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R&D INSIGHT REPORT

Canagliflozin: First Global Approval

Shelley Elkinson · Lesley J. Scott

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Abstract Canagliflozin (Invokana™), an oral selective sodium-glucose co-transporter 2 (SGLT2) inhibitor, is under global development with Mitsubishi Tanabe Pharma and Janssen Pharmaceuticals, a subsidiary of Johnson and Johnson, for the treatment of type 2 diabetes mellitus. SGLT2 are mainly located in the proximal tubule of the kidney and are involved in the reabsorption of filtered glucose from the glomeruli into the body. Inhibition of SGLT2 lowers blood glucose in an insulin independent manner as a consequence of blocking reabsorption of filtered glucose in the glomeruli, thereby increasing urinary excretion of glucose and, in turn, potentially reducing bodyweight. Canagliflozin is the first SGLT2 inhibitor to be approved in the USA and is under regulatory review in the EU. This article summarizes the milestones in the development of canagliflozin, leading to its first approval for use in adults with type 2 diabetes.

1 Introduction

Type 2 diabetes mellitus is a chronic, progressive condition that affects more than 220 million people worldwide, with approximately 8.3 % of the population in the USA having the disease [1]. It is characterized by hyperglycaemia resulting from pancreatic β-cell dysfunction and insulin resistance, and is associated with major microvascular and macrovascular complications [1, 2]. Various classes of drugs, in conjunction with lifestyle modifications, are utilized in the management of the disease, including oral biguanides (e.g. metformin), sulfonylureas (e.g. glibenclamide, glipizide, glimepiride), thiazolidinediones (e.g. pioglitazone) and dipeptidyl peptidase-4 inhibitors (e.g. sitagliptin, saxagliptin, linagliptin), and the injectable meglitinides (e.g. repaglinide, nateglinide), glucagon-like peptide 1 receptor agonists (e.g. exenatide, liraglutide) and insulins (e.g. insulin glargine, insulin lispro, Neutral Protamine Hagedorn insulin) [3].

International guidelines emphasise the need for an individualized approach to the management of diabetes, with the biguanide metformin (as an adjunct to diet and exercise) considered the optimal first-line drug [3]. Ultimately most patients will require combination therapy. The choice of individual agents, in addition to targeting glycaemic control, should aim to minimize the risk of adverse effects, particularly bodyweight gain and hypoglycaemia (both of which are considered cardiovascular risk factors), with sulfonylureas, meglitinides and insulins associated with an increased risk of hypoglycaemia and bodyweight gain, and thiazolidinediones associated with bodyweight gain [3]. However, despite the availability of various classes of antihyperglycaemic drugs with differing mechanisms of action, more than half of patients fail to achieve adequate glycaemic control; thus, novel pharmacological approaches are required to improve glycaemic control [1, 2].

The kidneys play an important role in glucose homeostasis and are responsible for approximately 20 % of total glucose released into the blood in normal fasting humans, thereby contributing to hyperglycaemia [1, 4]. Preventing

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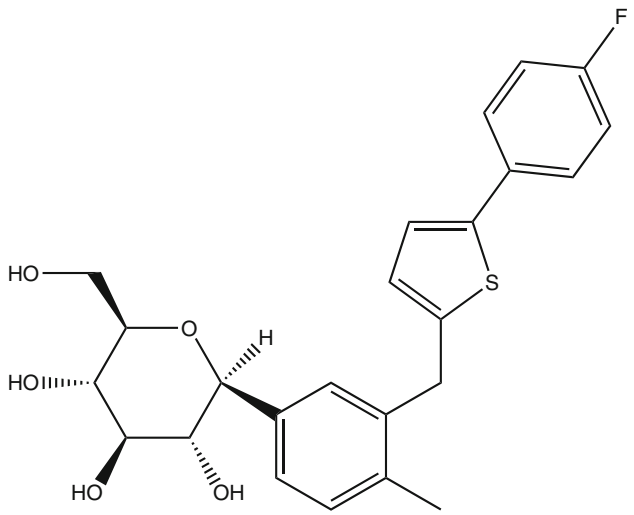
S. Elkinson (✉) · L. J. Scott
Adis R&D Insight, 41 Centorian Drive,
Private Bag 65901, Mairangi Bay, North Shore 0754,
Auckland, New Zealand
e-mail: dru@adis.com

Features and Properties of Canagliflozin

Alternative names	Invokana™; JNJ 28431754; JNJ-28431754; JNJ28431754; TA 7284; TA-7284; TA7284
Class	Glucosides, Small-molecules, Thiophenes
Mechanism of Action	Sodium-glucose co-transporter 2 inhibitor
Route of Administration	Oral
Pharmacodynamics	Significantly increases urinary glucose excretion; lowers fed and fasting blood glucose levels and HbA_{1c}, and; reduces bodyweight in patients with type 2 diabetes, obese adults and/or healthy adult volunteers
Pharmacokinetics	Rapid, dose-proportional absorption after oral administration, with steady-state plasma concentrations achieved in 4–5 days; extensively bound to plasma proteins
	Approximately 51 % of the drug is eliminated in the faeces (41.5 % as parent compound) and 33 % (mainly as metabolites) in the urine
Adverse events	
Most frequent (incidence ≥5 %)	Female genital mycotic infections, urinary tract infections and increased urination
ATC codes	
WHO ATC code	A08 (Antiobesity Preparations, Excl. Diet Products), A10B-X (Other oral blood glucose lowering drugs, excluding insulins)
EphMRA ATC code	A10X (Other Drugs Used in Diabetes), A8 (Antiobesity Preparations, Excluding Dietetics)
Chemical Name	(3R,4R,5S,6R)-2-[3-[[5-(4-Fluorophenyl)thiophen-2-yl]methyl]-4-methylphenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol

reabsorption of glucose from the proximal tubules via inhibition of the high-capacity, low-affinity sodium-glucose co-transporter 2 (SGLT2), which is responsible for up to 90 % of glucose reabsorption in animals, provides a novel insulin-independent mechanism for lowering blood glucose [1, 4]. In this newest class of antihyperglycaemic agents, the SGLT2 inhibitors, canagliflozin is approved in the USA [5] and dapagliflozin is approved in the EU [6], with empagliflozin and ipragliflozin in phase III development.

Canagliflozin, a new oral, once-daily SGLT2 inhibitor, was developed by Mitsubishi Tanabe Pharma (formerly Tanabe Seiyaku) and Johnson and Johnson for the treatment of type 2 diabetes [7]. In March 2013, canagliflozin was the first SGLT2 inhibitor to be approved in the USA for the treatment of adult patients with type 2 diabetes [7]. Canagliflozin is undergoing regulatory review in the EU [8] and is in phase III development in Asia, Australia, Canada, New Zealand and South America for the treatment of type 2 diabetes [9]. It is also in phase II development for the treatment of obesity in the USA and Europe [10]. In the USA, canagliflozin is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes [5]. The recommended starting dosage is 100 mg once daily taken before the first meal and, in patients with an estimated glomerular filtration rate (eGFR) of at least 60 mL/min/1.73 m^2 who require additional glycaemic control, the dosage may be increased to 300 mg once daily if required [5].



Chemical structure of canagliflozin

Janssen Pharmaceuticals, a subsidiary of Johnson and Johnson, submitted a New Drug Application (NDA) with the FDA in May 2012 [9]. In January 2013, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted to recommend approval of canagliflozin, proposed trade name of Invokana™, for this indication [11]. The submission was based on data from a phase III clinical trial programme comprising nine randomised, placebo- and active comparator-controlled, multicentre trials in over 10,000 patients, including three large trials conducted in older patients, patients with moderate renal impairment and patients who have or are at high risk of developing cardiovascular disease [11]. Along with the approval, the FDA have requested five postmarketing studies, including a cardiovascular outcomes trial (see subsequent discussion of the CANagliflozin cardioVascular Assessment Study [CANVAS]), an enhanced pharmacovigilance program, a

bone safety study and two paediatric studies [12]. Janssen submitted a Marketing Authorisation Application for canagliflozin to the European Medicines Agency in June 2012 for approval of the drug to treat adult patients with type 2 diabetes [13]. This application was based on the same clinical trial programme as the FDA application, with a decision expected in the third quarter of 2013.

Mitsubishi Tanabe Pharma plans to file an NDA for canagliflozin in Japan in 2013 [14]. Key phase II and III studies conducted in Japan have or are evaluating the glycaemic efficacy of monotherapy (NCT01413204 [15]; NCT01022112 [16, 17]; both completed) or combination therapy (NCT01387737; ongoing [18]) with canagliflozin in adult patients with type 2 diabetes.

1.1 Company Agreements

In July 2000, Tanabe Seiyaku and Johnson and Johnson entered into a research and development agreement for SGLT2 inhibitors providing Johnson and Johnson with exclusive worldwide development and marketing rights for SGLT2 inhibitors in North America, South America, Europe, the Middle East, Africa, Australia, New Zealand and parts of Asia, excluding Japan [7].

Mitsubishi Pharma Corporation and Tanabe Seiyaku Co. Ltd merged to form Mitsubishi Tanabe Pharma Corporation in October 2007 [19].

In March 2012, Mitsubishi Tanabe Pharma and Daiichi Sankyo entered into a sales agreement for canagliflozin and teneligliptin [14]. Under the agreement, both companies will conduct joint sales for both compounds in Japan, under a one-brand, two-channel framework.

2 Scientific Summary

2.1 Pharmacodynamics

Canagliflozin, is a highly selective SGLT2 inhibitor and, as a consequence, inhibits reabsorption of filtered glucose in the proximal tubules of the kidney and lowers the renal threshold for glucose (RT_G), thereby increasing urinary glucose excretion [5]. In in vitro studies, canagliflozin exhibited an approximately 200-fold higher selectivity for SGLT2 than for SGLT1; respective concentrations of canagliflozin required to produce 50 % inhibition were approximately 2.2 nmol/L and 0.44 μmol/L (reviewed by Bailey [2]).

The pharmacodynamic effects of canagliflozin in terms of inhibition of reabsorption of glucose and reducing RT_G have been demonstrated in animal studies [20] and in studies in healthy adult volunteers [21, 22], obese adults [23] and patients with type 2 diabetes [24, 25]. Dose dependent decreases in RT_G were observed after single and multiple doses of canagliflozin in patients with type 2 diabetes, with suppression occurring throughout the 24-hour dosing interval following canagliflozin 100 and 300 mg once daily and within the first day of dosing [5]. In phase I studies in patients with type 2 diabetes, maximal suppression of mean RT_G over a 24-h period occurred with canagliflozin 300 mg once daily (reduced from 240 mg/dL at baseline to $\approx$70–90 mg/dL) [5].

After 28 days, canagliflozin treatment significantly improved glycaemic control and reduced bodyweight compared with placebo in a study in 29 patients with type 2 diabetes with inadequate glycaemic control on insulin and up to one OAD [25]. A dose-ranging study in 80 obese adults also showed significant reductions in bodyweight during 2 weeks of canagliflozin treatment compared with placebo [23].

In single-dose studies in healthy adult volunteers [21] and patients with type 2 diabetes [26], a single dose of canagliflozin 300 mg prior to a mixed-meal delayed intestinal glucose absorption and reduced postprandial glucose levels. In addition, in healthy adult volunteers, single-dose canagliflozin reduced insulin excursion after a mixed meal [21].

In 16-day and 12-week studies in patients with type 2 diabetes, there were significant improvements in calculated measures of β-cell function at study end with canagliflozin ($\geq$100 mg/day) compared with placebo [27].

In 60 healthy adult volunteers, single oral doses of canagliflozin 300 mg or 1,200 mg (i.e. 4× maximum therapeutic dose) had no clinically relevant effects on the corrected QT interval in a double-blind, placebo- and active comparator-controlled, 4-way crossover study [28].

Key company agreements

Companies	Type of agreement	Key elements in agreement	Date of agreement	Agreement status
Tanabe Seiyaku & Johnson & Johnson	License	Worldwide license agreement to develop and market canagliflozin	31/07/2000	Completed/ active
Mitsubishi Pharma Corporation & Tanabe Seiyaku	Merger	Mitsubishi Pharma Corporation merged with Tanabe Seiyaku to form Mitsubishi Tanabe Pharma Corporation	1/10/2007	Completed/ active
Mitsubishi Tanabe Pharma & Daiichi Sankyo	License	Sales agreement for canagliflozin and teneligliptin in Japan	6/03/2012	Completed/ active

2.2 Pharmacokinetics

The pharmacokinetics of canagliflozin are similar in healthy adult volunteers and patients with type 2 diabetes [5].

After oral administration canagliflozin is rapidly absorbed in a dose-dependent manner across a dose range of 50–300 mg [5, 29], with the time taken to attain maximum plasma concentration (t_{max}) and the elimination half-life ($t_{½}$) of the drug being independent of dose [29]. After canagliflozin 100 or 300 mg, median t_{max} values occurred within 1–2 h, with steady-state levels attained after 4–5 days following multiple once daily doses [5]. Canagliflozin does not exhibit time-dependent pharmacokinetics and, following multiple 100 and 300 mg doses, accumulates in the plasma up to 36 % [5].

The mean absolute oral bioavailability is approximately 65 % [5]. Although there were no clinically relevant effects on the pharmacokinetics of canagliflozin when it was administered with a high-fat meal, based on its potential to reduce postprandial plasma glucose (PPG) excursions due to delayed intestinal glucose absorption, it is recommended that canagliflozin is taken before the first meal of the day [5].

The mean steady-state volume of distribution of canagliflozin after a single intravenous infusion was 119 L [5]. The drug is extensively (99 %) bound to plasma proteins, mainly albumin, with the extent of binding being independent of the plasma concentration of canagliflozin [5].

Canagliflozin is mainly metabolized via glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) 1A9 and UGT2B4 to two inactive *O*-glucuronide metabolites, with minor ($\approx$7 % in humans) metabolism by cytochrome P450 (CYP) 3A4 [5].

After a single radiolabelled oral dose of canagliflozin, 41.5, 7.0 and 3.2 % of the dose was recovered in the faeces as parent compound, a hydroxylated metabolite and an *O*-glucuronide metabolite, respectively [5]. Approximately 33 % of the drug was eliminated in the urine, mainly as *O*-glucuronide metabolites (30.5 %) [5], with <1 % of the dose eliminated in the urine as unchanged parent compound [5, 29].

The apparent $t_{½}$ of canagliflozin after 100 and 300 mg doses was 10.6 and 13.1 h [5]. Renal clearance of the drug after 100 and 300 mg doses ranged from 1.30 to 1.55 mL/min. Following intravenous administration, mean systemic clearance was 192 mL/min [5].

Gender, age, bodyweight and race did not alter the pharmacokinetics of canagliflozin to a clinically relevant extent [5].

Renal impairment did not affect maximum plasma concentrations (C_{max}) of canagliflozin and there were no clinically meaningful changes in area under the plasma concentration–time (AUC) values in patients with mild (eGFR 60–<90 mL/min/1.73 m^2), moderate (eGFR 30–<60 mL/min/1.73 m^2) or severe (eGFR 15–<30 mL/min/1.73 m^2) renal impairment compared with healthy volunteers (eGFR $\geq$ 90 mL/min/1.73 m^2) [5]. The pharmacodynamic response to canagliflozin declines with increasing severity of renal impairment, with a maximum recommended dosage of 100 mg once daily in those with moderate renal impairment (eGFR 45–<60 mL/min/1.73 m^2). Canagliflozin is not recommended in patients with an eGFR of <45 mL/min/1.73 m^2. Canagliflozin is negligibly removed by haemodialysis [5].

Mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment had no clinically meaningful effect on the pharmacokinetics of canagliflozin [5]. There is no clinical experience with canagliflozin in patients with severe (Child-Pugh class C) hepatic impairment and thus the drug is not recommended in these patients [5].

2.2.1 Potential Drug Interactions

In in vitro studies, canagliflozin did not induce CYP3A4, CYP2C9, CYP2C19, CYP2B6 and CYP1A2 enzyme expression or inhibit CYP1A2, CYP2A6, CYP2C19, CYP2D6 or CYP2E1 enzymes, although it weakly inhibited CYP2B6, CYP2C8, CYP2C9 and CYP3A4 [5].

The AUC value for canagliflozin was reduced by 51 % when it was coadministered with rifampin, a nonselective inducer of several UGT enzymes including UGT1A8 and UGT2B4 [5]. If an inducer of UGTs (e.g. rifampin, phenytoin, ritonavir) must be coadministered with canagliflozin, then consider increasing the dosage to 300 mg once daily based on the patient's tolerance of canagliflozin 100 mg once daily, renal function and requirement for additional glycaemic control. Consider using another antihyperglycaemic agent in patients with an eGFR 45–<60 mL/min/1.73 m^2 receiving concomitant therapy with a UGT inducer [5].

When canagliflozin was coadministered with digoxin, C_{max} and AUC values of digoxin were increased by 20 and 36 % [5]. Hence, patients receiving canagliflozin with concomitant digoxin should be monitored appropriately [5].

2.3 Therapeutic Trials

2.3.1 Monotherapy Trials in Patients with Type 2 Diabetes Mellitus

Monotherapy with oral canagliflozin 100 and 300 mg once daily for 26 weeks significantly reduced glycosylated haemoglobin (HbA_{1c}) levels from baseline compared with placebo in adult patients with type 2 diabetes inadequately controlled by diet and exercise in the CANagliflozin

Treatment And Trial Analysis (CANTATA)-M study ($n = 584$) [30]. The difference in least-square mean [LSM] change from baseline in HbA_{1c} level between canagliflozin 100 mg/day or 300 mg/day and placebo was −0.91 and −1.16 % (both $p < 0.001$) (primary endpoint), with a significantly ($p < 0.001$) greater proportion of canagliflozin than placebo recipients achieving an HbA_{1c} target level of <7.0 % at study end in this double-blind, multinational, phase III trial. There were no significant between-group differences in the proportion of patients achieving an HbA_{1c} level of <6.5 %. LSM changes in fasting plasma glucose (FPG) and bodyweight were also significantly ($p < 0.001$) greater in the canagliflozin 100 and 300 mg groups than in the placebo group [30].

In Japan, the glycaemic efficacy of high- and low-dose canagliflozin monotherapy compared with placebo was evaluated in adult (≥20 years of age) patients with type 2 diabetes in a 12-week, dose-ranging, phase II, double-blind, multicentre trial (NCT01022112; $n = 381$ evaluable) [16, 17] and a 24-week, phase III, double-blind, multicentre trial (NCT01413204; $n = 272$) [15]. In the dose-ranging study, at 12 weeks, mean reductions from baseline in HbA_{1c} (reduced by 0.61–0.88 % vs. an increase of 0.11 % with placebo) and FPG levels (by 24.7–38.3 vs. 3.0 mg/dL) were significantly greater with canagliflozin 50, 100, 200 and 300 mg once-daily than with placebo (no p values reported) [16].

2.3.2 *Combination Therapy Trials in Patients with Type 2 Diabetes*

Canagliflozin 100 or 300 mg once daily, as add-on combination therapy to stable dosages of metformin, significantly improved glycaemic control compared with placebo plus metformin in adult patients with type 2 diabetes inadequately controlled on metformin monotherapy in the 52-week, double-blind, multinational CANTATA-D study ($n = 1{,}284$) [5, 31]. At 26 weeks, there were significantly ($p < 0.001$) greater reductions from baseline in mean HbA_{1c} (reduced by 0.79 and 0.94 vs. 0.17 %) (primary endpoint), FPG (reduced by 27 and 38 mg/dL vs. increase of 2 mg/dL) and 2-h PPG (reduced by 48 and 57 vs. 10 mg/dL) levels in the canagliflozin 100 and 300 mg groups than in the placebo group [5]. In addition, significantly ($p < 0.001$) more patients in the canagliflozin 100 and 300 mg groups than in the placebo group achieved a target HbA_{1c} level of <7 % (46 and 58 vs. 30 %). Compared with placebo, canagliflozin recipients also experienced significantly ($p < 0.001$) greater reductions in bodyweight after 26 weeks [5]. The study also included a sitagliptin active-comparator control arm control [31].

In the 52-week CANTATA-SU study ($n = 1{,}450$), once daily canagliflozin 100 or 300 mg as add-on therapy to metformin was shown to be noninferior to glimepiride plus metformin in terms of reductions in HbA_{1c} level from baseline to 52 weeks (reduced by 0.82 and 0.93 vs. 0.81 %) (primary endpoint) in patients with type 2 diabetes with inadequate glycaemic control on stable dosages of metformin monotherapy [32]. Furthermore, canagliflozin 300 mg/day was shown to be superior to glimepiride plus metformin for this endpoint. Improvements in bodyweight at 52 weeks were also significantly ($p < 0.001$) better in the canagliflozin 100 and 300 mg groups than in the glimepiride group. In this double-blind, multinational trial, the dosage of glimepiride was titrated over 52 weeks up to 6 or 8 mg/day, with a mean dose of 5.6 mg [32].

In patients with type 2 diabetes inadequately controlled with metformin plus a sulfonylurea ($n = 469$), once-daily canagliflozin 100 or 300 mg as add-on therapy to stable dosages of metformin plus a sulfonylurea agent provided better glycaemic control than add-on placebo at 26 weeks in the double-blind, multinational CANTATA-MSU study [33]. After 26 weeks, LSM changes from baseline in HbA_{1c} levels were significantly ($p < 0.001$) greater in the canagliflozin 100 and 300 mg groups than in the placebo group (−0.85 and −1.06 vs. −0.13 %) (primary endpoint). There were also significantly ($p < 0.001$) greater improvements in FPG levels and bodyweight in the two canagliflozin groups than in the placebo group [33]. Moreover, add-on once-daily canagliflozin 100 or 300 mg significantly improved indices of β-cell function at 26 weeks compared with add-on placebo [34]. There were no significant between-group differences for changes from baseline in systolic blood pressure (SBP) and triglyceride levels [33].

After 52 weeks in the CANTATA-D2 study, canagliflozin 300 mg once daily as add-on therapy to metformin plus a sulfonylurea was shown to be noninferior to add-on sitagliptin 100 mg/day with respect to changes in HbA_{1c} levels (−1.03 vs. −0.66 %; primary endpoint) in patients with type 2 diabetes inadequately controlled with stable dosages of metformin plus a sulfonylurea agent ($n = 755$) [35]. A subsequent statistical analysis demonstrated the superiority of add-on canagliflozin treatment to that of add-on sitagliptin (LSM between-group difference for changes in HbA_{1c} −0.37 %; 95 % CI −0.50 to −0.25). There were also significantly ($p < 0.001$) greater reductions in FPG levels, bodyweight and SBP in canagliflozin than in sitagliptin recipients in this double-blind, multinational study. The proportion of patients achieving an HbA_{1c} level of <7 and <6.5 % in the canagliflozin group was 47.6 and 22.5 %, with respective rates in the sitagliptin group of 35.3 and 18.9 % [35].

In patients with type 2 diabetes inadequately controlled with stable dosages of metformin plus pioglitazone, add-on canagliflozin 100 or 300 mg once daily significantly

improved glycaemic control compared with placebo at 26 weeks in the double-blind, multinational CANTATA-MP study [36]. At 26 weeks, LSM changes from baseline in HbA_{1c} levels were −0.89 and −1.03 % in the canagliflozin 100 and 300 mg groups versus −0.26 % in the placebo group (both $p < 0.001$ vs. placebo) (primary endpoint). Canagliflozin recipients also experienced significantly ($p < 0.001$) greater reductions than placebo recipients in FPG levels, SBP and bodyweight at 26 weeks [5, 36]. In addition significantly more recipients of canagliflozin 100 and 300 mg/day than placebo recipients achieved an HbA_{1c} level of <7 % (46.9 and 64.3 vs. 32.5 %) [36].

The ongoing, double-blind, multinational, CANVAS evaluated add-on canagliflozin 100 or 300 mg once daily in patients with type 2 diabetes inadequately controlled on insulin with or without other antihyperglycaemic drugs and who had an elevated cardiovascular risk ($n = 4{,}330$) [37]. In a pre-specified substudy in 1,718 patients with type 2 diabetes inadequately controlled with stable insulin dosages, add-on once-daily canagliflozin 100 or 300 mg significantly reduced HbA_{1c} levels compared with placebo at 18 weeks (difference from placebo −0.65 and −0.73 %; both $p < 0.001$ vs. placebo) (primary endpoint), with significantly ($p < 0.001$) more patients in the canagliflozin groups than in the placebo group achieving an HbA1c level of <7.0 %. (20 and 25 vs. 8 %) [5, 37]. There were also significant ($p < 0.001$) improvements in other indices, including FPG levels, bodyweight and SBP [37].

An 18-week, phase III, double-blind, placebo-controlled, multinational trial conducted in Asia has evaluated the efficacy of canagliflozin 100 or 300 mg once daily in patients with type 2 diabetes with inadequate glycaemic control on metformin alone or in combination with a sulfonylurea (NCT01381900) [38].

The glycaemic efficacy of canagliflozin 50–300 mg once daily or 300 mg twice daily as add-on therapy to metformin was also shown in an earlier phase II, 12-week, dose-ranging, double-blind, placebo- and active comparator-controlled, multinational trial in adult patients with type 2 diabetes inadequately controlled on metformin (NCT00642278; $n = 451$) [39]. After 12 weeks, mean HbA_{1c} levels were reduced from baseline by 0.70–0.95 % with canagliflozin plus metformin (all $p < 0.001$ vs. placebo; mean reduction in placebo group −0.22 %) and by 0.74 % with sitagliptin plus metformin (active comparator-control group; no statistical comparison vs. canagliflozin groups). There were also significantly ($p < 0.001$) greater improvements from baseline in canagliflozin groups than in the placebo group in mean FPG levels (reduced by 16.2–27 mg/dL vs. an increase of 3.6 mg/dL with placebo) and bodyweight (reduced by 2.3–3.4 vs. 1.1 %) at 12 weeks [39].

2.3.3 In Special Patient Populations with Type 2 Diabetes

In older patients (aged 55–80 years) with type 2 diabetes with inadequate glycaemic control on antihyperglycaemic agents ($n = 714$), once-daily canagliflozin 100 or 300 mg as add-on therapy to stable dosages of antihyperglycaemic agents significantly ($p < 0.001$) reduced mean HbA_{1c} levels from baseline compared with placebo at 26 weeks (mean change −0.60 and −0.73 vs. −0.03 %) (primary endpoint) [40]. In this ongoing double-blind multinational study (NCT01106551), 76 % of patients were on two or more background antihyperglycaemic agents, which included metformin (85.3 % of patients), sulfonylureas (48.7 %) and insulin (32.7 %). There were also significantly (all $p < 0.001$) greater improvements from baseline in mean FPG levels, bodyweight, SBP and high-density lipoprotein cholesterol levels in the canagliflozin 100 mg and 300 mg groups than in the placebo group [40].

In adult patients with type 2 diabetes and moderate renal impairment (eGFR ≥30 to <50 mL/min/1.73 m^2) ($n = 269$), add-on therapy with canagliflozin 100 or 300 mg once daily for 26 weeks significantly ($p < 0.05$) improved HbA_{1c} levels from baseline compared with add-on placebo (mean reduction −0.33 and −0.44 vs. −0.03 %) [41]. In this double-blind, multinational study, 74 % of patients received background therapy with insulin and 31.2 % were receiving a sulfonylurea. Patients in both canagliflozin groups showed numerically greater improvements in FPG levels, bodyweight and SBP than those in the placebo group [41].

2.4 Adverse Events

Oral canagliflozin was generally well tolerated in patients with type 2 diabetes participating in clinical trials, including in older adults [40] and in patients with moderate renal impairment [41]. In a pooled analysis of four 26-week placebo-controlled studies (one monotherapy and four combination therapy studies) in 2,313 evaluable patients with type 2 diabetes (mean duration of canagliflozin exposure 24 weeks), the most common adverse events were female genital mycotic infections (10.4 % in the canagliflozin 100 mg group, 11.4 % in the canagliflozin 300 mg group and 3.2 % in the placebo group), urinary tract infection (5.9, 4.3 and 4.0 %) and increased urination (5.3, 4.6 and 0.8 %) [5]. Other adverse events occurring in at least 2% of patients receiving canagliflozin 100 or 300 mg/day and more frequently in canagliflozin than placebo recipients were male genital mycotic infections, vulvovaginal pruritus, thirst, constipation and nausea [5].

The nature and frequency of adverse events in a larger pooled analysis of eight placebo-controlled trials in patients with type 2 diabetes was consistent with the

Key clinical trials of canagliflozin in type 2 diabetes

Drugs	Study phase	Study status	Study location	Trial identifiers	Company
Canagliflozin (high-dose vs. low-dose) ± oral antihyperglycaemics	III	Enrolment completed	Japan	NCT01387737	Mitsubishi Tanabe Pharma
Canagliflozin + metformin + sulfonylurea vs. placebo + metformin + sulfonylurea	III	Completed	Multinational	NCT01106625 CANTATA-MSU	Johnson & Johnson
Canagliflozin + metformin vs. glimepiride + metformin	III	Completed	Multinational	NCT00968812 CANTATA-SU	Johnson & Johnson
Canagliflozin + metformin vs. placebo + metformin, (sitagliptin + metformin active control group)	III	Completed	Multinational	NCT01106677 CANTATA-D	Johnson & Johnson
Canagliflozin + metformin + pioglitazone vs. placebo + metformin + pioglitazone	III	Completed	Multinational	NCT01106690 CANTATA-MP	Johnson & Johnson
Canagliflozin + antihyperglycaemics vs. placebo + antihyperglycaemics	III	Ongoing	Multinational	NCT01106651	Johnson & Johnson
Canagliflozin + metformin + sulfonylurea vs. sitagliptin + metformin + sulfonylurea	III	Completed	Multinational	NCT01137812 CANTATA-D2	Johnson & Johnson
Canagliflozin vs. placebo	III	Completed	Multinational	NCT01081834 CANTATA-M	Johnson & Johnson
Canagliflozin + antihyperglycaemics vs. placebo + antihyperglycaemics	III	Completed	Multinational	NCT01064414	Johnson & Johnson
Canagliflozin + insulin ± oral antihyperglycaemics vs. placebo + insulin ± oral antihyperglycaemics	III	Ongoing	Multinational	NCT01032629 CANVAS	Johnson & Johnson
Canagliflozin + metformin ± sulfonylurea vs. placebo + metformin ± sulfonylurea	III	Completed	Multinational	NCT01381900	Johnson & Johnson
Canagliflozin vs. placebo	III	Completed	Japan	NCT01413204	Mitsubishi Tanabe Pharma
Canagliflozin + metformin vs. placebo + metformin	II	Completed	Multinational	NCT01340664	Johnson & Johnson
Canagliflozin (dose-ranging) vs. placebo	II	Completed	Japan	NCT01022112	Mitsubishi Tanabe Pharma
Canagliflozin + metformin vs. placebo + metformin (sitagliptin + metformin; active control group)	II	Completed	Multinational	NCT00642278	Johnson & Johnson

analysis of four placebo-controlled trials [5]. The mean duration of exposure to canagliflozin in this larger analysis was 38 weeks ($n = 6,177$), with 1,832 of these patients exposed to canagliflozin for more than 50 weeks. In this pooled analysis, the incidences of acute or chronic pancreatitis in the canagliflozin 100 mg ($n = 3092$), canagliflozin 300 mg ($n = 3085$) and comparator groups ($n = 3262$) were 2.7, 0.9 and 0.9 per 1000 patient-years of exposure, respectively [5].

In the larger pooled analysis, hypersensitivity-related adverse reactions, including erythema, rash, pruritus, urticaria and angioedema, occurred in 3–4 % of patients in the canagliflozin 100 mg, canagliflozin 300 mg and comparator groups [5]. Five canagliflozin recipients experienced serious hypersensitivity reactions; four cases of urticaria and once case of a diffuse rash and urticaria, which occurred within hours of exposure to canagliflozin. Two patients discontinued canagliflozin treatment, with one patient experiencing a recurrence of urticaria when canagliflozin was reinitiated [5].

In clinical studies, canagliflozin treatment was associated with a dose-dependent increase in volume depletion-related adverse reactions, including hypotension, postural dizziness, orthostatic hypotension, syncope and dehydration [5]. The use of loop diuretics, moderate renal impairment and age 75 years and older were the most common factors associated with the largest increase in this type of adverse event.

In the pooled analysis of four trials in which most patients had normal or mildly impaired renal function, 2.0, 4.1 and 2.1 % of patients in the canagliflozin 100 mg, canagliflozin 300 mg and placebo groups, respectively, experienced at least one event of significant renal function decline (i.e. eGFR <80 mL/min/1.73 m2 and an eGFR 30 % lower than baseline) [5]. In the study in patients with moderate renal

impairment [41], 18, 22.5 and 6.9 % of patients in the canagliflozin 100 mg, canagliflozin 300 mg and placebo groups, respectively, experienced at least one event of significant renal function decline (i.e. eGFR 30 % lower than baseline), with corresponding rates of a significant renal function decline by week 26 of 3.4, 3.4 and 4.6 % [5].

In the pooled analysis of four trials, female genital mycotic infections, including vulvovaginal mycotic infection, vulvovaginal candidiasis and vulvovaginitis, occurred in 10.4 % of patients receiving canagliflozin 100 mg/day, 11.4 % of patients receiving canagliflozin 300 mg/day and 3.2 % of patients receiving placebo [5]. These adverse events were more likely to occur in patients with a history of genital mycotic infections and female patients who developed genital mycotic infections during canagliflozin treatment were more likely to experience recurrence of infection and require appropriate pharmacotherapy [5].

Hypoglycaemia (i.e. any event regardless of symptoms where biochemical hypoglycaemia was documented as a glucose level of ≤70 mg/dL) occurred at higher rate when canagliflozin was coadministered with insulin or sulfonylureas in individual clinical trials [5]. In the CANTATA-M study, monotherapy with canagliflozin 100 or 300 mg/day was associated with a low incidence of hypoglycaemia, with the incidence being similar to that in the placebo group (2.6–3.6 % across treatment groups) [30]. The incidence was also low (≤5 %) across treatment groups when canagliflozin was coadministered with metformin in the CANTATA-D study or with metformin plus pioglitazone in the CANTATA-MP study [5]. In combination with metformin plus a sulfonylurea in the CANTATA-MSU study, the incidence of hypoglycaemia in the canagliflozin 100 mg, canagliflozin 300 mg and placebo groups was 27.4, 30.1 and 15.4 %, respectively [5]. In CANVAS, as add-on therapy to insulin with or without other antihyperglycaemic drugs, the incidence of hypoglycaemia during the first 18 weeks in the canagliflozin groups was 49 % and, in the add-on placebo group, it was 37 % [5].

In a pooled analysis of four clinical trials, dose-related increases in mean low-density lipoprotein cholesterol (LDL-C) were observed [5]. Relative to placebo, mean increases from baseline (140–147 mg/dL across groups) in LDL-C levels in the canagliflozin 100 and 300 mg groups were 4.4 (4.5 % increase) and 8.2 (8.0 %) mg/dL. During canagliflozin treatment patients should have their LDL-C levels monitored and be treated as per the standard of care [5].

In a pre-specified cardiovascular meta-analysis of phase III clinical trials, for which the primary outcome was adjudicated major cardiovascular adverse events (MACE)-plus (a composite endpoint including cardiovascular death, myocardial infarction, stroke and hospitalized unstable angina), the hazard ration (HR) of the combined canagliflozin group to the non-canagliflozin group was 0.91 (95 % CI 0.68–1.22) [12]. For the components of the composite MACE-plus endpoint, all HRs for the canagliflozin group to the non-canagliflozin group were <1, with the exception of fatal/nonfatal strokes (HR 1.47; 95 % CI 0.83–2.59). Overall, these results and an updated analysis suggest that canagliflozin is not associated with an increased occurrence of cardiovascular events and met the FDA guidance requirement for an NDA filing (i.e. the upper bound of the confidence interval is <1.8). The long-term, ongoing CANVAS trial will provide further evidence on the long-term safety profile of canagliflozin, with a mean duration of follow-up of approximately 5–6 years for all subjects [12].

2.5 Ongoing Trials

An ongoing 52-week, dose-ranging, phase III, open-label, multicenter trial will evaluate the efficacy of low-dose versus high-dose canagliflozin with or without OADs in Japanese patients with type 2 diabetes (NCT01387737; $n = 1{,}200$ planned enrollment) [18]. The primary endpoints are safety and tolerability assessed by adverse events, hypoglycaemic events, laboratory test, 12-lead ECG and vital signs, to be assessed over 52 weeks.

A 52-week, multinational study evaluating the efficacy and safety of canagliflozin in older patients with type 2 diabetes is ongoing (NCT01106651) [42]; 26-week data have been reported [40]. The primary outcome is the change in HbA_{1c} from baseline to week 26.

In addition, the large CANVAS study evaluating the risk of major cardiovascular events in patients with type 2 diabetes receiving add-on canagliflozin treatment is ongoing, with an estimated completion date of June 2018 (NCT01032629) [43]. Data from an 18-week pre-specified substudy evaluating the efficacy in patients receiving canagliflozin plus insulin have been reported [37]. The primary outcome measures for CANVAS are MACE-plus events over a time frame of up to 9 years [43].

3 Current Status

Oral canagliflozin received its first global approval on the 29th of March 2013 for the treatment of type 2 diabetes in the USA.

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