hypoglycemia or diabetic ketoacidosis during the previous month

Two or more episodes of diabetic ketoacidosis during the previous six months

eGFR < 45 ml/min/1.73m2

**Intervention**: sotagliflozin 400 mg vs. placebo

## METHODS

**Primary Endpoint(s):**

HbA1c <7% at week 24 with no episodes of severe hypoglycemia or diabetic ketoacidosis at week 24

- 28.6% (sotagliflozin) vs. 15.2% (placebo); difference 13.4; 95% CI 9 to 17.8; p< 0.001
- HbA1c ≥ 7% and ≥ 1 episode of severe hypoglycemia: 2.3% vs. 1.8%; difference 0.4; 95% CI –1 to 1.9; p= 0.56
- HbA1c ≥ 7% and ≥ 1 episode of diabetic ketoacidosis: 2.6% vs 0.6%; difference 2; 95% CI 0.7 to 3.3; p= 0.003

<u>Secondary Endpoint(s):</u>

Change from baseline in HbA1c level at week 24

- Difference –0.46%; p< 0.001 (favoring sotagliflozin)

Change from baseline in weight at week 24

- Difference –2.98 kg; p< 0.001 (favoring sotagliflozin)

Change from baseline in SBP at week 16

- SBP ≥ 130 mmHg: reduction in SBP was significantly greater in sotagliflozin group (difference –3.5 mmHg; p= 0.002)

Change from baseline in mean daily total, bolus, and basal dose of insulin (placebo-corrected reductions) at week 24

- Total: -5.3 units per day (-9.7%; p< 0.001); bolus: -2.8 units per day (-12.3%; p< 0.001); basal: -2.6 units per day (-9.9%; p< 0.001)

## CONCLUSIONS

**Conclusion**: Among patients with type 1 diabetes who were receiving insulin, the proportion of patients who achieved a glycated hemoglobin level lower than 7% with no severe hypoglycemia or diabetic ketoacidosis was larger in the group that received sotagliflozin than in the placebo group. However, the rate of diabetic ketoacidosis was higher in the sotagliflozin group.

**Limitation(s):** Given the short duration of the study, long-term effects could not be determined. Frequent glucose monitoring and investigator adjustment of insulin regimen may limit generalizability of these study results.

Documented hypoglycemia: 96.3% (sotagliflozin) vs. 95.3% (placebo); event rates were 69.8 per person-year and 77.9 per person-year, respectively

- Severe hypoglycemia: 3% (sotagliflozin) vs. 2.4% (placebo)

Overall rates of adverse events: 55.1% (sotagliflozin) vs. 52.5% (placebo)

- Serious adverse events: 6.9% vs. 3.3%
- Withdrawal from trial due to adverse event: 6.3% vs. 2.3%

Rate of one or more positively adjudicated episodes of diabetic ketoacidosis: 3% (sotagliflozin) vs. 0.6% (placebo)

*N = 41 • Posch et al., 2022 • Exploratory, phase 2a, single-center, randomized, double-blind, double-dummy, active-control, parallel-group study*

# Metabolic, intestinal, and cardiovascular effects of sotagliflozin compared with empagliflozin in patients with type 2 diabetes: A randomized, double-blind study

## POPULATION

41 patients were randomized to: sotagliflozin (n= 21) and empagliflozin (n= 20); baseline characteristics were similar between groups

Mean age: 61.2 years; 20% female; mean BMI: 29.6 kg/m2

Mean HbA1c: 7.6%; age at diabetes onset: 53.9 years; duration of diabetes: 8 years; duration of metformin treatment: 6.1 years; eGFR: 87.6 ml/min/1.73m2

Duration of hypertension: 7.3 years; on ACEi: 61%; on ARB: 30%

## METHODS

**Inclusion Criteria:**

Age 18 to 74 years of age

T2DM (diagnosed at least 1 year before the screening visit)

BMI 18-38 kg/m2

Hypertension grades 1 or 2 (BP between 140/90 and 179/109

Screening HbA1c between 6.5% and 11%

eGFR ≥ 60 mL/min/1.73m2

On stable treatment with metformin for 3 months and either an angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) as monotherapy for hypertension

**Exclusion Criteria:**

Severe anemia

Severe cardiovascular disease

Stage 3 or higher CKD

New York Heart Association stage III or IV heart failure

Myocardial infarction within 12 months prior to screening

## METHODS

**Primary Endpoint(s):**

During breakfast MMTT, sotagliflozin significantly reduced incremental area under the curve (AUC) values for postprandial glucose, insulin, and glucose-dependent insulinotropic polypeptide (GIP) and significantly increased AUCs for postprandial glucagon-like peptide 1 (GLP-1) compared to empagliflozin; changes waned during lunch and dinner MMTTs

- AUC glucose change after breakfast (h*mmol/L)
  - 0-2 hours (LSM difference sotagliflozin vs. Empagliflozin): -1 (95% CI –1.9 to –0.1; p= 0.0283)
  - 0-3 hours: -1.5 (95% CI -2.9 to –0.06; p= 0.0417)
  - 0-5 hours: -1.5 (95% CI –3.7 to 0.8; p= NS)
- Both treatments significantly lowered GIP incremental AUCs relative to baseline over the 14 hour MMTT interval

**Secondary Endpoint(s):**

Change in HbA1c at week 8

- Sotagliflozin: -0.51 ± 0.11%; empagliflozin: -0.57 ± 0.1%; p= 0.06518

Decrease in BP

- Sotagliflozin: 4.6 ± 1.5/2.3 ± 0.9 (SBP/DBP); empagliflozin 7.9 ± 1.4/3.7 ±0.9

No serious or severe adverse events were observed

## CONCLUSIONS

**Conclusion**: Changes from baseline in glycemic and blood pressure control, cardiovascular biomarkers, and other parameters were comparable between sotagliflozin and empagliflozin. However, sotagliflozin but not empagliflozin inhibited intestinal SGLT1 after breakfast as shown by larger changes in postprandial glucose, insulin, GIP, and GLP-1 AUCs, particularly after breakfast. Additional study is warranted to assess the clinical relevance of transient SGLT1 inhibition and differences in incretin response.

**Limitation(s):** The study was limited by its small sample size, single-center design, and use primarily of surrogate parameters rather than clinical endpoints. Additionally, long term outcomes were not assessed as the study duration was up to 8 weeks

| | | |
|---|---|---|
| **Intervention**: sotagliflozin 400 mg vs. empagliflozin 25 mg | | • Gastrointestinal disorders occurred at similar rates between groups; no episodes of diarrhea or abdominal pain reported in sotagliflozin group<br>Both treatments significantly lowered GIP incremental AUCs relative to baseline over the 14 hour MMTT interva |

## ADVERSE EFFECTS

| | **Sotagliflozin** (SOLOIST n = 605; SCORED n = 5,291) | **Placebo** (SOLOIST n = 611; SCORED n = 5,286) |
|---|---|---|
| **Genitourinary** | • Urinary Tract Infection (8.6%, 11.5%)<br>• Genital Mycotic Infection (0.8%, 2.4%) | • Urinary Tract Infection (7.2%, 11%)<br>• Genital Mycotic Infection (0.2%, 0.9%) |
| **Endocrine & Metabolic** | • Hypoglycemia (4.3%, 7.7%)<br>• Volume Depletion (9.3%, 5.2%)<br>• Dizziness (2.6%, 3.3%) | • Hypoglycemia (2.8%, 7.9%)<br>• Volume Depletion (8.8%, 4%)<br>• Dizziness (2.5%, 2.8%) |
| **Gastrointestinal** | • Diarrhea (6.9%, 8.4%) | • Diarrhea (4.1%, 6%) |

## CONTRA-INDICATIONS

Patients with a history of serious hypersensitivity reaction to sotagliflozin

## IMMUNOGENICITY

N/A

## DRUG INTERACTIONS

| **Interacting Drug/Class** | **Interaction** | **Clinical Management** |
|---|---|---|
| Digoxin | Increase in exposure of digoxin when coadministered with sotagliflozin 400mg | Patients taking sotagliflozin with concomitant digoxin should be monitored appropriately |
| Uridine 5'-diphospho-glucuronosyltransferase (UGT) inducer | The coadministration of rifampicin (an inducer of UGTs) with a single dose of 400mg sotagliflozin resulted in a decrease in exposure to sotagliflozin; this decrease in exposure to sotagliflozin may decrease efficacy. | Consider monitoring of clinical status. |

| | | |
|---|---|---|
| Lithium | 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 |

## 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)

# SAFETY CONSIDERATIONS

## BOXED WARNINGS

N/A

## WARNINGS & PRECAUTIONS

- Diabetic ketoacidosis in patients with type 1 diabetes mellitus (T1DM) and other ketoacidosis: in placebo-controlled trials of patients with T1DM, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to placebo; the risk may be greater with higher doses of sotagliflozin. Ketone monitoring can be considered and ketoacidosis should be assessed in patients who present with signs and symptoms consistent with severe metabolic acidosis, regardless of presenting blood glucose levels; if ketoacidosis is suspected, discontinue sotagliflozin and promptly evaluate and treat ketoacidosis if confirmed.
- Volume depletion: sotagliflozin may cause intravascular volume depletion that can manifest as symptomatic hypotension or acute transient changes in creatinine; there have been postmarketing reports of acute kidney injury in patients with T2DM receiving SGLT2 inhibitors. Patients with impaired renal function (eGFR < 60 mL/min/1.73 m2) elderly patients, or patients on loop diuretics may be at increased risk and should be monitored for signs and symptoms of hypotension and renal function after initiating therapy.
- Urosepsis and pyelonephritis: treatment with SGLT2 inhibitors increases the risk for urinary tract infections; urosepsis and pyelonephritis requiring hospitalization have been reported
- Hypoglycemia with concomitant use of insulin and insulin secretagogues: sotagliflozin may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue; a lower dose of insulin or insulin secretagogue may be required when used with sotagliflozin to minimize the risk of hypoglycemia
- Necrotizing fasciitis of the perineum (Fournier's Gangrene): reports have been identified in postmarketing surveillance in patients with DM receiving SGLT2 inhibitors
- Genital mycotic infections: sotagliflozin increases the risk of genital mycotic infections
- Positive urine glucose test: monitoring glucose levels with urine glucose test is not recommended, as SGLT2 inhibitors increase urinary glucose excretion leading to a positive urine glucose test
- Interference with 1,5-anhydroglucitol (1,5-AG) assay: measurements of 1,5-AG are unreliable in assessing glucose levels in patients taking SGLT2 inhibitors

## USE IN SPECIFIC POPULATIONS

| | |
|---|---|
| **Renal impairment** | No dosage adjustment necessary |
| **Hepatic impairment** | No dosage adjustment necessary |
| **Geriatrics** | No dosage change is recommended based on age. No differences in efficacy were detected between elderly patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients may be at increased risk for volume depletion adverse reactions, including hypotension. |
| **Pediatrics** | The safety and effectiveness of sotagliflozin in pediatric patients under 18 years of age have not been established |
| **Reproductive potential** | Sodium-glucose cotransporter 2 (SGLT2) inhibitors are not recommended for the treatment of heart failure in patients planning to become pregnant (AHA/ACC/HFSA [Heidenreich 2022]). |
| **Pregnancy** | Based on animal data showing renal effects, sotagliflozin is not recommended during the second and third trimesters of pregnancy. Available data with sotagliflozin are insufficient to evaluate for drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. |
| **Lactation** | There are no data on the presence of sotagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Sotagliflozin is present in rat milk; when a drug is present in animal milk, it is likely to be present in human milk. Since human kidney maturation occurs *in utero* and during the first two years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in a breastfed infant, advise women that breastfeeding is not recommended while taking sotagliflozin. |
| **Pharmacogenomics** | Not provided |

# DOSAGE & ADMINISTRATION

200 mg once daily not more than 1 hour before first meal of the day; increase to 400 mg once daily after > 2 weeks; may decrease to 200 mg once daily as necessary based on tolerability. No dosage adjustment necessary.

**Administration**

- Administer no more than 1 hour before the first meal of the day
- Swallow tablets whole, do not cut, crush, or chew.
- If a dose of sotagliflozin is missed by more than 6 hours, take the next dose as prescribed the next day
- Withhold sotagliflozin at least three days, if possible- prior to major surgery or procedures associated with prolonged fasting; resume sotagliflozin when the patient is clinically stable and has resumed oral intake

## REFERENCES


1. INPEFA (sotagliflozin tablet). Prescribing information. Lexicon Pharmaceuticals, Inc.; 2023.
2. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021;384(2):117-128. doi:10.1056/NEJMoa2030183
3. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med. 2021;384(2):129-139. doi:10.1056/NEJMoa2030186
4. Cherney DZI, Ferrannini E, Umpierrez GE, et al. Efficacy and safety of sotagliflozin in patients with type 2 diabetes and stage 3 chronic kidney disease. Diabetes Obes Metab. 2023;25(6):1646-1657. doi:10.1111/dom.15019
5. Cherney DZI, Ferrannini E, Umpierrez GE, et al. Efficacy and safety of sotagliflozin in patients with type 2 diabetes and severe renal impairment. *Diabetes Obes Metab*. 2021;23(12):2632-2642. doi:10.1111/dom.14513
6. Buse JB, Garg SK, Rosenstock J, et al. Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: The North American inTandem1 Study. Diabetes Care. 2018;41(9):1970-1980. doi:10.2337/dc18-0343
7. Danne T, Cariou B, Banks P, et al. HbA1c and hypoglycemia deductions at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with type 1 diabetes: The European inTandem2 Study. *Diabetes Care*. 2018;41(9):1981-1990. doi:10.2337/dc18-0342
8. Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. *N Engl J Med*. 2017;377(24):2337-2348. doi:10.1056/NEJMoa1708337
9. Posch MG, Walther N, Ferrannini E, et al. Metabolic, intestinal, and cardiovascular effects of sotagliflozin compared with empagliflozin in patients with type 2 diabetes: A randomized, double-blind study. Diabetes Care. 2022;45(9):2118-2126. doi:10.2337/dc21-2166