

RESEARCH MONOGRAPH . COMPOUND PROFILE

Canagliflozin

A thiophene-containing C-glucoside developed by Mitsubishi Tanabe Pharma and licensed to Janssen as the first SGLT2 inhibitor approved in the United States, distinguished by dual SGLT2/SGLT1 inhibition and landmark cardiovascular and renal outcomes evidence from the CANVAS Program and CREDENCE trial.

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ABSTRACT

Canagliflozin is a potent, orally bioavailable inhibitor of the sodium-glucose cotransporter 2 (SGLT2) and the first agent of its class to receive United States Food and Drug Administration approval for the treatment of type 2 diabetes mellitus. The compound acts through an insulin-independent mechanism by blocking the reabsorption of filtered glucose in the proximal tubule of the kidney, producing sustained glycosuria, reduction in plasma glucose, modest body weight loss, and reduction in systolic blood pressure. Structurally, canagliflozin is a C-glucoside bearing a thiophene ring in the aglycone region, conferring metabolic stability against glucosidase cleavage and contributing to oral bioavailability of approximately 65 percent. The inhibition constant for human SGLT2 is approximately 4.2 nM, with approximately 160-fold to 250-fold selectivity over SGLT1 (K_i approximately 710 to 910 nM), a selectivity ratio that permits modest intestinal SGLT1 inhibition at the 300 mg clinical dose, contributing to postprandial glucose lowering through delayed intestinal glucose absorption [1, 2].

The compound was discovered at Mitsubishi Tanabe Pharma through systematic optimization of C-glucoside scaffolds for SGLT2 potency, metabolic stability, and oral pharmacokinetics [1]. Janssen Pharmaceuticals obtained development and commercialization rights through a licensing agreement and advanced canagliflozin through a comprehensive Phase 3 program (nine controlled studies, approximately 10,285 subjects) culminating in FDA approval on 29 March 2013 under the trade name Invokana [3, 4]. The compound was subsequently approved

by the European Medicines Agency in November 2013 and in multiple additional jurisdictions. A fixed-dose combination with metformin (Invokamet) was approved in 2014.

The clinical evidence base for canagliflozin extends substantially beyond glycemic control. The CANVAS Program (Canagliflozin Cardiovascular Assessment Study and CANVAS-R; N = 10,142; mean follow-up 188.2 weeks), published by Neal et al. in the New England Journal of Medicine in 2017, demonstrated a statistically significant 14 percent reduction in the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke (hazard ratio 0.86; 95 percent confidence interval 0.75 to 0.97) [5]. The CREDENCE trial (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; N = 4,401; median follow-up 2.62 years), published by Perkovic et al. in the New England Journal of Medicine in 2019, demonstrated a 30 percent reduction in the primary composite of end-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death (hazard ratio 0.70; 95 percent confidence interval 0.59 to 0.82), establishing canagliflozin as the first SGLT2 inhibitor with a dedicated positive renal outcomes trial [6].

Pharmacokinetics are characterized by rapid oral absorption (time to peak 1 to 2 hours), dose-proportional exposure across a wide range (50 to 1600 mg), steady-state attainment within 4 to 5 days, and predominant elimination through hepatic O-glucuronidation by UGT1A9 and UGT2B4, producing two inactive metabolites (M5 and M7) [7]. The terminal elimination half-life is approximately 10.6 to 13.1 hours at steady state, supporting once-daily dosing. Approximately 60 percent of the administered dose is recovered in feces and 33 percent in urine. Clinically significant drug-drug interactions are limited; UGT enzyme inducers

(rifampin, phenytoin, ritonavir) reduce canagliflozin exposure and may require dose adjustment.

The safety profile includes class-related adverse events: genital mycotic infections (principally vulvovaginal candidiasis in women and balanitis in men; occurring in approximately 10 to 12 percent of patients), urinary tract infections, volume depletion events related to osmotic diuresis, and euglycemic diabetic ketoacidosis (rare but clinically significant). The CANVAS Program identified a signal for increased lower-extremity amputations (6.3 versus 3.4 per 1,000 patient-years; hazard ratio 1.97), predominantly at the toe and metatarsal level, prompting an FDA boxed warning in 2017 that was subsequently removed in 2020 after additional data, including the CREDENCE trial, did not confirm the excess risk at a comparable magnitude [5, 8]. Bone fracture risk was identified in CANVAS but not confirmed in CREDENCE. Fournier gangrene (necrotizing fasciitis of the perineum) has been reported rarely across the SGLT2 inhibitor class.

This monograph documents the chemistry, synthesis, and structure-activity relationships of canagliflozin; the molecular pharmacology of SGLT2 and SGLT1 inhibition; the comprehensive human pharmacokinetic record; preclinical pharmacology in animal models of diabetes and kidney disease; the clinical evidence base across glycemic, cardiovascular, and renal outcomes; sourcing and quality verification for research applications; reconstitution and handling; stack-interaction considerations; adverse-event signal including the amputation and ketoacidosis findings; and a structured comparative assessment of five SGLT2 inhibitor alternatives (dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin, and bexagliflozin) against canagliflozin on five competency standards: novelty, effect

size, promising potential, side-effect profile, and overall validation.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Canagliflozin.

Marketed names: Invokana (Janssen Pharmaceuticals, United States, European Union, and multiple additional jurisdictions). Invokamet and Invokamet XR (fixed-dose combinations with metformin hydrochloride immediate-release and extended-release, respectively). Sulisent (selected markets outside the United States).

Development codes: JNJ-28431754 (Janssen), TA-7284 (Mitsubishi Tanabe Pharma). The Janssen code is the canonical identifier in the clinical development literature; the Mitsubishi Tanabe code appears in the early discovery and preclinical pharmacology publications [1].

Chemical Abstracts Service registry numbers: 842133-18-0 (anhydrous free form), 928672-86-0 (hemihydrate). The hemihydrate is the pharmaceutical-grade solid form used in commercial formulations.

International Union of Pure and Applied Chemistry name: (1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol. The compound is a C-glucoside in which the glucose moiety is linked to the aglycone through a carbon-carbon bond at the anomeric position, conferring resistance to glucosidase-mediated hydrolysis that distinguishes C-glucosides from the earlier O-glucoside SGLT2 inhibitors (such as phlorizin and its derivatives) [1].

1.2 Structural class and chemistry

Canagliflozin is a C-aryl glucoside bearing a thiophene ring in the aglycone portion. The structural class places it within the diarylmethane C-glucoside family of SGLT2 inhibitors, a scaffold pioneered in the medicinal chemistry programs at Bristol-Myers Squibb (leading to dapagliflozin) and subsequently optimized at Mitsubishi Tanabe with the introduction of the thiophene heterocycle to replace the distal phenyl ring of earlier analogs [1].

Molecular formula: C₂₄H₂₅FO₅S (anhydrous free form); C₄₈H₅₂F₂O₁₁S₂ (hemihydrate, representing two molecules of canagliflozin plus one molecule of water).

Exact mass: 444.1407 g/mol (anhydrous free form, monoisotopic).

Molecular weight: 444.52 g/mol (anhydrous); 898.04 g/mol (hemihydrate, per formula unit).

Physical properties: White to off-white crystalline powder. The hemihydrate is the thermodynamically stable solid form and is used in commercial tablet formulations. Solubility in water is low (approximately 1.4 mg/mL at 25 degrees Celsius); the compound is freely soluble in dimethyl sulfoxide, soluble in methanol and ethanol, and sparingly soluble in ethyl acetate. Melting point of the hemihydrate is approximately 94 to 97 degrees Celsius.

Stereochemistry: Canagliflozin contains five stereocenters (those of the glucitol ring) and is supplied as the single (1S,2R,3R,4S,5R) diastereomer corresponding to the beta-D-glucopyranose configuration. The carbon-carbon bond at the anomeric position is in the beta configuration, consistent with the thermodynamic product of the C-glucosylation reaction. Investigators acquiring research-grade canagliflozin should confirm stereochemical integrity by chiral high-performance liquid chromatography or by comparison of optical rotation values against a certified reference standard.

1.3 Synthesis

The published synthesis of canagliflozin proceeds through two convergent stages: preparation of the aglycone (the arylthiophene component) and stereoselective C-glucosylation [1, 9].

Aglycone synthesis: 5-Bromo-2-methylbenzoyl chloride is condensed with 2-(4-fluorophenyl)thiophene under Friedel-Crafts acylation conditions (aluminum chloride catalyst, dichloromethane solvent) to produce the diaryl ketone intermediate. The ketone is reduced to the corresponding methylene bridge using triethylsilane and boron trifluoride diethyl etherate at low temperature, yielding the diarylmethane aglycone bearing the bromine substituent required for metalation.

C-Glucosylation: The brominated aglycone is treated with n-butyllithium at low temperature to generate the aryllithium species, which is coupled with 2,3,4,6-tetra-O-trimethylsilyl-beta-D-gluconolactone. The resulting lactol intermediate is desilylated and subjected to stereoselective reduction with triethylsilane and boron trifluoride etherate, producing the beta-C-glucoside with high diastereoselectivity.

The product is purified by recrystallization, typically from ethanol-water or isopropanol-water mixtures, and the hemihydrate is obtained by controlled crystallization under defined humidity conditions.

Industrial-scale syntheses have been optimized for the C-glucosylation step to achieve yields of 60 to 75 percent, with particular attention to diastereomeric purity (greater than 99 percent beta-anomer) and removal of residual palladium or lithium salts. The hemihydrate crystal form is characterized by X-ray powder diffraction and differential scanning calorimetry to confirm polymorphic identity [9].

2. Abstract

Canagliflozin (JNJ-28431754, TA-7284) is a potent, selective, orally bioavailable inhibitor of the sodium-glucose cotransporter 2 (SGLT2) and the first compound of the gliflozin class to receive approval from the United States Food and Drug Administration for the treatment of type 2 diabetes mellitus [3, 4]. The compound acts through an insulin-independent mechanism: by blocking SGLT2 in the S1 and S2 segments of the renal proximal tubule, it prevents the reabsorption of approximately 50 to 80 grams of filtered glucose per day at the 100 mg and 300 mg clinical doses, producing sustained glycosuria and corresponding reductions in plasma glucose, hemoglobin A1c, body weight, and blood pressure [10].

The SGLT2 inhibition constant is approximately 4.2 nM, with approximately 160-fold to 250-fold selectivity over SGLT1 [1, 2]. At the 300 mg dose, transient inhibition of intestinal SGLT1 contributes to delayed postprandial glucose absorption, a pharmacodynamic feature that distinguishes canagliflozin from the more SGLT2-selective agents dapagliflozin and empagliflozin and that may contribute to its cardiovascular and metabolic benefits [2, 11].

The clinical evidence base is anchored by three landmark programs. The Phase 3 registration program (nine controlled studies, approximately 10,285 subjects) demonstrated reductions in hemoglobin A1c of 0.77 to 1.16 percent at 100 mg and 0.97 to 1.32 percent at 300 mg compared to placebo, with additional benefits of 2.2 to 3.7 kg body weight loss and 3 to 5 mmHg systolic blood pressure reduction [4, 12]. The CANVAS Program (N = 10,142; mean follow-up 188.2 weeks) demonstrated a 14 percent reduction in major adverse cardiovascular events (MACE; hazard ratio 0.86; 95 percent CI 0.75 to 0.97), establishing cardiovascular benefit [5]. The CREDENCE trial (N = 4,401; median follow-up 2.62 years) demonstrated a 30 percent reduction in the primary renal composite endpoint (hazard ratio 0.70; 95 percent CI 0.59 to 0.82) in patients with type 2 diabetes and albuminuric chronic kidney disease, establishing canagliflozin as a renal-protective agent and the first SGLT2 inhibitor to demonstrate a positive dedicated renal outcomes result [6].

Pharmacokinetics are characterized by rapid absorption, dose-proportional exposure, moderate protein binding (approximately 99 percent, predominantly to albumin), a terminal half-life of 10.6 to 13.1 hours supporting once-daily dosing, and

predominant hepatic glucuronidation by UGT1A9 and UGT2B4 with minimal cytochrome P450-mediated oxidative metabolism [7].

The safety profile includes genital mycotic infections (the most common adverse event, approximately 10 to 12 percent incidence), urinary tract infections, volume depletion, euglycemic diabetic ketoacidosis (rare), and signals for lower-extremity amputation and bone fracture that were identified in the CANVAS Program but not confirmed at comparable magnitude in CREDENCE [5, 6, 8]. The FDA issued a boxed warning for amputation risk in 2017, which was removed in 2020 following reassessment.

3. Discovery and Development History

3.1 Origin

Canagliflozin was discovered at Mitsubishi Tanabe Pharma Corporation (Osaka, Japan) through a medicinal chemistry program aimed at developing potent, selective, and metabolically stable SGLT2 inhibitors with improved oral pharmacokinetics relative to the natural product phlorizin and its early synthetic O-glucoside analogs [1]. The key insight driving the program was the replacement of the O-glycosidic bond (susceptible to intestinal and hepatic glucosidase cleavage) with a C-glycosidic bond, a strategy that had been pioneered at Bristol-Myers Squibb in the development of dapagliflozin. Mitsubishi Tanabe introduced a thiophene ring as the distal aromatic component of the diarylmethane aglycone, replacing the chlorophenyl group of dapagliflozin. This modification improved SGLT2 potency (IC₅₀ approximately 2.2 to 4.4 nM for human SGLT2) while maintaining acceptable selectivity over SGLT1 and conferring favorable pharmacokinetic properties in pre-clinical species [1].

The discovery was published by Nomura et al. in the Journal of Medicinal Chemistry in 2010 under the title "Discovery of canagliflozin, a novel C-glucoside with thiophene ring, as sodium-dependent glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes mellitus" [1]. The compound was selected for clinical development on the basis of its in vitro potency, selectivity profile, oral bioavailability in multiple preclinical species (rat, dog, monkey), and efficacy in the Zucker diabetic fatty (ZDF) rat model of type 2 diabetes.

3.2 Licensing and clinical development

Janssen Pharmaceuticals (a division of Johnson and Johnson) obtained exclusive worldwide development and commercialization rights to canagliflozin through a licensing agreement with Mitsubishi Tanabe Pharma. Janssen initiated the clinical development program with Phase 1 single-ascending-dose and multiple-ascending-dose studies in healthy volunteers and patients with type 2 diabetes beginning in approximately 2007 [7].

The Phase 3 program comprised nine controlled clinical studies enrolling approximately 10,285 subjects with type 2 diabetes. These studies evaluated canagliflozin as monotherapy, as add-on to metformin, as add-on to metformin plus sulfonylurea, as add-on to metformin plus pioglitazone, and in comparison with glimepiride, sitagliptin, and placebo. Two dose levels were studied throughout the Phase 3 program: 100 mg and 300 mg once daily [4, 12].

3.3 Regulatory approvals

The United States FDA approved canagliflozin on 29 March 2013, making it the first SGLT2 inhibitor to receive marketing authorization in the United States [3]. The approval was granted on the basis of the Phase 3 glycemic efficacy data, with a requirement for a post-marketing cardiovascular outcomes trial (which became the CANVAS Program). The European Medicines Agency approved canagliflozin in November 2013. Subsequent approvals were granted in Japan, Canada, Australia, and multiple additional jurisdictions.

The fixed-dose combination of canagliflozin 50 mg or 150 mg with metformin hydrochloride (Invokamet) was approved by the FDA in August 2014. An extended-release formulation of the combination (Invokamet XR) followed in September 2016.

3.4 Post-approval landmark trials

The CANVAS Program, required by the FDA as a post-marketing commitment, was designed as an integrated analysis of two trials: CANVAS (initiated in 2009, 4,330 subjects) and CANVAS-R (initiated in 2014, 5,812 subjects). The combined analysis enrolled 10,142 subjects with type 2 diabetes and high cardiovascular risk; the primary endpoint was the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke (three-point MACE). Results were published by Neal et al. in June 2017 in the New England Journal of Medicine [5].

The CREDENCE trial was designed as a dedicated renal outcomes trial in patients with type 2 diabetes and albuminuric chronic kidney disease (estimated glomerular filtration rate 30 to less than 90 mL/min/1.73 m² and urinary albumin-to-creatinine ratio greater than 300 to 5000 mg/g). The trial randomized 4,401 subjects to canagliflozin 100 mg or placebo and was stopped early for efficacy at a prespecified interim analysis. Results were published by Perkovic et al. in June 2019 in the New England Journal of Medicine [6].

3.5 Regulatory safety actions

In May 2017, the FDA added a boxed warning to the canagliflozin label regarding an increased risk of lower-extremity amputations, based on the CANVAS Program data [8]. In August 2020, following review of additional data including the CREDENCE trial (which did not confirm the amputation signal at a comparable magnitude), the FDA removed the boxed warning, though the amputation risk remains described in the warnings and precautions section of the prescribing information [8].

In August 2018, the FDA issued a safety communication regarding Fournier gangrene (necrotizing fasciitis of the perineum) as a rare but serious risk for the entire SGLT2 inhibitor class. In 2015, the FDA had issued a warning regarding euglycemic diabetic ketoacidosis associated with SGLT2 inhibitors [13].

4. Mechanism of Action

Canagliflozin is principally a renal glucose reabsorption inhibitor. Its molecular targets are the sodium-glucose cotransporters SGLT2 and SGLT1, members of the SLC5 family of solute carriers. The compound produces its glycemic, cardiovascular, and renal effects through a composite of direct tubular actions, hemodynamic alterations, metabolic substrate shifts, and secondary neurohormonal adaptations.

4.1 SGLT2 inhibition

SGLT2 (SLC5A2) is a high-capacity, low-affinity sodium-glucose cotransporter expressed almost exclusively in the S1 and S2 segments of the renal proximal tubule. Under normal physiological conditions, SGLT2 is responsible for the reabsorption of approximately 90 percent of the 180 grams of glucose filtered daily by the glomeruli. The remaining 10 percent is reabsorbed by SGLT1 in the S3 segment [14].

Canagliflozin is a competitive inhibitor of SGLT2 with an inhibition constant (K_i) of approximately 4.2 nM and an IC_{50} of approximately 2.2 to 4.4 nM in cell-based assays using human SGLT2 expressed in CHO or HEK293 cells [1, 2]. The binding site is located on the extracellular face of the transporter; the compound is transported into the cell through the SGLT2 translocation pathway at a slow rate, a feature that may contribute to the sustained pharmacodynamic effect [2].

At clinical doses of 100 mg and 300 mg, canagliflozin lowers the renal threshold for glucose (RTG) from approximately 200 mg/dL to approximately 60 to 90 mg/dL and 40 to 60 mg/dL, respectively, resulting in urinary glucose excretion of approximately 50 to 80 grams per day in patients with type 2 diabetes and normal renal function [10]. The magnitude of glycosuria is proportional to the plasma glucose concentration, providing an intrinsic safeguard against hypoglycemia: as plasma glucose falls toward the euglycemic range, the filtered glucose load decreases and urinary glucose excretion diminishes correspondingly.

4.2 SGLT1 inhibition

SGLT1 (SLC5A1) is a low-capacity, high-affinity sodium-glucose cotransporter expressed in the S3 segment of the renal proximal tubule, in the brush border of intestinal enterocytes (where it mediates the active absorption of dietary glucose and galactose), and in the myocardium. Canagliflozin inhibits SGLT1 with a K_i of approximately 710 to 910 nM, giving an SGLT2:SGLT1 selectivity ratio of approximately 160-fold to 250-fold [1, 2].

At the 300 mg clinical dose, peak intestinal luminal concentrations of canagliflozin are estimated to exceed the SGLT1 IC_{50} transiently after oral administration, producing a brief delay in intestinal glucose absorption that attenuates postprandial glucose excursions [11]. This pharmacodynamic feature is absent or minimal at the 100 mg dose and distinguishes canagliflozin from the more SGLT2-selective agents dapagliflozin (approximately 1200-fold SGLT2:SGLT1 selectivity) and empagliflozin (approximately 2500-fold selectivity). The intestinal SGLT1 inhibition is transient; sustained systemic SGLT1 inhibition would be expected to produce glucose-galactose malabsorption and osmotic diarrhea, but these effects are not observed at clinical doses.

The dual SGLT2/SGLT1 pharmacology has been proposed as a contributor to the cardiovascular outcomes observed in the CANVAS Program, through reduction of postprandial hyperglycemia, augmentation of intestinal GLP-1 secretion (secondary to delivery of unabsorbed glucose to the distal intestine), and direct cardiac SGLT1 inhibition in the ischemic myocardium [11, 15].

4.3 Secondary and downstream mechanisms

The primary renal action of canagliflozin sets in motion several secondary mechanisms that contribute to the observed cardiovascular and renal benefits:

Tubuloglomerular feedback and hemodynamic effects: SGLT2 inhibition increases sodium delivery to the macula densa in the distal tubule, activating tubuloglomerular feedback and producing afferent arteriolar vasoconstriction. This reduces intraglomerular pressure and single-nephron glomerular filtration rate, a hemodynamic effect that is renoprotective in the setting of diabetic hyperfiltration and that manifests as an acute, reversible decline in estimated glomerular filtration rate of approximately 2 to 5 mL/min/1.73 m² followed by long-term stabilization of kidney function [6, 14].

Metabolic substrate shift: The sustained glycosuria reduces plasma glucose and insulin levels, shifting hepatic and peripheral metabolism toward increased fatty acid oxidation and mild ketogenesis. The resulting increase in circulating beta-hydroxybutyrate has been proposed as a more efficient myocardial fuel substrate (the "thrifty substrate" hypothesis), potentially contributing to the cardiovascular benefit observed in outcomes trials [16].

Natriuresis and volume effects: SGLT2 inhibition produces mild osmotic diuresis and natriuresis, reducing plasma volume and contributing to blood pressure reduction. The volume reduction is modest (estimated 5 to 10 percent reduction in plasma volume) and is accompanied by a compensatory increase in hematocrit [5].

Uric acid reduction: Canagliflozin reduces serum uric acid by approximately 10 to 15 percent through increased renal uric acid excretion, mediated by glucose-urate exchange in the proximal tubule via GLUT9 and URAT1 transporters. The uric acid reduction may contribute to renal protection [17].

4.4 Selectivity

Canagliflozin has been profiled against a broad panel of molecular targets. It does not show significant activity (IC₅₀ or K_i greater than 10 micromolar) at glucose transporters GLUT1 through GLUT4, at sodium-glucose cotransporter SGLT3, or at a standard panel of 65 receptors, ion channels, and enzymes [1]. The selectivity profile supports the interpretation that the clinical effects of canagliflozin are primarily attributable to SGLT2 and SGLT1 inhibition rather than to off-target pharmacology.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Canagliflozin is rapidly absorbed after oral administration, with time to peak plasma concentration (T_{max}) of 1 to 2 hours in the fasted state. Oral bioavailability is approximately 65 percent. Systemic exposure (AUC and C_{max}) increases in a dose-proportional manner across a wide dose range (50 to 1600 mg) [7]. High-fat meals delay T_{max} by approximately 1 hour and increase AUC by approximately 10 to 15 percent; this effect is not clinically meaningful and the compound may be administered without regard to food.

Mean peak plasma concentrations (C_{max}) following 100 mg and 300 mg doses at steady state are approximately 1,096 ng/mL and 3,480 ng/mL, respectively. Mean AUC values at steady state are approximately 6,800 ng $\cdot$ h/mL and 23,600 ng $\cdot$ h/mL for the 100 mg and 300 mg doses [7].

5.2 Distribution

Canagliflozin is extensively bound to plasma proteins (approximately 99 percent), predominantly to albumin. The volume of distribution at steady state is approximately 83.5 L, indicating moderate tissue distribution beyond the plasma compartment. The compound distributes to the kidney, the primary site of pharmacological action, and achieves proximal tubular concentrations sufficient for sustained SGLT2 inhibition throughout the 24-hour dosing interval [7].

5.3 Metabolism

The principal metabolic pathway is hepatic O-glucuronidation, catalyzed by uridine diphosphate glucuronosyltransferases UGT1A9 and UGT2B4. Two pharmacologically inactive glucuronide metabolites are produced: M5 (formed by UGT2B4) and M7 (formed by UGT1A9). Cytochrome P450-mediated oxidative metabolism contributes minimally (approximately 7 percent of total clearance), predominantly through CYP3A4 with minor contributions from CYP2C8 and CYP1A2 [7, 18].

The predominance of UGT-mediated glucuronidation rather than CYP-mediated oxidation is a favorable pharmacokinetic feature that limits the drug-drug interaction potential. Canagliflozin is not a significant inhibitor or inducer of the major CYP enzymes at therapeutic concentrations. The compound is a substrate of P-glycoprotein and breast cancer resistance protein (BCRP) efflux transporters, but transporter-mediated interactions at clinical doses are modest.

5.4 Elimination

The terminal elimination half-life at steady state is approximately 10.6 hours (100 mg dose) to 13.1 hours (300 mg dose), supporting once-daily dosing. Minimal accumulation occurs with repeated daily dosing (accumulation ratio approximately 1.36). Canagliflozin is eliminated primarily through non-renal pathways: approximately 60 percent of the administered dose is recovered in feces (predominantly as unchanged drug) and approximately 33 percent in urine (predominantly as glucuronide metabolites M5 and M7, with less than 1 percent as unchanged drug) [7].

Renal clearance of unchanged canagliflozin is low (approximately 1.3 mL/min), consistent with extensive protein binding and predominantly hepatic elimination. However, because the pharmacodynamic effect depends on renal filtration and proximal tubular SGLT2 inhibition, the glycemic efficacy is reduced in patients with moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m²), although cardiovascular and renal benefits are preserved [6].

5.5 Routes of administration

Canagliflozin is administered exclusively by the oral route as immediate-release film-coated tablets in strengths of 100 mg and 300 mg. The compound has not been developed for parenteral, intravenous, or subcutaneous administration. The tablet formulation contains the hemihydrate crystal form and standard pharmaceutical excipients.

5.6 Special populations

Renal impairment: Canagliflozin exposure (AUC) increases by approximately 15 percent, 29 percent, and 53 percent in patients with mild (eGFR 60 to less than 90), moderate (eGFR 45 to less than 60), and severe (eGFR 30 to less than 45) renal impairment, respectively, compared to subjects with normal renal function. The 100

mg dose is recommended for patients with eGFR 30 to less than 60 mL/min/1.73 m²; the compound is contraindicated for glycemic improvement in patients with eGFR below 30, although CREDENCE demonstrated renal and cardiovascular benefit in this population [6, 7].

Hepatic impairment: Mild and moderate hepatic impairment (Child-Pugh class A and B) do not produce clinically meaningful changes in canagliflozin pharmacokinetics. The compound has not been studied in severe hepatic impairment (Child-Pugh class C) and is not recommended in this population [7].

Geriatric patients: No dose adjustment is required for age. Elderly patients may be at increased risk for volume depletion-related adverse events.

Pediatric patients: Canagliflozin is not approved for use in patients under 18 years of age. Pharmacokinetic data in the pediatric population are limited.

6. Preclinical Pharmacology

6.1 In vitro characterization

Canagliflozin was characterized in vitro using cell lines stably expressing human SGLT2 and SGLT1 (CHO cells and HEK293 cells) [1, 2]. The IC₅₀ for inhibition of alpha-methyl-D-glucopyranoside (AMG) uptake through human SGLT2 was 2.2 to 4.4 nM; for human SGLT1, the IC₅₀ was 663 to 910 nM. Kinetic analysis demonstrated competitive inhibition of both transporters with respect to glucose [2]. The inhibition was shown to operate from the extracellular side of the transporter, consistent with the compound binding to the glucose recognition site in the outward-facing conformation of the transporter.

Polidori et al. (2013) characterized the interaction kinetics of canagliflozin with SGLT1 and SGLT2, demonstrating that canagliflozin is slowly transported through the SGLT2 translocation pathway, a property that may contribute to the prolonged pharmacodynamic effect and that distinguishes canagliflozin from some other SGLT2 inhibitors [2].

6.2 Animal pharmacology

The preclinical pharmacology of canagliflozin was characterized in normal and diabetic rodent models. In Zucker diabetic fatty (ZDF) rats, single and repeated oral doses of canagliflozin produced dose-dependent reductions in the renal threshold for glucose, increases in urinary glucose excretion, and reductions in plasma glucose [10]. At doses of 0.3 to 10 mg/kg, canagliflozin lowered the RTG from approximately 300 mg/dL to approximately 50 to 100 mg/dL in ZDF rats. Chronic dosing (4 weeks) produced sustained reductions in HbA1c, preservation of beta-cell function (as measured by insulin content of pancreatic islets), and reductions in body weight [10].

In diet-induced obesity mouse models, canagliflozin reduced body weight, improved glucose tolerance, and reduced hepatic steatosis, supporting the metabolic benefits observed subsequently in clinical trials [19].

6.3 Renal protection in preclinical models

Canagliflozin demonstrated renal-protective effects in multiple preclinical models of diabetic kidney disease. In the db/db mouse model, chronic canagliflozin treatment reduced albuminuria, attenuated glomerular hypertrophy, and decreased expression of renal inflammatory and fibrotic markers. The renal protection was associated with reduction of intraglomerular pressure (consistent with the tubuloglomerular feedback mechanism) and with attenuation of oxidative stress markers in renal tissue [20].

Recent preclinical work by Zhang et al. (2025) demonstrated that canagliflozin reduces blood glucose levels in the renal capillaries and protects the capillary network in diabetic rats, providing mechanistic support for the renal outcomes observed in the CREDENCE trial [21].

6.4 Hepatoprotective effects

Canagliflozin has been investigated as a potential therapeutic agent for non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma in preclinical models. Obara et al. (2018) demonstrated that canagliflozin attenuated the development of hepatocellular carcinoma in a mouse model of human NASH, with reductions in hepatic steatosis, inflammation, and fibrosis [22]. These findings have supported exploratory clinical investigation of SGLT2 inhibitors in non-alcoholic fatty liver disease.

7. Clinical Evidence Base

7.1 Glycemic efficacy

The Phase 3 registration program for canagliflozin comprised nine controlled clinical studies evaluating the compound as monotherapy and in various combination regimens. Key efficacy findings include the following [4, 12]:

Monotherapy (Study DIA3005): In treatment-naïve patients with type 2 diabetes inadequately controlled with diet and exercise, canagliflozin 100 mg and 300 mg once daily for 26 weeks reduced HbA1c by 0.77 percent and 1.03 percent, respectively, compared to placebo.

Add-on to metformin (Study DIA3006): In patients inadequately controlled on metformin monotherapy, canagliflozin 100 mg and 300 mg added to metformin for 26 weeks reduced HbA1c by 0.79 percent and 0.94 percent versus placebo.

Active comparator vs. sitagliptin (Study DIA3009): Canagliflozin 300 mg was non-inferior and statistically superior to sitagliptin 100 mg as add-on to metformin and sulfonylurea, with HbA1c reductions of 1.03 percent versus 0.66 percent at 52 weeks.

Active comparator vs. glimepiride (Study DIA3008): Canagliflozin 300 mg was non-inferior to glimepiride (titrated to 6 to 8 mg/day) as add-on to metformin at 52 weeks, with HbA1c reduction of 0.93 percent versus 0.81 percent and with significant weight loss (3.7 kg) versus weight gain (0.9 kg) in the glimepiride arm.

Across all Phase 3 studies, canagliflozin produced consistent secondary benefits: body weight reductions of 2.2 to 3.7 kg at 26 weeks (predominantly fat mass loss), systolic blood pressure reductions of 3 to 5 mmHg, and increases in HDL cholesterol of 5 to 9 percent [12].

7.2 Cardiovascular outcomes: CANVAS Program

The CANVAS Program integrated two companion trials (CANVAS and CANVAS-R) enrolling 10,142 subjects with type 2 diabetes and high cardiovascular risk (either established cardiovascular disease or at least two cardiovascular risk factors).

Subjects were randomized to canagliflozin (100 mg or 300 mg) or placebo in addition to standard of care; the primary endpoint was three-point MACE (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) [5].

Key results (mean follow-up 188.2 weeks):

- Three-point MACE: hazard ratio 0.86 (95 percent CI 0.75 to 0.97; P = 0.02 for superiority)
- Cardiovascular death: hazard ratio 0.87 (95 percent CI 0.72 to 1.06)
- Nonfatal myocardial infarction: hazard ratio 0.85 (95 percent CI 0.69 to 1.05)
- Nonfatal stroke: hazard ratio 0.90 (95 percent CI 0.71 to 1.15)
- Hospitalization for heart failure: hazard ratio 0.67 (95 percent CI 0.52 to 0.87)
- Progression of albuminuria: hazard ratio 0.73 (95 percent CI 0.67 to 0.79)

The cardiovascular benefit was consistent across prespecified subgroups defined by baseline kidney function, use of diuretics, baseline HbA1c, diabetes duration, and treatment intensity [5, 23].

7.3 Renal outcomes: CREDENCE trial

The CREDENCE trial randomized 4,401 subjects with type 2 diabetes and albuminuric chronic kidney disease (eGFR 30 to less than 90 mL/min/1.73 m²; urinary albumin-to-creatinine ratio greater than 300 to 5000 mg/g) to canagliflozin 100 mg or placebo. All subjects were receiving stable doses of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. The primary endpoint was the composite of end-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death [6].

Key results (median follow-up 2.62 years; trial stopped early for efficacy):

- Primary composite endpoint: hazard ratio 0.70 (95 percent CI 0.59 to 0.82; P = 0.00001)
- End-stage kidney disease: hazard ratio 0.68 (95 percent CI 0.54 to 0.86)
- Cardiovascular death, myocardial infarction, or stroke: hazard ratio 0.80 (95 percent CI 0.67 to 0.95)
- Hospitalization for heart failure: hazard ratio 0.61 (95 percent CI 0.47 to 0.80)
- Cardiovascular death: hazard ratio 0.78 (95 percent CI 0.61 to 1.00)

The renal benefit was consistent across subgroups defined by baseline eGFR, including the subgroup with eGFR 30 to less than 45 mL/min/1.73 m², supporting the use of canagliflozin in patients with significantly impaired kidney function [6, 24].

The CREDENCE trial was described by investigators as the first dedicated renal outcomes trial for an SGLT2 inhibitor to demonstrate a positive result, and the findings contributed to guideline updates by the American Diabetes Association, the Kidney Disease: Improving Global Outcomes (KDIGO) organization, and other professional bodies.

7.4 Pooled cardiovascular and renal analyses

Pooled analyses of the CANVAS Program and CREDENCE trial (total N approximately 14,500) have demonstrated consistent benefits across the full spectrum of type 2 diabetes with and without established cardiovascular or kidney disease. Mahaffey et al. (2019) reported that canagliflozin produced both primary and secondary cardiovascular prevention, with consistent reductions in MACE, hospitalization for heart failure, and renal outcomes irrespective of baseline cardiovascular disease status [25, 26].

Impact of diabetes duration on treatment response has been analyzed by Jardine et al. (2024), demonstrating that the kidney and cardiovascular benefits of canagliflozin are preserved regardless of diabetes duration (less than 10 years, 10 to less than 16 years, or 16 or more years) [27].

7.5 Heart failure

In the CANVAS Program, canagliflozin reduced hospitalization for heart failure by 33 percent (hazard ratio 0.67; 95 percent CI 0.52 to 0.87) [5]. Network meta-analyses of SGLT2 inhibitors in heart failure have ranked canagliflozin favorably for this outcome, with surface under the cumulative ranking curve (SUCRA) values of approximately 95.5 percent for reduction of hospitalization for heart failure in patients with type 2 diabetes [28]. Canagliflozin has not been the subject of a dedicated heart failure outcomes trial comparable to DAPA-HF (dapagliflozin) or EMPEROR-Reduced (empagliflozin), and it does not carry an FDA-approved indication for heart failure.

8. Sourcing and Quality Verification

Pharmaceutical-grade canagliflozin (Invokana brand or licensed generic) is available as 100 mg and 300 mg film-coated tablets for oral administration. The pharmaceutical-grade material is the preferred source for clinical research applications where regulatory equivalence to the approved product is required. Generic canagliflozin has been approved by the FDA and is commercially available.

Research-grade canagliflozin is supplied by multiple chemical and pharmaceutical research suppliers (Cayman Chemical, Selleck Chemicals, MedChemExpress, Sigma-Aldrich/MilliporeSigma, Toronto Research Chemicals, BOC Sciences, and others) at greater than 98 percent purity by HPLC. Supply is available in milligram to multi-gram quantities as the anhydrous form or the hemihydrate. Pricing is moderate, typically in the range of \$30 to \$150 per 100 milligrams of high-purity research-grade material at the time of monograph preparation.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography (HPLC) area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (445.15 for the protonated free form $[M+H]^+$, or 444.14 for the molecular ion)
- Nuclear magnetic resonance (1H -NMR and ^{13}C -NMR) confirmation of structure, with particular attention to the anomeric C-glucoside carbon signal
- Karl Fischer titration or thermogravimetric analysis for water content (the hemihydrate contains approximately 2.0 percent water by weight)
- Chiral HPLC or optical rotation measurement to confirm stereochemical purity of the beta-D-glucopyranose configuration
- Residual solvent analysis by gas chromatography if the synthesis involves dichloromethane, tetrahydrofuran, or other solvents of concern

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The research-grade canagliflozin market is well established given the commercial success of the pharmaceutical product; counterfeit material

is uncommon, but lot-to-lot variability in crystal form (anhydrous versus hemihydrate) is observed and may affect dissolution behavior in in vitro assays.

9. Reconstitution and Handling

Canagliflozin anhydrous is a white to off-white crystalline powder with limited aqueous solubility (approximately 1.4 mg/mL at 25 degrees Celsius). For in vitro research applications, stock solutions are typically prepared in dimethyl sulfoxide (DMSO) at concentrations of 10 to 100 mM, yielding clear, colorless solutions. The compound is stable in DMSO at room temperature for at least 3 months and at minus 20 degrees Celsius for at least 12 months when protected from moisture. Stock solutions in DMSO should be aliquoted to avoid repeated freeze-thaw cycles; stability through at least 5 freeze-thaw cycles has been reported without measurable potency loss.

For cell-based assays, DMSO stock solutions are diluted into aqueous cell culture media immediately before use. Final DMSO concentration should be maintained below 0.1 to 0.5 percent (v/v) to avoid solvent cytotoxicity; at these dilutions, canagliflozin remains in solution at concentrations up to approximately 5 to 10 micromolar.

For in vivo administration in rodent studies, canagliflozin is typically formulated as a suspension in 0.5 percent methylcellulose or 0.5 percent carboxymethylcellulose in water for oral gavage administration. The compound can also be formulated in standard vehicle systems containing polyethylene glycol 400, Tween 80, or cyclodextrin solutions for enhanced dissolution.

Storage of the solid form should be at room temperature (15 to 30 degrees Celsius) or refrigerated (2 to 8 degrees Celsius) in a tightly sealed container protected from moisture. The hemihydrate crystal form is the thermodynamically stable polymorph under ambient conditions; the anhydrous form may convert to the hemihydrate on exposure to humid environments. Investigators requiring the anhydrous form for crystallographic or physicochemical studies should store the material under desiccated conditions.

The pharmaceutical tablet formulation (Invokana) should be stored at controlled room temperature (20 to 25 degrees Celsius with excursions permitted to 15 to 30 degrees Celsius).

10. Stack Interactions and Combinations

Canagliflozin interacts with several drug classes through pharmacokinetic and pharmacodynamic mechanisms. Investigators conducting research with canagliflozin, especially in chronic dosing regimens or in combination with other agents, should consider:

UGT enzyme inducers: Rifampin (a potent inducer of UGT1A9 and multiple CYP enzymes) reduces canagliflozin AUC by approximately 51 percent and C_{max} by approximately 28 percent. Other UGT inducers (phenytoin, phenobarbital, ritonavir) may produce similar reductions. If co-administration with a UGT inducer is required, consider increasing the canagliflozin dose to 300 mg if the patient is currently tolerating 100 mg [7, 18].

Digoxin: Canagliflozin increased digoxin AUC by approximately 20 percent, a modest pharmacokinetic interaction mediated by inhibition of intestinal P-glycoprotein. Digoxin levels should be monitored when initiating or modifying canagliflozin therapy in patients on digoxin [7].

Insulin and insulin secretagogues: The combination of canagliflozin with insulin or sulfonylureas produces additive glucose-lowering and increases the risk of hypoglycemia. Dose reduction of insulin or the sulfonylurea is recommended when initiating canagliflozin. In the Phase 3 program, hypoglycemia rates with canagliflozin plus sulfonylurea were approximately 30 to 40 percent versus 15 to 20 percent with placebo plus sulfonylurea [4].

Diuretics: Canagliflozin produces osmotic diuresis and natriuresis; concurrent loop or thiazide diuretics increase the risk of volume depletion, hypotension, and acute kidney injury. Monitoring of volume status and renal function is recommended [5].

ACE inhibitors and angiotensin receptor blockers: These agents are frequently co-administered with canagliflozin in the setting of diabetic kidney disease (as in the CREDENCE trial). The combination is generally well tolerated and produces ad-

ditive renal protection. The potential for additive hyperkalemia should be monitored, although SGLT2 inhibitors tend to reduce serum potassium through increased renal potassium excretion [6].

Metformin: The fixed-dose combination of canagliflozin and metformin (Invokamet) is commercially available and widely used. No clinically meaningful pharmacokinetic interaction exists between the two compounds. The combination produces additive glycemic efficacy [4].

Other SGLT2 inhibitors: Concurrent use with another SGLT2 inhibitor is pharmacologically redundant and is not recommended.

Lithium: Canagliflozin may increase renal lithium clearance through its natriuretic and diuretic effects, potentially reducing lithium levels. Lithium levels should be monitored when initiating or modifying canagliflozin therapy in patients on lithium.

Bosentan: Bosentan (a moderate CYP3A4 inducer) may modestly reduce canagliflozin exposure; clinical significance is uncertain.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at approved doses (100 mg and 300 mg) observed across the Phase 3 program and post-marketing surveillance include [4, 5, 8]:

- Genital mycotic infections: approximately 10 to 12 percent in women (vulvo-vaginal candidiasis) and 4 to 5 percent in men (balanitis, balanoposthitis). The mechanism is direct: glycosuria provides a glucose-rich environment favoring *Candida* overgrowth. Most infections are mild to moderate and respond to standard antifungal therapy.
- Urinary tract infections: approximately 5 to 8 percent (similar to or modestly higher than placebo rates in some studies). The mechanism is multifactorial and may involve altered urinary composition.
- Volume depletion-related events (postural dizziness, orthostatic hypotension, dehydration, syncope): approximately 2 to 4 percent, more common in elderly patients and those on concurrent diuretics.
- Increased urination (pollakiuria, polyuria): approximately 5 to 7 percent, reflecting the osmotic diuretic mechanism.
- Thirst: approximately 2 to 3 percent.
- Constipation: approximately 1 to 2 percent.

11.2 Serious and notable adverse events

Lower-extremity amputations: The CANVAS Program identified a two-fold increase in lower-extremity amputations with canagliflozin compared to placebo (6.3 versus 3.4 per 1,000 patient-years; hazard ratio 1.97; 95 percent CI 1.41 to 2.75), predominantly at the toe and metatarsal level [5]. The mechanism remains incompletely characterized; proposed contributors include volume depletion-mediated peripheral hypoperfusion, altered wound healing, and pre-existing peripheral vascular disease in the study population. The CREDENCE trial did not demonstrate a statistically significant increase in amputations (12.3 versus 11.2 per 1,000 patient-years;

hazard ratio 1.11; 95 percent CI 0.79 to 1.56) [6]. The FDA removed the boxed warning for amputation risk in August 2020, though the risk remains in the warnings and precautions section [8].

Bone fractures: The CANVAS trial (but not CANVAS-R) identified a higher rate of fractures with canagliflozin versus placebo (15.4 versus 11.9 per 1,000 patient-years) [5]. The CREDENCE trial did not confirm this finding. The mechanism may involve bone mineral density effects; canagliflozin has been associated with modest increases in markers of bone resorption and decreases in bone mineral density at the hip in some studies.

Euglycemic diabetic ketoacidosis (DKA): A rare but clinically important adverse event (estimated incidence less than 1 per 1,000 patient-years) observed across the SGLT2 inhibitor class. The mechanism involves the metabolic substrate shift toward fatty acid oxidation and ketogenesis in the setting of relative insulin deficiency; blood glucose may be only mildly elevated or normal at presentation, complicating diagnosis [13]. Risk factors include low carbohydrate intake, dehydration, acute illness, reduced insulin dose, and excessive alcohol intake.

Fournier gangrene: Rare cases of necrotizing fasciitis of the perineum have been reported with SGLT2 inhibitors as a class. The FDA identified 12 cases across all SGLT2 inhibitors between March 2013 and May 2018. The mechanism may involve glycosuria-mediated perineal bacterial overgrowth [29].

Acute kidney injury: Volume depletion-mediated acute kidney injury has been reported, particularly in patients on concurrent diuretics, ACE inhibitors, or NSAIDs. Most cases are reversible with volume repletion and drug discontinuation.

11.3 Laboratory abnormalities

Canagliflozin produces predictable laboratory changes consistent with its mechanism of action: increased serum creatinine (acute, reversible, reflecting hemodynamic changes rather than structural injury), decreased eGFR (acute dip of approximately 2 to 5 mL/min/1.73 m² followed by stabilization), increased hematocrit (reflecting hemoconcentration), increased serum magnesium, increased serum phosphate, increased LDL cholesterol (5 to 10 percent), and decreased serum uric acid [7, 12].

11.4 Pregnancy and lactation

Canagliflozin is contraindicated in pregnancy (FDA former Category C; adverse effects on renal development observed in animal studies at exposures greater than clinical exposure). The compound is not recommended during the second and third trimesters of pregnancy on the basis of potential fetal renal toxicity. Limited data are available on excretion in human milk; a decision should be made whether to discontinue breastfeeding or to discontinue the drug.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five SGLT2 inhibitor alternatives against canagliflozin, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal SGLT2 inhibitors with substantive clinical outcomes evidence or with distinctive pharmacological features relevant to the research and clinical positioning of canagliflozin.

12.1 Dapagliflozin (Farxiga/Forxiga)

Mechanism: Selective SGLT2 inhibitor with high selectivity over SGLT1 (approximately 1200-fold). Dapagliflozin is an O-glucoside-derived C-glucoside (the original C-glucoside scaffold from Bristol-Myers Squibb) with a chlorophenyl aglycone rather than the thiophene of canagliflozin [30].

Development trajectory: Developed by Bristol-Myers Squibb and AstraZeneca. FDA-approved in January 2014 for type 2 diabetes. Subsequently approved for heart failure with reduced ejection fraction (DAPA-HF, 2020), heart failure with preserved ejection fraction (DELIVER, 2022), and chronic kidney disease (DAPA-CKD, 2021).

Novelty: Low. The C-glucoside SGLT2 inhibitor mechanism is shared with canagliflozin; the principal structural difference is the higher SGLT2:SGLT1 selectivity and the absence of the thiophene ring.

Effect size: DAPA-HF demonstrated a 26 percent reduction in cardiovascular death or worsening heart failure (hazard ratio 0.74) in patients with heart failure with reduced ejection fraction, irrespective of diabetes status [31]. DAPA-CKD demonstrated a 39 percent reduction in the primary renal composite endpoint (hazard ratio 0.61) in patients with chronic kidney disease with and without diabetes [32]. DELIVER demonstrated benefit in heart failure with preserved ejection fraction. These effect sizes are robust and represent substantial clinical impact.

Promising potential: High. Dapagliflozin has the broadest approved indication set of any SGLT2 inhibitor, spanning type 2 diabetes, heart failure (across the ejection fraction spectrum), and chronic kidney disease regardless of diabetes status.

Side-effect profile: Similar class-related adverse events (genital mycotic infections, urinary tract infections, volume depletion). No confirmed signal for amputation or fracture risk. Euglycemic DKA risk is shared across the class.

Overall validation: Very high. The compound has produced positive results across four major outcomes trials (DECLARE-TIMI 58, DAPA-HF, DAPA-CKD, DELIVER) and has the broadest evidence base of any SGLT2 inhibitor.

Comparison to canagliflozin: Dapagliflozin has broader approved indications (including heart failure and CKD irrespective of diabetes) and a cleaner safety profile (no amputation signal). Canagliflozin has the advantage of being first-to-market, having the first positive dedicated renal outcomes trial (CREDENCE preceded DAPA-CKD), and having the dual SGLT2/SGLT1 pharmacology that may confer additional postprandial glucose and cardiovascular benefits at higher doses.

12.2 Empagliflozin (Jardiance)

Mechanism: Highly selective SGLT2 inhibitor with approximately 2500-fold selectivity over SGLT1. Developed by Boehringer Ingelheim and Eli Lilly [33].

Development trajectory: FDA-approved in August 2014 for type 2 diabetes. The EMPA-REG OUTCOME trial (published 2015) was the first SGLT2 inhibitor cardiovascular outcomes trial to report, demonstrating a 14 percent reduction in three-point MACE and a 38 percent reduction in cardiovascular death [34]. Subsequently approved for cardiovascular death risk reduction, heart failure (EMPEROR-Reduced, EMPEROR-Preserved), and chronic kidney disease (EMPA-KIDNEY).

Novelty: Low. The mechanism is conventional SGLT2 inhibition within the same pharmacological class.

Effect size: EMPA-REG OUTCOME demonstrated a 38 percent reduction in cardiovascular death (hazard ratio 0.62), the largest mortality signal in any SGLT2 inhibitor outcomes trial [34]. EMPEROR-Reduced and EMPEROR-Preserved demonstrated consistent heart failure benefits. EMPA-KIDNEY demonstrated renal benefits in CKD populations with and without diabetes.

Promising potential: Very high. Empagliflozin has comprehensive outcomes evidence across cardiovascular, heart failure, and renal endpoints and has among the broadest approved indication sets.

Side-effect profile: Similar class-related adverse events. No confirmed amputation signal. Clean safety profile across outcomes trials.

Overall validation: Very high. The compound was the first SGLT2 inhibitor with published cardiovascular outcomes data (EMPA-REG OUTCOME) and has subsequently produced positive results in heart failure and CKD trials.

Comparison to canagliflozin: Empagliflozin has the advantage of the largest cardiovascular death signal, the broadest outcomes trial portfolio, and the cleanest safety profile among the leading SGLT2 inhibitors. Canagliflozin has the advantage of the first positive dedicated renal outcomes trial and the dual SGLT2/SGLT1 pharmacology. The cardiovascular death reduction in EMPA-REG OUTCOME (38 percent) was larger than in the CANVAS Program (13 percent, not significant for the cardiovascular death component individually), a difference that may reflect population differences, SGLT1 selectivity differences, or statistical variability.

12.3 Ertugliflozin (Steglatro)

Mechanism: Selective SGLT2 inhibitor with high selectivity over SGLT1 (approximately 2000-fold). Developed by Pfizer and Merck [35].

Development trajectory: FDA-approved in December 2017 for type 2 diabetes. The VERTIS-CV outcomes trial (published 2020) demonstrated non-inferiority for three-point MACE (hazard ratio 0.97; 95 percent CI 0.85 to 1.11) but did not demonstrate superiority for either the MACE or heart failure endpoints [36].

Novelty: Low. Conventional selective SGLT2 inhibitor mechanism.

Effect size: VERTIS-CV showed no significant benefit on three-point MACE or hospitalization for heart failure. Reductions in renal outcomes were observed but were secondary endpoints. The glycemic efficacy is comparable to other SGLT2 inhibitors at approved doses.

Promising potential: Low to moderate. The neutral cardiovascular outcomes trial and lack of approved indications beyond glycemic control limit the competitive positioning. Pfizer announced discontinuation of ertugliflozin commercializa-

tion in the United States.

Side-effect profile: Similar class-related adverse events. No amputation signal. Clean safety profile in VERTIS-CV.

Overall validation: Moderate. Glycemic efficacy is established; cardiovascular and renal outcomes evidence is weaker than for canagliflozin, dapagliflozin, or empagliflozin.

Comparison to canagliflozin: Canagliflozin has substantially stronger outcomes evidence (positive CANVAS and CREDENCE results versus neutral VERTIS-CV). Ertugliflozin has a cleaner safety profile regarding amputation risk but lacks the cardiovascular and renal benefit demonstration that distinguishes canagliflozin.

12.4 Sotagliflozin (Inpefa)

Mechanism: Dual SGLT1/SGLT2 inhibitor with lower selectivity for SGLT2 over SGLT1 (approximately 20-fold) than canagliflozin (approximately 160-fold to 250-fold). The substantially greater SGLT1 inhibitory activity produces more pronounced effects on intestinal glucose absorption, postprandial GLP-1 secretion, and postprandial glucose excursions [37].

Development trajectory: Developed by Lexicon Pharmaceuticals. FDA-approved in May 2023 for heart failure. Approved specifically for reducing the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visits in adults with heart failure. The SOLOIST-WHF and SCORED trials demonstrated significant benefits on heart failure endpoints in patients with and without diabetes.

Novelty: Moderate to high. The intentional dual SGLT1/SGLT2 mechanism represents a pharmacologically distinct approach within the gliflozin class, with SGLT1 inhibition as a therapeutic feature rather than a secondary activity.

Effect size: SOLOIST-WHF demonstrated a 33 percent reduction in cardiovascular death and heart failure events (hazard ratio 0.67). SCORED demonstrated a 26 percent reduction in the composite of cardiovascular death, hospitalization for heart failure, and urgent heart failure visits (hazard ratio 0.74) [37]. Network meta-analyses have suggested sotagliflozin may be among the most effective SGLT2 inhibitors for heart failure outcomes.

Promising potential: Moderate to high. The heart failure indication and the dual SGLT1/SGLT2 mechanism position sotagliflozin as a differentiated agent. However, the limited indication set (heart failure only in the United States) and the lack of comprehensive renal outcomes data limit the breadth of positioning relative to dapagliflozin and empagliflozin.

Side-effect profile: Diarrhea is more common with sotagliflozin than with SGLT2-selective agents (approximately 8 to 9 percent versus 2 to 3 percent), consistent with intestinal SGLT1 inhibition. Other class-related adverse events are similar. Euglycemic DKA risk may be modestly elevated relative to SGLT2-selective agents.

Overall validation: Moderate. The heart failure outcomes evidence is strong; glycemic and renal outcomes data are less comprehensive than for canagliflozin, dapagliflozin, or empagliflozin.

Comparison to canagliflozin: Sotagliflozin shares the dual SGLT1/SGLT2 pharmacological concept with canagliflozin but at a much more pronounced degree of SGLT1 inhibition. Canagliflozin has broader outcomes evidence (cardiovascular, renal) and broader approved indications. Sotagliflozin may have advantages in heart failure through its more potent SGLT1 inhibition. The two compounds are pharmacologically related and represent different points on the SGLT2:SGLT1 selectivity spectrum.

12.5 Bexagliflozin (Brenzavvy)

Mechanism: Selective SGLT2 inhibitor. Developed by TheracosBio. FDA-approved in January 2023 for type 2 diabetes [38].

Development trajectory: The most recently approved SGLT2 inhibitor in the United States. Clinical development included Phase 3 glycemic efficacy studies. No dedicated cardiovascular or renal outcomes trial has been published.

Novelty: Low. Conventional selective SGLT2 inhibitor mechanism without pharmacological differentiation from established agents.

Effect size: Glycemic efficacy (HbA1c reduction approximately 0.5 to 0.9 percent) is comparable to other SGLT2 inhibitors. No cardiovascular or renal outcomes data.

Promising potential: Low. The absence of outcomes data and the competitive landscape with well-established agents (dapagliflozin, empagliflozin, canagliflozin) with proven cardiovascular and renal benefits limit the market positioning and research interest.

Side-effect profile: Similar class-related adverse events. Limited post-marketing data relative to the established agents.

Overall validation: Low. Glycemic efficacy is established but outcomes evidence is absent.

Comparison to canagliflozin: Canagliflozin has vastly stronger clinical evidence (CANVAS, CREDENCE), broader indications, and more extensive post-marketing safety data. Bexagliflozin does not currently offer any advantage over canagliflozin for research or clinical applications.

12.6 Comparator summary

The five comparator SGLT2 inhibitors occupy distinct positions in the clinical and research landscape. **Dapagliflozin** has the broadest approved indication set and the most comprehensive outcomes trial portfolio across diabetes, heart failure, and CKD. **Empagliflozin** has the strongest cardiovascular mortality signal (EMPA-REG OUTCOME) and comprehensive outcomes evidence. **Ertugliflozin** has been commercially deprioritized following the neutral VERTIS-CV result. **Sotagliflozin** represents a pharmacologically distinct dual SGLT1/SGLT2 approach with strong heart failure outcomes data. **Bexagliflozin** is a late entrant without outcomes evidence.

Canagliflozin occupies a historically significant position as the first SGLT2 inhibitor approved in the United States and the first to demonstrate a positive dedicated renal outcomes trial (CREDENCE). Its dual SGLT2/SGLT1 pharmacology at the 300 mg dose provides a mechanistic distinction from the more selective agents that may contribute to postprandial glucose lowering and cardiovascular benefit. The amputation signal identified in the CANVAS Program, although subsequently attenuated by CREDENCE data and FDA label revision, remains a distinguishing safety consideration.

For research applications requiring an SGLT2 inhibitor tool compound, canagliflozin offers the advantages of extensive published pharmacology, well-characterized pharmacokinetics, commercial availability in research-grade material, and comprehensive clinical outcomes data for translational reference. The

principal research question for the field is whether the modest SGLT1 inhibitory activity of canagliflozin at the 300 mg dose confers a clinically meaningful benefit beyond that achieved by purely SGLT2-selective agents, and whether the dual mechanism explains differential outcomes across the SGLT2 inhibitor class.

13. References

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