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Canagliflozin: A Review in Type 2 Diabetes

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Abstract Canagliflozin (Invokana®) is a sodium-glucose co-transporter-2 (SGLT2) inhibitor indicated in various countries worldwide for the once-daily oral treatment of type 2 diabetes (T2D). Unlike many T2D therapies, canagliflozin lowers blood glucose levels independently of insulin, with the inhibition of SGLT2 reducing renal reabsorption of glucose and increasing excretion of glucose in the urine. In well-designed clinical trials, canagliflozin (as first-line monotherapy or add-on therapy to other antihyperglycaemic agents) improved glycaemic control in adults with T2D, including those of older age and/or at high cardiovascular (CV) risk, and also had beneficial effects on their bodyweight and BP; whether the drug impacts the CV risk profile of T2D is currently being evaluated in the large CV outcomes study CANVAS. Canagliflozin was generally well tolerated, had a low risk of hypoglycaemia and was most commonly associated with adverse events such as genital and urinary tract infections and increased urination, consistent with its mechanism of action. Thus, canagliflozin is a useful monotherapy and add-on therapy option for the management of T2D in adults, and its CV profile is eagerly awaited.

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Canagliflozin: clinical considerations in type 2 diabetes

Lowers blood glucose levels by increasing urinary glucose excretion, an effect independent of insulin

Provides effective glycaemic control as first-line monotherapy or as add-on therapy

Associated with reductions in bodyweight and BP

Generally well tolerated with a low risk of hypoglycaemia

1 Introduction

Type 2 diabetes (T2D) is a chronic progressive metabolic disease characterized by hyperglycaemia, due to insulin resistance/insufficient insulin production [1]. Patients are often obese, have lipid disturbances and elevated BP, and are at an increased risk of microvascular and macrovascular complications [1]. Achieving good glycaemic control [e.g. HbA_{1C} level <7%] is a key management goal, for which numerous antihyperglycaemic agents (AHAs) with varying mechanisms of action are now available [2]. Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a relatively recent AHA class. By inhibiting SGLT2 (a key protein in glucose resorption in the kidney), these drugs increase urinary glucose excretion (UGE), causing blood glucose levels to decline independently of insulin. One of the most widely available SGLT2 inhibitors is canagliflozin (Invokana®), which is approved for the treatment of T2D in various countries worldwide, including the USA and EU. This article reviews data relevant to the use of canagliflozin in T2D in the EU; fixed-dose canagliflozin/metformin tablets are also now available but are beyond the scope of this article.

2 Pharmacodynamic Properties

Canagliflozin is a potent competitive inhibitor of SGLT2 [3, 4], and thus reduces both renal glucose reabsorption and the renal threshold for glucose (RT_G), with subsequent increases in UGE [5-7]. These increases in UGE reduce plasma glucose levels [5-7], provide calorie and thus bodyweight loss (Sect. 4.2) and have an osmotic diuretic effect (that may reduce BP; Sect. 4.3) [7], although transient early increases in urine output with canagliflozin may also reflect increased natriuresis [8]. Maximal RT_G suppression in T2D patients was seen with canagliflozin 300 mg/day in phase 1 trials, with 24-h mean RT_G values reduced from ≈13 to 4–5 mmol/L (i.e. values greater than plasma glucose levels usually associated with hypoglycaemia symptoms, indicating a low hypoglycaemia risk; Sect. 5.3) [7].

Canagliflozin is highly selective for SGLT2 in vitro [3, 4], with one study, for instance, demonstrating ≈200-fold greater affinity of the drug for SGLT2 than SGLT1 [3]. However, as SGLT1 is key in gastrointestinal glucose absorption, canagliflozin in the small intestines after oral administration may transiently inhibit intestinal SGLT1, and thus glucose absorption [9]. Indeed, in small placebo-controlled crossover studies in T2D patients [10] or healthy volunteers [11], canagliflozin reduced postprandial glucose (PPG) excursions by both non-renal (possibly via intestinal SGLT1 inhibition) and renal (via SGLT2 inhibition) mechanisms. Notably, canagliflozin 300 mg/day was associated with less extensive PPG excursions, lower 24-h mean RT_G and greater 24-h UGE than dapagliflozin 10 mg/day in healthy volunteers [12]. Various measures of β-cell function improved with canagliflozin regimens in T2D trials [7, 13-17], likely as an indirect consequence of reduced glucotoxicity.

Canagliflozin (100 or 300 mg/day) was generally associated with small changes in serum electrolytes (including sodium, calcium, bicarbonate, phosphate, potassium and magnesium) [18], normalization of serum magnesium levels in hypomagnesaemia [19], and reductions in serum uric acid levels (possibly via increased urinary uric acid excretion) [20] in pooled (post hoc [19, 20]) analyses of phase 3 trials in T2D patients. The most common serum electrolyte abnormality of interest with canagliflozin 100 or 300 mg/day was potassium above the upper limit of normal plus >15% increase from baseline, both in patients with an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73m^2 (5 and 7 vs. 5% of placebo recipients) and in those with an eGFR ≥45 to <60 mL/min/1.73m^2 (5 and 9 vs. 6%) [18].

Elderly patients with T2D who added canagliflozin to their current AHA regimen in a phase 3 study (Sect. 4.4.2) had small but significant reductions in BMD at the total hip (but not other skeletal sites) over 104 weeks of therapy compared with adding placebo, with increases in biomarkers of bone turnover also seen over 52 weeks in the canagliflozin versus placebo groups; these changes were partly due to bodyweight loss, and bone strength was not impacted [21].

3 Pharmacokinetic Properties

Canagliflozin is rapidly absorbed after oral administration, reaching maximum plasma concentrations 1–2 h post-dose in T2D patients [5] and healthy volunteers [7]. The drug has a mean absolute oral bioavailability of ≈65% [22] and reaches steady-state in 4–5 days [5, 7]. Exposure increases in proportion to dose and there is up to 36% accumulation of the drug in plasma at the recommended dosages (100 or 300 mg/day) [5, 7]. Food does not impact canagliflozin pharmacokinetics [23], enabling it to be taken with or without food [7]; however, as canagliflozin may help reduce PPG excursions by delaying glucose absorption in the intestine (Sect. 2), administration before the first meal of the day is advised [7].

Canagliflozin is extensively (99%) plasma protein bound, and has a mean volume of distribution at steady state of 83.5 L after intravenous infusion [7]. Metabolism of canagliflozin occurs primarily via *O*-glucuronidation (by UGT1A9 and UGT2B4), producing two main inactive metabolites [24]; metabolism via CYP3A4 is minimal (≈7%) [7]. Canagliflozin is eliminated via the faeces (41.5% as parent drug; 10.2% as metabolites) and urine (33%, mainly *O*-glucuronide metabolites), and recommended doses have renal clearance rates of 1.30–1.55 mL/min [7]. The mean elimination half-life of canagliflozin 100 or 300 mg/day in T2D patients was 13.7 and 14.9 h [5].

Mild or moderate hepatic impairment does not alter canagliflozin pharmacokinetics to a clinically relevant extent [25] and does not necessitate dosage adjustment [7]; the drug has not been assessed, and is thus not recommended, in severe hepatic impairment [7]. Renal impairment increases canagliflozin exposure and reduces pharmacodynamic response to the drug [25]. The canagliflozin dosage does not require adjustment in patients with an eGFR of 60 to <90 mL/min/1.73 m^2; however, if eGFR persistently declines below 60 or 45 mL/min/1.73 m^2, dosage adjustment/consideration or discontinuation is necessary [7]. Canagliflozin should not be initiated in patients with an eGFR <60 mL/min/1.73 m^2 or used in patients with end-stage renal disease/on dialysis. Renal function monitoring is advised [7].

Higher than therapeutic concentrations of canagliflozin did not inhibit or induce key CYP isoenzymes in vitro, and there was no clinically relevant impact of canagliflozin on CYP3A4 in vivo [7]. However, as canagliflozin is metabolized by UGT1A9 and UGT2B4, and transported by p-gp and BCRP, drugs that induce these enzymes may reduce canagliflozin exposure; thus, if coadministered, canagliflozin dosage adjustment (and, in some instances, additional AHAs) may be necessary [7]. There is also potential for canagliflozin exposure to be reduced by cholestyramine, necessitating staggered administration [7]. Canagliflozin weakly inhibits p-gp and may thus increase plasma concentrations of p-gp substrates; monitoring is advised [5, 7]. Intestinal BCRP inhibition by canagliflozin cannot be ruled out and may increase exposure to drugs transported by BCRP [7]. Canagliflozin may augment the effects of diuretics, increasing dehydration and hypotension (Sect. 5.2) risks [7]. There is also an increased risk of hypoglycaemia if canagliflozin is used in combination with an insulin secretagogue or insulin (Sect. 5.3); reduction of the insulin or insulin secretagogue dosage may be required [7].

4 Therapeutic Efficacy

The clinical efficacy of oral canagliflozin, as monotherapy or add-on therapy, in adults with inadequately-controlled T2D, has been evaluated in numerous placebo- and/or active comparator-controlled trials of randomized, double-blind (or open-label [26]) design and 16–52-weeks' duration; some studies also had 26- to 78-week double-blind extensions. Unless otherwise specified, trials were phase 3 and used the change from baseline in HbA_{1C} (usually at 26 or 52 weeks; range 16–52 weeks) as the primary endpoint. Real-world data are also now available. Discussion focuses on recommended canagliflozin dosages (i.e. 100 or 300 mg/day); some data are from abstracts [27-32].

4.1 Glycaemic Parameters

In patients with T2D inadequately controlled by diet and exercise, monotherapy with canagliflozin 100 or 300 mg/day improved glycaemic control over 26 weeks, with each dosage significantly reducing HbA_{1C} and FPG levels relative to placebo; the proportion of patients achieving an HbA_{1C} target of <7% also significantly favoured the canagliflozin groups (Table 1) [13]. Improvements in glycaemic control were sustained over 52 weeks in canagliflozin recipients who continued to receive the drug in the 26-week extension of this trial (Table 1) [33]. Moreover, another study in this setting found canagliflozin 100 or 300 mg/day to be noninferior to metformin extended-release in improving HbA_{1C} over 26 weeks (Table 1) [27].

Canagliflozin was also an effective add-on therapy in patients with T2D inadequately controlled by their current AHA regimen. Indeed, as an add-on to metformin, canagliflozin 100 or 300 mg/day significantly improved HbA_{1C} and other glycaemic parameters over 26 weeks relative to placebo (Table 2) [34]. Moreover, compared with adding sitagliptin [34] or glimepiride [35] in this setting, adding canagliflozin 100 mg/day was noninferior and adding canagliflozin 300 mg/day was superior in lowering HbA_{1C} levels over 52 weeks (Table 2). A target HbA_{1C} of <7.0% was reached by 41–60% of patients at 52 weeks in these trials (Table 2) [34, 35], with the odds of achieving this target without concomitant hypoglycaemia being 2.1- and 2.9-fold greater with canagliflozin 100 or 300 mg/day than with glimepiride (post hoc analysis) [28]. Reductions in FPG were also significantly [34] or numerically [35] greater in the canagliflozin than in the active comparator groups at 52 weeks in these studies (Table 2). Longer term, the relative glycaemic benefits of the canagliflozin and glimepiride regimens were generally sustained over up to 104 weeks' therapy (Table 2) [36].

Similarly, in patients with T2D inadequately controlled by metformin plus either a sulfonylurea [14], pioglitazone [16] or sitagliptin [37], adding canagliflozin (100 or 300 mg/day) significantly lowered both HbA_{1C} and FPG levels and significantly increased the proportion of patients achieving HbA_{1C} levels <7% versus placebo over 26 weeks, with these benefits sustained up to 52 weeks [14, 16] (Table 2). Another trial in a similar patient population found adding canagliflozin 300 mg/day to metformin plus a sulfonylurea to be more effective in lowering HbA_{1C} and FPG levels over 52 weeks than adding sitagliptin, and numerically more canagliflozin than sitagliptin recipients achieved HbA_{1C} <7% (Table 2) [15].

4.2 Bodyweight

Canagliflozin (100 or 300 mg/day) significantly reduced bodyweight relative to placebo over 26 weeks, both when used as monotherapy in patients with T2D inadequately controlled by diet and exercise (Table 1) [13] and when used as add-on therapy in patients whose T2D was inadequately controlled by metformin, either alone [34] or in combination with another oral AHA [14, 16, 37] (Table 2). In all settings, weight loss was sustained with canagliflozin up to 52 weeks (Table 1 and Table 2) [14, 16, 33, 34].

In active comparator-controlled trials, adding canagliflozin (100 or 300 mg/day) to ongoing metformin monotherapy [34, 35] or metformin plus a sulfonylurea [15] significantly reduced bodyweight over 52 weeks compared with adding either sitagliptin [15, 34] or glimepiride [35], with the benefit of canagliflozin versus glimepiride being maintained over 104 weeks' treatment [36] (Table 2). Notably, in a post hoc analysis [38] of one of these studies [35, 36], more overweight/obese patients (BMI ≥25 kg/m^2) lost ≥4.5 kg in bodyweight with canagliflozin than with glimepiride over 52 and 104 weeks.

The weight loss associated with canagliflozin seems mainly due to fat mass reduction [35] and, according to a pooled analysis of four phase 3 placebo-controlled studies (n = 2250) [39], may contribute to some of the HbA_{1C}- (Sect. 4.1) and SBP- (Sect. 4.3) lowering benefits of the drug (≈15 and ≈42%, respectively).

4.3 Other Parameters

In general, BP was modestly lowered with canagliflozin (as monotherapy or add-on therapy) in the trials discussed so far. For instance, in placebo-controlled studies [13, 14, 16, 34, 37], mean changes from baseline (126–131 mmHg) in SBP over 26 weeks ranged from −5.8 to −3.3 mmHg with canagliflozin (100 or 300 mg/day) versus −2.7 to +1.5 mmHg with placebo, with the between-group difference being statistically significant ($p < 0.025$) in all but one trial [14]. Mean changes from baseline (76–79 mmHg) in DBP in the respective groups ranged from −3.5 to −1.7 mmHg and from −1.7 to +0.3 mmHg ($p = 0.002$ for canagliflozin vs. placebo, where reported/assessed [37]). Moreover, when four 26-week phase 3 placebo-controlled trials were pooled ($n = 2313$), the SBP- and DBP-lowering benefits of canagliflozin were seen regardless of whether antihypertensives were, or were not, taken concomitantly [40], and improvements in mean arterial pressure, pulse pressure and double product (a cardiac workload measure) were also seen with the drug [41].

In active comparator-controlled trials, adding canagliflozin (100 or 300 mg/day) to ongoing metformin monotherapy [34, 35] or metformin plus a sulfonylurea [15] reduced SBP over 52 weeks compared with adding either sitagliptin ($p < 0.001$) [15, 34] or glimepiride (no p-value; comparison not prespecified) [35], with DBP-lowering benefits also evident in the canagliflozin versus the comparator groups. The SBP- and DBP-lowering effects of canagliflozin were durable, being sustained over 104 weeks of treatment [36].

In terms of lipids, canagliflozin (as monotherapy or add-on therapy) was generally associated with modest increases in HDL-C and LDL-C levels (with minimal LDL-C:HDL-C ratio changes) and modest reductions in triglyceride versus placebo over 26 weeks in key clinical trials (between-group differences were significant/numerical) [13, 14, 34, 37]; similar findings were generally seen at 52 weeks [14, 16, 33]. In active comparator-controlled trials, adding canagliflozin to metformin-based therapy for 52 weeks appeared to increase HDL-C levels [15, 34, 35] and (in some studies [15, 35]) LDL-C levels, relative to adding sitagliptin [15, 34] or glimepiride [35]. During this period, canagliflozin also reduced triglyceride levels relative to glimepiride [35], but did not significantly differ from sitagliptin in terms of triglyceride changes [15, 34]. Longer-term data from the glimepiride-controlled trial at 104 weeks were generally consistent with these findings [36].

In a post hoc analysis [42] of this trial [36], canagliflozin also appeared to preserve renal function relative to glimepiride over 104 weeks. The annual slope of eGFR decline was significantly ($p < 0.01$) smaller with canagliflozin 100 or 300 mg/day than with glimepiride (0.5 and 0.9 vs. 3.3 mL/min/1.73 m^2), with canagliflozin 300 mg/day (but not 100 mg/day) also significantly ($p < 0.01$ vs. glimepiride) reducing the urinary albumin : creatinine ratio, independent of HbA_{1C} changes [42].

4.4 Special Patient Populations

The findings of trials and subgroup analyses assessing canagliflozin efficacy in various special patient groups are generally consistent with those of the pivotal trials already discussed; efficacy measures of particular relevance are summarized here.

4.4.1 High CVD Risk Patients

Clinical efficacy data for canagliflozin in patients with inadequately controlled T2D and an elevated risk of cardiovascular disease (CVD) are available from prespecified [43, 44] and post hoc [45] subgroup analyses of CANVAS, a trial designed primarily to assess the impact of canagliflozin on CVD risk [46]. In these patients, adding canagliflozin 100 or 300 mg/day to insulin ≥20 IU/day (with or without other AHAs) significantly improved HbA_{1C} and FPG measures over 18 weeks relative to adding placebo, and these benefits were sustained to week 52 (Table 3); findings were independent of insulin dosage [43]. Similarly, adding canagliflozin 100 or 300 mg/day to ongoing

sulfonylurea monotherapy [44] or a DPP4 inhibitor or GLP-1 receptor agonist (RA), with or without other AHAs [45], improved glycaemic measures over 18 weeks versus adding placebo, although some subgroups were small (Table 3). Over 18–52 weeks, canagliflozin, compared with placebo, reduced bodyweight by up to 3.5 kg across subgroups (Table 3) [43-45] and, in the largest substudy [43], reduced SBP and DBP and had minimal impact on the LDL-C: HDL-C ratio.

These findings are generally supported by a post hoc pooled analysis of four 26-week placebo-controlled phase 3 trials (n = 2313) in which canagliflozin (100 or 300 mg/day) regimens improved glycaemic control, bodyweight and SBP relative to placebo regardless of patient CVD history/risk factors [47].

4.4.2 Older Patients

In older patients (n = 714) aged 55–80 years with T2D inadequately controlled by oral/injectable AHA regimens, adding canagliflozin 100 or 300 mg/day significantly ($p < 0.001$) improved glycaemic control over 26 weeks versus adding placebo, as measured by mean changes from baseline in HbA_{1C} (−0.60 and −0.73 vs. −0.03%; overall baseline value 7.7% across groups) and FPG (−18.1 and −20.3 vs. +7.4 mmol/L; overall baseline value 157 mmol/L) levels [48]. Significant ($p < 0.001$) bodyweight loss also occurred with canagliflozin versus placebo during this period (mean changes from baseline −2.2 and −2.8 vs. −0.1 kg; overall baseline value 90 kg) [48]. Longer term, canagliflozin 100 or 300 mg/day largely maintained improvements versus placebo in HbA_{1C} levels (mean changes from baseline: −0.32 and −0.43 vs. +0.17%), as well as FPG levels and bodyweight, over 104 weeks in a 78-week extension (n = 624) [49].

Notably, canagliflozin (as monotherapy or combination therapy) improved glycaemic control versus placebo regardless of whether patients were aged ≥65 or <65 years (n = 445 and 1868) [50] or ≥75 or <75 years (n = 183 and 3975) [51] in pooled analyses of four [50] or six [51] phase 3 trials (plus CANVAS substudies [51]) of 18–26 weeks' duration. However, glycaemic improvements were slightly more pronounced in the younger patient groups [50, 51].

4.4.3 Other Patients

In Asian patients with T2D, canagliflozin 100 or 300 mg/day, as first-line monotherapy [26, 52] or added to oral AHA [26, 53] or insulin [54] regimens, significantly ($p < 0.05$) improved HbA_{1C}, FPG and bodyweight versus corresponding placebo regimens in phase 3 (or unspecified phase [54]) trials of 16–24 weeks' duration (total n = 146–676), with improvements in these parameters also seen in a 52-week noncomparative study (total n = 1299; primary endpoint not specified) [26]. Indeed, in post hoc analyses, race did not impact the glycaemic or bodyweight benefits of canagliflozin regimens in placebo-controlled trials (pooled; n = 124–3108 per racial group) [55-59] or in one (n = 307) [56] or three (n = 551; pooled) [59] active comparator-controlled studies.

Reductions in HbA_{1C} and bodyweight (of ≈0.5 and ≈2%) were also seen with canagliflozin (100 or 300 mg/day) versus placebo in T2D patients with renal impairment (eGFR 45 to <60 mL/min/1.73 m^2) in a pooled analysis (n = 721) of phase 3 trials; most (94%) patients in this analysis were receiving an AHA regimen at baseline [60]. Moreover, in patients with T2D who met metabolic syndrome criteria in two phase 3 trials (n = 1169 or 586; post hoc analysis), adding canagliflozin 100 or 300 mg/day to ongoing metformin-based therapy generally improved glycaemic (HbA_{1C}, FPG) as well as non-glycaemic (e.g. bodyweight, BMI, waist circumference, BP, HDL-C) metabolic parameters over 52 weeks relative to adding glimepiride or sitagliptin, although generally increased LDL-C levels [61].

4.5 Additional Analyses

Canagliflozin (100 or 300 mg/day), as monotherapy or add-on therapy, was effective in lowering HbA_{1C} levels in T2D patients, regardless of baseline patient/disease characteristics such as age [62], BMI [62], HbA_{1C} level [63], T2D

duration [63] or renal function (although efficacy declined with increasing renal impairment) [62], in post hoc pooled analyses of four (*n* = 2313) [63] or six (*n* = 4053) [62] placebo-controlled phase 3 trials of 18–26 weeks' duration.

Moreover, post hoc analyses of composite endpoints have confirmed the concomitant benefit of canagliflozin on glycaemic and other metabolic parameters (e.g. bodyweight, BP and lipids) in T2D patients [29, 64-66]. For instance, a reduction in both HbA_{1C} and bodyweight was achieved by 1.5- to 3.6-fold more recipients of canagliflozin (100 or 300 mg/day) than of placebo [29], glimepiride [66] or sitagliptin [67], when each was used for 18 [29] or 52 [66, 67] weeks as add-on therapy to ongoing AHA regimens in CANVAS [29], CANTATA-SU [66] or two other phase 3 trials (pooled; *n* = 1856) [67]. Notably, combined reductions in bodyweight and HbA_{1C} with canagliflozin may lead to improvements in liver enzyme levels in patients with T2D, according to additional pooled phase 3 study data [68].

4.6 Real-World Studies

The efficacy of canagliflozin in the real-world setting has been established in various analyses of US healthcare claims databases and/or healthcare datasets [30-32, 69-71]. Among those fully published (*n* = 826–1562 evaluable) [69-71], canagliflozin regimens reduced ($p < 0.001$, where specified [69, 71]) HbA_{1C} levels from baseline by a mean of 0.70–0.81% and increased the proportion of patients achieving HbA_{1C} levels <7.0% by approximately twofold ($p < 0.001$ where specified [71]) over 6 months [69] or mean of 67–185 days [70, 71]. Limited glycaemic data available from the other analyses (*n* = 1227–16,163) [30-32] were generally consistent with these findings, with one indicating significantly ($p = 0.004$) greater reductions in HbA_{1C} levels with canagliflozin than with DPP4 inhibitor regimens over ≈183 days' mean follow-up [32]. In another of these analyses (designed primarily to assess bodyweight), canagliflozin regimens were associated with significant ($p < 0.0001$) mean reductions from baseline in bodyweight, ranging from −1.8 kg at 3 months to −2.6 kg at 12 months in the overall population and −2.1 to −3.0 kg in patients with a baseline BMI of ≥30 kg/m^2 [31].

5 Tolerability

Oral canagliflozin, as monotherapy or add-on therapy, was generally well tolerated for up to 104 weeks in patients with T2D, including those of older age and/or at high CV risk, in the key phase 3 or 4 trials discussed in Sect. 4. In the pooled analysis of four placebo-controlled phase 3 trials (*n* = 2313) [72], treatment-related adverse events (AEs) occurred in up to 1.7-fold more canagliflozin 100 or 300 mg/day than placebo recipients over 26 weeks (20.5 and 22.9 vs. 13.2%) and, consistent with canagliflozin's mechanism of action (Sect. 2), the most common AEs associated with the drug were female genital mycotic infection (GMI) (10.4 and 11.4 vs. 3.2%), urinary tract infection (UTI) (5.9 and 4.3 vs. 4.0%), increased urination (5.3 and 4.6 vs. 0.8%) and male GMI (4.2 and 3.7 vs. 0.6%). AEs were generally mild or moderate and few patients experienced serious AEs (≈3% in each group) or death (<0.3% in each group) [72].

In active comparator-controlled studies, canagliflozin regimens were generally similar to sitagliptin or glimepiride regimens in terms of the incidence of treatment-related AEs (20–34 vs. 20–28%) and discontinuations because of AEs (3–7 vs. 3–6%) over 52 weeks [15, 34, 35], with 104-week data from the glimepiride-controlled trial being consistent with these findings [36]. Local prescribing information should be consulted for warnings and precautions relating to AEs such as diabetic ketoacidosis (rare but sometimes serious/fatal [7, 73]), elevated haematocrit, and GMIs [7].

5.1 Genitourinary Infections

Canagliflozin increases UGE (Sect. 2), which may contribute to GMIs [7]. Canagliflozin 300 mg/day significantly ($p < 0.00001$; 3.76-fold) increased the risk of GMIs versus placebo over 12–26 weeks in a meta-analysis of eight placebo-controlled trials (*n* = 1338) [74]. The most common GMIs with canagliflozin (100 or 300 mg/day) over 26 weeks

included vulvovaginal mycotic infection in women (5.9 and 5.3 vs. 1.3% with placebo) and balantitis in men (2.2 and 1.7 vs. 0%) in the pooled analysis of four placebo-controlled studies [72]. GMIs in this analysis were never serious, rarely (<1% of patients) led to therapy discontinuation and responded to standard antifungal treatment [72], lasting a median of 7 and 18 days in treated female and male canagliflozin recipients [75].

The likelihood of GMIs with canagliflozin 300 mg/day was significantly greater (4.95-fold; $p < 0.00001$) than with sitagliptin or glimepiride over 12–52 weeks in a meta-analysis of four active comparator-controlled trials ($n = 2510$) [74]. Similarly, in individual studies, the GMI incidence was numerically greater with canagliflozin (100 or 300 mg/day) than with sitagliptin or glimepiride regimens over 52 weeks both in men (2–9 vs. 0.5–1%) and women (10–15 vs. 2–4%) [15, 34, 35], although did not further increase versus glimepiride over 104 weeks [36].

Despite being a common AE with canagliflozin, UTIs did not significantly differ in incidence between canagliflozin 300 mg/day and placebo over 12–26 weeks in the meta-analysis of eight trials [74]. UTIs with canagliflozin (100 or 300 mg/day), although often symptomatic, were rarely serious (≤0.2% of patients) [76] and responded to standard therapy without canagliflozin discontinuation [7] when four placebo-controlled studies were pooled. Compared with other active agents, the UTI incidence with canagliflozin did not significantly differ from that with sitagliptin or glimepiride in the meta-analysis of four 12- to 52-week trials [74], with data from individual sitagliptin- or glimepiride-controlled studies of up to 104 weeks' duration generally supporting these findings [15, 34-36].

5.2 Osmotic Diuresis and Volume Depletion

By increasing UGE, canagliflozin can trigger osmotic diuresis. Treatment-related AEs related to osmotic diuresis (e.g. increased urine volume/frequency) occurred in 6.1-fold more canagliflozin (100 or 300 mg/day) than placebo recipients (4.9 and 4.9 vs. 0.8%) in the pooled analysis of four 26-week trials ($n = 2313$) [40]; these AEs typically occurred during the first 6 weeks of therapy and none were serious [72]. Consistent with these findings, over 12–52 weeks, canagliflozin significantly ($p < 0.01$) increased the risk of osmotic diuresis-related AEs compared with placebo, as well as active comparators (sitagliptin or glimepiride), in meta-analyses ($n = 3853$ and 5057) [74].

AEs related to volume depletion (e.g. postural dizziness, orthostatic hypotension) were rare (≈1% incidence) with canagliflozin in the pooled analysis of four placebo-controlled trials [40] and occurred predominantly in patients on antihypertensives [72]. Moreover, these AEs did not significantly differ in incidence between canagliflozin and placebo or active comparators (sitagliptin or glimepiride) in meta-analyses ($n = 3334$ and 4910) [74]. When risk factors for volume depletion-related AEs were assessed in a pooled analysis of eight phase 3 trials ($n = 9439$), the incidence was generally numerically greater with canagliflozin 100 or 300 mg/day than with comparators in patients who were receiving loop diuretics (3.2 and 8.8 vs. 4.7%), had a baseline eGFR of 30 to <60 mL/min/1.73 m^2 (4.8 and 8.1 vs. 2.6%) or were aged ≥75 years (4.9 and 8.7 vs. 2.6%) [7]. Similarly, in CANVAS (in which patients generally had more T2D complications), the incidence of volume depletion-related AEs was 2.8 and 4.6% with canagliflozin 100 or 300 mg/day versus 1.9% with placebo [7]. However, canagliflozin did not increase the incidence of volume depletion-related AEs that were serious or that led to discontinuation in these studies [7].

Volume depletion with canagliflozin may reduce eGFR, although the reductions are usually small, occur in the first few weeks of therapy [7, 72] and stabilize/attenuate thereafter [72, 77]. However, large (>30%), albeit transient, eGFR reductions have occurred with canagliflozin in patients more susceptible to volume depletion (such as the high-risk patients already discussed), although did not usually require treatment interruption [7]. Renal-related AEs (e.g. reduced GFR, increased blood creatinine) occurred with an incidence of <3% and were rarely serious (≤0.2% of patients) with canagliflozin or comparators over 26 [72] or 104 [78] weeks' therapy in pooled analyses of placebo- and/or active comparator-controlled trials [72, 78]. Nevertheless, a possible signal for acute renal injury was detected with

canagliflozin, as well as other SGLT2 inhibitors, when postmarketing data from the US FDA AE Reporting System were assessed [78].

5.3 Hypoglycaemia

Hypoglycaemia was relatively uncommon when canagliflozin (100 or 300 mg/day) was used as monotherapy [13, 33] or added to metformin (alone [34] or in combination with sitagliptin [37] or pioglitazone [16]) over 26 weeks (3−4 vs. 2−3% with placebo) or 52 weeks (4−7%) in placebo- and/or active comparator-controlled trials [13, 34, 37] and their extensions [16, 33]. In patients receiving metformin in active comparator-controlled studies, the incidence of hypoglycaemia with add-on canagliflozin (100 or 300 mg/day) was not markedly different from that with add-on sitagliptin (7 and 7 vs. 4%) [34] but was significantly ($p < 0.0001$) lower than with add-on glimepiride (6 and 5 vs. 34%) [35] over 52 weeks, with the benefit over glimepiride maintained at week 104 [36]. Severe hypoglycaemia was rare (<1%) with canagliflozin in these trials, where specified [13, 16, 34-37].

By contrast, hypoglycaemia tended to be relatively common when canagliflozin was added to an AHA regimen that included a sulfonylurea [14, 15, 44] or insulin [43] in phase 3 trials. For instance, in patients receiving metformin plus a sulfonylurea, the incidence of hypoglycaemia over 52 weeks was approximately twofold greater with add-on canagliflozin 100 or 300 mg/day than with add-on placebo (34 and 37 vs. 18%) [14] but did not markedly differ between add-on canagliflozin 300 mg/day and sitagliptin (43 vs. 41%) [15]; severe hypoglycaemia was not common (≤4% incidence) in any treatment group of either trial. Added to insulin therapy, canagliflozin 100 or 300 mg/day did not significantly differ from placebo in terms of hypoglycaemia (59 and 57 vs. 48%) or severe hypoglycaemia (5 and 6 vs. 4%) incidence over 52 weeks in CANVAS [43].

5.4 Cardiovascular and Other Events

Canagliflozin (100 or 300 mg/day, pooled) did not increase the risk of major CV events (MACE) relative to placebo and active comparators (combined) in a pre-specified interim meta-analysis of phase 2 or 3 trials ($n = 9632$; 44.9% were high CV risk patients from CANVAS). The hazard ratio (HR) was 0.91 (95% CI 0.68, 1.22) for the composite primary endpoint of time to CV death, non-fatal stroke, non-fatal myocardial infarction and unstable angina requiring hospitalization [7].

Lower limb amputations (mainly of the toes) appeared to increase in incidence with canagliflozin in T2D patients with, or at high risk of, CVD in ongoing long-term trials [7]. For instance, in an interim safety analysis of CANVAS (mean follow-up 4.5 years), lower limb amputation occurred with an approximately twofold greater incidence with canagliflozin 100 or 300 mg/day than with placebo (7 and 5 vs. 3 per 1000 patient-years) [79]. The mechanism underlying this risk has not yet been determined; patients at higher risk of amputation should be monitored and counselled appropriately, and canagliflozin may need to be discontinued if events such as skin ulcer, infection, osteomyelitis or gangrene develop in the lower extremities [7].

In addition, bone fracture risk was significantly increased with canagliflozin (100 or 300 mg/day, combined) relative to placebo over 104 weeks in CANVAS ($n = 4327$) (4.0 vs. 2.6% of patients; HR 1.51; 95% CI 1.04, 2.19), whereas pooled data from non-CANVAS studies found no significant fracture risk with these canagliflozin dosages over 52 ($n = 5867$) or 104 ($n = 2164$) weeks versus placebo/active agents (combined) [80]. The reason for the increased fracture risk with canagliflozin in CANVAS but not the non-CANVAS studies is unknown, although differences in factors such as patient age (mean 62 vs. 58 years), loop diuretic use (12 vs. 4% of patients) and eGFR (mean 77 vs. 85 mL/min) have been suggested.

6 Dosage and Administration

In the EU, canagliflozin is approved for use as monotherapy (as an adjunct to diet and exercise, when metformin is considered inappropriate) and as an add-on therapy (to other AHAs, including insulin) to improve glycaemic control in adults with T2D [7]. Canagliflozin tablets should be taken orally, preferably prior to the first food of the day. The initial dosage is 100 mg once daily; if tolerated (and eGFR is ≥60 mL/min/1.73 m^2), this can be increased to 300 mg once daily if necessary. Care is advised if increasing the dosage in patients for whom the initial diuresis associated with the drug may pose a risk (e.g. those aged ≥75 years or with known CVD) [7]. Local prescribing information should be consulted for further details, including drug interactions, use in special patient populations, contraindications and other warnings and precautions.

7 Place of Canagliflozin in T2D Management

Managing T2D requires an individualized stepwise approach [1, 2], taking into consideration common patient comorbidities (e.g. heart failure, coronary artery disease) and the likelihood that AHA-associated hypoglycaemia (thought to contribute to CV dysfunction and, in high-risk patients, CV events) may have untoward outcomes [2]. Among the numerous AHAs now available, metformin monotherapy remains the standard first-line option for most patients [1, 2], although sequential addition of drugs from other classes is often required to attain/maintain good glycaemic control.

Although most AHAs lower blood glucose levels by increasing insulin secretion and/or sensitivity, SGLT2 inhibitors (e.g. canagliflozin, dapagliflozin and empagliflozin [81]) act independently of insulin, enabling them to be used at any stage of T2D (i.e. regardless of insulin secretory capacity) and to complement a wide variety of AHAs as part of combination regimens [2, 82]. In treatment guidelines, SGLT2 inhibitors (as well as sulfonylureas, thiazolidinediones, DPP4 inhibitors, GLP-1 RAs and insulin) are generally recommended as second- and/or subsequent-line options for use in combination regimens, although can be used first line if metformin is contraindicated/not tolerated [1, 2] (provided a sulfonylurea or pioglitazone is inappropriate and a DPP4 inhibitor would otherwise be used [83]).

Canagliflozin is one of the most widely available SGLT2 inhibitors [81]. Its approval as a first-line monotherapy or as an add-on to other AHAs, including insulin, in adults with T2D (Sect. 6) was based on numerous well-designed clinical trials in these settings, in which the drug (at 100 or 300 mg/day) provided improved and sustainable glycaemic control over up to 104 weeks' therapy (Sect. 4). The glycaemic efficacy of canagliflozin 100 mg/day was noninferior to that of metformin as first-line monotherapy and to that of sitagliptin or glimepiride as an add-on therapy, whereas canagliflozin 300 mg/day was more effective than sitagliptin or glimepiride in the add-on setting (Sect. 4.1). Real-world data are also now available and support the use of canagliflozin in T2D management (Sect. 4.6).

In addition to hyperglycaemia, the common comorbidities of T2D, such as obesity, hypertension and dyslipidaemia, should also be addressed to minimize the overall CV risk of T2D [84]. Canagliflozin (like other SGLT2 inhibitors) induces moderate bodyweight loss (Sect. 4.2) through urinary loss of glucose (and thus calories) (Sect. 2) [2, 82]. The ability to reduce bodyweight is shared by few other AHAs (including GLP-1 RAs), with most increasing bodyweight (e.g. sulfonylureas, meglitinides, thiazolidinediones and insulin) or being bodyweight neutral (e.g. DPP4 inhibitors, metformin, α-glucosidase inhibitors) [2, 85]; as such, canagliflozin has a bodyweight profile more favourable than that of glimepiride or sitagliptin as an add-on therapy (Sect. 4.2). Bodyweight losses occur with canagliflozin even in combination with AHAs typically associated with bodyweight gain, and appear primarily due to reductions in fat (Sect. 4.2), which could (through improved insulin sensitivity) contribute to the glycaemic benefits of the drug.

Canagliflozin also appears to modulate various other non-glycaemic CVD risk factors, consistent with the SGLT2 inhibitor class [2]. For instance, the drug generally improved BP (Sect. 4.3) (possibly through weight loss, osmotic diuresis and/or mild natriuresis [86]), serum uric acid levels (Sect. 2) (possibly via increased urinary secretion) and markers of arterial stiffness (Sect. 4.3). It also modestly impacted serum lipid levels (generally increasing HDL-C and LDL-C and reducing triglyceride; Sect. 4.3), although it is not yet clear whether the net impact of the drug on lipids is of any clinical relevance.

However, the CV profile of canagliflozin is being investigated. At present, CV data for the drug are limited to a meta-analysis of T2D studies (including the large ongoing CV outcomes trial CANVAS), which demonstrated no increased MACE risk with canagliflozin (Sect. 5.4). Mature CV data from CANVAS are required to determine whether canagliflozin improves major CV outcomes in T2D patients at high CV risk, a benefit that has been seen with empagliflozin in a similar trial; to date, the only other AHAs to have demonstrated a reduction in MACE risk are GLP-1 RAs [87]. Thus, CANVAS CV data are awaited with interest.

Canagliflozin is generally well tolerated and, consistent with its mechanism of action, the most common AEs are genitourinary infections and increased urination (Sect. 5). As with other SGLT2 inhibitors and most other AHAs [2], hypoglycaemia is uncommon with canagliflozin, unless used in combination with drugs that increase the risk of the event (Sect. 5.3), among which are sulfonylureas, insulins and meglitinides [2].

Reductions in eGFR initially occur with canagliflozin due to volume depletion and may explain the signal of acute kidney injury identified with the drug (and other SGLT2 inhibitors) postmarketing (Sect. 5.2). However, over 104 weeks, eGFR reductions with canagliflozin were less than those with glimepiride, suggesting kidney function preservation (Sect. 4.3), possibly via albuminuria and glomerular hyperfiltration attenuation [78]. Notably, the effects of the drug on renal and CV outcomes in T2D patients with diabetic nephropathy (CREDENCE; NCT02065791) or increased risk of CV events (CANVAS-R; NCT01989754) are currently being evaluated, as are its effects in T2D patients with congestive heart failure (CANDLE; UMIN000017669). Other AEs related to volume depletion (such as dizziness and orthostatic hypotension) are generally uncommon with canagliflozin, but may limit its use in patients particularly susceptible to volume depletion, such as the elderly or those on antihypertensives or with CVD (Sect. 5.2); thus, any volume depletion should be corrected before initiating canagliflozin [7]. Further longer-term studies evaluating the benefits versus potential risks of canagliflozin and other SGLT2 inhibitors would be beneficial, including the potential for lower-limb amputations and bone fractures (Sect. 5.4).

Also of interest are robust trials directly comparing canagliflozin with AHAs such as other SGLT2 inhibitors or GLP-1 RAs. Currently, such comparisons are limited to network meta-analyses, across which canagliflozin was at least as effective in improving glycaemic control over 26 (or 26–104 [88]) weeks as empagliflozin [88-90], dapagliflozin [88-90], sitagliptin, pioglitazone or a sulfonylurea [90], when used as monotherapy [90] or as part of a dual [88] or triple [89] AHA regimen. Similar comparisons (including those vs. GLP-1 RAs) had more mixed findings, depending on the canagliflozin/comparator dosage and the timepoint and/or treatment setting assessed [91, 92]. Due to their indirect nature, findings from such analyses should be interpreted with caution.

Like most AHAs, canagliflozin and other SGLT2 inhibitors have the convenience of oral administration (unlike GLP-1 RAs and insulins, which are injectable), although the cost of SGLT inhibitors and other relatively recent AHA classes (e.g. DPP4 inhibitors, GLP-1 RAs) is high [2]. Various canagliflozin cost-utility analyses conducted from the NHS perspective of the UK [93, 94] or Spain [95, 96] are available. Their findings suggest that canagliflozin 100 mg may dominate (i.e. be cheaper with greater quality-adjusted life-year gains) and canagliflozin 300 mg may be cost effective versus both empagliflozin 25 mg and dapagliflozin 10 mg as monotherapy [94] and versus sitagliptin 100 mg as an add-on to metformin [96]. Both canagliflozin dosages may also dominate dapagliflozin 10 mg [95] and be cost effective versus a sulfonylurea [93] in the latter setting, and dominate sitagliptin as an add-on to metformin plus a sulfonylurea [96]. Additional cost analyses conducted in the UK [97] and from an Italian NHS perspective [98]

generally support these findings, with canagliflozin estimated to be cost saving versus other SGLT inhibitors [97], as well as sitagliptin and glimepiride [98], when used as add-on therapy. Further cost-utility analyses would be beneficial.

In conclusion, canagliflozin is an effective and generally well tolerated once-daily oral AHA for T2D management, with an insulin-independent mechanism of action that makes it a particularly useful option for use in combination regimens. Given the drug improves glycaemic control, as well as bodyweight and BP, and has a low risk of hypoglycaemia, its CV profile is highly anticipated.

Data selection sources: Database(s): EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data [searches last updated 12 May 2017]. Records were limited to those in English language.

Search terms: Canagliflozin, Canaglu, Invokana, JNJ-28431754, TA-7284, type 2, type II, T2DM, T2D

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Compliance with Ethical Standards

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Table 1 Efficacy of oral canagliflozin as first-line monotherapy in adults with inadequately-controlled T2D in 26-week double-blind phase 3 trials and a 26-week double-blind extension; changes from baseline are least squares means and baseline values are means

Study	Regimen (mg od) [no. of pts]	Week of eval	Change from BL [BL]		% pts with HbA_{1C} <7%	Change from BL [BL]
			HbA_{1C}[a] (%)	FPG (mmol/L)		Bodyweight (kg)
Stenlöf et al [13]	CAN 100 [195]	26	−0.77* [8.1]	−1.5* [9.6]	44.5*	−2.5* [85.9]
(CANTATA-M)	CAN 300 [197]		−1.03* [8.0]	−1.9* [9.6]	62.4*	−3.4* [86.9]
	PL [192]		+0.14 [8.0]	+0.5 [9.2]	20.6	−0.5 [87.5]
Stenlöf et al [33]	CAN 100 [166]	52	−0.81 [8.0]	−1.5 [9.5]	52.4	−2.8 [86.4]
(CANTATA-M ext)[b]	CAN 300 [166]		−1.11 [8.0]	−2.2 [9.4]	64.5	−3.9 [87.2]
Jodar et al [27]	CAN 100 [712[c]]	26	−1.37[d] [8.8[c]]	NR	38.8	NR
	CAN 300		−1.42[d]	NR	42.8	NR
	MET-XR		−1.30	NR	43.0	NR

BL baseline, *CAN* canagliflozin, *ext* extension, *eval* evaluation, *FPG* fasting plasma glucose, HbA_{1C} glycosylated haemoglobin, *MET-XR* metformin-extended release, *NR* not reported, *od* once daily, *PL* placebo, *pts* patients

* $p < 0.001$ vs. PL

[a] Primary endpoint at week 26

[b] Pts ($n = 155$) originally randomized to PL in CANTATA-M were switched to sitagliptin 100 mg od for this ext; efficacy data were not reported

[c] Value is for the whole trial population

[d] Noninferiority of CAN 100 or 300 mg od vs. MET-XR was established (no further details reported)

Table 2 Efficacy of oral canagliflozin as add-on therapy to metformin, with or without other oral antihyperglycaemic agents, in adults with inadequately-controlled T2D in randomized, double-blind, phase 3 (or phase 4 [37]) trials and a double-blind extension

Study (acronym)	Regimen (mg od) [no. of pts]	Week of eval	Change from BL [BL]		% of pts with HbA_{1C} <7%	Change from BL [BL]
			HbA_{1C}[a] (%)	FPG (mmol/L)		Bodyweight (kg)
Add-on to MET						
Lavalle-González et al [34]	CAN 100 + MET [368]	26	−0.79** [7.9]	−1.5** [9.4]	46**	−3.3** [88.7]
(CANTATA-D)	CAN 300 + MET [367]		−0.94** [8.0]	−2.1** [9.6]	58**	−3.6** [85.4]
	SIT 100 + MET [366]		−0.82[b] [7.9]	−1.1[b] [9.4]	55[b]	−1.1[b] [87.6]
	PL + MET [183]		−0.17 [8.0]	+0.1 [9.1]	30	−1.1 [86.7]
	CAN 100 + MET [368]	52	−0.73[c] [7.9]	−1.5† [9.4]	41[d]	−3.3† [88.7]
	CAN 300 + MET [367]		−0.88[c] [8.0]	−2.0† [9.6]	55[d]	−3.7† [85.4]
	SIT 100 + MET [366]		−0.73 [7.9]	−1.0 [9.4]	51	−1.2 [87.6]
Cefalu et al [35]	CAN 100 + MET [483]	52	−0.82[c] [7.8]	−1.35[b] [9.2]	54[b]	−3.7††[e] [86.8]
(CANTATA-SU)	CAN 300 + MET [485]		−0.93[c] [7.8]	−1.52[b] [9.1]	60[b]	−4.0††[e] [86.6]
	GLIM + MET [482]		−0.81 [7.8]	−1.02 [9.2]	56	+0.7 [86.6]
Leiter et al [36]	CAN 100 + MET [393]	104	−0.65 [7.8]	−1.1[f] [9.2]	43[b]	−4.1[f] [86.8]
(CANTATA-SU ext)	CAN 300 + MET [377]		−0.74[f] [7.8]	−1.3[f] [9.1]	50[b]	−4.2[f] [86.6]
	GLIM + MET [381]		−0.55 [7.8]	−0.6 [9.2]	44	+0.9 [86.6]
Add-on to MET + Other Oral Antihyperglycaemic Agent						
Wilding et al [14]	CAN 100 + MET + SU [157]	26	−0.85** [8.1]	−1.0** [9.6]	43**	−1.9**[e] [93.5]
(CANTATA-MSU)	CAN 300 + MET + SU [156]		−1.06** [8.1]	−1.7** [9.3]	57**	−2.5**[e] [93.5]
	PL + MET + SU [156]		−0.13 [8.1]	+0.2 [9.4]	18	−0.8 [90.8]
	CAN 100 + MET + SU [157]	52[b]	−0.74 [8.1]	−1.1 [9.6]	39	−2.0 [93.5]
	CAN 300 + MET + SU [156]		−0.96 [8.1]	−1.5 [9.3]	53	−3.1 [93.5]
	PL + MET + SU [156]		+0.01 [8.1]	+0.6 [9.4]	19	−1.0 [90.8]
Schernthaner et al [15]	CAN 300 + MET + SU [377]	52	−1.03[c] [8.1]	−1.7** [9.4]	48[b]	−2.3** [87.6]
(CANTATA-D2)	SIT 100 + MET + SU [378]		−0.66 [8.1]	−0.3 [9.1]	35	+0.1 [89.6]
Forst et al [16]	CAN 100 + MET + PIO [113]	26	−0.89** [8.0]	−1.5** [9.4]	47*	−2.6** [94.2]
	CAN 300 + MET + PIO [114]		−1.03** [7.8]	−1.8** [9.1]	64**	−3.7** [94.4]
	PL + MET + PIO[g] [115]		−0.26 [8.0]	+0.1 [9.1]	33	−0.2 [94.0]
	CAN 100 + MET + PIO [103]	52	−0.92 [8.0]	−1.5 [9.4]	52	−2.5 [94.2]
	CAN 300 + MET + PIO [96]		−1.03 [7.8]	−1.8 [9.1]	66	−3.6 [94.4]
Rodbard et al [37]	CAN[h] + MET + SIT [107]	26	−0.91** [8.5]	−1.7** [10.3]	32**	−3.1**[e] [93.8]
	PL + MET + SIT [106]		−0.01 [8.4]	−0.1 [10.0]	12	−1.6 [89.9]

Changes from BL are least squares means and BL values are means

BL baseline, *BGD* between-group difference, *CAN* canagliflozin, *ext* extension, *eval* evaluation, *FPG* fasting plasma glucose, *GLIM* glimepiride (uptitrated to 6 or 8 mg od), *HbA_{1C}* glycosylated haemoglobin, *MET* metformin (generally ≥2000 mg/day; ≥1500 mg/day if higher dosages not tolerated, *od* once daily, *PIO* pioglitazone (30 or 45 mg/day), *PL* placebo, *pts* patients, *SIT* sitagliptin, *SU* sulfonylurea (≥50% maximal dosage)

* $p < 0.01$, ** $p \leq 0.001$ vs. PL; † $p < 0.001$, †† $p < 0.0001$ vs. active comparator group

[a] Primary endpoint at week 26 [14, 16, 34, 37] or 52 [15, 35]

[b] No formal statistics performed/reported for CAN vs. PL [14], GLIM [35, 36] or SIT [15], or SIT vs. PL [34], for these endpoints/timepoints

[c] Based on prespecified criteria, CAN 100 was noninferior to, and CAN 300 more effective than, SIT [15, 34] and GLIM [35]

[d] Difference vs. SIT was not significant for CAN 300 but significant for CAN 100, based on the 95% CIs of the odds ratios

[e] P-values are for percentage changes in bodyweight, and are assumed to also apply to kg changes

[f] Significantly favoured CAN vs. GLIM, based on 95% CI for BGD

[g] Ninety pts in this group entered the 26-week ext, during which they received SIT + MET + PIO to maintain blinding

[h] Pts received CAN 100 or 300 mg od; pooled data for these groups are presented

Table 3 Efficacy of oral canagliflozin as add-on therapy to insulin- or incretin mimetic-based therapy or sulfonylurea monotherapy in prespecified [43, 44] or post hoc [45] subgroup analyses of the phase 3 CANVAS trial

Regimen (mg od) [no. of pts]	Week of eval	HbA_{1C} (%)		FPG (mmol/L)		% of pts with HbA_{1C} <7%	Bodyweight (kg)	
		Change from BL [BL]	Diff vs. PL	Change from BL	Diff vs. PL		Change from BL	Diff vs. PL
Add-on to INS therapy [43]								
CAN 100 + INS ± OAA [661]	18	−0.63[a] [8.3]	−0.62**	NR [9.2]	−1.2**	19.8**	NR [94.4]	−1.9**
CAN 300 + INS ± OAA [660]		−0.75[a] [8.3]	−0.73**	NR [9.2]	−1.6**	25.8**	NR [94.8]	−2.4**
PL + INS ± OAA [636]		−0.1[a] [8.3]		NR [9.2]		8.3	NR [94.8]	
CAN 100 + INS ± OAA [664]	52	−0.55 [8.3]	−0.58[b]	NR [9.2]	−1.1[b]	23.2	NR [94.4]	−2.8[b]
CAN 300 + INS ± OAA [664]		−0.69 [8.3]	−0.73[b]	NR [9.2]	−1.5[b]	28.6	NR [94.8]	−3.5[b]
PL + INS ± OAA [639]		+0.03 [8.3]		NR [9.2]		9.9	NR [94.8]	
Add-on to SU [44]								
CAN 100 + SU [42]	18	−0.70 [8.3]	−0.74**	−1.4 [10.3]	−2.1	25	−0.6 [85.1]	−0.4%
CAN 300 + SU [40]		−0.79 [8.3]	−0.83**	−2.0 [9.8]	−2.7**	33	−2.0 [80.4]	−1.8%*
PL + SU [45]		+0.04 [8.5]		+0.7 [10.3]		5	−0.2 [85.5]	
Add-on to incretin-mimetic therapy [45]								
CAN 100 + DPP4i ± OAA [103]	18	−0.46 [8.1]	−0.56[b]	NR	−1.1[b]	22	−2.7 [91.5]	−2.0[b]
CAN 300 + DPP4i ± OAA [111]		−0.64 [8.0]	−0.75[b]	NR	−1.5[b]	34[b]	−3.5 [92.4]	−2.7[b]
PL + DPP4i ± OAA [102]		+0.1 [8.1]		NR		15	−0.8 [88.6]	
CAN 100 + GLP-1ra ± OAA [35]	18	−0.83 [8.2]	−1.00[b]	NR	−1.8[b]	29[b]	−3.3 [109]	−2.7[b]
CAN 300 + GLP-1ra ± OAA [30]		−0.89 [8.3]	−1.06[b]	NR	−2.5[b]	35[b]	−3.9 [111]	−3.3[b]
PL + GLP-1ra ± OAA [30]		+0.17 [7.9]		NR		7	−0.6 [106]	

Changes from BL are least squares means, BL values are means. INS dosage was ≥20 IU/day; SU, DPP4i and GLP-1ra dosages were stable

BL baseline, *CAN* canagliflozin, *diff* difference, *DPP4i* dipeptidyl peptidase 4 inhibitor, *eval* evaluation, *FPG* fasting plasma glucose, GLP-1ra glucagon-like peptide-1 receptor agonist, HbA_{1C} glycosylated haemoglobin, *INS* insulin, *NR* not reported, *OAA* other antihyperglycaemic agent, *od* once daily, *PL* placebo, *pts* patients, *SU* sulfonylurea

* $p < 0.02$, ** $p < 0.001$ vs. PL

[a] Estimated from a graph

[b] Between-group difference significantly favoured CAN regimen based on the 95% CI (p-values not available, as outcome was not prespecified [43, 44] or the analysis did not perform statistical testing for CAN vs. PL [45])