**A safety evaluation of Canagliflozin: a first in class treatment for Type 2 Diabetes**

**Luke D. Boyle, John P.H. Wilding**

Address Correspondence to John PH Wilding:

John P H Wilding

Department of Obesity & Endocrinology

University of Liverpool

Clinical Sciences Centre

University Hospital Aintree

Longmoor Lane

Liverpool L9 7AL

Tel: +44 151 529 5885

Fax +44 151 529 5888

Email: j.p.h.wilding@liv.ac.uk

Abstract

**Introduction:** Type 2 diabetes mellitus (T2DM)is a public health challenge globally. Numerous treatments are available which can improve insulin sensitivity or stimulate its secretion including biguanides, sulphonylureas, and glitazones; as well as insulin, GLP-1 agonists and DPP-IV inhibitors. These are usually unable to halt progression with high resulting morbidity and mortality. New therapies are therefore being developed; inhibition of glucose reabsorption from the renal filtrate was proposed as a novel therapeutic target, and sodium/glucose co-transporter 2 (SGLT2) inhibitors were developed accordingly, with canagliflozin the first to launch in the US in 2013.

**Areas covered:** This evaluation includes a description of the mechanism of action of canagliflozin and summarises its pharmacokinetic data, before describing its clinical applications and efficacy data from clinical studies of both subjects with T2DM controlled on diet and exercise, and those on glucose-lowering agents and insulin. The evaluation focuses primarily on the safety of canagliflozin mainly in clinical trials conducted for initial registration due to very little postmarketing data available, and discusses its safety in special populations, before comparing its safety with existing therapies wherever such comparisons are possible.

**Expert opinion:** Canagliflozin offers a novel therapeutic approach to management of T2DM; advantages over other agents include weight loss and blood pressure lowering with a low intrinsic risk of hypoglycaemia. The main adverse effects likely to be seen in clinical practice are a very small increase in risk of urinary tract infections, and a modest risk of developing genital fungal infections. Studies suggest no increased risk of CV disease, but longer duration outcome studies are essential to prove long-term safety and efficacy.

Keywords

Canagliflozin, Safety, SGLT2, Type 2 Diabetes

Introduction

Type 2 diabetes mellitus (T2DM) is a rapidly growing public health challenge now at epidemic levels. The global prevalence of the disease is estimated at 285 million people, which represents 6.4% of the world’s adult population.

The general management of T2DM firstly involves patient education on diet & physical activity. Review of blood pressure and lipids is also essential and these should be appropriately treated if not responsive to lifestyle modification. Glucose control is assessed using glycated haemoglobin monitoring (HbA1c) – aiming for below 6.5% (48mmol/mol) in most newly diagnosed patients, although less stringent targets (7.5% (58mmol/mol) may be appropriate later in the course of the disease, particularly if complications have already developed. If this is inadequate, then pharmacotherapy and ultimately insulin therapy is recommended to help the patient reach glycaemic targets. In clinical practice, the first step is monotherapy – if the patient is overweight or obese, metformin is usually commenced, if not, either metformin or a sulphonylurea can be considered. A glitazone (pioglitazone), a DPP-IV inhibitor or a GLP-1 analogue can also be considered at this stage, particularly if metformin is contraindicated or not tolerated. Failing this, a dual or triple combination therapy can be employed. If inadequate glycaemic control persists on combination therapy, insulin is used and titrated up over time.1 A recent estimate suggesting that fewer than half of all patients with T2DM achieve adequate disease control suggests that novel treatment approaches are needed. The inhibition of glucose reabsorption the kidney was identified as one such solution, for two major reasons outlined below. Sodium/glucose co-transporter 2 (SGLT2) is a 672 amino-acid transmembrane protein responsible for the vast majority of glucose reabsorption by the nephron; the remainder is absorbed via SGLT1, a more widely expressed transporter that is also responsible for gut glucose absorption.

Familial Renal Glucosuria (caused by defects in the SGLT2 transporter gene, SLC5A2) can lead to significant glucosuria; up to 134g/day has been reported.32 Interestingly, most patients with this condition remain asymptomatic, typically reporting only polyuria, or they are diagnosed when glycosuria is found as an incidental finding,.[33](#_ENREF_16" \o "Lee, 2012 #147) Interestingly, Powell et al. have recently reported improved glycaemic control in SGLT2 knockout mice.[34](#_ENREF_17) It is therefore possible that humans lacking SGLT2 may have improved glycemic control, although this has not been formally tested.

The O-glycoside phlorizin originates from apples and the bark of the trees on which they grow – naturally it has become a component of the human diet. In 1886 it was reported to cause glucosuria and in the 1930s it was first used to investigate renal physiology. It has since been shown to lower glucose in experimental diabetes, with an effect independent of insulin. In 1987 phlorizin was used to show that correction of hyperglycaemia restores insulin sensitivity.[35](#_ENREF_18) Phlorizin is now known to be a non-specific inhibitor of SGLT1 and SGLT2, which together with its poor oral bioavailability, prevented the development of phlorizin as a therapy.. It is however on phlorizin that most SGLT2 inhibitors including canagliflozin are principally based.

Mechanism of action

 In non-diabetic individuals the kidney contributes up to 20% of gluconeogenesis (more post-prandially), uses approximately 10% of total body glucose and filters and reabsorbs up to approximately 180g of glucose per day. After filtering into the nephrons through the glomeruli, most of this glucose load is reabsorbed in the proximal convoluted tubule. Approximately 90% is reabsorbed in the S1 segment of the proximal convoluted tubule, with the remainderreabsorbed in theS2 and S3 segments before the filtrate reaches the Loop of Henle. Figure 1 illustrates this process.1

 **Negligible glucose**

 **in urine**

**Collecting duct**

**Glucose**

**SGLT2**

**SGLT1**

**S1 segment of**

**proximal tubule**

**Most**

**Glucose reabsorption**

**Remainder**

**Distal S2/3**

**segment of**

**Proximal tubule**

**FIGURE 1** Glucose reabsorption in the nephron

 The sodium/glucose co-transporters (SLC5 gene family), are active transporters, driving glucose reabsorption by the sodium gradient maintained by the Na+-K+ ATPase of the basal membrane. SGLT1 and SGLT2 are responsible for intestinal and renal glucose reabsorption respectively. SGLT1 is expressed mostly in the intestine (for dietary glucose absorption) with some found in the kidney, whereas SGLT2 is found almost exclusively in the kidney (for renal glucose absorption). These transporters differ in two other respects; unlike SLGT1, SGLT2 is specific for glucose (SGLT1 binds both glucose and galactose), and SGLT2 has a much higher capacity for transport than SGLT1. SGLT2 is responsible for reabsorption of almost all filtered glucose. Canagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor and a low-potency SGLT1 inhibitor, reducing glucose absorption in the intestine by 6% due to activity on SGLT1 in one study.1

***Pharmacokinetics***

Following oral administration, the median time to peak plasma concentration is 1-2hr and mean bioavailability is approximately 65%. Administration with a high-fat meal has no effect on the pharmacokinetics of canagliflozin. The area under the curve and peak concentrations increase in a dose-dependent manner. Steady state is reached in 4 to 5 days, and the steady-state volume of distribution is 119 L in healthy people. Canagliflozin is 99% bound to plasma proteins, mainly albumin. The elimination half-life is 10.6 and 13.1 hours for the 100 and 300 mg doses, respectively. Canagliflozin is metabolized primarily by glucuronidation via uridine diphosphate glucuronosyltransferase (UGT) 1A9 and UGT2B4 to 2 inactive metabolites. Approximately 7% of canagliflozin is oxidized by cytochrome P450 3A4. Following a single oral dose of radiolabeled canagliflozin, 41.5%, 7%, and 3.2% were recovered in the faeces as canagliflozin, a hydroxylated metabolite, and an O-glucuronide metabolite, respectively. Approximately 33% of the dose was recovered in urine, 30.5% as O-glucuronide metabolites and less than 1% as unchanged canagliflozin.2 3

Clinical applications and efficacy

Canagliflozin (Invokana®; Janssen Research and Development, LLC, Raritan, NJ, USA; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) was FDA approved on 29 March 2013 to be used with diet and exercise, to improve glycaemic control in adults with T2DM on the basis of the data generated from the clinical studies described below; it was subsequently approved in the European Union in October 2013.4 To date there have been fewer than ten major studies to evaluate the clinical efficacy and safety of canagliflozin – two in subjects with T2DM controlled by diet and exercise, with the others involving patients using oral agents or insulin.

***In subjects with T2DM controlled by diet and exercise***

In a 26-week, randomized, double blind, placebo-controlled, phase 3 trial, 584 subjects received canagliflozin 100 or 300 mg or placebo once daily. Stenlöf et al. reported significant reductions in HbA1c from baseline with canagliflozin 100 and 300 mg compared with placebo (−0.77, −1.03 and 0.14%, respectively; p < 0.001 for both). Both canagliflozin doses significantly decreased FPG, 2 hour post prandial glucose, body weight and systolic BP (p < 0.001 for all), and increased HDL-C compared with placebo (p < 0.01 for both).5 Inagaki et al. replicated these findings in a Japanese population, using a 12-week, randomised, double blind, placebo-controlled study of 383 patients aged between 20-80. Significant reductions in HbA1c were observed in all canagliflozin groups relative to placebo (−0.61, – 0.80, – 0.79 and −0.88% for 50, 100, 200 and 300 mg, respectively, versus +0.11% for placebo; all, p < 0.01). FPG and postprandial glycaemic parameters improved significantly in the canagliflozin groups. Body weight was significantly decreased.6

***In subjects with T2DM and taking oral agents or insulin***

 Yale et al. evaluated the efficacy and safety of canagliflozin in 269 subjects with T2DM and stage 3 chronic kidney disease (CKD3) using a randomized, double blind, placebo-controlled, phase 3 trial. Both canagliflozin 100 and 300mg reduced HbA1c from baseline compared with placebo at week 26 (–0.33, –0.44 and –0.03%; p < 0.05). Numerical reductions in FPG and higher proportions of subjects reaching HbA1c < 7.0% were observed with canagliflozin 100 and 300mg versus placebo (27.3, 32.6 and 17.2%).7 In a study of canagliflozin as an add-on to metformin in patients with T2DM (see Table 1) canagliflozin was associated with significant reductions in A1C from baseline (7.6–8.0%) to week 12: 0.79, 0.76, 0.70, 0.92, and 0.95% for canagliflozin 50, 100, 200, 300 mg QD and 300 mg BID, respectively, versus 0.22% for placebo (all P < 0.001) and 0.74% for sitagliptin. FPG was reduced by 216 to 227 mg/dL, and body weight was reduced by 2.3 to 3.4%.8 In the study by Lavalle-González et al. (Table 1), at week 26, canagliflozin 100 mg and 300 mg reduced HbA1c vs placebo (−0.79%, –0.94%, –0.17%, respectively; p < 0.001). At week 52, canagliflozin 100 mg and 300 mg demonstrated non-inferiority, and canagliflozin 300 mg demonstrated statistical superiority, to sitagliptin in lowering HbA1c (−0.73%, –0.88%, –0.73%, respectively); differences (95% CI) vs sitagliptin were 0% (−0.12, 0.12) and −0.15% (−0.27, –0.03), respectively. Canagliflozin 100 mg and 300 mg reduced body weight vs placebo (week 26: –3.7%, –4.2%, –1.2%, respectively; p < 0.001) and sitagliptin (week 52: –3.8%, –4.2%, –1.3%, respectively; p <0.001). Both canagliflozin doses reduced FPG and systolic BP vs placebo (week 26) and sitagliptin (week 52) (p <0.001).9

Safety evaluation

***Safety in clinical studies***

Stenlöf et al. reported the overall incidence of AEs as modestly higher for subjects treated with canagliflozin compared with placebo, with incidence of serious AEs low across treatment groups. Ten subjects in the canagliflozin groups (2.6%) discontinued treatment due to AEs, compared with two subjects (1.0%) in the placebo group; no single AE term accounted for more than a single discontinuation. Two deaths occurred during the treatment period (one with placebo and one with canagliflozin 100 mg); neither was considered to be drug-related. The incidence of genital mycotic infections was higher in both males and females with canagliflozin compared with placebo; these AEs were generally mild to moderate in severity, treated with topical and/or oral antifungal therapies and resolved without interruption of study drug treatment. There was a modest increase in lower UTIs with canagliflozin 100 and 300 mg compared with placebo, no upper UTIs, and all were mild to moderate in severity – none led to study discontinuation. AEs related to osmotic diuresis and reduced intravascular volume were ≤3.0% and led to few study discontinuations. The percentage of subjects with documented hypoglycaemia was similar with canagliflozin 100 and 300mg and placebo (3.6, 3.0 and 2.6%, respectively), with no report of severe hypoglycaemia. Interestingly, modest improvements in indices of liver function, including alanine aminotransferase (ALT) and alkaline phosphatase, were observed with canagliflozin relative to placebo.5

No deaths or drug-related serious AEs were reported and incidence of hypoglycaemia was low in the study by Inagaki et al. There was no dose-dependent increase in the incidence of AEs or hypoglycaemia in the canagliflozin groups. Specifically, overall 266 AEs occurred in 169 patients, including 43 AEs in 26 (34.7%) patients in the placebo group, 52 AEs in 37 (45.1%) patients in the 50 mg group, 60 AEs in 34 (45.9%) patients in the 100 mg group, 61 AEs in 38 (49.4%) patients in the 200mg group and 50 AEs in 34 (45.3%) patients in the 300 mg group. AEs leading to study discontinuation occurred only in 0 – 2 patients across the groups (lung adenocarcinoma, pollakiuria, oral discomfort and pruritus). Most of the AEs were mild; only one serious AE occurred (lung adenocarcinoma in one patient in the 50 mg group). Five patients with treatment- emergent AEs withdrew from the study although, in one of these, the primary reason for withdrawal was disease progression. The AEs reported in >3% patients were nasopharyngitis, increased blood ketone bodies, hypoglycaemia unawareness, hypoglycaemia, gastritis, periodontitis, upper respiratory tract infections and malaise, but there was no dose-dependent trend. Two vulvovaginal infections were reported in the canagliflozin group (one each of vulvovaginal candida infection in the 100 and 300mg groups). Volume-related AEs (dry mouth, dehydration, dizziness and palpitation) were reported in 0–3 patients in the canagliflozin groups and in 1 patient in the placebo group. Pollakiuria was reported in three patients in the canagliflozin groups and in none of the patients in the placebo group. No urinary tract infections were reported in any group. No clinically meaningful changes in electrocardiograms were observed, and there were no cardiovascular events. Although canagliflozin was associated with a decrease in blood pressure, no postural hypotension was reported. No clinically meaningful changes in serum electrolytes were observed in any of the groups. There were no remarkable changes in serum creatinine or the urinary albumin/creatinine ratio, suggesting that canagliflozin did not impair kidney function. Small increases in urinary N-terminal cross- linked telopeptide of type I collagen levels and serum C-terminal cross-linked telopeptide of type I collagen levels together with slight decreases in bone-specific alkaline phosphatase and 1,25-(OH)2 vitamin D levels from baseline to week 12 were reported in the canagliflozin groups. The clinical relevance of these small changes is unknown and there were no AEs suggestive of changes in bone-related markers.6

In a randomised, double blind placebo-controlled multicentre trial by Wilding et al. presented in 2012, 469 adult patients with T2DM inadequately controlled with metformin and a sulphonylurea were given oral canagliflozin 100 or 300mg/day or placebo for 26 weeks. The overall incidence of adverse events did not differ between groups; however, the canagliflozin treated patients experienced a higher incidence of genital fungal infections (18.7% vs 3.8% in women and 4.9% vs 1.3% in men). More patients in the canagliflozin groups also experienced hypoglycaemia (28.8% vs 15.4%). In another similar, but much smaller study involving only 29 patients, Devineni et al. reported that symptomatic hypoglycaemia occurred in 6 patients on canagliflozin 100mg, 3 patients in the 300mg group, and 3 patients in the placebo group. None of these hypoglycaemic episodes were classed as severe or serious.2

Canagliflozin treatment has been associated with several changes in fasting plasma lipids, including increases in HDL-Cholesterol and decreases in triglycerides, and increases in LDL-Cholesterol.

In the FDA analysis, the placebo-subtracted mean absolute change from baseline for LDL-C was 4.36 mg/dL and 8.15 mg/dL, for the canagliflozin 100 mg and 300 mg groups, respectively, equating to mean percent changes from baseline were 4.5% and 8.0%, respectively. In 52 week studies, no consistent further increases in LDL-C were observed from weeks 26 to 52. Further analysis by subgroup including by age, sex, race, BMI, eGFR, baseline statin use, and baseline LDL-C by tertile suggested that these subgroup factors had no meaningful impact on the change from baseline in LDL-C with canagliflozin. A post-hoc analysis was also conducted to determine if response to statin medications was altered in subjects on canagliflozin, which suggested no substantive differences in response to statin in subjects in the canagliflozin relative to the non-canagliflozin group.

The canagliflozin 2-year rat carcinogenicity study described an increase in LCTs, phaeochromocytomas, and renal tubular cell tumours; however the mechanistic toxicology program showed that the increase in LCTs was related to increased LH seen in canagliflozin-treated rats (an increase in LH is a well established mechanism of tumorigenesis in the rat); this rise in LH is not seen in clinical studies. The increase in phaeochromocytomas and RTTs was related to the induction of carbohydrate malabsorption and its metabolic consequences (canagliflozin does not cause significant carbohydrate malabsorption in humans). In addition, reports from the dapagliflozin, another SGLT2 inhibitor, showed a numerical imbalance in the occurrence of breast and bladder cancer events, therefore a careful assessment of the occurrence of these tumours has been conducted. These tumour adverse events occurred at a low and similar incidence across treatment groups in all studies to date, in fact few events of breast, bladder, or renal cancer and no events of phaeochromocytoma or LCTs were reported in the Phase 3 clinical program, correct as of 15 Nov 2012. There has been no meaningful imbalance in the events of breast, bladder, and renal cancers in the data reported since.

***Postmarketing data***

 Since Canagliflozin (Invokana®; Janssen Research and Development, LLC, Raritan, NJ, USA; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) was only relatively recently FDA approved (on 29 March 2013) to improve glycaemic control in adults with T2DM, little postmarketing data is available. However, the FDA is requiring five post-marketing studies for canagliflozin, including a CV outcomes trial, an enhanced pharmacovigilance programme (monitoring for malignancy, severe pancreatitis, severe hypersensitivity reactions, photosensitivity reactions, liver abnormalities, and adverse pregnancy outcomes), a bone safety study, and two paediatric studies.4 All of this data is awaited with interest.

***Safety in special populations***

 Three special populations in particular must be considered carefully when evaluating the safety of a novel antidiabetic agent; patients with chronic kidney disease (CKD), due to the large numbers of patients with T2DM who develop diabetic nephropathy & particularly relevant for agents where the kidney is the main site for drug action, elderly patients, since the risks of hypoglycaemia and postural hypotension are higher (and consequences often more serious) in this population, and they are more likely to have bone disease. In fact all patients with T2DM have an increased risk of bone fractures, for reasons yet to be fully understood, which can be amplified by some oral antidiabetic agents e.g. thiazolidinediones. Therefore, it is also important to assess the effects of SGLT2 inhibitors on bone structure and function.4

 Yale et al. found that in their cohort of patients with CKD stage 3, overall AE rates were similar for canagliflozin 100 and 300 mg and placebo (78.9, 74.2 and 74.4%). The overall incidence serious AEs and study discontinuations due to AEs was similar for canagliflozin 100 and 300 mg and placebo.

Canagliflozin was associated with higher rates of genital mycotic infections in males and females compared with placebo, but incidences were low across groups and none led to study discontinuation. The incidence of UTIs was higher with canagliflozin 300 mg compared with canagliflozin 100 mg and placebo, with no upper UTI AEs reported. All UTIs were considered mild or moderate in severity, with none leading to study discontinuation. Incidences of pollakiuria and AEs related to reduced intravascular volume (i.e. postural dizziness and orthostatic hypotension) were increased with canagliflozin 300mg relative to canagliflozin 100mg and placebo; these were low across groups, generally mild or moderate in intensity and infrequently led to discontinuation. There was no report of polyuria (increased urine volume) in any group.

Most subjects (96.3%) were on background therapy associated with an increased risk of hypoglycaemia (i.e. insulin or sulphonylurea agents). Among these subjects, the proportion with documented hypoglycaemia episodes was higher with canagliflozin 100 and 300 mg (52.9 and 51.2%, respectively) compared with placebo (36.4%). Six subjects experienced severe hypoglycaemia episodes [4 (4.7%), 1 (1.2%) and 1 (1.1%) with canagliflozin 100 and 300 mg and placebo, respectively]. There were no documented hypoglycaemia episodes reported among subjects who were not on insulin or a sulphonylurea agent.

Overall, only small differences in safety laboratory parameters were observed with canagliflozin 100 and 300 mg relative to placebo. At week 26, similar increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed with canagliflozin 100 mg (mean percent changes of 10.1 and 5.5%, respectively) and placebo (8.2 and 4.3%, respectively), whereas decreases were seen with canagliflozin 300 mg (–4.4 and –4.3%, respectively). Increases in serum magnesium were seen with canagliflozin 100 and 300 mg, whereas no change was observed with placebo (mean percent changes of 9.1, 14.6 and 0.0%, respectively). Dose-related increases in serum phosphate were seen with canagliflozin 100 and 300 mg compared with placebo (mean percent changes of 4.9, 9.5 and 1.0%, respectively). Canagliflozin 100 and 300 mg were associated with non–dose- related increases in haemoglobin compared with a minimal change with placebo (mean percent changes of 5.3, 3.1 and –0.5%, respectively); corresponding changes in haematocrit were observed (mean percent changes of 6.0, 4.8 and –0.1%, respectively).

Changes in renal function parameters were observed with both canagliflozin doses compared with placebo. Transient decreases in eGFR from baseline were observed in all treatment groups and were larger in the canagliflozin 100 and 300 mg groups relative to the placebo group: mean percent changes of –9.1, –10.1 and –4.5%, respectively. The reductions in eGFR with canagliflozin were largest at week 3 (the first post baseline measurement) and then trended back towards baseline over the 26-week treatment period. Increases in BUN were observed with canagliflozin 100 and 300 mg compared with placebo (mean percent changes of 12.1, 12.5 and 4.9%, respectively); these increases also occurred early and then trended towards baseline over the remaining treatment period. Canagliflozin 100 and 300 mg were associated with greater decreases in urine ACR compared with placebo, with median percent reductions of –29.9, –20.9 and –7.5%, respectively. Progression of albuminuria from baseline to week 26 was examined, with a lower proportion of subjects in the canagliflozin 100 and 300 mg groups progressing relative to those in the placebo group (5.1, 8.3 and 11.8%, respectively).7

Bode et al looked at the use of canagliflozin in an elderly population (ages 55–80 years) with T2DM uncontrolled by their current glucose-lowering regimen. This regimen could include any oral hypoglycaemic agent or injectable treatment (including insulin). This randomized double-blind phase III trial was completed over 26 weeks and is currently being followed with a 78 week extension period. Patients were randomized to receive canagliflozin 100 mg daily, 300 mg daily, or placebo. Rates of any AE were similar between the canagliflozin 100 mg group and placebo at 174 incidents each, but were slightly higher in the canagliflozin 300 mg group, with 184 incidents reported. A higher rate of mycotic infections was seen in the canagliflozin 100 mg and 300 mg groups compared to placebo with 22, 20, and 2 events, respectively, being reported. Pollakiuria was reported in five, six, and 12 cases and polyuria was observed in zero, four, and four subjects in the placebo, canagliflozin 100 mg, and canagliflozin 300 mg groups, respectively. Discontinuation due to any AE occurred in ten patients receiving placebo, five receiving canagliflozin 100 mg daily, and in 17 receiving canagliflozin 300 mg daily. As expected, hypoglycemia was seen more often in participants on multiple antidiabetic agents, including a slightly higher incidence in the canagliflozin 100 mg and 300 mg compared with placebo at 66, 76, and 82 events, respectively. There were no clinically significant changes in laboratory markers between study groups. Based on this trial, canagliflozin may be a reasonable option for elderly patients without cardiovascular disease.3

Relative to placebo, treatment with canagliflozin resulted in increases in bone resorption markers, beta-CTx (17.1% to 24.9%) and small decreases in the bone formation marker, procollagen type 1 N-terminal propeptide (P1 NP) (−5.7% to −6.9%), which was also found with dapagliflozin use in the general population. These changes in bone markers are similar to those changes seen with pioglitazone use, which resulted in increases in beta-CTx of 16.8% without decreases in P1 NP. However, there is no increase in the incidence of fracture compared to placebo. Dual-energy X-ray absorptiometry (DEXA) scan results with canagliflozin use showed minimal changes in bone mineral density (BMD) at the lumbar spine, distal forearm, femoral neck, and total hip. In contrast, pioglitazone, is known to have an increased rate of fractures of 5.1% over one year compared to 2.5% in those treated with placebo therapy.4

***Comparison with the safety of other agents***

A number of the clinical studies evaluating the efficacy of canagliflozin against existing therapies have made direct comparison of its safety compared with that of other agents possible – the safety data provided by these studies is summarised in Table 1.

**TABLE 1 Comparison of the safety of canagliflozin with that of other agents**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Design** | **Comparison agent** | **Adverse events** |
| Rosenstock et al.8 | Double-blind, placebo-controlled, parallel-group, multicentre, dose-ranging study in 451 subjects randomized to canagliflozin 50, 100, 200, or 300 mg once daily (QD) or 300 mg twice daily (BID), sitagliptin 100 mg QD, or placebo.  | Sitagliptin | Adverse events were transient, mild to moderate, and balanced across arms except for a non dose-dependent increase in symptomatic genital infections with canagliflozin (3–8%) versus placebo and sitagliptin (2%). Urinary tract infections were reported without dose dependency in 3–9% of canagliflozin, 6% of placebo, and 2% of sitagliptin arms. Overall incidence of hypoglycaemia was low.  |
| Lavalle-González et al.9 | Randomised, double blind, four-arm, parallel-group, Phase 3 study conducted at 169 centres in 22 countries between April 2010 and August 2012. Participants (N = 1,284) with T2DM aged ≥18 and ≤80 years who had inadequate glycaemic control (HbA1c ≥7.0% [53 mmol/mol] and ≤10.5% [91 mmol/mol]) on metformin therapy received canagliflozin 100 mg or 300 mg, sitagliptin 100 mg, or placebo (n =368, 367, 366, 183, respectively) for a 26 week, placebo- and active-controlled period followed by a 26 week, active-controlled period (placebo group switched to sitagliptin [placebo/sitagliptin]) and were included in a modified intent-to-treat analysis.  | Sitagliptin | Overall AE and AE-related discontinuation rates were generally similar across groups, but higher with canagliflozin 100mg. Genital mycotic infection and osmotic diuresis related AE rates were higher with canagliflozin; few led to discontinuations. Hypoglycaemia incidence was higher with canagliflozin.  |
| Cefalu et al.2 | 1,450 patients with T2DM inadequately controlled with metformin. Mean age was 56.2 years, mean HbA1c was 7.8%, mean FPG was 9.2 mmol/L, and mean body weight was 86.6 kg. Intervention: Canagliflozin 100 or 300 mg orally once daily or glimepiride at a titrated dose (mean, 5.6 mg) orally once daily for 52 weeks.  | Glimepiride | Overall incidence of adverse events did not differ between groups; however, the canagliflozin-treated patients experienced a higher incidence of genital fungal infections (14.3% with canagliflozin 100 mg and 23.8% with canagliflozin 300 mg vs 3.7% with glimepiride in women; 6.7% and 8.3% vs 1.1%, respectively, in men), UTIs (6.4% with both doses of canagliflozin vs 4.4% with glimepiride), and osmotic diuresis related adverse events (all less than 3%).  |
| Gross et al.2 | Randomized, double blind, active- controlled, multicentre study with 755 patients with T2DM inadequately controlled with metformin plus a sulfonylurea (mean age 56.7 years, mean HbA1c 8.1%, mean FPG 9.3 mmol/L and mean body weight 88.3kg)given oral canagliflozin 300mg once daily or sitagliptin 100mg once daily for 52 weeks.  | Sitagliptin | Overall adverse event rates were similar; however, superficial genital fungal infections were more common with canagliflozin (15.3% in the canagliflozin group vs 4.3% in the sitagliptin group in women; 9.2% vs 0.5% in men). Rates of UTIs and hypoglycaemia did not differ. |
| Schernthaner |  |  |  |

Conclusion

Canagliflozin has been associated with improved glycaemic control, lower fasting and post-prandial glucose levels, improved blood pressure control and body fat loss in large randomized-controlled trials. It can also be used with existing therapies with solid evidence of safety and efficacy. It is likely to take a significant role in the treatment of T2DM in the coming years, but must be used judiciously in combination therapy as second or third line treatments until concerns about its propensity to cause genital and urinary tract infections, and cardiovascular safety as well as efficacy in patients with CKD has been evaluated further.

Expert Opinion

 The primary advantage canagliflozin confers over other oral therapies is that of weight loss, which although modest, is approximately equivalent to what is seen with GLP1 receptor agonists. A low intrinsic risk of hypoglycaemia and reductions in blood pressure are also potential advantages. The fact that the mode of action that is independent of insulin allows use across the time course of type 2 diabetes, including in combination with insulin

 It is very unlikely that given the efficacy and safety of metformin that canagliflozin would be commonly used as first line agent, except in those with metformin intolerance It is more likely that canagliflozin would be most frequently used as a second line agent in combination with existing therapies, including insulin.

 The side effect profile could be considered generally favourable aside from an increased risk of genital and urinary tract infections, nevertheless there are some areas of potential concern that will require ongoing scrutiny. Perhaps the most important of these relates to the (as yet unexplained) effects on lipids, particularly the dose-dependent increase in LDL cholesterol. This has also been seen with other agents in the class so seems intrinsic to the mode of action. The reduction in blood pressure may potentially reduce CV risk, but the risk of postural hypotension in volume depleted patients, and the possibility of an increased thromboembolic risk, particularly during the early period of treatment where volume depletion appears to be most apparent is also a potential concern. The outcome data to date is reassuring, but only the planned long-term prospective studies can provide a definitive answer.The data we await with most interest is specifically on the CV safety of canagliflozin – this is coming with the CANVAS trial (primary endpoints: CV death, MI, stroke), which has already recruited 4,330 patients with T2DM. Additional data on the efficacy and potential renoprotective effects of canagliflozin in patients with CKD is also important, although it seems unlikely that the agent will ever be of use in those with more advanced renal disease (CKD 4 and above), given that its mode of action is dependent on GFR. The effects on bone markers and fracture risk described above also require ongoing observation and study.

 The next 5 years may herald further interest in the efficacy and safety of SGLT1 blockade or dual blockade of SGLT1 and SGLT2, SGLT1 inhibition presents additional challenges and as it is more widely expressed than SLGT2, particularly as high level of inhibition seems likely to result in significant GI side effects. However the evidence that canagliflozin does weakly inhibit SGLT1 and that this might make a small contribution to its glucose-lowering effect suggests that this concept can be explored further. Combination preparations with existing therapies are gaining favour because of the large numbers of medicines taken by many people with diabetes; a combination preparation of canagliflozin and metformin is already in development and may well prove popular amongst prescibers and patients.

Drug Summary Box

|  |  |
| --- | --- |
| Drug name | Canagliflozin |
| Phase | FDA Approved |
| Indication | Type 2 Diabetes – second line combination agent |
| Mechanism of action | Inhibition of kidney sodium/glucose co-transporter 2, reducing glucose reabsorption from the renal filtrate |
| Route of administration | Oral |
| Chemical structure |  |
| Pivotal trials | Stenlöf et al.Yale et al.Rosenstock et al. |

References

1. Boyle LD, Wilding JPH. Emerging sodium/glucose co-transporter 2 inhibitors for type 2 diabetes. *Expert Opin Emerg Drugs*. 2013;18:375–91. doi:10.1517/14728214.2013.831405.

2. Cada DJ, Ingram KT, Levien TL, Baker DE. Canagliflozin. *Hosp Pharm*. 2013;48:855–67. doi:10.1310/hpj4810-855.

3. Dietrich E, Powell J, Taylor JR. Canagliflozin: a novel treatment option for type 2 diabetes. *Drug Des Devel Ther*. 2013;7:1399–408. doi:10.2147/DDDT.S48937.

4. Rosenwasser, Rebecca; Sultan, Senan; Sutton, David; Choksi, Rushab; Epstein B. SGLT-2 inhibitors and their potential in the treatment of diabetes. *Diabetes, Metab Syndr Obes Targets Ther*. 2013;6:453–467. doi:10.2147/DMSO.S34416.

5. Stenlöf K, Cefalu WT, Kim K, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab*. 2013;15:372–82. doi:10.1111/dom.12054.

6. Inagaki N, Kondo K, Yoshinari T, Maruyama N, Susuta Y, Kuki H. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. *Diabetes Obes Metab*. 2013;15:1136–45. doi:10.1111/dom.12149.

7. Yale J, Bakris G, Cariou B. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes, Obes …*. 2013:463–473. Available at: http://onlinelibrary.wiley.com/doi/10.1111/dom.12090/full.

8. Rosenstock J, Aggarwal N, Polidori D, et al. Dose-Ranging Effects of Canagliflozin, a Sodium-Glucose Cotransporter 2 Inhibitor, as Add-On to Metformin in Subjects With Type 2 Diabetes. *Diabetes Care*. 2012;35:1232–1238. doi:10.2337/dc11-1926.

9. Lavalle-González FJ, Januszewicz A, Davidson J, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia*. 2013;56:2582–92. doi:10.1007/s00125-013-3039-1.