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MONOGRAPH

CANAGLIFLOZIN

Rec INN; USAN

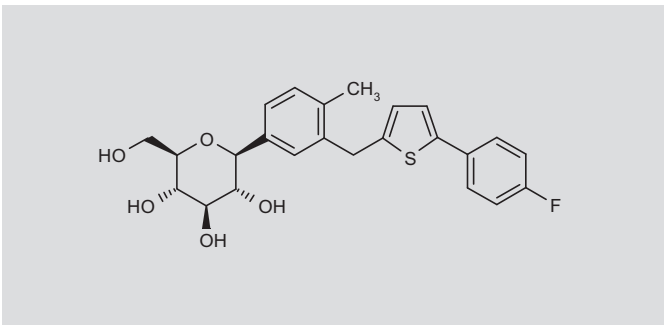
Sodium/Glucose Cotransporter 2 Inhibitor
Treatment of Type 2 Diabetes
Treatment of Obesity

JNJ-28431754
TA-7284

1-Deoxy-1-[3-[5-(4-fluorophenyl)thien-2-ylmethyl]-4-methylphenyl]-β-D-glucopyranoside

1,5-Anhydro-1(S)-[3-[5-(4-fluorophenyl)thien-2-ylmethyl]-4-methylphenyl]-D-glucitol

InChI: 1S/C24H25FO5S/c1-13-2-3-15(24-23(29)22(28)21(27)19(12-26)30-24)10-16(13)11-18-8-9-20(31-18)14-4-6-17(25)7-5-14/h2-10,19,21-24,26-29H,11-12H2,1H3/t19-,21-,22+,23-,24+/m1/s1



$C_{24}H_{25}FO_5S$

Mol wt: 444.516

CAS: 842133-18-0

CAS: 928672-86-0

EN: 455923

SUMMARY

Sodium/glucose cotransporters (SGLTs) serve a critical role in the reclamation of glucose in the kidney. Blocking this reabsorption, and thus increasing the amount of glucose excretion, has been proposed as a novel strategy for treating diabetes. Canagliflozin is a C-glucoside with a thiophene ring that acts as a sodium/glucose cotransporter 2 (SGLT2) inhibitor. Although further data from multiple ongoing phase III clinical trials of canagliflozin and other SGLT2 inhibitors are forthcoming, results to date suggest that the benefits of SGLT2 inhibition may be achieved without causing significant adverse effects. This review will provide a description of the role of the kidney in glucose homeostasis and summarize the preclinical and clinical studies published thus far on canagliflozin.

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*Synthesis prepared by R. Pandian, J. Bolòs, R. Castañer, N. Díaz. Thomson Reuters, Provença 398, 08025 Barcelona, Spain.

SYNTHESIS*

Canagliflozin can be prepared by three strategies:

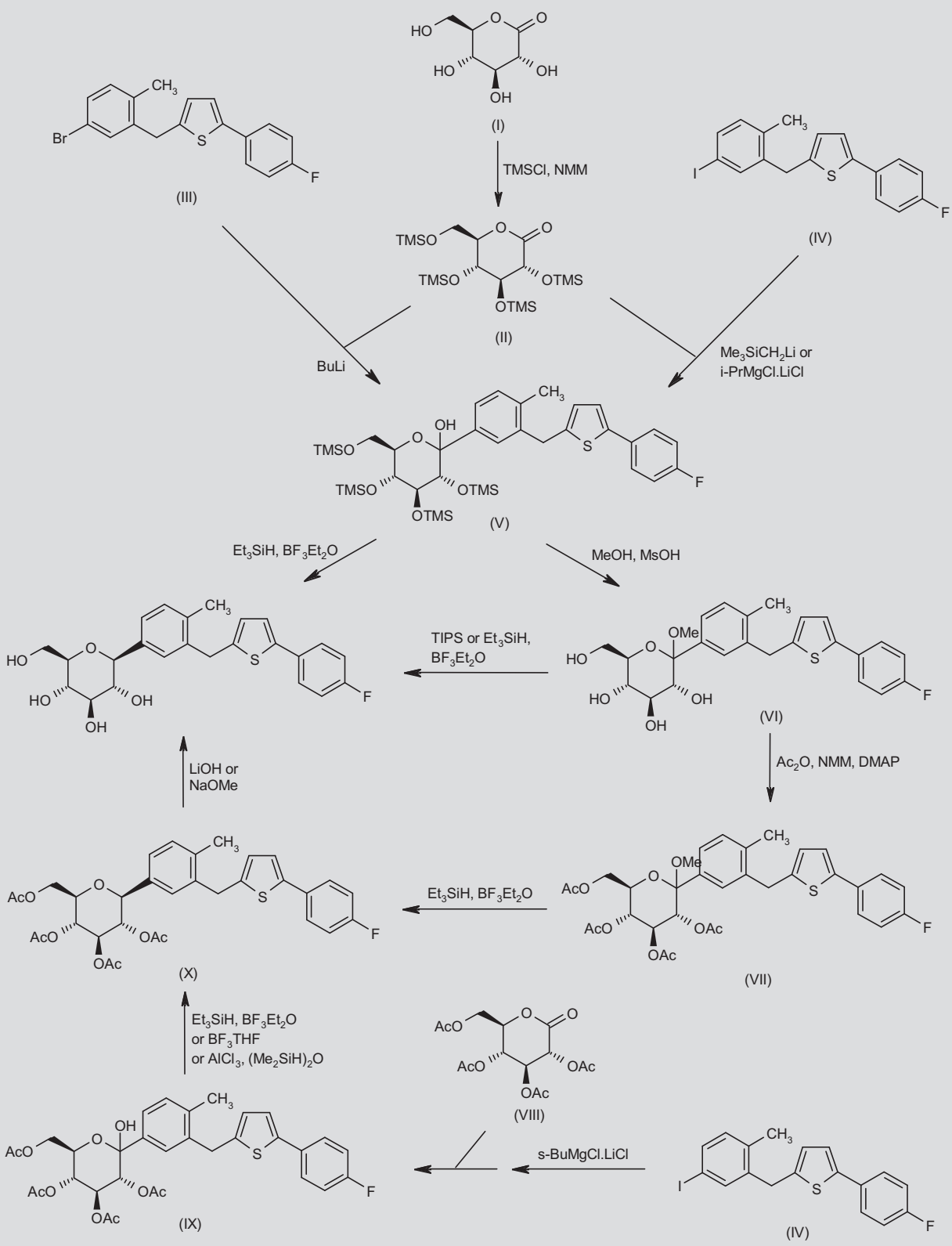
O-Protection of gluconolactone (I) with TMSCl in the presence of NMM in THF yields the tetrasilylgluconolactone (II) (1, 2), which by coupling with either 2-(5-bromo-2-methylbenzyl)-5-(4-fluorophenyl)thiophene (III), with previous treatment with BuLi in THF/toluene at −78 °C (3, 4), or with iodobenzyl derivative (IV), with previous treatment with Me_3SiCH_2Li in THF at −40 °C (1) or *i*-PrMgCl·LiCl in THF at 0 °C (5), provides the D-glucopyranose derivative (V) (1, 3-5). Finally, D-glucopyranose (V) is desilylated and reduced stereospecifically by means of Et_3SiH and $BF_3{\cdot}Et_2O$ in dichloroethane (1). Scheme 1.

Alternatively, glucosidation and cleavage of the silyl protecting groups in intermediate (V) with MeOH and MsOH affords the methyl D-glucopyranoside derivative (VI) (3-5), which then undergoes enantiospecific reduction in the presence of TIPS (3) or Et_3SiH (4) and $BF_3{\cdot}Et_2O$ (3, 4). Scheme 1.

Acetylation of the hydroxyl groups of the methyl D-glucopyranoside (VI) with Ac_2O in the presence of NMM and DMAP in toluene/EtOAc leads to tetraacetate derivative (VII), which is then reduced by means of Et_3SiH and $BF_3{\cdot}Et_2O$ in acetonitrile to give stereospecifically the D-glucitol derivative (X). Finally, glucitol (X) is hydrolyzed with $LiOH{\cdot}H_2O$ in MeOH/THF or with NaOMe in refluxing MeOH and subsequently treated with AcOH (5). Scheme 1.

D-Glucitol derivative (X) can also be prepared by treatment of iodobenzyl derivative (IV), with *s*-BuMgCl·LiCl in THF at 2 °C and addition of the resulting Grignard reagent to a solution of the tetraacetyl gluconolactone (VIII) in THF at −35 °C to give the D-glucopyranose derivative (IX), which then undergoes enantiospecific reduction by means of Et_3SiH and $BF_3{\cdot}Et_2O$ or $BF_3{\cdot}$THF in acetonitrile or in the presence of $AlCl_3$ and $(Me_2SiH)_2O$ in acetonitrile (5). Scheme 1.

Scheme 1. Synthesis of Canagliflozin



Intermediate (IV) can be prepared by two methods:

In one method, metalation of 1-bromo-4-fluorobenzene (XI) with Mg in 2-MeTHF at 90 °C gives 4-fluorophenyl magnesium bromide (XII), which then couples with 2-bromothiophene (XIII) in the presence of $NiCl_2$·dppe and AcOH in 2-MeTHF at 22 °C or in the presence of $Pd(OAc)_2$ and DPPP in THF to yield 2-(4-fluorophenyl)thiophene (XIV). Finally, this compound undergoes Friedel–Crafts acylation with 5-iodo-2-methylbenzoic acid (XV) (initially chlorinated with $SOCl_2$ in CH_2Cl_2) using $AlCl_3$ in CH_2Cl_2, and subsequent reduction with $(Me_2SiH)_2O$ in refluxing acetonitrile (5). Scheme 2.

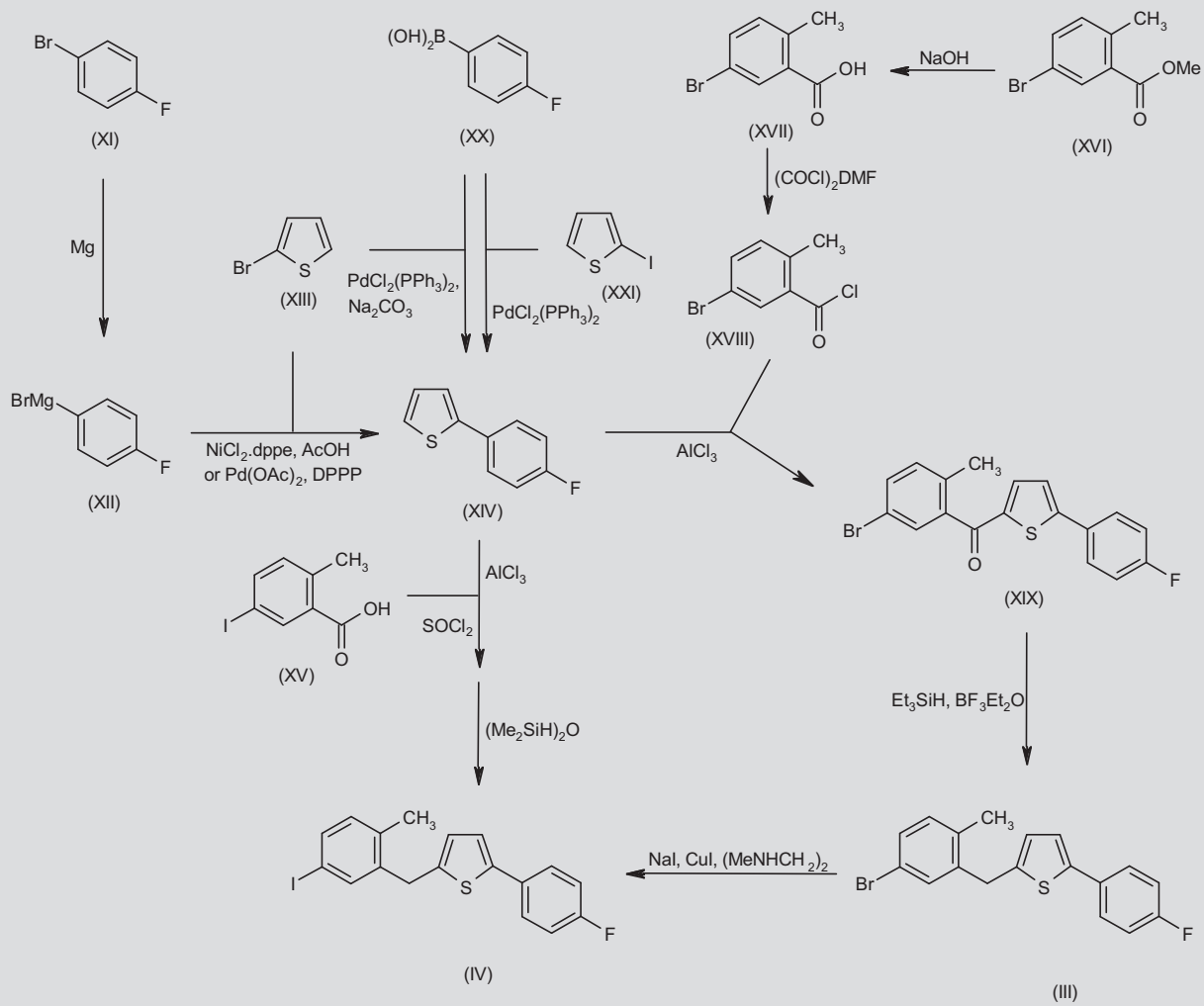
In another method, hydrolysis of methyl 5-bromo-2-methylbenzoate (XVI) with NaOH in MeOH at 50 °C gives rise to the benzoic acid (XVII) (3), which is then chlorinated with $(COCl)_2$ in the presence of DMF in CH_2Cl_2 to yield 5-bromo-2-methylbenzoyl chloride (XVIII). Friedel–Crafts reaction of acyl chloride (XVIII) with 2-(4-fluorophenyl)thiophene (XIV) in the presence of $AlCl_3$ in CH_2Cl_2 affords ketone (XIX), which is then reduced by means of Et_3SiH and BF_3·Et_2O in CH_2Cl_2/acetonitrile to afford 2-(5-bromo-2-methylbenzoyl)-5-(4-fluorophenyl)thiophene (III) (1, 3, 4). Finally, compound (III) is iodinated with NaI and CuI in the presence of $(MeNHCH_2)_2$ in refluxing toluene/diglyme (IV) (1, 5). Scheme 2.

Alternatively, coupling of 4-fluorophenylboronic acid (XX) with either 2-bromothiophene (XIII) in the presence of $PdCl_2(PPh_3)_2$ and Na_2CO_3 in dimethoxyethane at 75-80 °C (5) or with 2-iodothiophene (XXI) in the presence of $PdCl_2(PPh_3)_2$ at 50 °C (3) affords 2-(4-fluorophenyl)thiophene (XIV) (3, 5). Scheme 2.

BACKGROUND

Diabetes is a chronic disease that has reached epidemic proportions. The estimated global prevalence of type 2 diabetes has increased substantially, from 151 million in 2000 to 285 million in 2010, and is projected to affect 438 million individuals worldwide by 2030 (6).

Scheme 2. Synthesis of Intermediate (IV)



Type 2 diabetes represents approximately 90% of all cases of diabetes. This disease is marked by insulin resistance and hyperglycemia. Chronic hyperglycemia is toxic to beta cells. This glucose toxicity results in increased apoptosis and decreased insulin gene transcription, and leads to beta cell failure. Insulin synthesis and secretion thus decrease (7).

As the disease advances, complications stem from hyperglycemia, such as microvascular disease (retinopathy, neuropathy and nephropathy) and macrovascular disease (cardiovascular, cerebral and peripheral vascular disease) (8). Efforts to treat type 2 diabetes with currently available agents are often hampered by significant adverse effects. Metformin can cause gastrointestinal side effects, including nausea and diarrhea, and rarely, lactic acidosis. Sulfonylureas and insulin can result in weight gain and hypoglycemia (9). Thiazolidinediones are associated with edema and weight gain (9), while the newer incretin mimetics may cause nausea, vomiting and diarrhea (10). Glycemic control can be challenging to attain, even with a combination of the currently available multiple oral agents and insulin. Consequently, the quest to develop therapeutic agents with novel mechanisms of action without these adverse effects continues.

Although the focus of diabetes therapy has centered on the pancreas and liver, the kidney plays a unique, key role in regulating glucose homeostasis by mediating the reabsorption of glucose back into the plasma. Glucose uptake is matched by glucose production, primarily performed by the liver, and to a lesser extent by the kidney. Under normal circumstances, the approximately 180 g of glucose that is filtered daily is essentially completely reabsorbed by the kidney (11). While retaining calories is a crucial evolutionary adaptation, this process contributes to the sustained elevation of plasma glucose levels in individuals with diabetes. Glycosuria has traditionally been regarded as a marker of metabolic decompensation. Harnessing glycosuria as a potential new therapeutic mechanism thus represents a significant paradigm shift.

As cell membranes are impermeable to glucose, transport across the cell membrane of this polar compound requires the assistance of carrier proteins located within the cell membrane. Two sodium/glucose cotransporters –SGLT2 and SGLT1– mediate glucose reabsorption, with SGLT2 accounting for approximately 90% of this function. SGLT2 is a high-capacity, low-affinity transporter located mainly in the S1 segment, but also found in the S2 segment of the renal proximal convoluted tubule (PCT) (Fig. 1) (12). SGLT1 is a low-capacity, high-affinity transporter that is found in the more distal S2/S3 segment of the PCT. Once plasma glucose has been filtered in the kidney by the glomeruli, glucose is actively transported across the luminal membrane of the PCT epithelial cell by coupled downhill transport with sodium (Fig. 2). Intracellular glucose diffuses passively out of the cell via facilitative glucose transporters (GLUTs) located on the basolateral membrane (13).

Plasma glucose concentrations are usually maintained within a narrow range, which is crucial for normal function. The filtered load of glucose is the product of the plasma glucose concentration and the glomerular filtration rate. As the plasma concentration of glucose increases, the filtered load of glucose increases linearly. When the threshold for glucose excretion, at a plasma concentration of ~200-

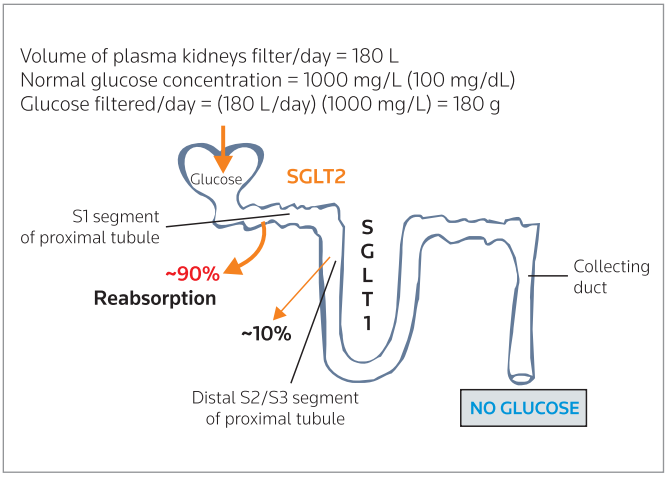


Figure 1. Glucose handling in the kidney in a nondiabetic individual. The locations for the sodium/glucose cotransporters SGLT2 and SGLT1 are indicated (23). Copyright Informa Healthcare 2009. Reproduced with permission.

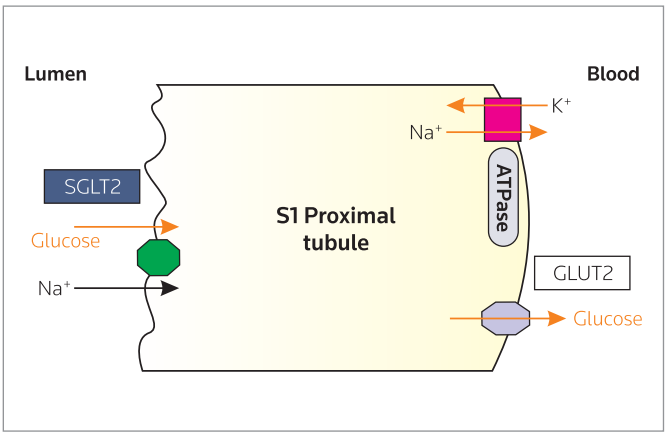


Figure 2. The sodium/glucose cotransporter SGLT2 mediates renal glucose reabsorption. SGLT2 catalyzes the active transport of glucose (against a concentration gradient) across the luminal membrane by coupling it with the downhill transport of Na^+. The inward Na^+ gradient across the luminal epithelium is maintained by active extrusion of Na^+ across the basolateral (antiluminal) surface into the intercellular fluid, which is in equilibrium with the blood. Glucose passively diffuses out of the cell down a concentration gradient via basolateral facilitative transporters, GLUT2 (and GLUT1) (24). Used with permission from The American Physiological Society.

250 mg/100 mL, has been exceeded, the SGLTs are saturated, meaning that the maximum capacity of the renal tubule for glucose reabsorption, the t_{max}, has been exceeded. Some of the filtered glucose is thus not reabsorbed, but is excreted in the urine (Fig. 3).

Patients with type 2 diabetes must contend with hyperglycemia and its glucotoxic effects due to significantly higher numbers of SGLT2 and glucose transporter type 2 (GLUT2), which also transport more glucose than in healthy individuals, as demonstrated in cultured PCT cells (14). These individuals with type 2 diabetes also

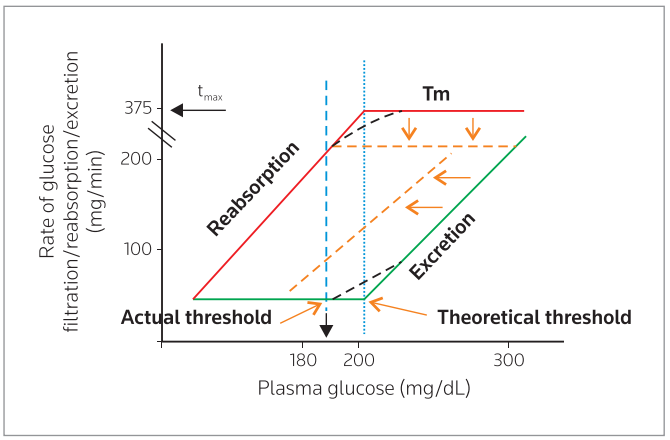


Figure 3. Renal glucose handling before and following inhibition of SGLT2. With gradual infusion of glucose, as the plasma glucose concentration increases, the reabsorption progressively increases following the line marked reabsorption curve (in red). At plasma glucose concentrations < 200 mg/dL, all the filtered glucose is reabsorbed and there is no excretion. When glucose reaches a threshold, around 200-250 mg/dL, the maximum capacity of the renal tubule to reabsorb glucose – or the t_{max} – is exceeded, and once it passes this, glucose begins to be excreted into the urine (green line, labeled "excretion"). The breaking point, however, is not abrupt –splay (the curved dotted lines between the actual and theoretical thresholds) represents glucose excretion in the urine before saturation (t_{max}) is fully attained, and is explained by some nephrons releasing glucose at a slightly lower threshold, some slightly higher, and the relatively low affinity of the sodium/glucose carriers. The dotted yellow lines depict renal glucose handling after SGLT2 inhibition. The SGLT2 inhibitors lower the t_{max} of glucose, which in turn increases the excretion of glucose via the kidneys (27). Reprinted from Endocrine Practice, Vol. 14, Abdul-Ghani, M., DeFronzo, R.A. *Inhibition of renal glucose reabsorption: a novel strategy for achieving glucose control in type 2 diabetes*, pp. 782-90, Copyright 2008, with permission from the American Association of Clinical Endocrinologists.

generate glycosuria as a result of overwhelming the renal capacity to reabsorb glucose. Although both unchecked hyperglycemia and the therapeutic inhibition of renal glucose reabsorption share the manifestation of glycosuria, only SGLT2 blockade involves decreasing the threshold for renal glucose excretion, which serves to reduce the level of hyperglycemia.

Phlorizin was first isolated from the root bark of the apple tree by French chemists in 1835. When given to rats who had undergone partial pancreatectomy to induce diabetes, this agent produced glycosuria, which normalized both fasting and postprandial plasma glucose levels (15). Insulin resistance was thus completely reversed. This agent was not further developed as a therapy for diabetes due to poor intestinal absorption, and thus low bioavailability. Phlorizin was also nonselective –it acts on both SGLT2 and SGLT1– and thus caused diarrhea, dehydration and malabsorption of both glucose and galactose. Other SGLT2 inhibitors, including T-1095, sergliflozin and remogliflozin, were not viable candidates, presumably secondary to unfavorable side effect and efficacy profiles.

PRECLINICAL PHARMACOLOGY

Canagliflozin is a C-glucoside with a thiophene ring. In preclinical studies, a single oral dose of 3 mg/kg of canagliflozin decreased plasma glucose levels independent of food intake in mice on a high-fat, hyperglycemic diet. In normoglycemic mice, canagliflozin administration led to a minimal change in plasma glucose levels. Canagliflozin had a longer plasma half-life and greater oral bioavailability compared with its predecessor T-1095 (4).

PHARMACOKINETICS AND METABOLISM

Limited information on these topics is available, as there is only one published paper on pharmacokinetics at present. Oral administration of canagliflozin at 30 mg/kg to male Sprague-Dawley rats resulted in glucose excretion over 24 hours of 3696 mg/200 g of body weight. After intravenous (i.v.) doses of 3 mg/kg and oral (p.o.) doses of 10 mg/kg, the $t_{1/2}$ (p.o.) was 5.2 hours, the area under the curve (AUC_{0-inf}) (p.o.) was 35,980 ng.h/mL and the oral bioavailability was 85% (4).

SAFETY

No deaths or serious adverse events, including severe hypoglycemic episodes, were reported in clinical studies. Generally, adverse events that were noted were mild to moderate in intensity, transient and balanced across the groups studied.

Rosenstock et al. (16) reported observing urinary tract infections at rates ranging from 3% to 9% across the canagliflozin arms, but this did not exhibit a dose-dependent relationship. Urinary tract infections were detected in 2% of the sitagliptin-treated and 6% of the placebo-treated groups. The 50 mg once daily, 100 mg once daily, 300 mg once daily and 300 mg b.i.d. arms included 64 subjects, and the 200 mg once daily and sitagliptin arms were each composed of 65 individuals. Schwartz et al. (17) found no urinary tract or genital infections. In a study in 40 obese male and 40 obese female volunteers by Sarich et al. (18), adverse events were generally noted to be mild to moderate and transient; no specific details on the nature of these events were provided, except for a specific report on one event: one female subject receiving canagliflozin 300 mg b.i.d. sustained an asymptomatic urinary tract infection post-treatment. There was a non-dose-dependent elevation in symptomatic genital infections in the Rosenstock study: 3-8% in the canagliflozin cohorts, 2% in the sitagliptin cohort and 2% in the placebo group. Schwartz et al. documented no genital infections. Sha et al. (19) reported one case of vaginal candidiasis. Hypoglycemia was present in 0-6% of the canagliflozin groups, 5% of those on sitagliptin and 2% of those on placebo in the Rosenstock study. Schwartz and his group found that 1 or more non-severe hypoglycemic events occurred in 12 of 29 subjects: 6 of 10 patients on canagliflozin 100 mg once daily, 3 of 10 subjects receiving canagliflozin 300 mg b.i.d. and 3 of 9 individuals administered placebo. No significant changes in vital signs, electrocardiogram or laboratory analyses were seen in the abstracts presented by Rosenstock, Sarich, Schwartz or Sha.

CLINICAL STUDIES

All clinical studies to date have been published in abstract form, and were presented at the 70th Scientific Sessions of the American Diabetes Association in June 2010. A phase I clinical trial by Sha et al. found that single doses of canagliflozin of 10, 30, 100, 200, 400, 600 and 800 mg once daily or 400 mg b.i.d. were well tolerated

(20, 21). The agent significantly increased urinary glucose excretion in a dose-dependent manner, with a maximum mean 24-hour urinary glucose excretion of 70 g at doses exceeding 200 mg –ranging from 5 g at 10 mg of canagliflozin to approximately 70 g at > 200 mg. The renal threshold for glucose excretion declined in a dose-dependent manner. The doses of 100 and 200 mg resulted in near-maximal reduction of the renal threshold during the first 13 hours after dosing.

Sha et al. also investigated the response to multiple doses of canagliflozin versus placebo –30, 100, 200 and 400 mg once daily or 300 mg b.i.d. after discontinuing the subjects' diabetes medications for 2 weeks (19). Volunteers had a mean age of 53 years, mean glycated hemoglobin (HbA1c) of 8% and a mean body weight of 91.8 kg; there were 27 females and 70 males. All individuals followed an isocaloric diet. In a dose-dependent manner, 24-hour urinary glucose excretion increased and the renal threshold for glucose excretion decreased. For placebo subjects, the change in 24-hour urinary glucose excretion was –10 g; for the subjects on 30 mg, 69 g; for 100 mg, 76 g; for 200 mg, 88 g; for 400 mg, 113 g; and for 300 mg b.i.d., 88 g ($P < 0.01$ compared with placebo for all canagliflozin arms). The mean 24-hour renal threshold for placebo declined from 241 mg/dL 1 day before dosing to 232 mg/dL on day 16; for the 30 mg group, it decreased from 259 mg/dL to 152 mg/dL; for 100 mg, from 243 mg/dL to 116 mg/dL; for 200 mg, from 247 mg/dL to 101 mg/dL; for 400 mg, from 261 mg/dL to 90 mg/dL; and for 300 mg b.i.d., from 240 mg/dL to 90 mg/dL. Weight decreased approximately 1-1.5 kg versus placebo.

The study by Rosenstock et al. evaluated 451 subjects with type 2 diabetes with inadequate glycemic control on metformin in a double-blind clinical study (16). Subjects were randomized to placebo, canagliflozin 50, 100, 200 or 300 mg once daily, 300 mg b.i.d. or sitagliptin 100 mg once daily. The changes in HbA1c at week 12 were statistically significant for all arms: –0.45% for 50 mg once daily; –0.51% for 100 mg once daily; –0.54% for 200 mg once daily; –0.71% for 300 mg once daily; –0.73% for 300 mg b.i.d.; and –0.56% for sitagliptin 100 mg once daily. Significant decreases in fasting plasma glucose were also observed, ranging from –16.2 mg/dL to –32.4 mg/dL. All canagliflozin arms demonstrated dose-related weight reductions, from –1.3% to –2.3%; there was a +0.4% increase in the sitagliptin group.

Canagliflozin was also studied in 29 subjects with type 2 diabetes not controlled on stable insulin doses (17). These patients had a body mass index of 32.3 kg/m^2 and a median age of 50 years; patients were studied at two centers and were assigned to 100 mg once daily or 300 mg b.i.d. of canagliflozin, or to placebo. HbA1c declined by 0.73% in the group given canagliflozin 100 mg once daily (–0.98 to –0.11, 90% confidence interval [CI]) and by 0.92% in those taking 300 mg once daily (–1.25 to –0.22, 90% CI); the placebo group showed a decrease of 0.19%. Fasting plasma glucose was –38.1 mg/dL on canagliflozin 100 mg once daily (–7.4 to –19.7, 90% CI) and –42.4 mg/dL (–80.7 to –21.6, 90% CI), compared with +8.7 mg/dL for placebo. Body weight also decreased: –0.7 kg (–1.44 to –0.08, 90% CI) and –1.2 kg (–2.21 to –0.23, 90% CI) in the groups treated with canagliflozin 100 mg once daily and 300 mg b.i.d., respectively. Placebo subjects showed no weight change. Urinary glucose excretion increased: +71.9 g/day (39.6-94.8, 90% CI) on canagliflozin 100 mg once daily and +129.2 g/day (125.2-181.9, 90% CI) on canagliflozin 300 mg b.i.d., compared to –3.2 g/day for placebo.

A multiple-ascending-dose study in 40 female and 40 male obese subjects on a fixed weight-maintaining diet found that body weight decreased at a statistically significant level for all but 1 group randomized to canagliflozin at day 14: –2.9 kg for 30 mg once daily ($P = 0.002$); –2.7 kg for 100 mg once daily ($P = 0.008$); –2.1 kg for 300 mg once daiy ($P = 0.13$); –3.4 kg for 600 mg once daily ($P < 0.0001$); and –3.5 kg for 300 mg b.i.d. ($P < 0.0001$) (18). While body weight decreased, no significant changes in self-reported satiety and appetite measures were noted. Canagliflozin significantly increased 24-hour urinary glucose excretion but did not alter fasting plasma glucose, mean 24-hour plasma glucose or insulin levels. Canagliflozin at 100 mg resulted in near-maximal lowering of the renal threshold for glucose excretion during the first 13 hours after dosing, and doses of 300 mg b.i.d. and 600 mg once daily yielded near-maximal lowering over 24 hours.

In the study by Rossetti et al., diminished beta cell function in rats was reversed when normal glucose levels were restored in hyperglycemic rats (15). A trial conducted by Polidori et al. examined canagliflozin to assess whether the same improvement could also be detected in human beta cells (22). In this 16-day study, beta cell function was assessed using a model-based method that determines the insulin secretion rate at specified plasma glucose concentrations using plasma glucose and C-peptide concentrations sampled frequently over a 24-hour period. The results showed significant improvement in the insulin secretion rate compared to placebo at doses of 100, 200 and 400 mg once daily and 300 mg b.i.d. (change from baseline to day 16: 94 ± 8, 86 ± 18, 94 ± 19 and 120 ± 23 pmol/min/m^2, respectively, at 10 mM glucose; 132 ± 12, 125 ± 19, 136 ± 26 and 163 ± 35 pmol/min/m^2, respectively, at 12 mM glucose). In a 12-week phase II trial in subjects with type 2 diabetes by the same investigators, beta cell function was assessed using HOMA2-B%. HOMA, the Homeostasis Model Assessment, is a computer model that predicts the steady-state (fasting) concentrations of plasma glucose and insulin that result from differing degrees of beta cell deficiency and insulin resistance. Steady-state beta cell function is expressed as B% = 20 x insulin/(glucose - 3.5), as a percentage of a normal reference population (25). An updated HOMA model (HOMA2) also accounts for factors such as hepatic glucose resistance (26). Again, significant improvement was observed compared to placebo (change from baseline to week 12: 14 ± 3, 15 ± 5, 18 ± 3 and 16 ± 3%, respectively, at 100 mg/day, 200 mg/day, 300 mg/day and 300 mg b.i.d.; sitagliptin 10 ± 5% at 100 mg/day; placebo 2 ± 2%).

DRUG INTERACTIONS

There are no published studies to date on potential drug interactions between canagliflozin and other medications. A study is under way to further investigate possible interactions between canagliflozin and warfarin.

CONCLUDING REMARKS

Canagliflozin is an SGLT2 inhibitor that is currently undergoing phase III clinical trials. Data from studies thus far have suggested

efficacy and a relatively low incidence of adverse effects, such as urinary tract infections and genitourinary fungal infections. Agents such as canagliflozin represent a potentially more appealing therapeutic approach, given that they do not act on insulin secretion. Further investigations are needed to examine the efficacy, safety and use of these SGLT2 inhibitors in treating diabetes.

SOURCES

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DISCLOSURES

The author states no conflicts of interest.

REFERENCES

1. Abdel-Magid, A.F., Chisholm, M., Mehrman, S. et al. (Janssen Pharmaceutica NV; Mitsubishi Tanabe Pharma Corp.). *Process for the preparation of compounds useful as inhibitors of SGLT*. CN 101801371, EP 2200606, JP 2010539092, WO 2009035969.
2. Ellsworth, B., Washburn, W.N., Sher, P.M., Wu, G., Meng, W. (Bristol-Myers Squibb Co.). *C-Aryl glucoside SGLT2 inhibitors and method.* EP 1506211, JP 2005531588, JP 2009275050, US 2002137903, US 6515117, WO 2003099836.
3. Nomura, S., Ueta, K., Kawanishi, E. (Mitsubishi Tanabe Pharma Corp.). *Novel compounds having inhibitory activity against sodium-dependant transporter.* EP 1651658, JP 2007518683, JP 2008266328, WO 2005012326.
4. Nomura, S., Sakamaki, S., Hongu, M. et al. *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.* J Med Chem 2010, 53(17): 6355-60.
5. Filliers, W.F.M., Broeckx, R.L.M., Nieste, P.H.J., Hatsuda, M., Yoshinaga, M., Yada, M. (Janssen Pharmaceutica NV; Mitsubishi Tanabe Pharma Corp.). *Process for the preparation of compounds useful as inhibitors of SGLT*. US 2010099883, WO 2010043682.
6. International Diabetes Foundation Diabetes Atlas. http://www.diabetesatlas.org/content/foreword. Accessed December 4, 2010.
7. Kaiser, N., Leibowitz, G., Nesher, R. *Glucotoxicity and beta-cell failure in type 2 diabetes mellitus.* J Pediatr Endocrinol Metab 2003, 16(1): 5-22.
8. Porte, D. Jr. *Clinical importance of insulin secretion and its interaction with insulin resistance in the treatment of type 2 diabetes mellitus and its complications*. Diabetes Metab Res Rev 2001, 17/3): 181-8.
9. Inzucchi, S.E. *Oral antihyperglycemic therapy for type 2 diabetes*. JAMA 2002, 287(3): 360-72.
10. Buse, J.B., Henry, R.R., Han, J., Kim, D.D., Fineman, M.S., Baron, A.D.; Exenatide-113 Clinical Study Group. *Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes*. Diabetes Care 2004, 27(11): 2628-35.
11. Wright, E.M. *Renal Na(+)-glucose cotransporters.* Am J Physiol Renal Physiol 2001, 280(1): F10-18.
12. Wright, E.M., Turk, E. *The sodium/glucose cotransport family SLC5*. Pflugers Arch 2004, 447(5): 510-8.
13. Lee, Y.J., Han, H.J. *Regulatory mechanisms of Na+/glucose cotransporter in renal proximal tubule cells.* Kidney Int Suppl 2007, 106: S27-35.
14. Rahmoune, H., Thompson, P.W., Ward, J.M., Smith, C.D., Hong, G., Brown, J. *Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes*. Diabetes 2005, 54(12): 3427-34.
15. Rossetti, L., Smith, D., Shulman, G.I., Papachristou, D., DeFronzo, R.A. *Correction of hyperglycemia with phlorizin normalizes tissues sensitivity to insulin in diabetic rats*. J Clin Invest 1987, 79(5): 1510-5.
16. Rosenstock, J., Arbit, D., Usiskin, K. *Canagliflozin, an inhibitor of sodium glucose co-transporter 2 (SGLT2), improves glycemic control and lowers body weight in subjects with type 2 diabetes (T2D) on metformin.* Diabetes [70th Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 25-29, Orlando) 2010] 2010, 59(Suppl. 1): Abst 77-OR.
17. Schwartz, S., Morrow, L., Hompesch, M. et al. *Canagliflozin improves glycemic control in subjects with type 2 diabetes (T2D) not optimally controlled on stable doses of insulin*. Diabetes [70th Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 25-29, Orlando) 2010] 2010, 59(Suppl. 1): Abst 564-P.
18. Sarich, T., Damayanthi, D., Ghosh, A. et al. *Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2 (SGLT2), increases 24-h urinary glucose excretion and decreases body weight in obese subjects.* Diabetes [70th Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 25-29, Orlando) 2010] 2010, 59(Suppl. 1): Abst 567-P.
19. Sha, S., Damayanthi, D., Ghosh, A. et al. *Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2, improved glucose control in subjects with type 2 diabetes and was well tolerated.* Diabetes [70th Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 25-29, Orlando) 2010] 2010, 59(Suppl. 1): Abst 568-P.
20. Sha, S., Damayanthi, D., Ghosh, A. et al. *Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2, induces dose-dependent urinary glucose excretion in healthy subjects.* Diabetes [70th Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 25-29, Orlando) 2010] 2010, 59(Suppl. 1): Abst 76-OR.
21. Sha, S., Devineni, D., Ghosh, A. et al. *Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2, dose-dependently reduces calculated renal threshold for glucose excretion and increases urinary glucose excretion in healthy subjects*. Diabetes Obes Metab 2011, Epub ahead of print.
22. Polidori, D., Zhao, Y., Sha, S., Canovatchel, W. *Canagliflozin treatment improves beta cell function in subjects with type 2 diabetes.* Diabetes [70th Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 25-29, Orlando) 2010] 2010, 59(Suppl. 1): Abst 646-P.
23. Bays, H. *From victim to ally: The kidney as an emerging target for the treatment of diabetes mellitus*. Curr Med Res Opin 2009, 25(3): 671-81.
24. Hediger, M.A., Rhoads, D.B. *Molecular physiology of sodium-glucose cotransporter*. Physiol Rev 1994, 74(4): 993-1026.
25. Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F., Turner, R.C. *Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man*. Diabetología 1985, 28(7): 412-9.
26. Wallace, T.M., Levy, J.C., Matthews, D.R. *Use and abuse of HOMA modeling*. Diabetes Care 2004, 27(6): 1487-95.
27. Abdul-Ghani, M., DeFronzo, R.A. *Inhibition of renal glucose reabsorption: A novel strategy for achieving glucose control in type 2 diabetes.* Endocr Pract 2008, 14(6): 782-90.