Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update with New Drug Evaluation: SGLT2 Inhibitors

Date of Review: August 2023

Generic Name: bexagliflozin
Generic Name: sotagliflozin

Date of Last Review: October 2022
Dates of Literature Search: 08/01/2022 - 04/24/2023
Brand Name (Manufacturer): Brenzavvy (TheracosBio, LLC)
Brand Name (Manufacturer): Inpefa (Lexicon Pharmaceuticals, Inc.)
Dossiers Received: no

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this class update is to evaluate new evidence for safety and harms of sodium-glucose co-transporter 2 (SGLT-2) inhibitors. The evidence for the new SGLT-2 inhibitors, bexagliflozin and sotagliflozin, will be evaluated and recommendations for place in therapy will be presented.

Plain Language Summary:
- This review looks at new research published for drugs called sodium-glucose co-transporter 2 (SGLT2) inhibitors. These medicines are used to lower blood sugar in people with type 2 diabetes. They have also shown to prevent damage to the heart and kidneys in people with and without diabetes.
- A high quality guideline from the National Institute for Health and Care Excellence recommends SGLT2 inhibitors for adults with chronic heart failure.
- Several different guidelines have made recommendations for the use of SGLT2 inhibitors in people with type 2 diabetes in addition to their ability to decrease blood sugar levels. These include evidence of benefit to the kidney and heart.
- There is a new drug approved by the Food and Drug Administration called bexagliflozin. The research on how well bexagliflozin lowers blood sugars showed bexagliflozin works the same as other SGLT2 inhibitors and has similar adverse reactions, such as yeast infections, bladder infections and increased urination. It was also found to lower blood sugars a similar amount as 2 other medicines used to manage type 2 diabetes called sitagliptin and glimepiride.
- There is a second new drug approved in this class called sotagliflozin. It has shown benefit in people with heart failure or in those with type 2 diabetes, chronic kidney disease and other cardiovascular risk factors, such as heart failure or high blood pressure. It has similar adverse events as other SGLT2 inhibitors, such as bladder infections, diarrhea and very low blood sugars.
- The Drug Use Research and Management Group recommends no changes to the preferred SGLT2 inhibitors in this class. The new drugs, bexagliflozin and sotagliflozin should go through the prior authorization process to ensure appropriate use.

Author: Kathy Sentena, PharmD

Research Question

1. In patients with type 2 diabetes (T2D), what is the comparative evidence for efficacy or harms of SGLT2 inhibitors for important outcomes (e.g., hemoglobin A1c [HbA1C], microvascular outcomes, macrovascular outcomes and mortality)?
2. Are there specific subpopulations (e.g., those with comorbidities) for which SGLT2 inhibitors may be better tolerated or more effective than other available antidiabetic therapies when used for glucose lowering?
3. What is the evidence for the effectiveness and harms of bexagliflozin in patients with T2D?
4. Are there specific subpopulations for which bexagliflozin may be specifically indicated, more effective, or associated with less harm?
5. What is the evidence for the effectiveness and harms of sotagliflozin in patients with HF or T2D, CKD and other CV risk factors?
6. Are there specific subpopulations for which sotagliflozin may be specifically indicated, more effective, or associated with less harm?

Conclusions:

- Included in this update are the following: 4 high quality guidelines, 3 new indications, one new safety warning, 3 randomized controlled trials and 2 new drug evaluations.
- National Institutes for Health and Care Excellence (NICE) guidance recommends the use of SGLT-2 inhibitors for adults with chronic heart failure (HF).[1]
- Updated guidelines by the Kidney Disease: Improving Global Outcomes (KDIGO) strongly recommend SGLT-2 inhibitors for adults with T2D and chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) $\geq$ 20 ml/min per 1.73 m^2, with or without hyperglycemia (Strong recommendation).[2]
- The Canadian Cardiovascular Society strongly recommends the use of SGLT2 inhibitors, based on moderate evidence, for adults with T2D for the treatment of HF and CKD.[3]
- The American Diabetes Association (ADA) recommends the use of SGLT2 inhibitors for glucose lowering and for CV and renal benefits in those with T2D.[4,5]
- Dapagliflozin and empagliflozin received additional Food and Drug Administration (FDA) approved indications for reducing cardiovascular (CV) risk in adults.[6,7]
- Empagliflozin monotherapy and in combination with metformin, received approval for use in children and adolescents 10 years of age and older with T2D.[8]
- A safety warning was added to SGLT2 labeling due to a drug interaction with lithium causing reduced lithium concentrations.
- A new SGLT2 inhibitor, bexagliflozin, was approved in January of 2023.[9] Moderate-quality evidence showed bexagliflozin efficacy is similar to other SGLT2 inhibitors with HbA1c lowering of -0.38% to -0.48%. Active treatment comparisons found bexagliflozin to be non-inferior to sitagliptin and glimepiride (moderate quality of evidence). Common adverse events are female genital mycotic infections, urinary tract infection and increased urination.[9]
- Moderate-quality evidence shows sotagliflozin reduces the risk of CV death, hospitalization for HF and urgent HF visits in adults with HF or T2D, CKD and other CV risk factors.[10] Sotagliflozin is not approved for glucose lowering at this time. Adverse reactions are similar to other SGLT2 inhibitors. When studied in patients with type 1 diabetes (T1D), sotagliflozin had an increased incidence of diabetic ketoacidosis (DKA) compared to placebo.
- Limitations to the data include lack of ethnic diversity and the enrollment of populations that are older than those in the fee-for-service (FFS) Medicaid program.

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on a review of recent clinical evidence.
- Update prior authorization (PA) criteria to allow for preferred SGLT2 therapies to be used first-line in treatment of T2D.
- Maintain bexagliflozin and sotagliflozin as non-preferred.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- The SGLT2 inhibitor class was reviewed in October of 2022. The committee voted to maintain the PA criteria for preferred SGLT2 inhibitors as second line therapy after metformin in patients with diabetes and update the PA to clarify that renal function should be evaluated on an annual basis.
- Evidence was presented that demonstrated that SGLT2 inhibitors were more effective than placebo in people with T2D and atherosclerotic cardiovascular disease (ASCVD) or who were at high risk of ASCVD for the following outcomes: CV death or hospitalization for heart failure (HF), all-cause mortality, major adverse cardiovascular events (MACE), and hospitalizations for HF or emergency department visits for HF.

Background:

Approximately 287,000 adult Oregonians have T2D.[11] It is estimated that over 38,000 of these patients are Oregon Health Plan (OHP) members and over 10,000 Oregon FFS members have a T2D diagnosis.[11] The OHP paid $106 million in direct medical claims for diabetes and diabetes-related complications in 2012.[11] The overall cost to the state is estimated at $3 billion a year.[11] According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have T2D by 2050.[12] Despite a variety of treatment options, a significant number of patients fail to meet HbA1c goals within 3 years of being diagnosed and 50% of patients require combination therapy to control their T2D.[13,14]

Underlying characteristics that lead to hyperglycemia and T2D are insulin resistance and impaired insulin secretion. While evidence has shown the importance of lifestyle modifications, such as diet and exercise changes, antidiabetic treatments are necessary to reduce glucose levels in most patients with T2D.[15] Pharmacotherapy improves hyperglycemia by increasing glucose uptake, increasing glucose secretion and/or increasing insulin sensitivity. Goal glucose levels are dependent upon patient characteristics, such as age and comorbidities; however, guidelines recommend a goal HbA1c of less than 7% for most patients but a range of less than 6.5% to less than 8% may be appropriate in certain patients. Currently available classes of non-insulin antidiabetic agents are: alpha-glucosidase inhibitors, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), insulins, meglitinides, SGLT2 inhibitors, sulfonylureas, thiazolidinediones, bile acid sequestrants, dopamine-2 agonists and amylin mimetics. Current evidence and guidelines recommend metformin as a first-line treatment in most patients with T2D due to its safety profile, low risk of hypoglycemia and potential CV benefit.[16–18] In patients with CV or renal comorbidities some guidelines recommend the use of therapies such as SGLT2 inhibitors and GLP-1 RAs, that have evidence of CV and renal benefits, as first line therapy.[4,5] There is no consensus on a universally recognized second-line treatment, and therefore, selection should depend on the degree of glucose lowering required to assist in obtaining goal HbA1c levels, patient specific characteristics including comorbidities, and harms of therapy.[16] People that may benefit from weight loss should consider SGLT2 inhibitors or GLP-1 RAs, which have high quality evidence demonstrating weight reductions with use.[17] This update will focus on new evidence for the use of SGLT2 inhibitors (**Table 1**).

Sodium glucose cotransporter-2 inhibitors block the reabsorption of glucose from the renal glomerular filtrate in the renal proximal tubule.[19] The result is a reduction in renal absorption of filtered glucose and increased urinary glucose excretion. An additional mechanism of action is reduced sodium reabsorption and increased sodium delivery to the distal tubule.[19] In addition to glucose lowering, some SGLT-2 inhibitors have evidence of reducing CV death (e.g., canagliflozin, dapagliflozin, and empagliflozin) and adverse renal outcomes in those with diabetic nephropathy and albuminuria (e.g., canagliflozin) in adults with T2D. Benefits of SGLT2 inhibitors have also been demonstrated in adults without diabetes with HF (e.g., dapagliflozin, empagliflozin) and in those with chronic kidney disease (e.g., dapagliflozin).

Table 1. Cardiovascular and Renal Outcomes for SGLT2 Inhibitors compared to Placebo[17,20]

	All-Cause Mortality	Stroke	CV Death/ CV Events	Myocardial Infarction	Hospitalization for Heart Failure	Chronic Kidney Disease
SGLT-2 Inhibitors	*No effect (moderate quality evidence)* Benefit: Empagliflozin Neutral: Canagliflozin Dapagliflozin	*No effect (low quality evidence)* Neutral: Canagliflozin Dapagliflozin Empagliflozin	*Reduced Risk (moderate quality evidence)* Benefit: Canagliflozin* Dapagliflozin* Empagliflozin∞*	*No effect (moderate quality evidence)* Neutral: Canagliflozin Dapagliflozin Empagliflozin	*Significant risk reduction (moderate quality evidence)* Benefit: Canagliflozin Dapagliflozin* Empagliflozin* Ertugliflozin	*Reduced risk of eGFR decline, end stage kidney disease CV death and hospitalization for HF in adults with* CKD *(moderate quality evidence)* Benefit: Dapagliflozin* Canagliflozin*

* FDA indicated for this outcome

Abbreviations: CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ER = extended release; GLP-1 = glucagon-like peptide 1; HR = heart failure; inj = injection; SGLT-2 = sodium-glucose cotransporter-2

Important outcomes in patients with diabetes are microvascular and macrovascular complications, mortality, HbA1c reduction, severe adverse events and hypoglycemia. Hemoglobin A1C reduction is often used as a surrogate marker to assess comparative efficacy of different antidiabetic therapies, as hyperglycemia is associated with increased microvascular complications, and possibly macrovascular outcomes as well. A clinically relevant change in HbA1c is considered to be a decrease of 0.3% or more.[21] Available data for most new drugs are limited to short-term studies, which prevents the assessment of the durability of most antidiabetic treatments to control glucose levels long-term.

Abbreviated Drug Utilization Evaluation:

Ninety-five percent of SGLT-2 utilization is for preferred products: canagliflozin, dapagliflozin and empagliflozin. There were almost 100 claims for SGLT-2 inhibitors in fourth quarter of 2022, which represents a modest cost to the OHP. All SGLT-2 inhibitors require PA.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, twenty one systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[22–27, 23,28–39, 40–42]

New Guidelines:
High Quality Guidelines:

NICE – Chronic Heart Failure in Adults
The National Institute for Health and Care Excellence updated guidance for the use of dapagliflozin and empagliflozin in 2021 and 2022, respectively, for the management of people with HF.[1] The recommendation is that those adults with chronic HF and reduced ejection fraction (i.e., ejection fraction less than 40%) should be offered SGLT-2 inhibitors, if appropriate based on patient specific factors, along with other HF medications (e.g., ACE inhibitors, ARBs, beta-blockers, mineralocorticoid receptor antagonists [MRAs] and angiotensin receptor/neprilysin inhibitor [ARNIs]).[1]

Specific recommendations for the management of HF with reduced ejection fraction from NICE include:[1]
- ACE and beta-blockers as first-line treatment.
- ARBs licensed for HF as an alternative to ACE inhibitors in people who are unable to tolerate an ACE inhibitor.
- MRAs, SGLT-2 inhibitors, and sacubitril/valsartan have demonstrated improved outcomes and should be added to optimize the standard of care if advised by a specialist.

KDIGO 2022 Clinical Practice Guideline
In 2022 KDIGO updated their 2020 recommendations with an emphasis on glucose lowering therapies in patients with CKD, highlighting the use of SGLT-2 inhibitors. Guideline methodology was well described; however, authors had a significant number of conflicts of interest.[2] Recommendations were graded from Grade A (high quality of evidence) to Grade D (very low quality of evidence).

Optimal management of people with diabetes and CKD has important consequences on minimizing kidney failure and CV events (e.g., myocardial infarction [MI], stroke, ischemia, and HF) and other diabetes-related complications.[2] SGLT-2 inhibitors are an important component of first-line drug therapy recommendations that also include metformin, renin-angiotensin-system [RAS] inhibitors and moderate- or high-intensity statin. In addition to the composite kidney outcomes, SGLT2 inhibitors conferred less annual eGFR decline and a reduction in albuminuria or decreased progression to severely increased albuminuria.[2]

Recommendations pertaining to SGLT-2 utilization:[2]
- SGLT-2 inhibitors should be used to treat people with T2D and CKD with an eGFR $\geq$20 ml/min per 1.73 m^2, with or without hyperglycemia (Strong recommendation; Grade 1A).
- In Patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2 inhibitor therapy, or who are unable to use those medications, a long-acting GLP-1 RA is recommended (Grade 1B).

Other Considerations with using SGLT-2 inhibitors in people with T2D and CKD[2]:
- People treated with other glucose lowering therapy should still be considered for treatment with an SGLT2.

- SGLT-2 inhibitors with evidence of kidney and CV benefit (e.g., canagliflozin 100 mg, dapagliflozin 10 mg and empagliflozin 10 mg) should be considered in treatment choice.
- SGLT-2 inhibitors should be held if the patient undergoes a prolonged fast, surgery or critical medical illness.
- For patients at risk of hypovolemia, consider decreasing dose of thiazide or loop diuretic dose before initiating SGLT-2 therapy and counsel patients on symptoms of volume depletion.
- Upon initiation of SGLT-2 therapy a reversible decrease in eGFR may occur and most likely therapy does not have to be discontinued.
- If a patient has been initiated on a SGLT-2 inhibitor, it may be continued even if the eGFR falls below of 20 ml/min per 1.73 m^2 unless it is not tolerated or kidney replacement therapy is initiated.
- SGLT-2 inhibitors have not been adequately studied in kidney transplant recipients.

The recommendation for the use of SGLT2 inhibitors is based on evidence of benefit that demonstrated kidney and CV protection.[2] Improved outcomes in patients with CKD using SGLT-2 inhibitors have been demonstrated in those without diabetes as well. There is insufficient evidence to recommend the use of SGLT-2 inhibitors in patients with type 1 diabetes (T1D).

2022 Canadian Cardiovascular Society Guideline for Use of GLP-1 receptor agonists and SGLT2 inhibitors for Cardiorenal Risk Reduction in Adults

A 2022 guideline from the Canadian Cardiovascular Guideline updated recommendations for the use of SGLT2 inhibitors in patients with T2D.[3] Methods were clearly presented; however, all but three of 25 panel members had conflicts of interest. Recommendations were based on a high quality systematic review and meta-analysis. Recommendations were evaluated by the GRADE approach. Recommendations ranged from "strong" to "weak" based on the quality of evidence are are presented in **Table 2**.

Table 2. Recommendations for the Use of SGLT2 inhibitors for Cardiorenal Risk Reduction[3]

Recommendation	Rationale	Strength of recommendation; quality of evidence
SGLT2 inhibitors are recommended for adults with HF and an LVEF less than or equal to 40%	To reduce the risk of all-cause and CV mortality, hospitalization for HF and the composite end point of significant decline in eGFR progression to end-stage kidney disease or death due to kidney disease	Strong; moderate
SGLT2 inhibitors are recommended for adults with HF and LVEF greater than 40%	To reduce hospitalizations for HF	Strong; moderate
SGLT2 inhibitors are recommended for adults with CKD (UACR >20 mg/mmol and eGFR $\geq$25 ml/min/1.73m^2)	To reduce the composite of significant decline in eGFR, progression to end stage kidney disease, or kidney death, all cause and CV mortality, nonfatal MI, and hospitalization for heart failure.	Strong; moderate
SGLT2 inhibitors and GLP-1 RAs are recommended for adults with T2D and either established ASCVD or multiple risk factors for ASCVD	To reduce the risk of all-cause or CV mortality or MACE	Strong; moderate

SGLT2 inhibitors are recommended for adults with T2D and either established ASCVD or multiple risk factors for ASCVD	To reduce the risk of hospitalization for HF or the composite for significant decline in eGFR, progression to end stage kidney disease or kidney death	Strong; moderate
Abbreviations: ASCVD – atherosclerotic cardiovascular disease; CKD – chronic kidney disease; CV – cardiovascular; eGFR – estimated glomerular filtration rate; GLP-1 RA – glucagon-like peptide-1 receptor agonists; HF – heart failure; LVEF – left ventricular ejection fraction; MACE – major adverse cardiovascular events; SGLT2 – sodium-glucose co-transporter 2; T2D – type 2 diabetes; UACR – urine albumin-creatinine ratio		

ADA – Standards in Diabetes Update 2023

The annual update from the ADA on the standards of care in diabetes was published in January in 2023. New updates include recommendations for the use of SGLT2 inhibitors to slow progression of chronic kidney disease.

Pharmacotherapy recommendations include using therapies to achieve and maintain goal treatment levels. Choice of medications should include consideration of patient comorbidities and selecting therapies which provide benefit, such as weight management or reduction in cardiorenal risk. Recommendations for the use of SGLT2 inhibitors include the use of SGLT2 inhibitors that have demonstrated CV benefit, irrespective of glucose levels, in those who are high risk or have atherosclerotic disease CV disease, HF (with preserved or reduced ejection fraction), and/or CKD to reduce cardiorenal risk as part of their glucose lowering regimen (Grade A). Specifically SGLT2 inhibitors are recommended for people with T2D and diabetic kidney disease to reduce progression and CV events in those with an eGFR of 20 ml/min/1.73 m^2, or greater, and urinary albumin of 200 mg/g creatinine or greater (Grade A). This recommendation is also extended to those with an eGFR of 20 ml/min/1.73 m^2, or greater, and urinary albumin ranging from normal to 200 mg/g creatinine (Grade B). The use of SGLT2 inhibitors for CV risk reduction in people with T2D (with an eGFR of 20 ml/min/1.73 m^2 or greater) and diabetic kidney disease is also recommended (Grade A).

Canagliflozin, dapagliflozin and empagliflozin have evidence of CV benefit and canagliflozin and dapagliflozin have evidence for slowing the progression of diabetic kidney disease. Canagliflozin, dapagliflozin, empagliflozin and ertugliflozin have demonstrated benefit for HF. SGLT2 inhibitors are also recommended for those for glycemic management (high recommendation) and for achievement and maintenance of weight management (intermediate recommendation). The glucose lowering effect of SGLT2 inhibitors is reduced in people with lower eGFR.

Combination therapy with a SGLT2 inhibitor (with demonstrated CV benefit) and a GLP-1 RA (with demonstrated CV benefit) may be considered in those with T2D and established atherosclerotic CV disease or multiple risk factors for atherosclerotic CV disease to help reduce the risk of adverse CV and kidney events (Grade A).

New Formulations or Indications:

Dapagliflozin (FARXIGA) – In May of 2023 dapagliflozin received an expanded indication to reduce the risk of CV death, HF hospitalizations, and urgent visits due to HF in all adult patients.[6] The expanded indication applies to patients with HF that have all ranges of ejection fractions.

Empagliflozin and metformin (SYNJARDY AND SYNJARDY XR) – In February of 2023 the combination product containing empagliflozin and metformin received an additional indication to reduce the risk of CV death and hospitalization for HF in adults with HF.[43] The new indication was based off previously presented trials, Emperor-preserved and Emperor-reduced.

Empagliflozin and metformin (JARDIANCE and SNJARDY) – In June of 2023 empagliflozin and empagliflozin/metformin were approved for the use in children and adolescents, 10 years and older with T2D, to improve blood sugar control as an adjunct to diet and exercise.[8] Evidence for use was demonstrated in a 26-week, placebo-controlled, randomized, double-blind study which evaluated the use of empagliflozin and linagliptin.

New FDA Safety Alerts:

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
All SGLT2 inhibitors	Not applicable	October 2023	Warnings	Risk of drug interactions with lithium, which may decrease lithium concentrations. Serum lithium levels should be monitored more frequently if initiating or changing doses of a SGLT2 inhibitor.

Randomized Controlled Trials:

A total of 76 citations were manually reviewed from the initial literature search. After further review, 73 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Soloman, et al[44] DELIVER DB, MC, PG, Phase 3, RCT	1. Dapagliflozin 10 mg orally once daily* 2. Placebo* * In addition to usual therapy Median study duration: 2.3 years	Adult patients, with or without diabetes, with HF and left ventricular ejection fraction of more than 40% N = 10,418	Composite of worsening HF (unplanned hospitalization for HF or urgent visit for heart failure) or CV death	1. 512 (16.4%) 2. 610 (19.5%) HR 0.82 (95% CI, 0.73 to 0.92) P<0.001	In patients with mildly reduced or preserved ejection fraction, dapagliflozin was more effective than placebo at reducing the risk of worsening HF or CV death (ARR 3.1%/NNT 33)
Laffel, et al[45] DINAMO DB, MC, PG, Phase 3, RCT	1. Empagliflozin 10 mg orally once daily* 2. Linagliptin 5 mg orally once daily 7. Placebo * Those who did not have and HbA1c < 7% by week 12 were	Patients 10-17 years of age with a history of diabetes for at least 8 weeks before screening N = 158	Change from baseline in HbA1c at 26 weeks	1. -0.17% (pooled doses) 2. 0.33% 3. 0.68% Empagliflozin compared to placebo: Mean change -0.84% (95% CI, -1.50 to -0.19) P=0.012	In patients with a mean age of 14 years and obese, empagliflozin reduced HbA1c more than placebo or linagliptin.

	underwent a second randomization at week 14 to either stay on 10 mg or increase to 25 mg 26 weeks			Linagliptin vs. placebo: Mean change -0.34% (95% CI, -0.99 to 0.30) P=0.29	
EMPA-KIDNEY Collaborative Group[46] EMPA-KIDNEY DB, MC, PC, Phase 3, RCT	1. Empagliflozin 10 mg orally once daily* 2. Placebo* * In addition to usual therapy Median follow-up: 2 years	Adults with chronic kidney disease who had an eGFR of at least 20 but less than 45 ml/min/1.73 m2 or an eGFR of at least 45 but less than 90 ml/min/1.73 m2 with an urinary to albumin-to-creatinine ratio of at least 200 N=6609	Composite of progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to <10 ml/min/1.73 m2, sustained decrease in eGFR of 40% or greater from baseline or death from renal causes) or death from CV disease	1. 432 (13.1%) 2. 558 (16.9%) HR 0.72 (95% CI, 0.64 to 0.82) P<0.001	Results were similar in those with or without diabetes. Empagliflozin was more effective than placebo at reducing progression of kidney disease or death from CV causes (ARR 3.8%/NNT 27)

Abbreviations: ARR = absolute risk reduction; DB = double-bind; CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure, HR = hazard ratio; MC = multicenter; NNT = number needed to treat; PG = parallel group, RCT = randomized controlled trial

NEW DRUG EVALUATION: BEXAGLIFLOZIN

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Bexagliflozin (Brenzavvy®) is a SGLT-2 inhibitor approved for use as an adjunct to diet and exercise for controlling glucose levels in adults with T2D.[9] Approval was based on 6 phase 3 studies, in which 3 have been published.[47–49] The published trials, including a phase 2 trial, are described in Table 6. In these trials, bexagliflozin was compared to placebo in 2 trials and compared to active treatment, sitagliptin and glimepiride, in the remaining two. Participants in the trials had T2D with baseline HbA1c levels ranging from 7.98% to over 8.5%.[19] The average age of the participants was 61 years and predominately of White ethnicity. All of the trials were small (n= 283 to 426). In one trial the participants had moderate renal impairment.[48] The primary outcome in all of the trials was change in HbA1c. Changes in body mass and the percent of patients obtaining an HbA1c <7% were relevant secondary endpoints.

Bexagliflozin lowered HbA1c in all the trials with difference from placebo ranging from 0.37% to 0.79%.[47–49] In the FDA Integrated review, the placebo-adjusted estimate of the treatment effect of bexagliflozin ranged from -0.38% to -0.48%.[19] Bexagliflozin was found to be non-inferior to both sitagliptin and glimepiride, as add-on therapy to metformin. Bexagliflozin demonstrated reductions in body mass in placebo and active treatment comparison trials ranging from -2.0 kg to -3.75 kg. The mean number of patients obtaining a HbA1c <7% was 34% with bexagliflozin vs. 21.5% for placebo (p-value not reported; secondary outcome).[48]

Limitations to the evidence include the data from small, short-term studies for the majority of the evidence. In the non-inferiority trial comparing bexagliflozin to glimepiride, the max dose of glimepiride was 6 mg daily, which is less than then maximum approved dose of 8 mg daily, which could underestimate the glucose lowering effects of glimepiride.

Clinical Safety:

The most common adverse reactions with bexagliflozin are female genital mycotic infections, urinary tract infection and increased urination.[8] Bexagliflozin should not be used in people with a GFR less than 30 mL/min/ 1.73 m2 and is contraindicated in people on dialysis. Any volume depletion should be corrected before treatment initiation. Severe adverse events include: ketoacidosis, lower limb amputations, volume depletion, urosepsis and pyelonephritis, hypoglycemia with insulin and insulin secretagogues concomitant use, and necrotizing fasciitis of the perineum, all of which are similar to other SGLT-2 inhibitors.[9] A summary of adverse reactions observed in clinical trials is presented in **Table 4**.

Table 4. Adverse Reactions in Adult with Type 2 Diabetes (+/- metformin) that Occurred in at Least 2% of Patients[9]

Adverse Reaction	Placebo (n=300)	Bexagliflozin (n=372)
Increased urination	3	7
Urinary tract infection	4	6
Female genital mycotic infection	0	6
Thirst	2	3
Vaginal pruritus	0	3
Male genital mycotic infection	1	2
Hypoglycemia	1	2

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Change in HbA1c
2) Cardiovascular mortality
3) All-cause mortality
4) Progression of renal disease
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change in HbA1 over 24 to 60 weeks

Table 5. Pharmacology and Pharmacokinetic Properties.[9]

Parameter

Mechanism of Action	Sodium-glucose co-transporter 2 inhibitor, which blocks the reabsorption of the majority of glucose from the renal glomerular filtrate in the renal proximal tubule. This reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, increasing urinary glucose excretion.
Oral Bioavailability	78%
Distribution and Protein Binding	93% protein bound to plasma protein Volume of distribution is 262 L
Elimination	51.1% in the feces and 40.5% in the urine
Half-Life	12 hours
Metabolism	Metabolized by UGT1A9 and to a lesser extent by CYP3A4

Abbreviations: CYP = cytochrome P450; L = liters; UGT = Uridine 5'-diphospho-glucuronosyltransferase.

Table 6. Comparative Evidence Table for Bexagliflozin.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Halvorsen, et al[2] (2019) DB, DD, MC, NI, PG, Phase 3, RCT	1. Bexagliflozin 20 mg 2. Sitagliptin 100 mg * On background metformin in both arms 24-weeks	Demographics: Age: 59.4 years Male: 64.1% Asian: 16.1% White: 81.8% Disease duration: 8.79 years Baseline HbA1c: 7.99% Key Inclusion Criteria: - T2DM - ≥18 years of age - Metformin dose of 1500 mg or more - HbA1c 7% - 11% - BMI of ≤ 45 kg/m2 Key Exclusion Criteria: - T1DM - Pregnant or breastfeeding - Pancreatitis - Genitourinary infections	ITT: 1. 192 2. 194 PP: 1. 180 2. 189 Attrition: 1. 12 (6.3%) 2. 5 (2.6%)	Primary Endpoint: Mean change from baseline in HbA1c at week 24: 1. Bexagliflozin: -0.74% 2. Sitagliptin: -0.82% MD 0.08% (95% CI, -0.07 to 0.22%) NI achieved; prespecified margin was 0.35% Secondary Endpoints: Fasting blood glucose: 1. Bexagliflozin: -1.82 mmol/L 2. Sitagliptin: -1.44 mmol/L MD -0.37 (95% CI, -0.70 to -0.05) P=0.0123 Body mass: 1. Bexagliflozin: -3.35 kg/m2 2. Sitagliptin: -0.81 kg/m2 MD -2.54 (95% CI, -3.15 to -1.92) P<0.0001	NA NA NA	Severe Adverse Events: 1. Bexagliflozin: 7 (3.7%) 2. Sitagliptin: 4 (2.1%) Hypoglycemia: 1. Bexagliflozin: 6 (3.1%) 2. Sitagliptin: 10 (5.2%) Nasopharyngitis: 1. Bexagliflozin: 15 (7.9%) 2. Sitagliptin: 25 (13.0%) Treatment Discontinuations due to AE: 1. Bexagliflozin: 6 (3.1%) 2. Sitagliptin: 1 (0.5%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Computer generated random assignment based on an interactive web response system. Baseline characteristics were similar between groups. Performance Bias: (Low) All patients took two identical investigational products. Detection Bias: (Unclear) Not described. Attrition Bias: (Low) Attrition was low in both groups. Reporting Bias: (Low) Study protocol followed as outlined. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: The results are most applicable to White males with moderately uncontrolled diabetes as an adjunct to metformin therapy. This population is older than the Oregon FFS demographic. Intervention: The intervention is appropriate. Bexagliflozin 20 mg was studied in phase 2 studies. Comparator: Sitagliptin 100 mg is an appropriate comparator. Outcomes: Change in HbA1c is a standard outcome to determine efficacy of glucose lowering agents. Setting: 52 sites across the United States, Czech Republic, Hungary, Spain, Poland and Japan.

2. Allegretti, et al[48] DB, MC, PC, PG, Phase 3, RCT	1. Bexagliflozin 20 mg 2. Placebo 24 weeks	Demographics: Mean Age: 69.6 yrs Male: 62.8% White: 54.8% Asian: 38.5% CKD stage 3a: 166 CKD stage 3b: 146 Mean duration of diabetes: 16 years Mean baseline HbA1c: 7.98% Insulin use: 56% Metformin use: 41.7% Key Inclusion Criteria: - Ages 20 years or older - Patients with CKD stage 3a or 3b - T2DM - HbA1c 7.0% to 10.5% - GFR 30-59 ml/min/1.73m2 - BMI 45 kg m2 or less - Taking oral hypoglycemic agents without changes in the previous 8 weeks Key Exclusion Criteria: - T1DM - History of hypoglycemia more than 1 episode a week - Cancer (not in remission), MI, stroke or hospitalization for unstable angina/HF within previous 3 months	ITT: 1. 157 2.155 PP: 1. 152 2.144 Attrition: 1. 4 (3%) 2. 7 (5%)	Primary Endpoint: Change in HbA1c from baseline to week 24: Bexagliflozin: -0.61% Placebo: -0.24% MD -0.37% (95% CI, -0.20 to -0.54%) P <0.001 Secondary Endpoints: Changes in body weight at 24 weeks: Bexagliflozin: -2.0 kg Placebo: -0.39 kg MD -1.61 kg (95% CI, -1.00 to -2.2) P <0.001 Percent of Patients Achieving a HbA1c <7%: Bexagliflozin: 52 (34.2%) Placebo: 32 (21.5%) p-value not reported	NA NA NA	Severe Adverse Events: 1. Bexagliflozin: 11 (7.0%) 2. Placebo: 9 (6%) Treatment Discontinuations due to AE: 1. Bexagliflozin: 1 (1%) 2. Placebo: 4 (3%) Hypoglycemia: 1. Bexagliflozin: 39 (25%) 2. Placebo: 38 (25%) Urinary Tract Infections: 1. Bexagliflozin: 11 (7%) 2. Placebo: 5 (3%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized 1:1 ratio via a central interactive web response system. Performance Bias: (Low) Investigators, patients and sponsors blinded to treatment allocation. Allocation codes managed by statistician not involved in the study operations. Detection Bias; (Unclear) Not described. Attrition Bias: (Low) Low attrition. Results analyzed with ITT and LOCF. Reporting Bias: Study protocol followed as outlined. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: The results are most applicable to patients with long-term diabetes that are moderately controlled with CKD stage 3a or 3b. Intervention: Bexagliflozin 20 mg is appropriate Comparator: Placebo comparison is appropriate; however, active treatment comparison would be more helpful in determining place in therapy. Outcomes: Change in HbA1c is a standard outcome to determine efficacy of glucose lowering agents. Setting: 54 sites in the United States, Spain, France and Japan.
3. Halvorsen, et al (2023)[49]	1. Bexagliflozin 20 mg 2. Glimepiride 2-6 mg	Demographics: Mean Age: 59.6 yrs Male: 58.2% White: 94.4% Asian: 3.1%	ITT: 1. 213 2. 213 PP:	Primary Endpoint: Change in HbA1c from baseline to week 60: 1. Bexagliflozin: -0.70% 2. Glimepiride: -0.66%		Severe Adverse Events: 1. Bexagliflozin: 25 (12%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized via an interactive web-response system. There were more females in the bexagliflozin arm.

DB, DD, MC, NI, PG, Phase 3, RCT	(titrated up if SMG measurements were >100 mg/dL) 96 weeks	Mean duration of diabetes: 5.8 years Body mass index: 89.09 kg Baseline FPG: 9.62 mmol/L (173 mg/dL) Baseline HbA1c: 8.01% Metformin use: 64.3% Key Inclusion Criteria: - Ages 18 years or older - Inadequately controlled on metformin 1500 mg daily for at least 8 weeks - Not taking more than one other OHA - T2DM - HbA1c 7.0% to 10.5% - GFR 30-59 ml/min/1.73m^2 - BMI 45 kg m^2 or less - Taking oral hypoglycemic agents without changes in the previous 8 weeks Key Exclusion Criteria: - T1DM or maturity onset diabetes of the young - History of genitourinary infections - Cancer, uncontrolled hypertension, eGFR less than 60 mL/min/1.73 m^2	1. 180 2. 177 Attrition: 1. 33 (15.5%) 2. 36 (17%)	MD -0.05% (95% CI, -0.21 to 0.11%) Prespecified margin of 0.35% for the upper boundary of the 95% CI was met for noninferiority Secondary endpoints; Body mass changes at week 60 in those that with a BMI of 25 kg /m2 or greater: 1. Bexagliflozin: -3.75 kg 2. Glimepiride: 0.6 kg MD -4.31 kg (95% CI, -5.10 to -3.52) P<0.0001	NA NA	2. Glimepiride: 26 (12%) Treatment Discontinuations due to AE: 1. Bexagliflozin: 8 (3.8%) 2. Glimepiride: 11 (5.2%) Hypoglycemia: 1. Bexagliflozin: 36 (16.9%) 2. Glimepiride: 71 (33.3%) Urinary Tract Infections: 1. Bexagliflozin: 25 (11.7%) 2. Glimepiride: 10 (4.7%)		Performance Bias: (Low) All patients received identical products as a placebo and active therapy Detection Bias: (High) An independent data and safety monitoring committee reviewed unblinded data for safety and efficacy issues and a blinded clinical endpoint committee adjudicated major CV events. Attrition Bias: (high) Greater than 10% attrition. Results analyzed with ITT and missing data imputed via multiple imputations. Reporting Bias: Study protocol followed as outlined. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: The results are most applicable to patients who were predominately white, inadequately controlled by metformin who are overweight or obese. Intervention: Bexagliflozin 20 mg is appropriate Comparator: Glimepiride 2-6 mg. The maximum dose of glimepiride is 8 mg so the bexagliflozin efficacy could potentially be underestimated. Outcomes: Change in HbA1c is a standard outcome to determine efficacy of glucose lowering agents. Setting: 38 sites in the United States, Germany, Poland and Spain.
4. Halvorsen, et al[37] (2019) DB, MC, PG, Phase 2, RCT	1. Bexagliflozin 20 mg 2. Placebo	Demographics: Mean Age: 55.6 yrs Male: 41% White: 77.7% Mean duration of diabetes: 7.47 years	ITT: 1. 145 2. 138 PP: 1. 126	Change in HbA1c at 24 weeks: 1. Bexagliflozin: -0.28% 2. Placebo: 0.51% MD -0.79% (95% CI, -0.53 to -1.06%)	NA	Severe Adverse Events: 1. Bexagliflozin: 4 (2.8%) 2. Placebo: 12 (8.5%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized via an interactive web-response system using a computer generated sequence. There were more females in the bexagliflozin arm. Performance Bias: (Unclear) Not described.

	96 weeks	Body mass index: 30.1 kg m2 Baseline FPG: 9.44 mmol/L (169.9 mg/dL) Baseline HbA1c < 8.5%: 65% Baseline HbA1c ≥ 8.5%: 35% Key Inclusion Criteria: - Ages 18 years or older - T2DM - HbA1c 7.0% to 10% - FPG < 250 mg/dl if treatment naïve or < 240 mg/dl if taking only oral hypoglycemic agent. - BMI 45 kg m2 or less Key Exclusion Criteria: - Parenteral antidiabetic medication - eGFR < 50 ml/min/1.73 m2 - History of genitourinary infections - Abnormal LFTs - Cancer, uncontrolled hypertension	2. 122 Attrition: 1. 33 (13.1%) 2. 16 (11.6%)	P<0.0001 Secondary endpoints; Body mass changes at week 60 in those that with a BMI of 25 kg /m2 or greater: 1. Bexagliflozin: -2.63 kg 2. Placebo: 0.67 kg MD -1.96 kg (95% CI, -5.10 to -3.52) P<0.0001	NA	Treatment Discontinuations due to AE: 1. Bexagliflozin: 2 (1.4%) 2. Placebo: 0 (0%) Hypoglycemia: 1. Bexagliflozin: 24 (16.6%) 2. Placebo: 25 (17.7%) Urinary Tract Infections: 1. Bexagliflozin: 21 (14.5%) 2. Placebo: 29 (20.6%)		Detection Bias: (High) Unblinded data and safety monitoring board to review study data. Attrition Bias: (High) Greater than 10% attrition. Results analyzed with ITT and missing data with LOCF. Reporting Bias: One site had to be closed due to improbable data. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: The results are most applicable to patients who were predominately white females who are obese who have been previously treated with antidiabetic therapy. Intervention: Bexagliflozin 20 mg is appropriate Comparator: Placebo is appropriate; however, active treatment comparison would be more helpful in determining place in therapy. Outcomes: Change in HbA1c is a standard outcome to determine efficacy of glucose lowering agents. Setting: 27 sites in the United States, Columbia and Mexico.
Abbreviations: ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; DB = double-blind; DD = double-dummy; eGFR = estimated glomerular filtration rate; ITT = intention to treat; LOCF = last observation carried forward; MC = multi-center; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NI = non-inferiority; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; PG = parallel group; PP = per protocol, RCT = randomized controlled trial								

NEW DRUG EVALUATION: SOTAGLIFLOZIN

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Sotagliflozin (Inpefa®) is a SGLT2 inhibitor indicated to reduce the risk of CV death, hospitalization for HF and urgent HF visits in adults with HF or T2D, CKD and other CV risk factors. Sotagliflozin inhibits both SGLT2 and SGLT1.[10] Inhibition of SGLT1 reduces intestinal absorption of glucose and sodium, which may lead to diarrhea. The inhibition of SGLT2 reduces renal absorption of glucose and sodium leading to downregulation of sympathetic activity. The exact mechanism conferring CV benefit with the SGLT2 inhibitor class is not fully know but is thought to be due to changes in volume status/diuresis.[51] Sotagliflozin is initiated as a 200 mg dose before the first meal of the day and increased to 400 mg daily if tolerated.[10]

Sotagliflozin was studied for HF, CKD, and T1D in 7 phase 3 trials (Table 9). Sotagliflozin was approved in Europe as an adjunct to insulin therapy to improve glucose control in people with T1D and later withdrawn due to commercial reasons.[52] The FDA did not approve sotagliflozin for glucose lowering in patients with T1D due to the incidence of DKA.[53] The trials will be discussed below based on indication. The SOLOIST and SCORED trials were used for FDA approval.[51,54]

The SCORED trial was a phase 3, placebo-controlled randomized trial in 10,584 patients with T2D, CKD (eGFR 25 to 60 ml/min/1.73 m^2) and at risk for CV disease. The mean age was 69 years, majority of participants were white (83%), taking glucose lowering medication (97%), had poorly controlled diabetes with an mean HbA1c of 8.3% at risk of CV disease (89%) or had HF (31%).[54] Those with a history of DKA were excluded. The primary outcome was a composite of total CV death from CV causes, hospitalizations for HF and urgent visits for HF. Sotagliflozin was found to lower the risk for the primary endpoint with 5.6 events/100 patient-years compared to 7.5 events/100 patient-years for placebo (HR 0.74; 95% CI, 0.63 to 0.88; p<0.001).[54]

In a second phase 3 trial, sotagliflozin was studied in patients (n=1222) with T2D and worsening HF who had been admitted to the hospital, HF unit, infusion center or emergency department.[51] Patients were a median age of 70 years old, predominately White (93%) with a baseline eGFR of 50 ml/min/1.73 m^2, baseline HbA1c of 7.2%, taking glucose lowering medication (85%) and any renin-angiotensin-aldosterone system (RAAS) inhibitor (91%).[51] Exclusion criteria included need for oxygen therapy, systolic blood pressure of less than 100 mg Hg, need for intravenous inotropic or vasodilator therapy (excluding nitrates) and currently on IV diuretic therapy. The primary endpoint is was total number of deaths from CV causes and hospitalizations and urgent visits for HF. Sotagliflozin reduced the primary endpoint more than placebo, 245 events compared to 355 (HR 0.67; 95% CI, 0.52 to 0.85; p<0.001).[51] Hospitalizations and urgent visits for HF were reduced with sotagliflozin, 194 events versus 297 for placebo (HR 0.64; 95% CI, 0.49 to 0.83; p<0.001).[51]

Sotagliflozin was studied in two trials in patients with T2D and renal disease.[55,56] One trial included patients with severe renal dysfunction (eGFR 30 to 59 mL/min/1.73 m^2) and the second trial included patients with stage 3 chronic kidney disease. The placebo-adjusted HbA1c reduction was -0.1% to -0.46% for sotagliflozin in placebo-controlled trials in patients with renal disease, which was not statistically significant from placebo.[55,56] The glucose lowering effect is attenuated in patients with reduced renal function. Small decreases in eGFR were seen in patients with CKD3 but returned toward baseline.

Sotagliflozin was also studied in patients with T1D for glucose lowering; however, it is not approved for this indication at this time. The 3 inTandem trials had the same study design and evaluated the efficacy and safety of sotagliflozin in people with T1D on insulin.[57–59] All trials were phase 3, placebo-controlled, double-blind trials. In the InTandem1 trial participants were randomized to sotagliflozin 200 mg and 400 mg with a baseline HbA1c of 7.57%, average age of 46.1 years and BMI of 29.66 kg/m^2.[57] The inTandem2 study enrolled participants in Europe and Israel with a baseline HbA1c of 7.75%, mean of age of 41.2 years and BMI of 22.77 kg/m^2.[58] The inTandem3 trial enrolled people with uncontrolled T1D (mean HbA1c 8.2%) taking insulin who were also overweight (mean BMI 28 kg/m^2).[59] The primary outcome was change in HbA1c from baseline in all 3 trials, in which sotagliflozin reduced HbAC1 by -0.35% to -0.79% versus placebo.

Trials in participants with T1D were of short duration so it is unknown if glucose lowering could be sustained long-term. Trials conferring CV benefit were studied in patients who were older and at high risk of developing a CV event. The benefits seen in the CV composite outcomes were driven by reductions in HF hospitalizations. Across all trials, sotagliflozin was associated with weight loss of -1.0 kg to -3.45 kg.

Clinical Safety:

Sotagliflozin use has similar adverse events as other SGLT2 inhibitors. In placebo controlled trials adverse events that occurred in 5% or more of patients include the following: urinary tract infection, volume depletion, diarrhea, and hypoglycemia (**Table 7**).[10] Serious adverse events which occurred with sotagliflozin are ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia with insulin and insulin secretagogues, necrotizing fasciitis and genital mycotic infections.

Table 7. Adverse Events Occurring in 2% or more of Patients Treated with Sotagliflozin versus Placebo[10]

Adverse Reaction	SOLOIST Trial		SCORED Trial	
	Placebo (n=611)	Sotagliflozin (N=605)	Placebo (N=5,286)	Sotagliflozin (N=5,291)
Urinary tract infection	7.2%	8.6%	11.0%	11.5%
Volume depletion	8.8%	9.3%	4.0%	5.2%
Diarrhea	4.1%	6.9%	6.0%	8.4%
Hypoglycemia	2.8%	4.3%	7.9%	7.7%
Dizziness	2.5%	2.6%	2.8%	3.3%
Genital mycotic infection	0.2%	0.8%	0.9%	2.4%

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Change in HbA1c
2) Cardiovascular mortality
3) All-cause mortality
4) Progression of renal disease
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Composite of total CV deaths from CV causes, hospitalizations for HF, and urgent visits for HF
2) Change in HbA1c over 24 weeks

Table 8. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Inhibition of SGLT1 and SGLT2. Inhibition of SGLT2 reduces renal absorption of glucose and sodium, which lowers pre-load, and afterload of the heart and reducing sympathetic activity. Blocking SGLT1 causes reduction in intestinal glucose absorption, which may cause diarrhea. The exact mechanism of the CV benefit is unknown.

Oral Bioavailability	25%
Distribution and Protein Binding	Distribution is 9000 L and 93% protein bound
Elimination	Urine 57% and Feces 37%
Half-Life	5-10 hours
Metabolism	Metabolized by UGT1A9 and to a lesser extend CYP3A4

Abbreviations: L = liter; SGLT1 = sodium-glucose cotransporter-1; SGLT2 = sodium glucose cotransporter-2

Table 9. Comparative Evidence Table for Sotagliflozin.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
HEART FAILURE TRIALS								
1. Bhatt, et al[10] SCORED DB, MC, PC, Phase 3, RCT	1. Sotagliflozin 200 mg* 2. Placebo * Increased to 400 mg if tolerated Median follow-up: 16 months	Demographics: Mean Age: 69 yrs Male: 55% White: 83% Asian: 7% Ejection fraction 40% or less or hospitalization for heart failure during previous 2 years: 20% History of HF: 31% CV risk factors: 89% Previous MI: 20% Baseline eGFR: 44 ml/min/1.73 m^2 Baseline HbA1c: 8.3% Any glucose-lowering medication: 97% Key Inclusion Criteria: - 18 years of age and older - T2D - HbA1c of 7% or higher - CKD (25 to 60 min/ml/1.73 m2) - Additional CV risk factors (e.g., at least one major CV risk factor in those 18 years and older, or at least 2 minor CV risk factors in those 55 years or older Key Exclusion Criteria: - History of diabetic ketoacidosis - Antihyperglycemic treatment (if applicable) that has been unstable in the 12 weeks prior to study initiation - Use of other SGLT2 inhibitor currently or within 1 month of screening - Lower extremity complications - Uncontrolled hypertension - End-stage HF	ITT: 1. 5292 2. 5292 PP: 1. 5232 2. 5210 Attrition: 1. 60 (1.1%) 2. 82 (1.5%)	Primary Endpoint: Composite of total CV deaths from CV causes, hospitalizations for HF, and urgent visits for HF: 1.Sotagliflozin: 5.6 events per 100 patient-years 2. Placebo: 7.5 events per 100 patient-years HR 0.74 (95% CI, 0.63 to 0.88) P<0.001 Secondary Endpoint: Total number of hospitalizations for heart failure: 1. Sotagliflozin: 3.5 events per 100 patient-years 2. Placebo: 5.1 events per 100 patient-years HR 0.67 (95% CI, 0.55 to 0.82) P<0.001 Deaths from CV causes: 1. Sotagliflozin: 2.2 events per 100 patient-years 2. Placebo: 2.4 events per 100 patient-years HR 0.90 (95% CI, 0.73 to 1.12) P=0.35	NA NA NS	Urinary tract infection: 1. Sotagliflozin: 610 (11.5%) 2. Placebo: 585 (11.1%) P=0.45 Diarrhea: 1. Sotagliflozin: 448 (8.5%) 2. Placebo: 315 (6.0%) P<0.001 Volume Depletion: 1. Sotagliflozin: 278 (5.3%) 2. Placebo: 213 (4.0%) P=0.003 Serious treatment emergent adverse events: 1. Sotagliflozin: 1236 (23.4%) 2. Placebo: 1331 (25.2%) P=0.03 Serious treatment emergent adverse event leading to discontinuation: 1. Sotagliflozin: 112 (2.1%) 2. Placebo: 94 (1.8%) P=0.21	NA ARR 2.5%/ NNH 40 ARR 1.3%/ NNH 77 ARR 1.8%/ NNH 56 NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomization done by interactive response technology. Baseline characteristics were well matched. Performance Bias: (Low) Matched placebo indistinguishable from sotagliflozin. Investigators blinded to treatment assignment. Detection Bias: (Low) Adjudication committee to evaluate primary endpoint assigned in a blinded manner. Attrition Bias: (Low) Results analyzed via an ITT analysis. Attrition was low in both treatment groups. Reporting Bia: (High) Primary endpoint changed during trial. Trial ended early due to loss of funding. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: Results are most applicable to older patients with T2D and chronic kidney disease and at risk of CV disease. This demographic is older than the average Medicaid enrollee. Intervention: Sotagliflozin dose is appropriate. Comparator: Placebo comparison is appropriate. Outcomes: Composite outcomes may overestimate treatment effect of sotagliflozin. Outcomes are appropriate. Setting: 54 countries including the United States.

2. Bhatt, et al[51] SOLOIST-WHF DB, MC, PC, Phase 3, RCT	1. Sotagliflozin 200 mg* 2. Placebo * Increased to 400 mg if tolerated Median follow-up: 9 months	Demographics: Median Age: 70 yrs Male: 66.4% White: 93% Black: 4% Ejection fraction 50% or less: 79% Median Baseline eGFR: 50 ml/min/1.73 m^2 Baseline HbA1c: 7.2% Median body-mass index: 31 kg/m^2 Any glucose-lowering medication: 85% Any RAAS inhibitor: 91% Key Inclusion Criteria: - 18 to 85 years - hospitalized due to signs and symptoms of heart failure and received treatment with IV diuretic therapy - T2D or laboratory evidence to support a T2D diagnosis - Elevated natriuretic peptide levels (at least 150 pg/ml B-type natriuretic peptide or at least 600 pg/ml for N-terminal pro-B type natriuretic peptide - not on oxygen therapy - systolic BP of 100 mg Hg or greater - not on IV inotropic or vasodilator therapy (excluding nitrates) - transitioned from IV to oral diuretic therapy Key Exclusion Criteria: - End-stage HF or recent acute coronary syndrome - Stroke - PCI or coronary bypass - eGFR of 30 ml/min/1.73 m^2 or less	ITT: 1. 608 2. 614 PP: 1. 588 2. 591 Attrition: 1. 20 (3.3%) 2. 23 (3.7%)	Primary Endpoint: Total number of deaths from CV causes and hospitalizations and urgent visits for HF : 1. Sotagliflozin: 245 events (51.0%) 2. Placebo: 355 events (76.3%) HR 0.67 (95% CI, 0.52 to 0.85) P<0.001 Secondary Endpoints: Hospitalizations and urgent visits for heart failure: 1. Sotagliflozin: 194 events (40.4%) 2. Placebo: 297 (63.9%) HR 0.64 (95% CI, 0.49 to 0.83) P<0.001 Deaths from CV causes: 1. Sotagliflozin: 51 events (10.6%) 2. Placebo: 58 events (12.5%) HR 0.84 (95% CI, 0.58 to 1.22) P=0.36	NA NA NS	Urinary tract infection: 1. Sotagliflozin: 29 (4.8%) 2. Placebo: 31 (5.1%) Diarrhea: 1. Sotagliflozin: 37 (6.1%) 2. Placebo: 21 (3.4%) Hypotension: 1. Sotagliflozin: (6.0%) 2. Placebo: 28 (4.6%) Serious treatment emergent adverse events: 1. Sotagliflozin: 235 (38.8%) 2. Placebo: 251 (41.1%) Treatment discontinuations due to AE: 1. Sotagliflozin: 29 (4.8%) 2. Placebo: 23 (3.8%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized centrally via an interactive-response technology and stratified by LVEF and geographic region. Performance Bias: (Low) Double-blind design with placebo matched tablets. Detection Bias: (low) Independent data monitoring committee and independent clinical endpoint adjudication committee that evaluated events in a treatment-blinded manner. Attrition Bias: (Low) Results analyzed by ITT analysis and low attrition. Reporting Bias: (High) Primary endpoint was changed mid-trial and trial was ended early due to loss of funding from sponsor. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: These trial results are most applicable to people with T2D recently hospitalized for worsening heart failure Intervention: Sotagliflozin dose is appropriate. Comparator: Placebo comparison is appropriate. Outcomes: Composite outcomes may overestimate treatment effect of sotagliflozin. Outcomes are appropriate. Setting: Thirty-two countries with 72 (6%) patients enrolled in US centers.

TYPE 1 DIABETES TRIALS								
3. Buse, et al[57] inTandem1 DB, PC, Phase 3. RCT	1. Sotagliflozin 200 mg daily 2. Sotagliflozin 400 mg daily 3. Placebo Study duration: 52 weeks * All patients underwent a 6-week insulin optimization phase	Demographics: Median Age: 46.1 yrs Male: 48.3% White: 92.2% Black: 3.5% Hispanic: 3.8% Baseline HbA1c: 7.57% Mean weight (kg): 86.92 Mean body mass index: 29.66 kg/m^2 Insulin dose: 65.36 IU/day Key Inclusion Criteria: - T1D treated with insulin - Age 18 years and over - HbA1c 7.0 % to 11.0% Key Exclusion Criteria: - Use of other antidiabetic therapies - Severe hypoglycemic episode within 1 month - Beta-hydroxybutyrate >0.6 mmol/L	ITT: 1. 263 2. 262 3. 268 PP: 1. 236 2. 240 3. 236 Attrition: 1. 27 (10.3%) 2. 22 (8.4%) 3. 32 (11.9%)	Mean placebo-adjusted change in HbA1c from baseline at 24 weeks: 1. Sotagliflozin 200 mg: -0.37% 2. Sotagliflozin 400 mg: -0.35% Sotagliflozin 200 mg vs. placebo: LSM -0.37% (95% CI, -0.48 to -0.25); P<0.001 Sotagliflozin 400 mg vs. placebo: LSM -0.35% (95% CI, -0.47 to -0.24); P<0.001 Secondary outcomes (at week 24): Composite of the proportion of patients with HbA1C <7%, no episode of severe hypoglycemia and no episode of diabetic ketoacidosis: 1. Sotagliflozin 200 mg: 33.46% 2. Sotagliflozin 400 mg: 43.51% 3. Placebo: 21.64% Sotagliflozin 200 mg vs. placebo: LSM 11.82% (95% CI, 3.90 to 19.73); P=0.002 Sotagliflozin 400 mg vs. placebo: LSM 21.87% (95% CI, 13.72 to 30.02); P<0.001 Placebo-adjusted change from baseline in body weight: 1. Sotagliflozin 200 mg: -2.35 kg 2. Sotagliflozin 400 mg: -3.45 kg Sotagliflozin 200 mg vs. placebo: LSM -2.35 kg (95% CI, -2.85 to -1.85); P<0.001 Sotagliflozin 400 mg vs. placebo: LSM -3.45 kg (95% CI, -3.95 to -2.94); P<0.001	NA NA NA NA NA NA	Urinary tract infection: 1. Sotagliflozin 200: 26 (9.9%) 2. Sotagliflozin 400: 11 (4.2%) 3. Placebo: 19 (17.1%) Genital mycotic infections: 1. Sotagliflozin 200: 24 (9.1%) 2. Sotagliflozin 400: 34 (13.0%) 3. Placebo: 9 (3.4%) Diarrhea: 1. Sotagliflozin 200: 22 (8.4%) 2. Sotagliflozin 400: 27 (10.3%) 3. Placebo: 18 (6.7%) Volume Depletion: 1. Sotagliflozin 200: 8 (3.0%) 2. Sotagliflozin 400: 4 (1.5%) 3. Placebo: 4 (1.5%) Serious adverse events: 1. Sotagliflozin 200: 27 (10.3%) 2. Sotagliflozin 400: 29 (11.1%) 3. Placebo: 20 (7.5%) Diabetic ketoacidosis: 1. Sotagliflozin 200: 4 (1.5%) 2. Sotagliflozin 400: 4 (1.5%) 3. Placebo: 0 Serious treatment emergent adverse event leading to discontinuation: 1. Sotagliflozin 200: 13 (4.9%) 2. Sotagliflozin 400: 17 (6.5%) 3. Placebo: 11 (4.1%) Severe Hypoglycemia (>1 episode): 1. Sotagliflozin 200: 1 (0.4%) 2. Sotagliflozin 400: 0 (0%) 3. Placebo: 2 (0.7%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Unclear) Randomization not described. Performance Bias: (Unclear) Double-blind design stated but no details provided. Detection Bias: (Low) Independent data monitoring committee was blinded to treatment status. Attrition Bias: (High) Results analyzed by mITT analysis with missing observations imputed as non-responders. High attrition in the sotagliflozin 200 mg and placebo groups. Reporting Bias: (Low) Trial conducted as outlined in protocol. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: These trial results are most applicable to people with T1D receiving insulin and who were overweight. Intervention: Sotagliflozin dose is appropriate. Comparator: Placebo comparison is appropriate. Outcomes: Changes in HbA1c is a standard outcome to measure effectiveness. Setting: 75 sites in the United States and Canada.

4. Danne, et al[58] inTandem2 DB, PC, Phase 3, RCT	1. Sotagliflozin 200 mg daily 2. Sotagliflozin 400 mg daily 3. Placebo Study duration: 52 weeks * All patients underwent a 6-week insulin optimization phase	Demographics: Median Age: 41.2 yrs Male: 51.9% White: 96.2% Black: 1% Hispanic: 18% Baseline HbA1c: 7.75% Mean weight (kg): 81.66 Mean body mass index: 27.77 kg/m^2 Insulin dose: 61.17 IU/day Key Inclusion Criteria: - see above Key Exclusion Criteria: - see above	ITT: 1. 261 2. 263 3. 258 PP: 1. 235 2. 236 3. 238 Attrition: 1. 26 (10.0%) 2. 27 (10.3%) 3. 20 (7.8%)	Mean placebo-adjusted change in HbA1c from baseline at 24 weeks: 1. Sotagliflozin 200 mg: -0.37% 2. Sotagliflozin 400 mg: -0.35% Sotagliflozin 200 mg vs. placebo: LSM -0.37% (95% CI, -0.48 to -0.25); P<0.001 Sotagliflozin 400 mg vs. placebo: LSM -0.35% (95% CI, -0.47 to -0.24); P<0.001 Secondary outcomes: Composite of the proportion of patients with HbA1C <7%, no episode of severe hypoglycemia and no episode of diabetic ketoacidosis at week 24: 1. Sotagliflozin 200 mg: 31.42% 2. Sotagliflozin 400 mg: 32.32% 3. Placebo: 15.12% Sotagliflozin 200 mg vs. placebo: LSM 16.3% (95% CI, 8.79 to 23.82) P<0.001 Sotagliflozin 400 mg vs. placebo: LSM 17.20% (95% CI, 9.67 to 24.73); P<0.001 Placebo-adjusted change from baseline in body weight at week 24: 1. Sotagliflozin 200 mg: -1.98 kg 2. Sotagliflozin 400 mg: -2.58 kg Sotagliflozin 200 mg vs. placebo: LSM -1.98 kg (95% CI, -2.53 to -1.44); P<0.001 Sotagliflozin 400 mg vs. placebo: LSM -2.58 kg (95% CI, -3.12 to -2.04); P<0.001	NA NA NA NA NA NA	Urinary tract infection: 1. Sotagliflozin 200: 11 (4.2%) 2. Sotagliflozin 400: 18 (6.8%) 3. Placebo: 13 (5%) Genital mycotic infections: 1. Sotagliflozin 200: 24 (9.2%) 2. Sotagliflozin 400: 29 (11%) 3. Placebo: 6 (2.3%) Diarrhea: 1. Sotagliflozin 200: 12 (4.6%) 2. Sotagliflozin 400: 19 (7.2%) 3. Placebo: 9 (3.5%) Volume Depletion: 1. Sotagliflozin 200: 6 (2.3%) 2. Sotagliflozin 400: 2 (0.8%) 3. Placebo: 1 (0.4%) Serious adverse events: 1. Sotagliflozin 200: 26 (10%) 2. Sotagliflozin 400: 21 (8%) 3. Placebo: 17 (6.6%) Diabetic ketoacidosis: 1. Sotagliflozin 200: 0 2. Sotagliflozin 400: 4 (1.5%) 3. Placebo: 0 Serious treatment emergent adverse event leading to discontinuation: 1. Sotagliflozin 200: 7 (2.7%) 2. Sotagliflozin 400: 12 (4.6%) 3. Placebo: 6 (2.3%) Severe Hypoglycemia (>1 episode): 1. Sotagliflozin 200: 0 2. Sotagliflozin 400: 0 3. Placebo: 0	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized centrally by an interactive voice/web response system Performance Bias: (Low) Double blind design that extended to investigators, patient, sponsor or designee. Detection Bias: (Unclear) Independent data monitoring committee with unknown blinding status. Attrition Bias: (High) Results analyzed by mITT analysis with missing observations imputed as non-responders. High attrition in the active treatment groups. Reporting Bias: (Low) Trial conducted as outlined in protocol. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: These trial results are most applicable to people with T1D receiving insulin and who were overweight. Intervention: Sotagliflozin dose is appropriate. Comparator: Placebo comparison is appropriate. Outcomes: Changes in HbA1c is a standard outcome to measure effectiveness. Setting: Nineteen countries with 96 study sites in Europe and Israel.

5. Garg, et al InTandem3 DB, MC, PC, PG, Phase 3, RCT	1. Sotagliflozin 400 mg daily 3. Placebo Study duration: 24 weeks	Demographics: Median Age: 43 yrs Male: 49.7% White: 88% Hispanic: 7% Baseline HbA1c: 8.2% Mean body-mass index: 28.2 Duration of diabetes: 20 yrs. Daily total insulin dose: 0.70 IU/kg Key Inclusion Criteria: - T1D - stable insulin use - HbA1c. 7.0% to 11.0% - BMI at least 18.5 Key Exclusion Criteria: - Severe hypoglycemia - Diabetic ketoacidosis - eGFR 45 ml/min/1.73 m^2	mITT: 1. 700 2. 705 PP: 1. 601 2. 602 Attrition: 1. 99 (14%) 2. 103 (15%)	HbA1c levels lower than 7% at week 24 (with no episodes of severe hypoglycemia or diabetic ketoacidosis after randomization): 1. Sotagliflozin 400 mg: 200 (28.6%) 2. Placebo: 107 (15.2%) MD 13.4 (95% CI, 9.0 to 17.8) P<0.001 Secondary Endpoints (at week 24): Change from baseline in HbA1c: 1. Sotagliflozin: -0.79% 2. Placebo: -0.33% LSMD 0.46% (CI not provided) P<0.001 Change from baseline in body weight: 1. Sotagliflozin: -2.21 kg 2. Placebo: 0.77 kg LSMD -2.98 kg (95% CI, -3.31 to -2.66); P<0.001 Change from baseline SBP (for those with SBP >130 at baseline): 1. Sotagliflozin: -9.2 mmHg 2. Placebo: -5.7 mmHg LSMD -3.5 mmHg (95% CI, -5.7 to -1.3); P=0.002	NA NA NA NA	Urinary tract infection: 1. Sotagliflozin: 25 (3.6%) 2. Placebo: 27 (3.8%) Genital mycotic infections: 1. Sotagliflozin: 45 (6.4%) 2. Placebo: 15 (2.1%) Diarrhea: 1. Sotagliflozin: 29 (4.1%) 2. Placebo: 16 (2.3%) Volume Depletion: 1. Sotagliflozin: 13 (1.9%) 2. Placebo: 2 (0.3%) Serious adverse events: 1. Sotagliflozin: 48 (6.9%) 2. Placebo: 23 (3.3%) Diabetic ketoacidosis: 1. Sotagliflozin: 21 (3.0%) 2. Placebo: 4 (0.6%) Serious treatment emergent adverse event leading to discontinuation: 1. Sotagliflozin: 44 (6.3%) 2. Placebo: 16 (2.3%) Severe Hypoglycemia (>1 episode): 1. Sotagliflozin: 21 (3%) 2. Placebo: 17 (2.4%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized centrally by an interactive voice/web response system Performance Bias: (Low) Double blind design that extended to investigators, patient, sponsor or designee. Detection Bias: (Unclear) Independent data monitoring committee with unknown blinding status. Attrition Bias: (High) Results analyzed by mITT analysis with missing observations imputed as non-responders. High attrition in both groups. Reporting Bias: (Low) Trial conducted as outlined in protocol. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: These trial results are most applicable to people with T1D receiving insulin and who were overweight. Intervention: Sotagliflozin dose is appropriate. Comparator: Placebo comparison is appropriate. Outcomes: Changes in HbA1c is a standard outcome to measure effectiveness. Setting: Nineteen countries with 133 study sites.

RENAL TRIALS								
6. Cherney, et al[55] (2021) DB, MC, PC, PG, Phase 3, RCT	1. Sotagliflozin 200 mg daily 2. Sotagliflozin 400 mg daily 3. Placebo Study duration: 52 weeks	Demographics: Median Age: 67 yrs Male: 48.8% White: 81.9% Black: 5.8% Hispanic: 38.6% Mean baseline HbA1c: 8.1% Mean body mass index: 31.6 kg/m^2 Insulin use: 80.1% Antihypertensive use: 97% Mean eGFR: 24 ml/min/1.73 m^2 CDK3A: 50.1% CDK3B: 49.9% Key Inclusion Criteria: - T2D - CKD - eGFR 15 to 30 ml/min/1.73 m^2 - Age 18 years and over - HbA1c 7.0 % to less than 11.0% Key Exclusion Criteria: - history of DKA - severe hypoglycemic - BMI of 20 kg/m^2 or less or >45 kg/m^2 - SBP <120 mmHg or diastolic BP <60 mmHg - dialysis - renal disease requiring immunosuppressive therapy	ITT: 1. 92 2. 92 3. 93 PP: 1. 64 2. 70 3. 66 Attrition: 1. 28 (30.4%) 2. 22 (24%) 3. 27 (29%)	HbA1c reduction at 26 weeks (sotagliflozin 400 mg dose only): 1. Sotagliflozin 400 mg*: -0.4% 2. Sotagliflozin 200 mg: -0.07% 3. Placebo: -0.1% Sotagliflozin 200 mg vs. placebo: LSMD 0.05% (95% CI, -0.3 to 0.4) P=0.812 Sotagliflozin 400 mg vs. placebo: LSMD -0.3% (95% CI, -0.6 to 0.05); P=0.096 Secondary Endpoints: Percent of patients achieving a HbA1c of <7% at week 26: 1. Sotagliflozin 200 mg: 16.3% 2. Sotagliflozin 400 mg: 17.4% 3. Placebo: 4.3% Sotagliflozin 200 mg vs. placebo: LSMD 12% (95% CI, -3.5 to 20.6) P=0.007 Sotagliflozin 400 mg vs. placebo: LSMD 13% (95% CI, 4.3 to 21.8) P=0.004 Placebo-adjusted change from baseline in body weight at week 24: 1. Sotagliflozin 200 mg: -0.4 kg 2. Sotagliflozin 400 mg: -1.0 kg 3. Placebo: 0.4 kg Sotagliflozin 200 mg vs. placebo: LSMD -0.8 kg (95% CI, -2.2 to 0.6) P=0.24 Sotagliflozin 400 mg vs. placebo: LSMD -1.4. kg (95% CI, -2.8 to -0.01); P=0.049	NA NA ARR 12/ NNT 9 ARR 13/ NNT 8 NA NA	Urinary tract infection: 1. Sotagliflozin 200: 16 (17%) 2. Sotagliflozin 400: 9 (10%) 3. Placebo: 18 (19.4%) Genital mycotic infections: 1. Sotagliflozin 200: 1 (1.1%) 2. Sotagliflozin 400: 0 3. Placebo: 0 Diarrhea: 1. Sotagliflozin 200: 5 (5.3%) 2. Sotagliflozin 400: 5 (5.6%) 3. Placebo: 3 (3.2%) Volume Depletion: 1. Sotagliflozin 200: 6 (6.4%) 2. Sotagliflozin 400: 1 (1.1%) 3. Placebo: 4 (4.3%) Serious adverse events: 1. Sotagliflozin 200: 18 (19.1%) 2. Sotagliflozin 400: 20 (22.2%) 3. Placebo: 21 (22.6%) Diabetic ketoacidosis: 1. Sotagliflozin 200: 0 2. Sotagliflozin 400: 0 3. Placebo: 0 Serious treatment emergent adverse event leading to discontinuation: 1. Sotagliflozin 200: 2 (2.1%) 2. Sotagliflozin 400: 1 (1.1%) 3. Placebo: 1 (1.1%) Severe Hypoglycemia (>1 episode): 1. Sotagliflozin 200: 0 2. Sotagliflozin 400: 3 (3.2%) 3. Placebo: 0	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Unclear) Randomization not described. Performance Bias: (Unclear) Double blind design but no details were provided. Detection Bias: (Unclear) Not described. Attrition Bias: (High) Results analyzed by mITT analysis. High attrition in all groups. Reporting Bias: (Low) Trial conducted as outlined in protocol. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: These trial results are most applicable to people with T2D and severe renal impairment (eGFR 30 to 59 ml/min/1.73 m^2). Intervention: Sotagliflozin dose is appropriate. Comparator: Placebo comparison is appropriate. Outcomes: Changes in HbA1c is a standard outcome to measure effectiveness. Setting: 15 countries and 92 centers in North and South America, Europe, and Asia.

7. Cherney, et al[56] (2023) DB, MC, PC, PG, Phase 3, RCT	1. Sotagliflozin 200 mg daily 2. Sotagliflozin 400 mg daily 3. Placebo Study duration: 52 weeks (26 week treatment and 26 week extension)	Demographics: Median Age: 69.5 yrs Male: 56% White: 84.6% Black: 5.2% Hispanic: 25.2% Mean baseline HbA1c: 8.3% Mean body mass index: 32.4 kg/m^2 Insulin use: 64.3% Antihypertensive use: 96.6% Mean eGFR: 45.0 ml/min/1.73 m^2 Key Inclusion Criteria: - T2D - Stage 3 CKD - eGFR 30 to 59 ml/min/1.73 m^2 - Age 18 years and over - HbA1c 7.0 % to less than 11.0% Key Exclusion Criteria: - history of DKA - severe hypoglycemic - BMI of 20 kg/m^2 or less or >45 kg/m^2 - SBP >180 mmHg or diastolic BP >100 mmHg - reversible renal failure	ITT: 1. 267 2. 260 3. 260 PP: 1. 233 2. 222 3. 225 Attrition: 1. 34 (12.7%) 2. 38 (14.6%) 3. 35 (13.4%)	HbA1c reduction at 26 weeks: 1. Sotagliflozin 400 mg*: -0.46% 2. Sotagliflozin 200 mg: -0.32% 3. Placebo: -0.22% Sotagliflozin 200 mg vs. placebo: LSMD -0.10% (95% CI, -0.25 to 0.05) P=0.2095 Sotagliflozin 400 mg vs. placebo: LSMD -0.24% (95% CI, -0.39 to 0.09) P=0.0021 Secondary Endpoints: Percent of patients achieving a HbA1c of <7% at week 26: 1. Sotagliflozin 200 mg: 19.4% 2. Sotagliflozin 400 mg: 20.8% 3. Placebo: 13.5% Sotagliflozin 200 mg vs. placebo: LSMD 6% (95% CI, -0.2 to 12.2); P=0.0614 Sotagliflozin 400 mg vs. placebo: LSMD 7.4% (95% CI, 1.1 to 13.7); P=0.0230 Placebo-adjusted change from baseline in body weight at week 24: 1. Sotagliflozin 200 mg: -1.7 kg 2. Sotagliflozin 400 mg: -1.2 kg 3. Placebo: -0.4 kg Sotagliflozin 200 mg vs. placebo: LSMD -1.3 kg (95% CI, -1.9 to -0.6); P<0.0001 Sotagliflozin 400 mg vs. placebo: LSMD -0.8. kg (95% CI, -1.5 to -0.2); P=0.0155	NA NA NS ARR 7.4/ NNT 14 NA NA	Urinary tract infection: 1. Sotagliflozin 200: 34 (12.7%) 2. Sotagliflozin 400: 28 (10.8%) 3. Placebo: 27 (10.4%) Genital mycotic infections: 1. Sotagliflozin 200: 4 (1.5%) 2. Sotagliflozin 400: 5 (1.9%) 3. Placebo: 2 (0.8%) Diarrhea: 1. Sotagliflozin 200: 19 (7.1%) 2. Sotagliflozin 400: 24 (9.2%) 3. Placebo: 15 (5.8%) Volume Depletion: 1. Sotagliflozin 200: 8 (3.0%) 2. Sotagliflozin 400: 10 (3.8%) 3. Placebo: 4 (1.5%) Serious adverse events: 1. Sotagliflozin 200: 43 (16.1%) 2. Sotagliflozin 400: 44 (16.9%) 3. Placebo: 48 (18.5%) Diabetic ketoacidosis: 1. Sotagliflozin 200: 0 2. Sotagliflozin 400: 0 3. Placebo: 0 Serious treatment emergent adverse event leading to discontinuation: 1. Sotagliflozin 200: 18 (6.7%) 2. Sotagliflozin 400: 31 (11.9%) 3. Placebo: 13 (5.0%) Severe Hypoglycemia (>1 episode): 1. Sotagliflozin 200: 1 (0.4%) 2. Sotagliflozin 400: 3 (1.2%) 3. Placebo: 2 (0.8%)		**Risk of Bias (low/high/unclear)**: Selection Bias: (Unclear) Randomization not described. Performance Bias: (Unclear) Double blind design but no details were provided. Baseline characteristics were well matched between groups. Detection Bias: (Unclear) Not described. Attrition Bias: (high) Results analyzed by mITT analysis and missing data was imputed by the multiple imputation methods. Attrition was high in all groups. Reporting Bias: (Low) Trial conducted as outlined in protocol. Other Bias: (Unclear) Industry funded. **Applicability**: Patient: These trial results are most applicable to people with T2D that is not well controlled and chronic kidney disease (eGFR 30 to 59 ml/min/1.73 m^2). Intervention: Sotagliflozin dose is appropriate. Comparator: Placebo comparison is appropriate. Outcomes: Changes in HbA1c is a standard outcome to measure effectiveness. Setting: 150 sites in North and South America, Europe, and Asia.

Key: * Primary endpoint was comparison between the 400 mg dose only.
Abbreviations: ARR = absolute risk reduction; BMI = body mass index; BP = blood pressure; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; DB = double-blind; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; HF = heart failure; HR = hazard ratio; ITT = intention to treat; IV = intravenous; LSMD = least squares mean difference; LVEF = left ventricular ejection fraction; MC = multi-center; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = controlled; PCI = percutaneous coronary intervention; PP = per protocol; RAAS = renin-angiotensin-aldosterone system; RCT = randomized controlled trial; T1D = type 1 diabetes; T2D = type 2 diabetes

References:

1. National Institute for Health and Care Excellence. Chronic heart failure in adults. Quality Standard. June 29, 2023. Available at: www.nice.org.uk/guidance/qs9. Accessed May 15, 2023. Published online 2023.

2. Rossing P, Caramori ML, Chan JCN, et al. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney International*. 2022;102(5):S1-S127. doi:10.1016/j.kint.2022.06.008

3. Mancini GBJ, O'Meara E, Zieroth S, et al. 2022 Canadian Cardiovascular Society Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults. *Can J Cardiol*. 2022;38(8):1153-1167. doi:10.1016/j.cjca.2022.04.029

4. ElSayed NA, Aleppo G, Aroda VR, et al. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2023. *Diabetes Care*. 2023;46(Supplement_1):S158-S190. doi:10.2337/dc23-S010

5. ElSayed NA, Aleppo G, Aroda VR, et al. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2023. *Diabetes Care*. 2023;46(Supplement_1):S191-S202. doi:10.2337/dc23-S011

6. Farxiga (dapagliflozin) [prescribing information]. Wilmington, DE. AstraZeneca Pharmaceuticals LP. April 2022.

7. Jardiance (empagliflozin) [prescribing information]. Ridgefield, CT. Boehringer Ingelheim Pharamceuticals, Inc. January 2020.

8. Jardiance (empagliflozin) [prescribing information]. Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals, Inc. June 2023.

9. Brenzavvy (bexagliflozin prescribing information). Marlborough, MA; TheracosBio, LLC. January 2023.

10. Inpefa (sotagliflozin [prescribing information]. The Woodlands, TX; Lexicon Pharmaceuticals, Inc. May 2023.

11. Oregon Health Authorit. Oreogn Diabetes Report - A report on the burden of diabetes in Oregon and progress on the 2009 strategic plan to slow the rate of diabetes. Published online January 2015. http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Diabetes/Documents/OregonDiabetesReport.pdf

12. Centers for Disease Control and Prevention Press Release. Number of Americans with Diabetes Projected to Double or Triple by 2050. Published online 2010. Accessed July 23, 2013. http://www.cdc.gov/media/pressrel/2010/r101022.html

13. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38(1):140-149. doi:10.2337/dc14-2441

14. Redmon B, Caccamo D, Flavin P. Diagnosis and management of type 2 diabetes mellitus in adults. *Institute for Clincal Systems Improvement*. Published online July 2014. https://www.icis.org/_asset/3rrm36/Diabetes.pdf

15. Johansen MY, MacDonald CS, Hansen KB, et al. Effect of an Intensive Lifestyle Intervention on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial. *JAMA*. 2017;318(7):637-646. doi:10.1001/jama.2017.10169

16. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. *NICE Guideline*. 2022;NG28.

17. American Diabetes Association. Pharmacological Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes -2022. Diabetes Care 2022;45:S125-S143.

18. Lin GA, Brouwer E, Nikitin D, et al. Tirzepatide for Type 2 Diabetes; Final Report. *Institute for Clinical and Ecomomic Review*. Published online February 15, 2022.

19. Food and Drug Administration. Bexagliflozin Integrated Review (Application number: 214373Orig1s000). Center for Drug Evaluation and Research. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/214373Orig1s000IntegratedR.pdf. Accessed June 3, 2023.

20. American Diabetes Association Professional Practice Committee. Chronic Kidney Disease and Risk Management: Standards of Medical Care in Diabetes—2022. Diabetes Care 2022;45:S175-S184. *Diabetes Care*. 2022;45(Supplement_1):S175-S184. doi:10.2337/dc22-S011

21. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. [Review]. *Annals of Internal Medicine*. 2016;164(11):740-751. doi:10.7326/M15-2650

22. Zheng XD, Qu Q, Jiang XY, Wang ZY, Tang C, Sun JY. Effects of Dapagliflozin on Cardiovascular Events, Death, and Safety Outcomes in Patients with Heart Failure: A Meta-Analysis. *American Journal of Cardiovascular Drugs*. 2021;21(3):321-330. doi:10.1007/s40256-020-00441-x

23. Butt JH, Docherty KF, Claggett BL, et al. Association of Dapagliflozin Use With Clinical Outcomes and the Introduction of Uric Acid-Lowering Therapy and Colchicine in Patients With Heart Failure With and Without Gout: A Patient-Level Pooled Meta-analysis of DAPA-HF and DELIVER. *JAMA Cardiology*. 2023;8(4):386-393. doi:10.1001/jamacardio.2022.5608

24. Chen MB, Wang H, Zheng QH, Xu HL, Cui WY. Effect of sodium-dependent glucose transporter inhibitors on glycated hemoglobin A1c after 24 weeks in patients with diabetes mellitus: A systematic review and meta-analysis. *Medicine*. 2021;100(1):e24101. doi:10.1097/MD.0000000000024101

25. Zhou B, Shi Y, Fu R, et al. Relationship Between SGLT-2i and Ocular Diseases in Patients With Type 2 Diabetes Mellitus: A Meta-Analysis of Randomized Controlled Trials. *Frontiers in Endocrinology*. 2022;1:907340. doi:10.3389/fendo.2022.907340

26. Fakhrolmobasheri M, Abhari AP, Manshaee B, et al. Effect of sodium-glucose cotransporter 2 inhibitors on insulin resistance; a systematic review and meta-analysis. *Acta Diabetologica*. 2023;60(2):191-202. doi:10.1007/s00592-022-01981-1

27. Mori Y, Duru OK, Tuttle KR, et al. Sodium-Glucose Cotransporter 2 Inhibitors and New-onset Type 2 Diabetes in Adults With Prediabetes: Systematic Review and Meta-analysis of Randomized Controlled Trials. *Journal of Clinical Endocrinology & Metabolism*. 2022;108(1):221-231. doi:10.1210/clinem/dgac591

28. Jhund PS, Kondo T, Butt JH, et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. *Nature Medicine*. 2022;28(9):1956-1964. doi:10.1038/s41591-022-01971-4

29. Younes AM, Salem M, Maraey A, et al. Safety outcomes of SGLT2i in the heart failure trials: A systematic review and Meta-analysis. *International Journal of Cardiology*. 2022;1:51-56. doi:10.1016/j.ijcard.2022.06.059

30. Patoulias D, Dimosiari A. Meta-analysis Addressing the Cardiovascular Safety of Bexagliflozin in Patients With Type 2 Diabetes Mellitus. *American Journal of Cardiology*. 2022;1:178-179. doi:10.1016/j.amjcard.2022.05.005

31. Zhou B, Shi Y, Fu R, et al. Relationship Between SGLT-2i and Ocular Diseases in Patients With Type 2 Diabetes Mellitus: A Meta-Analysis of Randomized Controlled Trials. *Frontiers in Endocrinology*. 2022;1:907340. doi:10.3389/fendo.2022.907340

32. Ahmad Y, Madhavan MV, Stone GW, et al. Sodium-glucose cotransporter 2 inhibitors in patients with heart failure: a systematic review and meta-analysis of randomized trials. *European Heart Journal Quality of Care & Clinical Outcomes*. 2022;8(4):383-390. doi:10.1093/ehjqcco/qcab072

33. Xu X, Xu W, Zhuo Q, Yan Y. The efficacy and safety of dapagliflozin combined with oral hypoglycemic agents in patients with type 2 diabetes: a systematic review and meta-analysis. *Annals of Palliative Medicine*. 2022;11(3):1028-1037. doi:10.21037/apm-22-121

34. Shi FH, Li H, Yue J, et al. Clinical Adverse Events of High-Dose vs Low-Dose Sodium-Glucose Cotransporter 2 Inhibitors in Type 2 Diabetes: A Meta-Analysis of 51 Randomized Clinical Trials. *Journal of Clinical Endocrinology*. 2020;105(11). doi:10.1210/clinem/dgaa586

35. Ong HT, Teo YH, Teo YN, et al. Effects of Sodium/Glucose Cotransporter Inhibitors on Atrial Fibrillation and Stroke: A Meta-Analysis. *Journal of Stroke & Cerebrovascular Diseases*. 2022;31(1):106159. doi:10.1016/j.jstrokecerebrovasdis.2021.106159

36. Hu X, Yang Y, Hu X, et al. Effects of sodium-glucose cotransporter 2 inhibitors on serum uric acid in patients with type 2 diabetes mellitus: A systematic review and network meta-analysis. *Diabetes, Obesity & Metabolism*. 2022;24(2):228-238. doi:10.1111/dom.14570

37. Chenchula S, Varthya SB, Padmavathi R. Rationality, Efficacy, Tolerability of Empagliflozin Plus Linagliptin Combination for the Management of Type 2 Diabetes Mellitus: A Systematic Review of Randomized Controlled Trials and Observational Studies. *Current Diabetes Reviews*. 2022;18(4):e100921196392. doi:10.2174/1573399817666210910165402

38. Egolum UO, Cates DW, McGraw-Senat C, Ling H. Impact of Dapagliflozin on Mortality in Patients With Heart Failure and Reduced Ejection Fraction: A Meta-analysis. *American Journal of Therapeutics*. 2022;29(5):e578-e579. doi:10.1097/MJT.0000000000001354

39. Vaduganathan M, Docherty KF, Claggett BL, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet*. 2022;400(10354):757-767. doi:10.1016/S0140-6736(22)01429-5

40. Neuen BL, Oshima M, Agarwal R, et al. Sodium-Glucose Cotransporter 2 Inhibitors and Risk of Hyperkalemia in People With Type 2 Diabetes: A Meta-Analysis of Individual Participant Data From Randomized, Controlled Trials. *Circulation*. 2022;145(19):1460-1470. doi:10.1161/CIRCULATIONAHA.121.057736

41. Nuffield Department of Population Health Renal Studies Group, SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet*. 2022;400(10365):1788-1801. doi:10.1016/S0140-6736(22)02074-8

42. Mannucci E, Gallo M, Giaccari A, et al. Effects of glucose-lowering agents on cardiovascular and renal outcomes in subjects with type 2 diabetes: An updated meta-analysis of randomized controlled trials with external adjudication of events. *Diabetes, Obesity and Metabolism*. 2023;25(2):444-453. doi:10.1111/dom.14888

43. Synjardy (empagliflozin and metformin) [prescribing information]. Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals, Inc. February 2023.

44. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2022;387(12):1089-1098. doi:10.1056/NEJMoa2206286

45. Laffel LM, Danne T, Klingensmith GJ, et al. Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial. *The Lancet Diabetes & Endocrinology*. 2023;11(3):169-181. doi:10.1016/S2213-8587(22)00387-4

46. The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, et al. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2023;388(2):117-127. doi:10.1056/NEJMoa2204233

47. Halvorsen YD, Lock JP, Zhou W, Zhu F, Freeman MW. A 24-week, randomized, double-blind, active-controlled clinical trial comparing bexagliflozin with sitagliptin as an adjunct to metformin for the treatment of type 2 diabetes in adults. *Diabetes Obes Metab*. 2019;21(10):2248-2256. doi:10.1111/dom.13801

48. Allegretti AS, Zhang W, Zhou W, et al. Safety and Effectiveness of Bexagliflozin in Patients With Type 2 Diabetes Mellitus and Stage 3a/3b CKD. *Am J Kidney Dis*. 2019;74(3):328-337. doi:10.1053/j.ajkd.2019.03.417

49. Halvorsen YD, Lock JP, Frias JP, et al. A 96-week, double-blind, randomized controlled trial comparing bexagliflozin to glimepiride as an adjunct to metformin for the treatment of type 2 diabetes in adults. *Diabetes Obes Metab*. 2023;25(1):293-301. doi:10.1111/dom.14875

50. Halvorsen YDC, Walford GA, Massaro J, Aftring RP, Freeman MW. A 96-week, multinational, randomized, double-blind, parallel-group, clinical trial evaluating the safety and effectiveness of bexagliflozin as a monotherapy for adults with type 2 diabetes. *Diabetes Obes Metab*. 2019;21(11):2496-2504. doi:10.1111/dom.13833

51. 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

52. EMA. Zynquista. European Medicines Agency. Published February 27, 2019. Accessed July 7, 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/zynquista

53. Dunleavy, K K, 2022 08:55am. Persistent Lexicon still working to get an audience with FDA on Type 1 diabetes prospect. Fierce Pharma. Published December 1, 2022. Accessed July 7, 2023. https://www.fiercepharma.com/pharma/persistent-lexicon-still-working-get-audience-fda-type-1-diabetes-drug-sotagliflozin

54. 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

55. 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

56. 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

57. 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

58. Danne T, Cariou B, Banks P, et al. HbA1c and Hypoglycemia Reductions 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

59. 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

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
canagliflozin	INVOKANA	TABLET	Y
dapagliflozin propanediol	FARXIGA	TABLET	Y
empagliflozin	JARDIANCE	TABLET	Y
canagliflozin/metformin HCl	INVOKAMET XR	TAB BP 24H	N
canagliflozin/metformin HCl	INVOKAMET	TABLET	N
dapagliflozin/metformin HCl	XIGDUO XR	TAB BP 24H	N
dapagliflozin/saxagliptin HCl	QTERN	TABLET	N
empaglifloz/linaglip/metformin	TRIJARDY XR	TAB BP 24H	N
empagliflozin/linagliptin	GLYXAMBI	TABLET	N
empagliflozin/metformin HCl	SYNJARDY XR	TAB BP 24H	N
empagliflozin/metformin HCl	SYNJARDY	TABLET	N
ertugliflozin pidolate	STEGLATRO	TABLET	N
ertugliflozin/metformin	SEGLUROMET	TABLET	N
ertugliflozin/sitagliptin phos	STEGLUJAN	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

Solomon, Rudolf A de Boer , David DeMets , et al

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure and cardiovascular death among patients with chronic heart failure and a left ventricular ejection fraction of 40% or less. Whether SGLT2 inhibitors are effective in patients with a higher left ventricular ejection fraction remains less certain.

Methods: We randomly assigned 6263 patients with heart failure and a left ventricular ejection fraction of more than 40% to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo, in addition to usual therapy. The primary outcome was a composite of worsening heart failure (which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death, as assessed in a time-to-event analysis.

Results: Over a median of 2.3 years, the primary outcome occurred in 512 of 3131 patients (16.4%) in the dapagliflozin group and in 610 of 3132 patients (19.5%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.92; P<0.001). Worsening heart failure occurred in 368 patients (11.8%) in the dapagliflozin group and in 455 patients (14.5%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.69 to 0.91); cardiovascular death occurred in 231 patients (7.4%) and 261 patients (8.3%), respectively (hazard ratio, 0.88; 95% CI, 0.74 to 1.05). Total events and symptom burden were lower in the dapagliflozin group than in the placebo group. Results were similar among patients with a left ventricular ejection fraction of 60% or more and those with a left ventricular ejection fraction of less than 60%, and results were similar in prespecified subgroups, including patients with or without diabetes. The incidence of adverse events was similar in the two groups.

Conclusions: Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction. (Funded by AstraZeneca; DELIVER ClinicalTrials.gov number, NCT03619213.).

Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial

Lori M Laffel, Thomas Danne, Georgeanna J Klingensmith, et al

Background: The incidence of type 2 diabetes in young people is increasing, but treatments remain limited. We aimed to assess the efficacy and safety of an empagliflozin dosing regimen versus placebo and linagliptin versus placebo on glycaemic control in young people with type 2 diabetes.

Methods: In this double-blind, placebo-controlled trial done in 108 centres in 15 countries, participants with type 2 diabetes (aged 10-17 years; HbA_{1c} 6·5-10·5% [48-91 mmol/mol]) who had been previously treated with metformin or insulin were randomly assigned (1:1:1) to oral empagliflozin 10 mg, oral linagliptin 5 mg, or placebo. Participants in the empagliflozin group who did not have HbA_{1c} below 7·0% (<53 mmol/mol) by week 12 underwent a second double-blinded randomisation (1:1) at week 14, either remaining on 10 mg or increasing to 25 mg. Participants in the placebo group were randomly reassigned (1:1:1) in a double-blinded manner at week 26 to linagliptin 5 mg or one of the empagliflozin doses (10 mg or 25 mg). Investigators were masked throughout the trial and received assignments of blinded medication kits through interactive response technology for all participants at the initial randomisation and for the re-randomisations at weeks 14 and 26. The primary outcome was change from baseline in HbA_{1c} at 26 weeks. For empagliflozin, results were based on a pooled analysis for all participants on empagliflozin. Safety was assessed until week 52. This trial is registered with ClinicalTrials.gov, NCT03429543.

Findings: Between April 26, 2018, and May 26, 2022, of 262 screened participants, 158 (60%) were randomly assigned to treatment (53 [34%] to placebo, 52 [33%] to empagliflozin 10 mg, and 53 [34%] to linagliptin). For the primary outcome, the adjusted mean HbA_{1c} change from baseline at week 26 was -0·84% [-9·2 mmol/mol] in the empagliflozin pooled group versus placebo (95% CI -1·50 to -0·19 [-16·4 to -2·1]; p=0·012); the corresponding change from baseline for linagliptin versus placebo was -0·34% [-3·8 mmol/mol; 95% CI -0·99 to 0·30 [-10·8 to 3·3]; p=0·29). Adverse events occurred in 34 (64%) participants in the placebo group, 40 (77%) in the empagliflozin pooled group, and 37 (71%) in the linagliptin group, up to week 26. Of these, severe adverse events were reported in two (4%) participants in the placebo group, one (2%) in the empagliflozin pooled group, and one (2%) in the linagliptin group. Hypoglycaemia was the most frequently reported adverse event with higher rates for those on active drug treatment compared with placebo. No severe hypoglycaemia cases were reported.

Interpretation: Empagliflozin provided clinically relevant placebo-corrected reductions in HbA_{1c}, whereas linagliptin did not, and might offer a new treatment option for young people with type 2 diabetes.

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group; William G Herrington, Natalie Staplin, et al

Background: The effects of empagliflozin in patients with chronic kidney disease who are at risk for disease progression are not well understood. The EMPA-KIDNEY trial was designed to assess the effects of treatment with empagliflozin in a broad range of such patients.

Methods: We enrolled patients with chronic kidney disease who had an estimated glomerular filtration rate (eGFR) of at least 20 but less than 45 ml per minute per 1.73 m^2 of body-surface area, or who had an eGFR of at least 45 but less than 90 ml per minute per 1.73 m^2 with a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 200. Patients were randomly assigned to receive empagliflozin (10 mg once daily) or matching placebo. The primary outcome was a composite of progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to <10 ml per minute per 1.73 m^2, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from cardiovascular causes.

Results: A total of 6609 patients underwent randomization. During a median of 2.0 years of follow-up, progression of kidney disease or death from cardiovascular causes occurred in 432 of 3304 patients (13.1%) in the empagliflozin group and in 558 of 3305 patients (16.9%) in the placebo group (hazard ratio, 0.72; 95% confidence interval [CI], 0.64 to 0.82; P<0.001). Results were consistent among patients with or without diabetes and across subgroups defined according to eGFR ranges. The rate of hospitalization from any cause was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.86; 95% CI, 0.78 to 0.95; P = 0.003), but there were no significant between-group differences with respect to the composite outcome of hospitalization for heart failure or

death from cardiovascular causes (which occurred in 4.0% in the empagliflozin group and 4.6% in the placebo group) or death from any cause (in 4.5% and 5.1%, respectively). The rates of serious adverse events were similar in the two groups.
Conclusions: Among a wide range of patients with chronic kidney disease who were at risk for disease progression, empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo. (Funded by Boehringer Ingelheim and others; EMPA-KIDNEY ClinicalTrials.gov number, NCT03594110; EudraCT number, 2017-002971-24.).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to April 24, 2023

Search Strategy:

#	Searches	Results
1	canagliflozin.mp. or Canagliflozin/	1732
2	dapagliflozin.mp.	2543
3	empagliflozin.mp.	2675
4	ertugliflozin.mp.	254
5	bexagliflozin.mp.	14
6	1 or 2 or 3 or 4 or 5	5620
7	limit 6 to (english language and humans and yr="2022 - 2023")	798
8	limit 7 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	76

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BRENZAVVY™ safely and effectively. See full prescribing information for BRENZAVVY.

BRENZAVVY (bexagliflozin) tablets, for oral use
Initial U.S. Approval: 2023

----------INDICATIONS AND USAGE----------
BRENZAVVY is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitation of Use: Not recommended in patients with type 1 diabetes mellitus. May increase the risk of diabetic ketoacidosis in these patients (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dose: 20 mg once daily, taken in the morning, with or without food. Do not crush or chew the tablet. (2.2)
- Assess renal function before initiating BRENZAVVY and as clinically indicated. Correct volume depletion before initiating (2.1)
- Not recommended if eGFR less than 30 mL/min/1.73 m^2. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 20 mg (3)

----------CONTRAINDICATIONS----------
- Hypersensitivity to bexagliflozin or any excipient in BRENZAVVY
- Patients on dialysis (4)

----------WARNINGS AND PRECAUTIONS----------
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue, evaluate, and treat promptly. Before initiating, consider risk factors for ketoacidosis. Patients may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.1)
- *Lower limb amputation:* Consider factors that may increase the risk for amputations before initiating BRENZAVVY. Monitor patients for signs and symptoms of infection or ulcers of the lower limbs, and discontinue if these occur (5.2).
- *Volume depletion:* May result in acute kidney injury. Before initiating BRENZAVVY, assess and correct volume status in patients with impaired renal function or low systolic blood pressure, elderly patients or patients on diuretics. Monitor for signs and symptoms during therapy (5.3)
- *Urosepsis and pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.4)
- *Hypoglycemia:* Consider a lower dose of insulin or insulin secretagogue to reduce risk of hypoglycemia when used in combination with BRENZAVVY (5.5)
- *Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):* Serious, life-threatening cases have occurred in both females and males treated with SGLT2 inhibitors. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment (5.6).
- *Genital mycotic infection*: Monitor and treat as appropriate. (5.7)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > 5%) are female genital mycotic infections, urinary tract infection and increased urination (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TheracosBio at 1-855-273-6928 (1-855-BRENZAV) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters. BRENZAVVY is not recommended during the second and third trimesters of pregnancy (8.1)
- *Lactation:* Not recommended when breastfeeding. (8.2)
- *Geriatric patients:* Higher incidence of adverse reactions related to volume depletion. (5.3, 8.5)
- *Renal Impairment:* Higher incidence of adverse reactions related to reduced renal function (5.3, 8.6)
- *Hepatic Impairment:* Not recommended for patients with severe hepatic impairment (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2023

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use INPEFA safely and effectively. See full prescribing information for INPEFA.

INPEFA™ (sotagliflozin) tablets, for oral use
Initial U.S. Approval: 2023

----------INDICATIONS AND USAGE----------
INPEFA is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with:

- heart failure (1) or
- type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors (1)

----------DOSAGE AND ADMINISTRATION----------
Correct volume status before starting INPEFA at 200 mg daily and titrate to 400 mg as tolerated. (2.2) In patients with decompensated heart failure, begin dosing when patients are hemodynamically stable. (2.1)

Withhold INPEFA at least 3 days, if possible, prior to major surgery or procedures associated with prolonged fasting. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 200 mg and 400 mg (3)

----------CONTRAINDICATIONS----------
- History of serious hypersensitivity reaction to INPEFA. (4)

----------WARNINGS AND PRECAUTIONS----------
- *Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis:* Consider ketone monitoring in patients with type 1 diabetes mellitus and consider ketone monitoring in others at risk for ketoacidosis, as indicated. Assess for ketoacidosis regardless of presenting blood glucose levels and discontinue INPEFA if ketoacidosis is suspected. Monitor patients for resolution of ketoacidosis before restarting. (5.1)
- *Volume Depletion:* Before initiating, correct volume status. Monitor for signs and symptoms of hypotension during therapy. (5.2)
- *Urosepsis and Pyelonephritis:* Monitor for signs and symptoms during therapy and treat promptly. (5.3)
- *Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues:* Lower dose of insulin or insulin secretagogue may be required. (5.4)
- *Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)*: Monitor for pain, tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. Discontinue INPEFA and treat urgently. (5.5)
- *Genital Mycotic Infections*: Monitor and treat as appropriate. (5.6)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥ 5%) are urinary tract infection, volume depletion, diarrhea, and hypoglycemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lexicon at 1-855-330-2573 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Digoxin: Monitor digoxin levels. (7.1)
Uridine 5'-diphospho-glucuronosyltransferase Inducers (e.g., rifampin): Sotagliflozin exposure is reduced. Consider monitoring of clinical status. (7.2)
Lithium: Monitor serum lithium concentrations. (7.3)

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
Lactation: INPEFA is not recommended when breastfeeding. (8.2)
Geriatrics: Higher incidence of adverse reactions related to volume depletion. (5.2, 8.5)
Renal Impairment: Higher incidence of adverse reactions related to volume depletion. (5.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 05/2023

Appendix 5: Key Inclusion Criteria

Population	People with T2D, heart failure and chronic kidney disease
Intervention	SGLT2 inhibitors
Comparator	Placebo or active treatment
Outcomes	HbA1c, worsening cardiac or renal disease, mortality
Timing	Not applicable
Setting	Outpatient

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2 Inhibitors)

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All non-preferred SGLT-2 inhibitors require a PA

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 code	
2. Will the prescriber consider switching to a preferred product? Message: • Preferred products do not require a PA. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Does the patient have type 2 diabetes?	**Yes:** Approve for up to 12 months	**No:** Go to #4

Approval Criteria		
4. Does the patient have heart failure and is requesting an SGLT-2 inhibitor with demonstrated cardiovascular benefit (e.g., dapagliflozin, empagliflozin, or sotagliflozin)?	**Yes:** Approve for up to 12 months	**No:** Go to #5
5. Does the patient have chronic kidney disease and is requesting an SGLT-2 inhibitor with demonstrated renal and cardiovascular benefits (e.g., dapagliflozin)?	**Yes:** Approve for up to 12 months	**No: No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *10/23 (KS), 10/22 (KS), 8/21 (KS), 8/20 (KS), 6/20, 7/18, 9/17; 9/16; 3/16; 9/15; 1/15; 9/14; 9/13*
Implementation: *11/1/23; 1/1/23; 9/1/20; 8/15/18; 10/13/16; 2/3/15; 1/1/14*