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REVIEW

Update on developments with SGLT2 inhibitors in the management of type 2 diabetes

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Abstract: The importance of the kidney's role in glucose homeostasis has gained wider understanding in recent years. Consequently, the development of a new pharmacological class of anti-diabetes agents targeting the kidney has provided new treatment options for the management of type 2 diabetes mellitus (T2DM). Sodium glucose co-transporter type 2 (SGLT2) inhibitors, such as dapagliflozin, canagliflozin, and empagliflozin, decrease renal glucose reabsorption, which results in enhanced urinary glucose excretion and subsequent reductions in plasma glucose and glycosylated hemoglobin concentrations. Modest reductions in body weight and blood pressure have also been observed following treatment with SGLT2 inhibitors. SGLT2 inhibitors appear to be generally well tolerated, and have been used safely when given as monotherapy or in combination with other oral anti-diabetes agents and insulin. The risk of hypoglycemia is low with SGLT2 inhibitors. Typical adverse events appear to be related to the presence of glucose in the urine, namely genital mycotic infection and lower urinary tract infection, and are more often observed in women than in men. Data from long-term safety studies with SGLT2 inhibitors and from head-to-head SGLT2 inhibitor comparator studies are needed to fully determine their benefit–risk profile, and to identify any differences between individual agents. However, given current safety and efficacy data, SGLT2 inhibitors may present an attractive option for T2DM patients who are failing with metformin monotherapy, especially if weight is part of the underlying treatment consideration.

Keywords: anti-diabetes agents, efficacy, hyperglycemia, safety, sodium glucose co-transporter type 2 inhibitors, type 2 diabetes mellitus

Renal glucose handling in the kidney in glucose-tolerant individuals

The human kidney regulates glucose homeostasis via gluconeogenesis, glucose uptake from the circulation, and by glucose reabsorption from the urine filtered in the renal glomeruli.[1]

Approximately 160–180 g/day of glucose is filtered by the kidneys.[1] In healthy (ie, glucose-tolerant) individuals, virtually all glucose filtered by the glomeruli is reabsorbed by the proximal renal tubule and returned into the circulation, so almost no glucose is excreted into the urine. The ability of the proximal tubule to reabsorb glucose increases as the filtered glucose load increases, which can occur by increasing plasma glucose concentration or glomerular filtration rate (GFR),[2] until the maximum glucose transport capacity (known as Tm glucose) is reached. Once this level is exceeded, surplus glucose cannot be reabsorbed and is excreted into the urine, resulting in urinary glucose excretion (UGE; ie, glucosuria). In a healthy adult, Tm glucose equates to a filtration

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rate of 260–350 mg/min/1.73 m,[2,3] which is equivalent to a plasma glucose concentration of approximately 200 mg/dL (11.0 mmol/L).[4] The plasma glucose concentration at which Tm glucose is reached is known as the renal threshold for glucose excretion.

Glucose reabsorption from the glomerular filtrate is mediated by sodium glucose co-transporter (SGLT) proteins in a process that is independent of insulin (Figures 1 and 2), unlike the action of the major facilitative glucose transporter (GLUT) GLUT4 that is responsible for glucose uptake into insulin-sensitive tissues, such as adipose tissue and muscle. SGLTs are membrane-bound proteins that actively transport glucose against its concentration gradient and, thus, require an energy source to drive the sodium pump.[5] Details of the SGLT family are summarized in Table 1.[5] Around 90% of filtered renal glucose is reabsorbed in the brush-border of cells in the first segment of the proximal convoluted tubule by SGLT2, a low-affinity, high-capacity transporter, and the remaining 10% is removed in the distal straight segment by SGLT1, a related high-affinity, low-capacity transporter.[5,6] SGLT1 is also extensively expressed in the small intestine where it has a significant role in glucose absorption.[5] A second group of glucose transporters, the facilitative glucose transporters or GLUTs, then enable the passive diffusion of glucose from the basolateral membrane of cells in the proximal convoluted tubule into the bloodstream, mainly via GLUT2 and to a minor degree via GLUT1.[5–7]

SGLT2 is encoded by the *SLC5A2* gene, and a range of loss-of-function mutations in this gene results in the rare disorder of familial renal glucosuria.[8] Familial renal glucosuria is characterized by UGE in the presence of normal plasma glucose concentrations, without any signs of renal tubular dysfunction.[8] Homozygous mutations in the gene encoding SGLT2 result in significant UGE (>10–100 g/1.73 m^2/day), whereas heterozygous mutations generally result in lower degrees of UGE (<10 g/1.73 m^2/day).[8] Nevertheless, most individuals affected by familial renal glucosuria are asymptomatic and only rarely suffer from hypoglycemia or hypovolemia,[8] and most of the commonly cited descriptions of this syndrome do not mention an increased risk of genito-urinary infections. In comparison, loss-of-function mutations in the gene encoding SGLT1, *SLC5A1*, cause glucose-galactose malabsorption in the gut,[9] with little or no glucosuria, which results in severe watery diarrhea in affected newborns;[9] however, dietary tolerance to glucose appears to develop in adulthood, possibly due to development of gastrointestinal flora that aid in its metabolization.[10]

Renal glucose handling in the kidney of an individual with diabetes mellitus

Individuals with type 2 diabetes mellitus (T2DM) have increased renal glucose output in the post-absorptive state, causing increased release of glucose into the blood not only

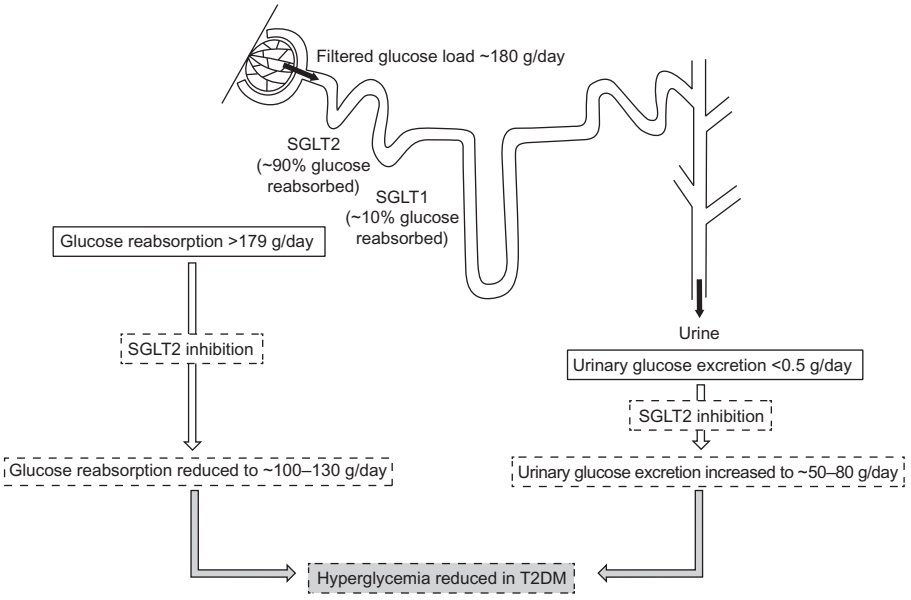

Figure 1 Renal tubular reabsorption of glucose.
Notes: Most of the glucose in the glomerular filtrate is reabsorbed by SGLT2 in the proximal convoluted tubule and the remainder is reabsorbed by SGLT1 in the distal straight segment of the tubule, so virtually no glucose is lost in the urine. The facilitative glucose transporters (GLUTs) then enable passive diffusion of glucose from the renal tubule into the bloodstream. Pharmacological inhibition of SGLT2 reduces glucose reabsorption, causing glucose to remain in the filtrate for subsequent urinary excretion.
Abbreviations: SGLT, sodium glucose co-transporter; T2DM, type 2 diabetes mellitus.

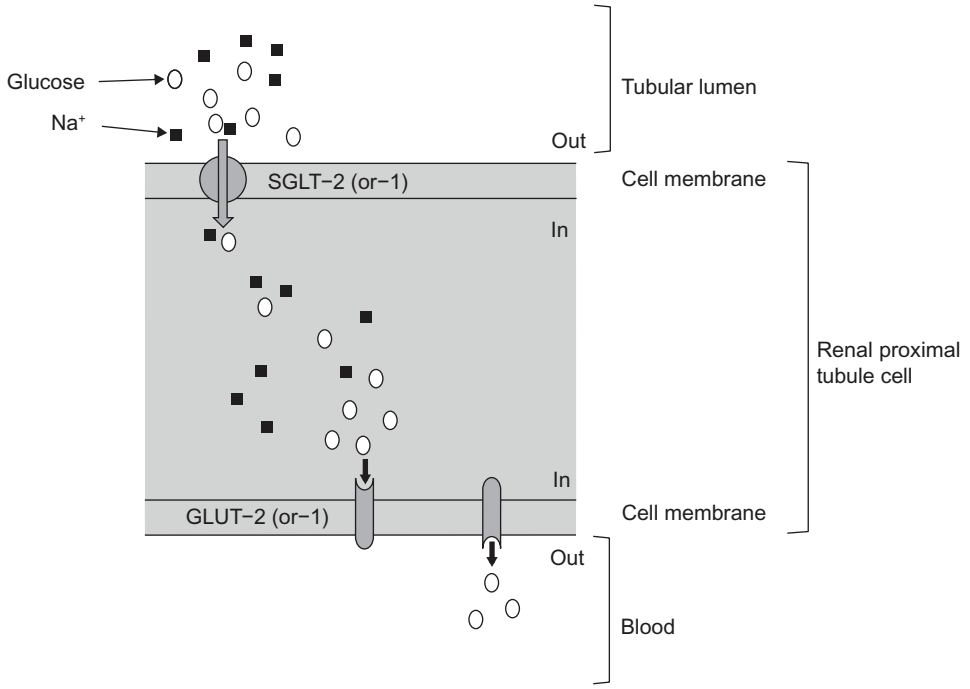

Figure 2 Renal glucose transport.
Notes: Glucose and sodium (1:1) enter the renal tubule cells with assistance from glucose transport proteins. Active transport of glucose across the luminal membrane occurs via SGLT2 (and SGLT1) and is driven by coupling glucose transport with sodium co-transport. Glucose then diffuses passively across the basolateral membrane, facilitated by GLUT2 (and GLUT1).
Abbreviations: GLUT, facilitative glucose transporter; Na^+, sodium; SGLT, sodium glucose co-transporter.

from the liver, but also with a significant contribution by the kidneys.[11] Greater postprandial elevation of renal glucose release is also observed in individuals with T2DM versus those with normal glucose tolerance.[12] Moreover, renal glucose uptake is increased in both post-absorptive and postprandial states in individuals with T2DM versus non-diabetic individuals.[11,12]

As demonstrated in an early study of individuals with type 1 DM (T1DM), hyperglycemia may occur without the expected degree of glucosuria, resulting from increased glucose reabsorption from the glomerular filtrate: the mean Tm glucose was reported to be up to 20% higher in individuals with T1DM than in healthy individuals.[13] In addition, increased expression and activity of SGLT2 mRNA and protein have been demonstrated in vitro.[14,15] There may also be over-expression of SGLT1 in the gastrointestinal tract in patients with diabetes.[16] A recent study also demonstrated a change in renal glucose kinetics in response to SGLT2 inhibition in healthy subjects and those with T2DM,[17] whereby administration of the SGLT2 inhibitor dapagliflozin (10 mg/day for 7 days) reduced Tm glucose by approximately 55% in both groups.[17] Moreover, dapagliflozin reduced the plasma glucose threshold at which glucose excretion began to concentrations well below fasting levels (ie, 4.7–6.0 mmol/L [85–108 mg/dL]) in both groups: glucosuria threshold was reduced to 1.2±2.6 mmol/L (21±46 mg/dL) in subjects with T2DM and to 2.0±2.2 mmol/L (37±40 mg/dL) in healthy subjects ($P<0.001$ for both groups).[17]

In healthy glucose-tolerant individuals, having a Tm glucose of approximately 200 mg/dL (11.0 mmol/L) that is well above the normal filtered glucose load of approximately 100 mg/dL (5.5 mmol/L) allows the kidney to conserve this energy source for future use when glucose availability is scarce; however, this process may become maladaptive in

Table 1 Sodium-glucose co-transporter (SGLT) family

SGLT member	Substrate	Distribution in human tissue
SGLT1	Glucose, galactose	Intestine, trachea, kidney, heart, brain, testis, prostate
SGLT2	Glucose	Kidney, brain, liver, thyroid, muscle, heart
SGLT3	Glucose	Intestine, testis, uterus, lung, brain, thyroid
SGLT4	Glucose, mannose	Intestine, kidney, liver, brain, lung, trachea, uterus, pancreas
SGLT5	Glucose, galactose	Kidney
SGLT6	D-chiro-inositol	Brain, kidney, intestine

Note: Table adapted with permission from Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. *Physiol Rev.* 2011;91(2):733–794.[5]

individuals with DM.[18] Instead of excreting excess glucose into the urine in the presence of hyperglycemia, the kidneys of a diabetic person continue to reabsorb glucose, due to an elevation of the Tm glucose.[18] Consequently, hyperglycemia remains uncorrected and contributes to the ensuing problem of glucose toxicity. Thus, if SGLT2 activity promotes glucose conservation and hinders normalization of plasma glucose levels in DM, it is postulated that inhibition of SGLT2 might decrease the threshold for UGE (glucosuria) and reduce hyperglycemia[18,19]

Early SGLT2 inhibitors

Early investigations into renal glucose handling were carried out on phlorizin (Figure 3), a naturally occurring glucoside found in the root bark of fruit trees.[20] Studies from the 1950s revealed that phlorizin blocked sugar transport in several tissues, including the kidney and small intestine.[21] This was later found to be due to inhibition of SGLT proteins: phlorizin is a competitive inhibitor of SGLT1 and SGLT2 but has greater affinity for SGLT2.[5,20] In the 1980s, a rat model of diabetes was used to demonstrate that phlorizin-induced glucosuria was associated with normalization of plasma glucose without hypoglycemia.[22,23] Phlorizin also normalized insulin sensitivity in partially pancreatectomized rats but did not affect insulin action in the control animals.[22] The ensuing glucosuria reversed insulin resistance, and discontinuation of phlorizin led to the return of hyperglycemia and insulin resistance.[22] However, phlorizin was unsuitable for clinical development in diabetes due to its poor oral bioavailability: phlorizin is metabolized to phloretin by glucosidase in the gut and, thus, must be given parenterally. Moreover, phloretin is a potent inhibitor of GLUT1,[20] the suppression of which could result in reduced glucose transport to other tissues, such as the central nervous system.[24]

Consequently, pharmaceutical research has pursued phlorizin derivatives that possess increased stability/bioavailability and SGLT2 selectivity, and both O- and C-glucoside entities have been evaluated (Figure 3). O-glucoside candidates, such as sergliflozin and T-1095,[25] were investigated first, but were discontinued in early clinical development for reasons probably related to nonselective SGLT2 inhibition,[26] and/or bioavailability issues.[27] C-glucoside candidates possessed increased resistance to enzymatic breakdown[28] and have fared more successfully during clinical development with a number of C-glucoside compounds progressing to marketing application and approval.

General characteristics of SGLT2 inhibitors

As the mode of action of SGLT2 is independent of insulin, SGLT2 inhibitors would be expected to act independently of pancreatic beta-cell function and insulin resistance. Consequently, there could be limited loss of potency in SGLT2 inhibitors (ie, maintained glucose lowering effect) when beta-cell function inevitably deteriorates over time, as is observed with other types of glucose-lowering agents. Furthermore, as inhibition of SGLT2 neither interferes with normal endogenous glucose production in response to hypoglycemia,[29] nor stimulates insulin release,[22,30] the mode of action of SGLT2 inhibitor therapy should not increase the risk of hypoglycemic episodes. The novel mechanism of action of SGLT2 inhibitor therapy also suggests that it can be given in combination with any of the existing glucose-lowering agents, including insulin, as they share no common mechanistic pathways.

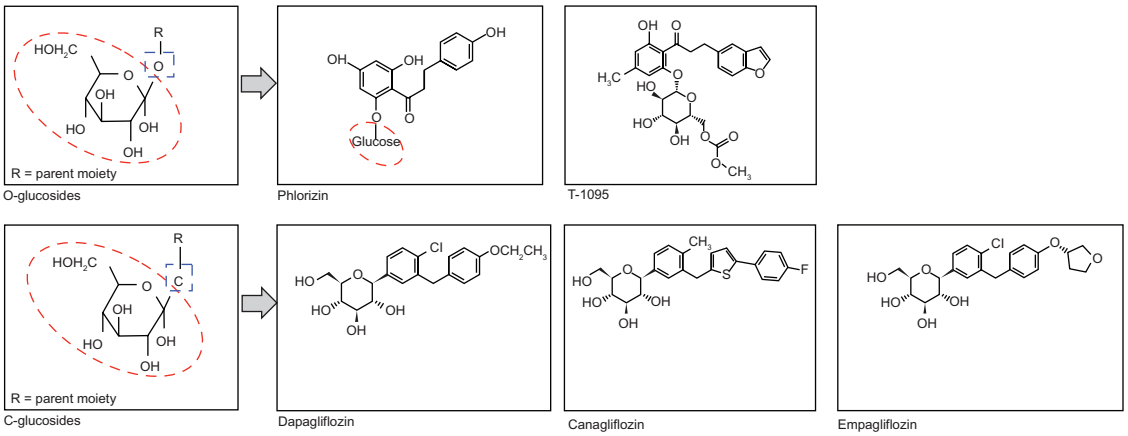

Figure 3 Structure of phlorizin and candidate SGLT2 inhibitors.
Abbreviation: SGLT, sodium glucose co-transporter.

As well as these predicted benefits, several potential safety issues may be anticipated from the known pharmacodynamic effects of SGLT2 inhibitors. For example, as SGLT2 inhibitors cause a modest osmotic diuresis, there may be a risk of hypotension and hypovolemia; although, lowering of blood pressure (BP) may be of benefit in some individuals with T2DM. The ability of SGLT2 inhibition to increase UGE depends upon the presence of a normal GFR, so the glycemic effectiveness of an SGLT2 inhibitor would be expected to be lower in patients with chronic kidney disease (CKD) and a reduced GFR. The continual presence of glucose in the urine caused by SGLT2 inhibition theoretically increases the risk of urinary tract infections and mycotic genital tract infections. Furthermore, given the renal tubular mechanism of action of SGLT2 inhibitors, this class of compounds has the hypothetical ability to alter the absorption and excretion of calcium and phosphate and, in so doing, potentially affect bone metabolism. Although the various SGLT2 inhibitors in clinical development have a structural similarity, they differ in their respective selectivity profiles for SGLT2 over SGLT1: empagliflozin has the highest degree of selectivity (>2,500-fold), followed by tofogliflozin (>1,875-fold), dapagliflozin (>1,200-fold), ipragliflozin (>550-fold), and canagliflozin (>250-fold).[31] Inhibitors with lower selectivity for SGLT2 versus SGLT1 may incur safety issues arising from SGLT1 inhibition, such as diarrhea caused by glucose-galactose malabsorption. Although, recent data suggest that transient inhibition of SGLT1 by SGLT2 inhibitors may lower postprandial glucose by reducing intestinal glucose absorption.[32]

Clinical data from SGLT2 inhibitor trials

A summary of SGLT2 inhibitors currently known to be in clinical development is presented in Table 2. Phase II through IV clinical trials with SGLT2 inhibitors are listed in Table S1. At the time of writing, dapagliflozin and canagliflozin are marketed in the US and EU and empagliflozin gained recent approval from the European Medicines Agency and the US Food and Drug Administration. Outside of the US and EU marketing applications for ipragliflozin, luseogliflozin, and tofogliflozin were submitted to Japan's Phar-

Table 2 SGLT2 inhibitors in advanced clinical development

Compound (sponsor)	Development status	Other information
Dapagliflozin (Bristol-Myers Squibb, AstraZeneca)	Launched in Europe EMA approval given in November 2012 Launched in the US FDA approval given in January 2014	http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002322/human_med_001546.jsp&mid=WC0b01ac058001d124 http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm380829.htm
Canagliflozin (Mitsubishi Tanabe Pharma, Janssen)	Launched in the US FDA approval given in March 2013 Launched in Europe EMA approval given in November 2013	http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm345848.htm http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002649/human_med_001707.jsp&mid=WC0b01ac058001d124
Empagliflozin (Boehringer Ingelheim, Eli Lilly)	EMA approval given in May 2014 FDA approval given in August 2014	http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm407637.htm
Ipragliflozin (Astellas, Kotobuki Pharmaceutical)	Launched in Japan Japanese MHLW approval given in January 2014	http://www.astellas.com/en/corporate/news/detail/approval-of-suglat-tablets-a-s.html
Luseogliflozin (Taisho, Novartis)	Pre-registration Marketing application made to MHLW, Japan in April 2013	http://www.taisho-holdings.co.jp/en/ir/development/ http://www.taisho-holdings.co.jp/en/release/2013/2013041801-e.pdf
Tofogliflozin (Chugai, Kowa, Sanofi)	Pre-registration Marketing application made to MHLW, Japan in June 2013	http://www.chugai-pharm.co.jp/hc/ss/english/ir/reports_downloads/pipeline.html http://www.chugai-pharm.co.jp/hc/ss/english/news/detail/20121026150000.html
Ertugliflozin [PF04971729] (Pfizer, Merck and Co)	Phase III trials commenced in October 2013	http://clinicaltrials.gov/ct2/results?term=ertugliflozin http://www.mercknewsroom.com/press-release/research-and-development-news/merck-co-inc-and-pfizer-enter-worldwide-collaboration-ag
Sotagliflozin [LX4211] (Lexicon Pharmaceuticals)[a]	Phase III trials are expected to begin in 2014	http://www.lexgen.com/pipeline/lx4211.html

Notes: [a]Sotagliflozin [LX4211] is a dual SGLT1 and SGLT2 inhibitor.
Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; MHLW, Ministry of Health, Labour and Welfare; SGLT, sodium glucose co-transporter.

maceuticals and Medical Devices Agency, and ipragliflozin was recently approved. Developmental SGLT2 inhibitors are listed in Table S2. In addition, several fixed dose combination products utilizing SGLT2 inhibitors plus another class of oral anti-diabetes agents are currently in clinical development: dapagliflozin plus metformin (in 5 mg/850 mg and 5 mg/1,000 mg tablets) gained marketing authorization in the EU in early 2014,[33] and single-pill combination products containing dapagliflozin plus saxagliptin, canagliflozin plus metformin, and empagliflozin plus linagliptin or plus metformin, respectively, are in Phase III clinical trials.

The SGLT2 inhibitors currently marketed are indicated as monotherapy for patients with T2DM and inadequate glycemic control from diet and exercise (US and EU indications),[34–37] who are unable to use metformin (EU-specific),[35,37] and as an add-on therapy with other glucose-lowering agents, including insulin (EU-specific).[35,37] In Europe, the recommended dose of dapagliflozin is 10 mg once daily, whether given as a monotherapy or as an add-on therapy combined with other glucose-lowering agents.[35] In the US, the recommended starting dose is 5 mg once daily, which can be increased to 10 mg once daily in patients without renal impairment who tolerate the drug and who require additional glycemic control.[36] The use of dapagliflozin is generally not recommended when eGFR is below 60 mL/min/1.73 m^2. The recommended starting dose of canagliflozin is 100 mg once daily, which can be increased to 300 mg once daily in patients (without renal impairment) who require additional glycemic control, provided the estimated glomerular filtration rate (eGFR) is 60 mL/min/1.73 m^2 or greater.[34,37] Canagliflozin is generally not recommended when eGFR is below 45 ml/min/1.73 m^2. In pre-registration Phase III trials, empagliflozin was independently dosed at 10 mg and 25 mg once daily as monotherapy and as add-on combination therapy to other glucose-lowering agents, including insulin.

Clinical efficacy

A summary of efficacy data from key clinical trials of SGLT2 inhibitors (as registered in ClinicalTrials.gov) that are available, or expected to soon be available, in the US and EU is presented in Table S3. Selected efficacy data are also presented in Figure 4. Dapagliflozin, canagliflozin, and empagliflozin are the most advanced of the SGLT2 inhibitors in terms of clinical development, and have the largest amount of published clinical data currently available. Pooled analyses of Phase III study data and data from US and EU regulatory reports were also available for dapagliflozin and canagliflozin, whereas data for empagliflozin were principally obtained from publications of individual Phase III studies. Other SGLT2 inhibitors were earlier in clinical development and had fewer publications available at the time of writing, or had no clinical trials registered in ClinicalTrials.gov due to their current development occurring outside the US.

Glycemic efficacy

Several meta-analyses have demonstrated a significant improvement of glycemic control in patients with T2DM who were treated with SGLT2 inhibitors.[60–62] The largest of these included data from 58 SGLT2 inhibitor trials, predominantly involving dapagliflozin and canagliflozin, and reported that this drug class had a favorable effect on reducing glycosylated hemoglobin (HbA_{1c}; mean difference versus placebo, –0.7% [95% confidence interval {CI} –0.7, –0.6]; mean difference versus active comparator, –0.1% [95% CI –0.2, 0.05]).[60] Dapagliflozin 10 mg provided statistically significant and clinically relevant improvements in glycemic control compared with placebo (with mean placebo-corrected HbA_{1c} decrease in the different studies ranging from –0.5% to –0.7% at 24 weeks), when given as monotherapy or as add-on therapy to metformin, sulfonylurea, thiazolidinediones, or insulin.[63] As add-on therapy to metformin, dapagliflozin 10 mg was shown to have non-inferior efficacy versus glipizide after 52 weeks.[41] Dapagliflozin 10 mg was also shown to have non-inferior efficacy versus metformin extended release when both were given as monotherapy for 24 weeks.[39] Furthermore, the glucose-lowering effect of dapagliflozin as add-on therapy was maintained over periods of 48–102 weeks.[42,64,65]

Pooled data for canagliflozin 300 mg and 100 mg gave an overall mean change from baseline in HbA_{1c} relative to placebo of –0.8% (95% CI –0.9, –0.8) and 0.7% (95% CI –0.75, –0.6), respectively.[66] Individual studies over 52 weeks using canagliflozin as monotherapy,[67] or with a background of metformin,[46,47] or with metformin plus sulfonylurea,[48] reported that efficacy in terms of reduced HbA_{1c} was maintained over this longer period. Furthermore, canagliflozin (300 mg) was superior in lowering HbA_{1c} when compared to glimepiride,[46] or sitagliptin.[47,48]

Empagliflozin 10 mg and 25 mg also led to statistically significant and clinically meaningful improvements in HbA_{1c}.[53–57] In monotherapy and compared with placebo, adjusted mean differences in change from baseline HbA_{1c} at week 24 were –0.7% (95% CI –0.9, –0.6; $P<0{\cdot}0001$) for empagliflozin 10 mg, –0.9% (95% CI –1.0, –0.7; $P<0.0001$) for empagliflozin 25 mg, versus –0.7% (95% CI

–0.9, –0.6; $P<0{\cdot}0001$) for sitagliptin.[53] Placebo-corrected changes in HbA_{1c} after 24 weeks for empagliflozin added to metformin were –0.6% (95% CI –0.7, –0.4; $P<0.001$) for empagliflozin 10 mg and –0.6% (95% CI –0.8, –0.5; $P<0.001$) for empagliflozin 25 mg.[54]

Larger reductions in HbA_{1c} were observed in patients with higher baseline levels of HbA_{1c} for each of these three SGLT2 inhibitors.[38,45,53] Changes in HbA_{1c} and fasting plasma glucose from individual key trials using dapagliflozin, canagliflozin, and empagliflozin are presented in Table S3.

Changes in body weight and composition

Meta-analysis demonstrated SGLT2 inhibitors reduced body weight compared with other anti-diabetes agents (mean difference –1.8 kg [95% CI –3.5, –0.1]).[60] Body weight reductions of approximately 2–3 kg were observed

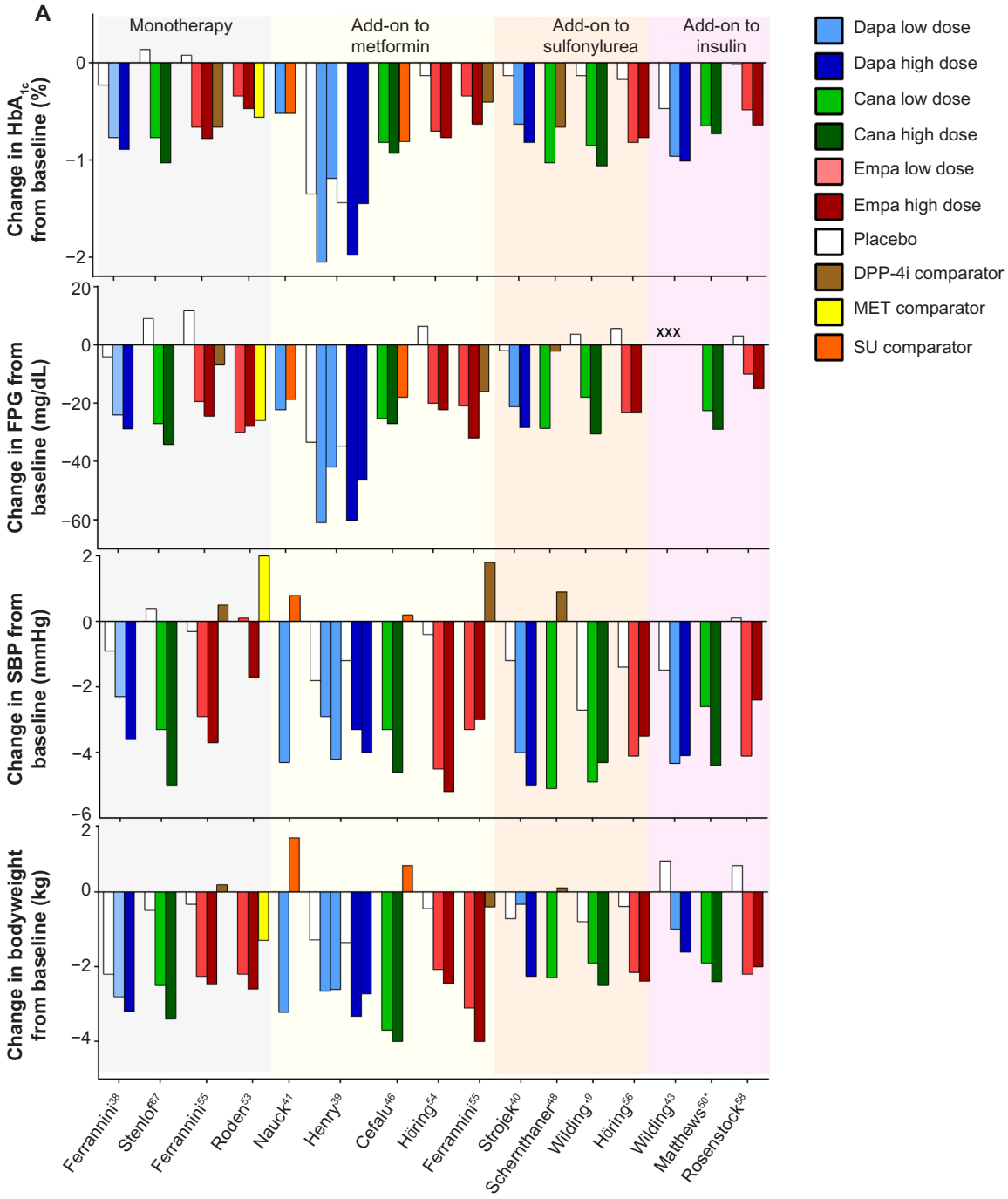

Figure 4 (*Continued*)

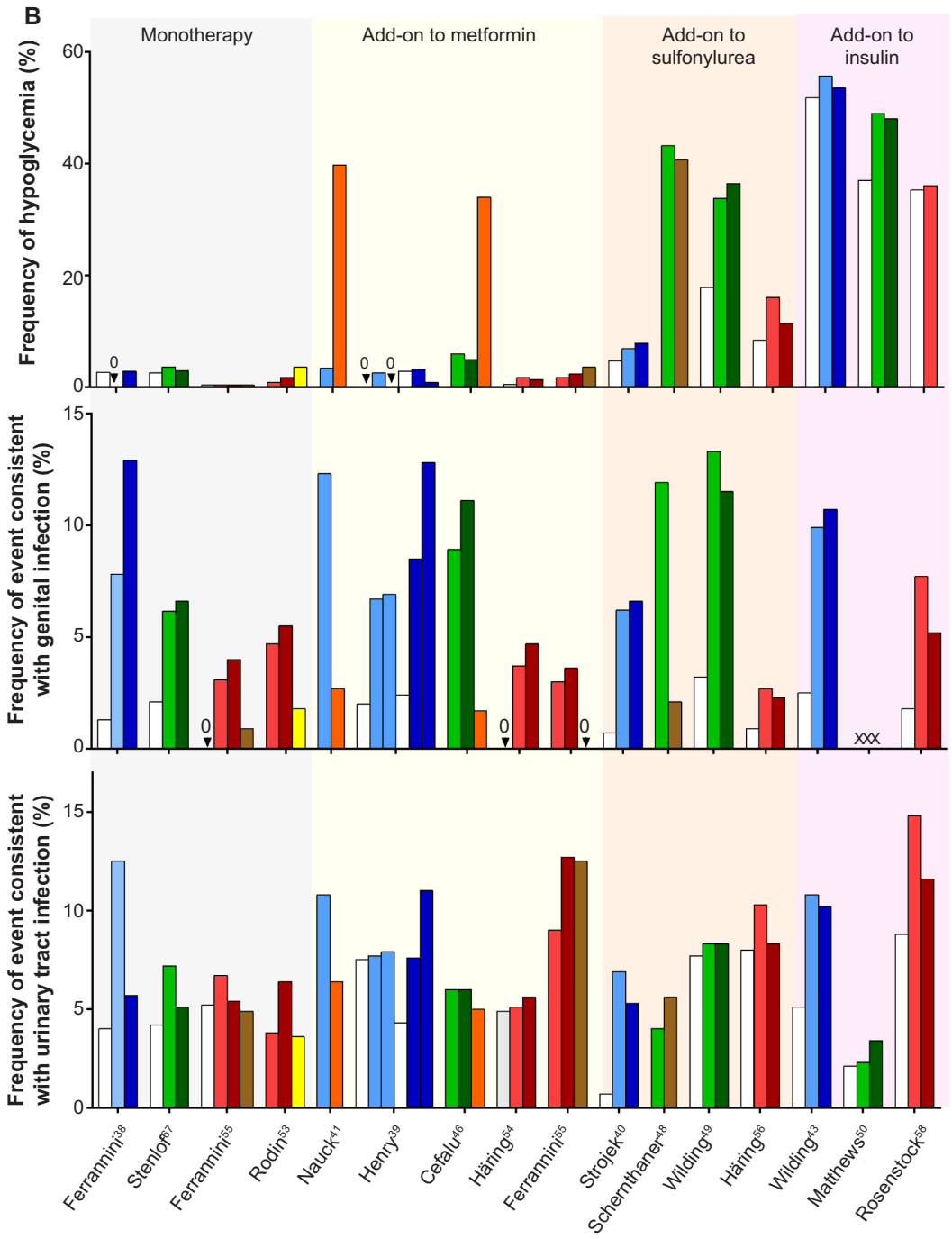

Figure 4 Efficacy and safety data from representative Phase III studies of dapagliflozin, canagliflozin, and empagliflozin.
Notes: (**A**) efficacy data; (**B**) safety data. Phase III studies were selected in which the SGLT2 inhibitor was given as monotherapy, or with background therapy of metformin, or sulfonylurea, or insulin. *Change versus placebo; X Not reported.
Abbreviations: SGLT, sodium glucose co-transporter; FPG, fasting plasma glucose; SBP, systolic blood pressure; DPP-4i, dipeptidyl peptidase-4 inhibitor; MET, metformin; SU, sulfonylurea; Dapa, dapagliflozin; Cana, canagliflozin; Empa, empagliflozin; HbA_{1c}, glycosylated hemoglobin.

in most dapagliflozin Phase III studies, as stated in the European Medicines Agency (EMA) assessment report.[63] The effect was maintained over 102 weeks in a study of dapagliflozin 10 mg added to metformin therapy, with a body weight reduction –4.5 kg versus –2.1 kg for placebo plus metformin.[68] Dual-energy X-ray absorptiometry revealed this reduction in body weight was principally due to a reduction in body fat mass, rather than a loss of fluid or lean tissue.[68] For canagliflozin, the change in body weight from baseline was generally consistent across placebo-controlled

Phase III studies, but was lower where sulfonylurea was a background therapy: the US Food and Drug Administration (FDA) briefing document stated the placebo-subtracted mean reduction in body weight (excluding sulfonylurea background) was −1.8% to −3.8% for the 300 mg dose and −1.6% to −2.4% for the 100 mg dose.[69] For empagliflozin monotherapy, mean placebo-corrected changes in body weight from baseline after 24 weeks were −1.9 kg (95% CI −2.4, −1.4; $P<0.0001$) and −2.1 kg (95% CI −2.6, −1.7; $P<0.0001$) for 10 mg and 25 mg groups, respectively, versus 0.5 kg (95% CI 0.04, 1.0; $P=0.0355$) for the sitagliptin comparator group.[53] When empagliflozin was added to metformin the mean change in body weight after 24 weeks was greater for empagliflozin groups versus placebo (mean change standard error [SE] −2.1 [0.2] kg and −2.5 [0.2] kg for 10 mg and 25 mg groups, respectively, versus −0.45 [0.2] kg for placebo; $P<0.001$ for each dose versus placebo).[54]

Blood pressure-lowering effects

In a meta-analysis of six studies, SGLT2 inhibitors reduced systolic BP compared with other anti-diabetes agents (mean difference −4.5 mmHg [95% CI −5.7, −3.2 mmHg]).[60] A decrease in systolic BP was observed consistently across the dapagliflozin studies (Table S3).[63] In a small study (n=75) directly comparing dapagliflozin with an antihypertensive, treatment with placebo, dapagliflozin (10 mg/day), or hydrochlorothiazide (25 mg/day) resulted in adjusted changes from baseline in 24-hour ambulatory mean systolic BP of −0.9 (95% CI −4.2, 2.4), −3.3 (95% CI −6.8, 0.2), and −6.6 (95% CI −9.9, −3.2) mmHg, respectively, at week 12.[70] The study data suggest that dapagliflozin may have a diuretic-like capacity to lower BP in addition to beneficial effects on glycemic control.[70]

Canagliflozin demonstrated a dose-dependent and significant placebo-subtracted mean reduction in systolic BP, except when used as an add-on to sulfonylurea, ranging from 2.6–5.7 mmHg and 3.5–7.9 mmHg for the 100 mg and 300 mg doses, respectively.[69] This was supported by a recent pooled analysis of six Phase III studies (n=4,158) using canagliflozin, in which modest reductions in systolic BP were observed relative to placebo (−3.3 and −4.5 mmHg for 100 mg and 300 mg, respectively).[71]

A pooled analysis of data from four Phase III trials (n=2,477) investigating empagliflozin 10 mg or 25 mg given for 24 weeks as monotherapy or as add-on therapy (with metformin, or metformin plus sulfonylurea, or pioglitazone ± metformin) reported reductions in systolic blood pressure (SBP) for empagliflozin groups versus placebo (placebo-corrected change from baseline −3.4 mmHg and −3.8 mmHg for empagliflozin 10 mg and 25 mg, respectively).[72] A study of patients (n=823) with T2DM and hypertension found that empagliflozin 10 mg and 25 mg significantly reduced mean 24 hour SBP, measured via ambulatory BP monitoring, versus placebo (−2.95 and −3.68 mmHg versus 0.48 mmHg, respectively; $P<0.001$ versus placebo for each dose).[73]

Clinical safety

As defined for Table S3, a summary of safety data from key clinical trials of SGLT2 inhibitors is presented in Table S4 and selected safety data are presented in Figure 4.

Urinary tract infections and genital tract infections

In a meta-analysis of eight studies using canagliflozin and dapagliflozin that compared the SGLT2 inhibitors with other anti-diabetes agents, urinary tract infections were more common with SGLT2 inhibitors (odds ratio, 1.42 [95% CI 1.06, 1.90]), as were genital tract infections (odds ratio, 5.06 [95% CI 3.44, 7.45]).[60] Safety data from a pooled retrospective analysis of data from the short-term, double-blind periods of 12 placebo-controlled trials (n=4,545) using dapagliflozin reported that genital tract infections and lower urinary tract infections were more common with dapagliflozin than placebo; however, between-group differences were less marked for urinary tract infections (genital tract infection 4.1%–5.7% dapagliflozin versus 0.9% placebo; urinary tract infection 3.6%–5.7% dapagliflozin versus 3.7% placebo).[74,75] Similar findings were reported from pooled analyses of canagliflozin and empagliflozin.

A pooled analysis of four 26 week Phase III studies (n=2,313) of canagliflozin found higher proportions of subjects with urinary tract infections and genital tract infections occurred in the canagliflozin groups than with placebo (urinary tract infection 5.1% canagliflozin versus 4.0% placebo; genital tract infection 7.5% canagliflozin versus 1.9% placebo).[76,77]

A pooled analysis of four Phase III studies (n=2,477) using empagliflozin found that empagliflozin was associated with an increased frequency of genital tract infections compared with placebo (approximately 4% versus 1%, respectively), but this was not the case for urinary tract infections (frequency of approximately 8%–9% for each).[78]

For dapagliflozin, canagliflozin, and empagliflozin studies, events of genital tract infections and urinary tract infections were more common in women than in men in all treatment groups (Table S4), and patients usually experienced

only a single episode, which was usually mild in intensity and responded to standard treatment.[74–78]

Hypoglycemia

The incidence of hypoglycemia during SGLT2 inhibitor treatment was generally low, except for groups receiving background therapy of sulfonylureas or insulin. A meta-analysis of SGLT2 inhibitor (dapagliflozin and canagliflozin) trials concluded that hypoglycemic risk was similar to that of other agents (odds ratio versus placebo, 1.28 [95% CI 0.99, 1.65; I^2=0%]: odds ratio versus other anti-diabetes agents, 0.44 [95% CI 0.35, 0.54; I^2=93%]).[60] There were no major episodes of hypoglycemia when dapagliflozin was used as monotherapy, but an increased risk of hypoglycemic events, which were mainly minor in nature (defined as either a symptomatic episode with a capillary or plasma glucose measurement <3.5 mmol/L [<63 mg/dL] regardless of the need for external assistance or an asymptomatic capillary or plasma glucose measurement <3.5 mmol/L [<63 mg/dL], that does not qualify as a major episode), was observed when it was added to sulfonylurea or insulin.[40,43,63]

Similar findings were observed with canagliflozin, with a low risk of hypoglycemia among subjects treated with canagliflozin taken as monotherapy, or in combination with other anti-hyperglycemic agents not associated with hypoglycemia. An increased incidence of hypoglycemia was observed when canagliflozin was used in combination with insulin or sulfonylureas.[34,49,50] The prescribing information for both canagliflozin and dapagliflozin recommend using a lower dose of insulin or insulin secretagogue to reduce the risk of hypoglycemia when used in combination with the respective SGLT2 inhibitor.[34,36]

The rate of hypoglycemia was also low with empagliflozin monotherapy and was comparable to placebo.[53] For empagliflozin added to metformin plus sulfonylurea, the frequency of confirmed hypoglycemia was greater for empagliflozin versus placebo, but none of these events required assistance.[56] When empagliflozin was added to basal insulin, no increased risk of hypoglycemia was reported versus placebo.[58]

Renal safety and volume depletion events

Approximately 375 mL of extra urinary volume is produced per day with dapagliflozin 10 mg therapy.[35] A pooled safety analysis of dapagliflozin using data from the double-blind periods of 12 placebo-controlled trials (n>4,500) reported that volume depletion events occurred in 0.6%–1.2% for dapagliflozin groups (2.5–10 mg) versus 0.4% for placebo groups,[79] indicating a slightly elevated risk and a need to maintain an adequate fluid intake. Hypotension occurred more frequently in dapagliflozin-treated groups than placebo groups for subjects who were elderly, had moderate renal impairment, or were treated with loop diuretics.[63] Dapagliflozin treatment was not associated with increased risk of acute renal toxicity or deterioration of renal function.[80] The estimated GFR (eGFR) decreased initially then returned to baseline by week 24 and was maintained to week 102, while mean serum creatinine showed minimal change (± 0.01 mg/dL) from baseline to week 24 in all groups.[80] As a safety measure, the dapagliflozin Summary of Product Characteristics recommends against its use in patients receiving loop diuretics or who are volume depleted, or who have moderate to severe renal impairment (defined as patients with creatinine clearance <60 mL/min or eGFR <60 mL/min/1.73 m^2), and encourages monitoring of volume status in cases where intercurrent conditions could lead to volume depletion.[35] A 104-week Phase III study of dapagliflozin treatment in T2DM patients with moderate renal impairment reported events of renal impairment or renal failure were uncommon (2.4% and 9.4% for dapagliflozin 5 mg and 10 mg, respectively; 7.1% for placebo), and volume depletion events were more frequent with dapagliflozin (9.6% and 12.9% for dapagliflozin 5 mg and 10 mg, respectively; 6.0% for placebo).[44]

Analysis of a pooled dataset from the canagliflozin FDA briefing document stated that volume depletion-related adverse events, most commonly hypotension, occurred in 1.2% and 1.3% of canagliflozin 100 mg and 300 mg groups, respectively, versus 1.1% in placebo groups;[69] furthermore, none of these events in the canagliflozin groups were serious or led to study discontinuation.[69] In a pooled analysis of eight clinical trials (placebo- and active-controlled), volume depletion-related adverse events occurred in 2.3% and 3.4% of canagliflozin 100 mg and 300 mg groups, respectively, versus 1.5% in the comparator groups.[34] Risk factors for these events were similar to those identified for dapagliflozin (eg, patient's age ≥75 years, eGFR <60 mL/min/1.73 m^2, and use of loop diuretics).[34] A Phase III trial of canagliflozin use in T2DM patients with stage 3 CKD (eGFR ≥30 and <50 mL/min/1.73 m^2) reported larger decreases in eGFR from baseline in canagliflozin treatment groups (least square mean change, –9.1% and –10.1% for 100 mg and 300 mg, respectively, versus –4.5% for placebo).[51] The reductions in eGFR with canagliflozin were largest at week 3 (the first post-baseline measurement) and then returned back toward baseline over the 26-week treatment period.[51] A lower proportion of subjects in the canagliflozin 100 mg

and 300 mg groups progressed to albuminuria (ie, from normoalbuminuria to micro- or macro-albuminuria, or from micro- to macro-albuminuria) versus those in the placebo group (5.1%, 8.3%, and 11.8%, respectively; odds ratio [95% CI], 0.33 [0.08, 1.48] for canagliflozin 100 mg versus placebo, and 0.51 [0.14, 1.91] for canagliflozin 300 mg versus placebo).[51]

A pooled analysis of empagliflozin data (>11,000 T2DM patients from Phase I, II, and III trials) reported that the percentage of patients with volume depletion events was similar with empagliflozin (10 mg dose group 1.4%; 25 mg dose group 1.5%) and placebo (1.4%).[81] More patients receiving diuretics reported these events than those not receiving diuretics (2.2%–2.7% versus 0.9%–1.0%, respectively).[81] Treatment with empagliflozin in patients with T2DM and stage 2 or 3 CKD (eGFR ≥60 to <90 mL/min/1.73 m^2 and 30 to <60 mL/min/1.73 m^2, respectively) significantly reduced mean HbA_{1c} from baseline (placebo adjusted mean reduction in HbA_{1c} at week 24 was −0.52% [95% CI −0.72, −0.32] and −0.68% [95% CI −0.88, −0.49] for stage 2 CKD receiving empagliflozin 10 mg and 25 mg, respectively, and −0.42% [95% CI −0.56, −0.28] for stage 3 CKD receiving empagliflozin 25 mg [empagliflozin 10 mg was not used]; $P<0.0001$ for each),[59] and the effect was sustained at week 52. However, empagliflozin 25 mg did not reduce HbA_{1c} at week 24 or week 52 in patients with stage 4 CKD (eGFR ≥15 to <30 mL/min/1.73 m^2).[59] In patients with stage 2, 3, or 4 CKD, small decreases in eGFR were noted in the empagliflozin groups, which returned to baseline by the end of the 3 week follow-up after treatment completion.[59] In patients with stage 3 CKD, fewer patients on empagliflozin 25 mg than placebo shifted from no albuminuria at baseline to microalbuminuria, or from microalbuminuria at baseline to macroalbuminuria, at end of treatment (12.2% with empagliflozin versus 22.2% with placebo, and 2.0% with empagliflozin versus 11.4% with placebo, respectively).[59]

Venous thromboembolic events

As volume depletion may increase the risk of hemoconcentration and venous thromboembolism (VTE), VTE events were monitored in trials using SGLT2 inhibitors.

Patients receiving dapagliflozin had a similar rate of VTE events to those in the comparator group (0.3% for both groups).[63] For canagliflozin, the rate of VTE in Phase III trials was also low (0.2% and 0.3% for canagliflozin 100 mg and 300 mg groups, respectively, versus 0.2% for non-canagliflozin groups).[69] VTE data have not yet been reported for empagliflozin.[82,83]

Bone safety

There was no clear evidence that dapagliflozin induced bone demineralization or increased fracture rates in people with diabetes and normal or mildly impaired renal function (eGFR >90 mL/min/1.73 m^2 and ≥60 to <90 mL/min/1.73 m^2, respectively),[63,84] but bone fractures were more common in dapagliflozin-treated patients with moderate renal impairment (eGFR >30 to <60 mL/min/1.73 m^2; 4.8% and 9.4% for 5 mg and 10 mg groups, respectively, versus 0% for placebo-treated subjects).[63] A 102 week study (n=140) did not identify any meaningful changes from baseline in markers of bone turnover or bone mineral density in patients receiving dapagliflozin added to metformin, when compared with placebo.[68] No meaningful changes in bone density were observed with canagliflozin treatment over 26 weeks, according to the FDA briefing report,[69] but there was an increase in overall bone fracture events with canagliflozin (2.5% for 100 mg and 2.3% for 300 mg) compared to control (1.7%; includes placebo and active comparators, both with various background therapies). A 104-week trial (26-week double-blind phase + 78-week double-blind extension phase) evaluating canagliflozin in older patients (aged 55–80 years) with T2DM (ClinicalTrials.gov identifier: NCT01106651) included an assessment of bone density, which will be reported separately from the main efficacy/safety analysis.[52] However, no discernible changes in bone density were observed at 26 weeks.[85] In a pooled analysis of data from more than 11,000 patients with T2DM from Phase I, II, and III trials, empagliflozin was not associated with an increased frequency of bone fractures versus placebo (1.6% and 1.1% for empagliflozin 10 mg and 25 mg, respectively, versus 1.6% for placebo).[86]

Cardiovascular safety

SGLT2 inhibitors have favorable effects on cardiovascular (CV) risk factors by reducing hyperglycemia, body weight, and BP,[87] but changes in lipid profiles have caused some concern,[88] and information on major CV outcomes such as stroke, heart attack, and other vascular complications is currently limited.[89] Several large, long-term studies with CV endpoints are ongoing and will provide data in the next 2–6 years (Table 3).[90,91] Results from a meta-analysis on CV outcomes and death with SGLT2 inhibitors showed overall no evidence for an increased CV risk with SGLT2 inhibitor treatment.[60] The EMA assessment report on dapagliflozin stated that an independently confirmed meta-analysis of Phase IIb/III studies did not show an increased CV risk in dapagliflozin-treated patients.[63] The estimated hazard ratio

Table 3 Registered cardiovascular clinical trials of SGLT2 inhibitors

Trial details	Reference
DECLARE TIMI58 – Dapagliflozin Effect on Cardiovascular Events **Full title:** Dapagliflozin Effect on Cardiovascular Events: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients With Type 2 Diabetes **Primary outcome measure:** Time to first event included in the composite endpoint of CV death, MI or ischemic stroke **Patients:** Aged ≥40 years; T2DM; high risk for CV events **Estimated enrollment:** 22,200 (recruiting) **Estimated study completion date:** 2Q 2019	http://www.clinicaltrials.gov/ct2/show/NCT01730534
CANVAS – Canagliflozin Cardiovascular Assessment Study **Full title:** A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ 28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus **Primary outcome measure:** Major adverse cardiovascular events, including CV death, nonfatal MI, and nonfatal stroke **Patients:** Aged ≥30 years; T2DM; high risk for CV events **Enrollment:** 4,330 **Estimated study completion date:** 2Q 2017	http://www.clinicaltrials.gov/ct2/show/NCT01032629 Neal[90]
BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG-OUTCOME™) **Full title:** A Phase III, Multicentre, International, Randomised, Parallel Group, Double Blind Cardiovascular Safety Study of BI 10773 (10 mg and 25 mg Administered Orally Once Daily) Compared to Usual Care in Type 2 Diabetes Mellitus Patients With Increased Cardiovascular Risk **Primary outcome measure:** Time to the first occurrence of any of the following adjudicated components of the primary composite endpoint: cardiovascular death (including fatal stroke and fatal MI), non-fatal MI and non-fatal stroke **Patients:** Aged >18 years; T2DM; confirmed history of MI, unstable angina, multi-vessel percutaneous coronary intervention, multi-vessel coronary artery bypass grafting, ischemic or hemorrhagic stroke, peripheral occlusive arterial disease **Estimated enrollment:** 7,000 **Estimated study completion date:** 2Q 2015	http://www.clinicaltrials.gov/ct2/show/NCT01131676 Zinman[91]
Cardiovascular Outcomes Following Treatment with Ertugliflozin in Participants with Type 2 Diabetes Mellitus and Established Vascular Disease **Primary outcome measure:** Time to the first occurrence of any component of the composite endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke **Patients:** T2DM; established vascular disease **Estimated enrollment:** 3,900 (currently recruiting) **Estimated study completion date:** 2Q 2020	http://www.clinicaltrials.gov/ct2/show/NCT01986881

Abbreviations: CV, cardiovascular; MI, myocardial infarction; Q, quarter; T2DM, type 2 diabetes mellitus; SGLT, sodium glucose co-transporter.

for the primary composite endpoint (time to first event of the following adjudicated events: CV death, myocardial infarction, stroke, and hospitalization for unstable angina) using a Cox proportional hazards method was 0.674 (95% CI 0.421, 1.078).[63] Similarly, a meta-analysis to assess CV safety for canagliflozin was presented in the FDA report,[69] and included all Major Adverse Cardiovascular Events Plus (MACE-Plus; defined as a composite endpoint consisting of the following adjudicated events: CV death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina) in nine Phase III trials (including interim data from the canagliflozin cardiovascular assessment study [CANVAS]). The estimated hazard ratio was 0.91 (95% CI 0.68, 1.22) for the risk of MACE-Plus comparing canagliflozin to all comparators (via the pre-specified primary Cox proportional hazards model fit to all trials including CANVAS).[69]

Changes in lipid profiles observed with SGLT2 inhibitor therapy have caused some concern.[88] Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed with canagliflozin, as shown in a pooled analysis of data from four 26-week placebo-controlled trials in which the mean percentage increases from baseline in LDL-C were 4.5% and 8.0% for 100 mg and 300 mg canagliflozin, respectively, relative to placebo.[92] Canagliflozin labeling information recommends LDL-C should be monitored and treated according to standard care after initiating canagliflozin therapy.[92] Statistically significant increases in high-density lipoprotein

cholesterol (HDL-C) from baseline were observed with canagliflozin in four of eight placebo-controlled Phase III trials, but decreases in triglyceride levels with canagliflozin were small and were generally not statistically significant.[93] For patients receiving dapagliflozin in Phase III trials, overall small mean changes in HDL-C (+2.1% to +9.3%), triglyceride (−0.9% to −10.6%), and LDL-C (−0.5% to +9.5%) were observed, but there was no clinically significant effect on lipid levels in the individual dapagliflozin studies concerned.[94] For empagliflozin, a pooled analysis of four placebo-controlled Phase III trials reported small increases in HDL-C and LDL-C and small decreases in triglycerides with empagliflozin versus placebo after 24 weeks.[72]

Malignancies

A pooled analysis of data for all dapagliflozin doses from 19 Phase IIb/III trials revealed that the incidence rates for malignancies were similar for dapagliflozin (1.4%) and placebo/comparator (1.3%),[79] and there was no carcinogenicity or mutagenicity signal in animal data.[35] However, breast and bladder cancer adverse events were numerically greater with dapagliflozin than placebo/comparator.[35,63,79,95] The US prescribing information for dapagliflozin states that the drug should not be used in patients with active bladder cancer and should be used with caution in patients with a history of this disease.[36] Furthermore, the dapagliflozin Summary of Product Characteristics does not recommend the use of dapagliflozin in patients being treated with pioglitazone, as epidemiological data suggest a small increased risk of bladder cancer with pioglitazone.[35] Adverse events for breast and bladder cancer, plus renal cell cancer, were also monitored in the clinical studies for canagliflozin.[69] The incidences of these tumor events were low and they occurred at a similar rate across treatment groups (breast cancer 0.38%–0.46% versus 0.4%; bladder cancer 0.06%–0.09% versus 0.11%; renal cell cancer 0.06%–0.09% versus 0.08% for canagliflozin 100 mg and 300 mg groups versus non-canagliflozin groups, respectively).[69] No data on malignancy rates from trials using empagliflozin (or any of the other SGLT2 inhibitors) have been reported to date. Nevertheless, these safety signals raised concerns and further data are required to exclude the possibility of an elevated risk of certain types of cancer occurring with SGLT2 inhibitor treatment.

Current and future roles for SGLT2 inhibitors

Currently available published clinical trial data for SGLT2 inhibitors document their use as add-on therapy with metformin, insulin, sulfonylureas, dipeptidyl peptidase (DPP-4) inhibitors, or thiazolidinediones. SGLT2 inhibitors may also have a role as monotherapy; for example, in patients who are intolerant to metformin due to ensuing gastrointestinal side effects. Data from published trials indicate that various SGLT2 inhibitors have a similar ability to improve glucose control with a low risk of hypoglycemia, together with promoting modest reductions in BP and body weight. The properties of SGLT2 inhibitors present for the first time the possibility of a triple combination (ie, metformin, DPP-4 inhibitor, and SGLT2 inhibitor), with the expected net effect of weight reduction and freedom from hypoglycemic episodes. This could be particularly attractive in Europe, where triple oral combinations have not been popular (presumably, because at least one of the combination components introduced undesired adverse events, such as weight gain and/or hypoglycemia). At present, there is no evidence suggesting preference of any one SGLT2 inhibitor over another: any differences between individual SGLT2 inhibitors may be revealed when clinical head-to-head comparator studies are carried out, although no such studies are currently reported to be underway. A Phase I study comparing the pharmacodynamics of canagliflozin and dapagliflozin was recently completed and publication of the data is awaited (ClinicalTrials.gov identifier: NCT01877889), the primary outcome measure was the between-treatment difference in 24-hour mean renal threshold for glucose.

The effect of SGLT2 inhibition on preserving beta-cell function and improving insulin sensitivity has also been reported. Data from a study using an insulin-resistant animal model of T2DM found that sustained glucose lowering with dapagliflozin improved insulin sensitivity and pancreatic islet function and morphology.[96] The authors suggested that reduction of hyperglycemia by dapagliflozin, through an insulin-independent mechanism, may improve core defects present in T2DM; however, further research is needed before firm conclusions can be drawn.[96] Recently published and independent studies using dapagliflozin and empagliflozin in patients with T2DM reported increased insulin sensitivity following SGLT2 inhibitor therapy,[97,98] and empagliflozin-induced UGE also improved beta-cell function.[98] SGLT2 inhibition with either of these agents increased to some extent endogenous glucose production, despite reducing fasting plasma glucose, and this may be at least partially explained by concentration change in the insulin to glucagon ratio which has been observed with SGLT2 inhibitor therapy.[89,90] There is also preliminary evidence to suggest that SGLT2 inhibitors with lower selectivity towards SGLT1 (ie, canagliflozin)

achieve intra-intestinal levels after oral dosing that may be sufficiently high to transiently inhibit intestinal SGLT1 and reduce intestinal glucose absorption,[32,99] resulting in increased release of glucagon-like peptide-1 and peptide YY.[32,100] These factors together may make SGLT2 inhibitors an attractive choice for T2DM patients who are failing with metformin and who need to lose weight.

Furthermore, SGLT2 inhibitors may have the potential to be used as an insulin-sparing agent in T2DM patients using insulin.[43,58,64] A long-term study of dapagliflozin in T2DM patients using insulin reported the mean insulin dose increased by 18.3 IU/day and body weight increased by 1.8 kg in the placebo group after 104 weeks, whereas insulin dose was stable and body weight decreased by 0.9 kg in the dapagliflozin groups.[64] A similar trend was reported after 78 weeks of empagliflozin treatment.[58] SGLT2 inhibitors could possibly be used transiently instead of insulin treatment in patients who are otherwise well controlled but who develop temporary acute hyperglycemia, due to factors such as short-term immobility, infectious diseases, etc. Additionally, SGLT2 inhibitors may have a role in improving glucose tolerance in pre-diabetic individuals. However, to allow the use of these agents in patients without established disease, clinical trials with SGLT2 inhibitors would need to show a reduced risk for relevant clinical endpoints (eg, CV, etc) as well as robust safety data.

Pilot studies using SGLT2 inhibitors in patients with T1DM are also in progress (ClinicialTrials.gov identifiers: NCT01498185, NCT01392560, NCT01742208), and preliminary results have been presented.[101,102] A further possible use of SGLT2 inhibitors in T1DM is the concept that SGLT2 inhibition may have renal effects by lowering intra-glomerular pressure, which has recently been demonstrated with empagliflozin in patients with T1DM.[103] This observation could explain the reduction of albuminuria with SGLT2 treatment described in Phase III studies. In addition, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE; ClinicialTrials.gov identifier: NCT02065791) study has just commenced, and is a renal outcome study to investigate whether SGLT2 inhibition has renal potential beyond its glucose-lowering properties.

As a final point, it is of interest to note that current SGLT2 inhibitors only inhibit 30%–50% of the filtered glucose load, ie, 50–80 g of the ~180 g filtered per day. The possible pharmacokinetic reasons for this imbalance are discussed in a report by Liu et al,[104] and a novel hypothesis to explain this conundrum was recently postulated by Abdul-Ghani et al.[105] Namely, complete inhibition of SGLT2 causes SGLT1 to reabsorb glucose at full capacity; therefore, only the fraction of filtered glucose that escapes SGLT1 will be excreted in the urine.[105] A better understanding of renal SGLT2 inhibitor handling may help to develop future agents that can inhibit a larger proportion of filtered glucose and further reduce HbA_{1c} levels,[104] for example, agents with the capacity to also partially inhibit renal SGLT1 and produce a more vigorous UGE than those that are highly specific for SGLT2 inhibition only.[105]

There is potentially much more to come from this novel class of drugs, and we wait with interest to see what further developments and therapeutic applications may arise.

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The author was fully responsible for all content and editorial decisions, was involved at all stages of manuscript development, and has approved the final version of the manuscript that reflects the author's interpretation and conclusions.

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Supplementary material

Table S1 SGLT2 inhibitor clinical trials (Phase II+)

Trial ID	Title	Status	Phase	Other trial ID numbers
	Dapagliflozin Phase II and III studies			
NCT00663260	Glycemic Efficacy and Renal Safety Study of Dapagliflozin in Subjects With Type 2 Diabetes Mellitus and Moderate Renal Impairment	Completed	Phase II Phase III	MB102-029
NCT00528372	A Phase III Study of BMS-512148 (Dapagliflozin) in Patients With Type 2 Diabetes Who Are Not Well Controlled With Diet and Exercise	Completed	Phase III	MB102-013
NCT00859898	Study of Dapagliflozin in Combination With Metformin XR to Initiate the Treatment of Type 2 Diabetes	Completed	Phase III	MB102-034 EudraCT #: 2008-007548-33
NCT01095666	A Phase III Study of BMS-512148 (Dapagliflozin) in Asian Patients With Type 2 Diabetes Who Are Not Well Controlled on Metformin Alone	Active, not recruiting	Phase III	MB102-055
NCT01095653	A Phase III Study of BMS-512148 (Dapagliflozin) in Asian Patients With Type 2 Diabetes Who Are Not Well Controlled With Diet and Exercise	Completed	Phase III	MB102-054
NCT01606007	Safety and Efficacy of Combination Saxagliptin and Dapagliflozin Added to Metformin to Treat Subjects With Type 2 Diabetes	Recruiting	Phase III	CV181-169 | 2012-000679-18
NCT00673231	Efficacy and Safety of Dapagliflozin, Added to Therapy of Patients With Type 2 Diabetes With Inadequate Glycemic Control on Insulin	Completed	Phase III	D1690C00006
NCT01498185	BMS – Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Dapagliflozin in Type 1 Diabetes	Completed	Phase II	MB102-072
NCT00680745	Efficacy and Safety of Dapagliflozin in Combination With Glimepiride (a Sulphonylurea) in Type 2 Diabetes Patients	Completed	Phase III	D1690C00005
NCT00643851	An Efficacy and Safety Study of BMS-512148 in Combination With Metformin Extended Release Tablets	Completed	Phase III	MB102-021
NCT00162305	A Phase IIA Study of BMS-512148 to Assess Safety, Exposure, and Biological Effects in Stable Type 2 Diabetic Subjects	Completed	Phase II	MB102-003
NCT01195662	A Study of BMS-512148 (Dapagliflozin) in Patients With Type 2 Diabetes With Inadequately Controlled Hypertension on an ACEI or ARB and an Additional Antihypertensive Medication	Completed	Phase III	MB102-077 | 2010-019798-13
NCT01137474	A Study of BMS-512148 (Dapagliflozin) in Patients With Type 2 Diabetes With Inadequately Controlled Hypertension on an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB)	Completed	Phase III	MB102-073 | 2010-019797-32
NCT00972244	Trial to Evaluate the Efficacy and Safety of Dapagliflozin in Japanese Type 2 Diabetes Mellitus Patients	Completed	Phase II	D1692C00005
NCT00855166	Evaluation of the Effect of Dapagliflozin in Combination With Metformin on Body Weight in Subjects With Type 2 Diabetes	Completed	Phase III	D1690C00012
NCT01730534	Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events	Not yet recruiting	Phase III	D1693C00001
NCT00736879	Safety and Efficacy of Dapagliflozin as Monotherapy in Subjects With Type 2 Diabetes	Completed	Phase III	MB102-032
NCT00984867	Dapagliflozin DPPIV Inhibitor add-on Study	Completed	Phase III	D1690C00010
NCT00528879	A Phase III Study of BMS-512148 (Dapagliflozin) in Patients With Type 2 Diabetes Who Are Not Well Controlled on Metformin Alone	Completed	Phase III	MB102-014
NCT01217892	Evaluation of Dapagliflozin Taken Twice-daily	Completed	Phase III	D1691C00003
NCT00831779	Effects of Dapagliflozin on Insulin Resistance and Insulin Secretion in Subjects With Type 2 Diabetes	Completed	Phase II	MB102-045
NCT00976495	Effects of Dapagliflozin on Kidney Function (Glomerular Filtration Rate) in Subjects With Type 2 Diabetes	Completed	Phase II	MB102-035 | EudraCT #: 2009-010221-39

NCT01392677	Evaluation of Safety and Efficacy of Dapagliflozin in Subjects With Type 2 Diabetes Who Have Inadequate Glycemic Control on Background Combination of Metformin and Sulfonylurea	Active, not recruiting	Phase III	D1693C00005
NCT00660907	Efficacy and Safety of Dapagliflozin in Combination With Metformin in Type 2 Diabetes Patients	Active, not recruiting	Phase III	D1690C00004
NCT01646320	Safety and Efficacy of Dapagliflozin in Triple Therapy to Treat Subjects With Type 2 Diabetes	Recruiting	Phase III	MB102-129 | 2011-006324-20
NCT00357370	A Pilot Study of BMS-512148 in Subjects With Type 2 Diabetes	Completed	Phase II| Phase III	MB102-009
NCT00683878	Add-on to Thiazolidinedione (TZD) Failures	Completed	Phase III	MB102-030
NCT01294423	Evaluate Efficacy and Safety in Japanese Subjects With Type 2 Diabetes Mellitus	Completed	Phase III	D1692C00006
NCT01257412	Evaluation of Efficacy and Safety of Dapagliflozin as Monotherapy in Subjects With Type 2 Diabetes Who Have Inadequate Glycemic Control With Diet and Exercise Alone	Suspended	Phase III	D1693C00002
NCT01042977	Efficacy and Safety in Patients With Type 2 Diabetes Mellitus and Cardiovascular Disease	Completed	Phase III	D1690C00019
NCT01031680	Efficacy and Safety in Patients With Type 2 Diabetes Mellitus, Cardiovascular Disease and Hypertension	Completed	Phase III	D1690C00018
NCT00263276	A Trial of BMS-512148 in Patients With Type 2 Diabetes Mellitus	Completed	Phase II	MB102-008
NCT01619059	Safety and Efficacy of Saxagliptin in Triple Therapy to Treat Subjects With Type 2 Diabetes	Recruiting	Phase III	CV181-168| 2011-006323-37
NCT01294436	Evaluate Safety as Mono or Combination Therapies With Anti-diabetes Mellitus Drugs in Japanese Subjects With Type 2 Diabetes Mellitus	Completed	Phase III	D1692C00012
NCT02096705	Phase III Insulin Add-On Asia Regional Program	Not yet recruiting	Phase III	MB102-137
	Canagliflozin Phase II through IV studies			
NCT01809327	A Study to Evaluate the Effectiveness, Safety, and Tolerability of Canagliflozin in Combination With Metformin in the Treatment of Patients With Type 2 Diabetes Mellitus With Inadequate Glycemic Control With Diet and Exercise	Recruiting	Phase III	CR100034|28431754DIA3011| 2011-000400-17
NCT01340664	An Efficacy, Safety, and Tolerability Study of Canagliflozin in the Treatment of Patients With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Monotherapy	Completed	Phase II	CR017914|28431754DIA2003| 2010-024256-28
NCT01939496	Evaluation of Blood Pressure Reduction, Safety, and Tolerability of Canagliflozin in Patients With Hypertension and Type 2 Diabetes Mellitus on Stable Doses of Anti-hyperglycemic and Anti-hypertensive Agents	Not yet recruiting	Phase IV	CR102208|28431754DIA4002
NCT01081834	The CANTATA-M (CANagliflozin Treatment and Trial Analysis – Monotherapy) Trial	Completed	Phase III	CR017011|28431754DIA3005
NCT01106690	The CANTATA-MP Trial (CANagliflozin Treatment and Trial Analysis – Metformin and Pioglitazone)	Completed	Phase III	CR017032|28431754DIA3012
NCT01106625	The CANTATA-MSU Trial (CANagliflozin Treatment And Trial Analysis – Metformin and SUlphonylurea)	Completed	Phase III	CR017005|28431754DIA3002
NCT01064414	An Efficacy, Safety, and Tolerability Study of Canagliflozin in Patients With Type 2 Diabetes Mellitus Who Have Moderate Renal Impairment	Completed	Phase III	CR017008|28431754DIA3004
NCT01106677	The CANTATA-D Trial (CANagliflozin Treatment and Trial Analysis – DPP-4 Inhibitor Comparator Trial)	Completed	Phase III	CR017023|28431754DIA3006
NCT01106651	A Safety and Efficacy Study of Canagliflozin in Older Patients (55 to 80 Years of Age) With Type 2 Diabetes Mellitus	Active, not recruiting	Phase III	CR017014|28431754DIA3010
NCT01381900	An Efficacy, Safety, and Tolerability Study of Canagliflozin in Patients With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Alone or in Combination With a Sulphonylurea	Completed	Phase III	CR018541|28431754DIA3014

(*Continued*)

Table S1 (*Continued*)

Trial ID	Title	Status	Phase	Other trial ID numbers
NCT01137812	The CANTATA-D2 Trial (CANagliflozin Treatment And Trial Analysis – DPP-4 Inhibitor Second Comparator Trial)	Completed	Phase III	CR017185|28431754DIA3015
NCT00968812	CANagliflozin Treatment And Trial Analysis-Sulfonylurea (CANTATA-SU) SGLT2 Add-on to Metformin Versus Glimepiride	Completed	Phase III	CR016480|28431754DIA3009
NCT01032629	CANVAS – CANagliflozin cardioVascular Assessment Study	Active, not recruiting	Phase III	CR016627|28431754DIA3008
NCT00642278	An Efficacy, Safety, and Tolerability Study of Canagliflozin (JNJ-28431754) in Patients With Type 2 Diabetes	Completed	Phase II	CR014587|28431754DIA2001
NCT00650806	A Study of the Safety and Effectiveness of Canagliflozin (JNJ-28431754) in Promoting Weight Loss in Overweight and Obese Patients Who do Not Have Diabetes	Completed	Phase II	CR014578|28431754OBE2001
NCT01413204	Efficacy and Safety Study of TA-7284 in Patients With Type 2 Diabetes	Completed	Phase III	TA-7284-05
NCT01022112	An Efficacy, Safety, and Tolerability Study for TA-7284 in Patients With Type 2 Diabetes	Completed	Phase II	TA-7284-04
NCT01387737	Long-Term Safety Study of TA-7284 in Patients With Type 2 Diabetes Mellitus	Completed	Phase III	TA-7284-06
NCT02025907	A Study to Evaluate the Efficacy and Safety of the Addition of Canagliflozin in Participants With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sitagliptin	Recruiting	Phase IV	CR103477|2013-004819-40|284317544004
NCT01989754	A Study of the Effects of Canagliflozin (JNJ-28431754) on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus	Recruiting	Phase IV	CR102647|2013-003050-25|28431754DIA4003
NCT02065791	Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy	Recruiting	Phase III	CR103517|2013-004494-28|28431754DNE3001
NCT02053116	A 6-Week Study To Determine The Safety And Effect Of An Investigational Drug (PF-05175157) Given With Canagliflozin In Adults With Type 2 Diabetes Mellitus Taking Metformin	Recruiting	Phase II	B1731006
	Empagliflozin Phase II and III studies			
NCT01289990	Safety and Efficacy of Empagliflozin (BI 10773) and Sitagliptin Versus Placebo Over 76 Weeks in Patients With Type 2 Diabetes	Completed	Phase III	1245.31|2010-022718-17
NCT01193218	Empagliflozin (BI 10773) Dose Finder Study in Japanese Patients With Type 2 Diabetes Mellitus	Completed	Phase II	1245.38
NCT01422876	Efficacy and Safety of Empagliflozin (BI 10773)/Linagliptin (BI 1356) Fixed Dose Combination in Treatment naïve and Metformin Treated Type 2 Diabetes Patients	Completed	Phase III	1275.1|2011-000383-10
NCT01649297	A 16 Weeks Study on Efficacy and Safety of Two Doses of Empagliflozin (BI 10773) (Once Daily Versus Twice Daily) in Patients With Type 2 Diabetes Mellitus and Preexisting Metformin Therapy	Active, not recruiting	Phase II	1276.10|2012-000905-53
NCT01177813	Efficacy and Safety of Empagliflozin (BI 10773) Versus Placebo and Sitagliptin Over 24 Weeks in Patients With Type 2 Diabetes	Completed	Phase III	1245.20|2009-016243-20
NCT01778049	Linagliptin as Add on Therapy to Empagliflozin 10 mg or 25 mg With Background Metformin in Patient With Type 2 Diabetes	Recruiting	Phase III	1275.10|2012-002271-34
NCT01719003	Safety and Efficacy Study of Empagliflozin and Metformin for 24 Weeks in Treatment Naïve Patients With Type 2 Diabetes	Recruiting	Phase III	1276.1|2010-021375-92
NCT01370005	12 Week Efficacy and Safety Study of Empagliflozin (BI 10773) in Hypertensive Patients With Type 2 Diabetes Mellitus	Completed	Phase III	1245.48|2011-000347-25
NCT00885118	4 Weeks Treatment With Empagliflozin (BI 10773) in Japanese Type 2 Diabetic Patients (T2DM)	Completed	Phase II	1245.15
NCT01159600	Efficacy and Safety Study With Empagliflozin (BI 10773) vs Placebo as add-on to Metformin or Metformin Plus Sulfonylurea Over 24 Weeks in Patients With Type 2 Diabetes	Completed	Phase III	1245.23|2009-016258-41
NCT01164501	Efficacy and Safety of Empagliflozin (BI 10773) in Patients With Type 2 Diabetes and Renal Impairment	Completed	Phase III	1245.36|2009-016179-31
NCT01210001	Efficacy and Safety of Empagliflozin (BI 10773) in Type 2 Diabetes Patients on a Background of Pioglitazone Alone or With Metformin	Completed	Phase III	1245.19|2009-016154-40

NCT01248364	A Study to Determine Acute (After First Dose) and Chronic (After 28 Days) Effects of Empagliflozin (BI 10773) on Pre and Postprandial Glucose Homeostasis in Patients With Impaired Glucose Tolerance and Type 2 Diabetes Mellitus and Healthy Subjects	Completed	Phase II	1245.39|2010-018708-99
NCT01368081	Empagliflozin (BI 10773) Comprehensive add-on Study in Japanese Subjects With Type 2 Diabetes Mellitus	Completed	Phase III	1245.52
NCT01131676	BI 10773 Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients	Active, not recruiting	Phase III	1245.25|2009-016178-33
NCT01011868	Efficacy and Safety of BI 10773 in Combination With Insulin in Patients With Type 2 Diabetes	Completed	Phase II	1245.33|2009-013668-38
NCT01306214	Safety and Efficacy of BI 10773 as add-on to Insulin Regimen in Patients With Type 2 Diabetes Mellitus	Completed	Phase III	1245.49|2010-019968-37
NCT00881530	Empagliflozin (BI 10773) in Type Two Diabetes (T2D) Patients, Open Label Extension	Completed	Phase II	1245.24|2008-007938-21
NCT01947855	Post Prandial Glucose (PPG) Study of Empagliflozin in Japanese Patients With Type 2 Diabetes Mellitus	Not yet recruiting	Phase III	1245.35
NCT01392560	Safety and Efficacy of Empagliflozin (BI 10773) in Type 1 Diabetes Mellitus Patients With or Without Renal Hyperfiltration	Completed	Phase II	1245.46
NCT01167881	Efficacy and Safety of Empagliflozin (BI 10773) With Metformin in Patients With Type 2 Diabetes	Active, not recruiting	Phase III	1245.28|2009-016244-39
NCT01734785	Safety and Efficacy of the Combination of Empagliflozin and Linagliptin Compared to Linagliptin Alone Over 24 Weeks in Patients With Type 2 Diabetes	Recruiting	Phase III	1275.9|2012-002270-31
NCT01867307	Effect of Empagliflozin Kinetics on Renal Glucose Reabsorption in Patients With Type II Diabetes and Healthy Controls	Recruiting	Phase II	1245.66
NCT00789035	12 Weeks Treatment With 3 Different Doses of BI 10773 in Type 2 Diabetic Patients	Completed	Phase II	1245.9|EudraCT No 2008-000640-14
NCT00749190	BI 10773 add-on to Metformin in Patients With Type 2 Diabetes	Completed	Phase II	1245.10|EudraCT 2008-000641-54
NCT01257334	Patients With Type 2 Diabetes Mellitus With Insufficient Glycaemic Control Despite Treatment With Metformin Alone or Metformin in Combination With a Sulfonylurea	Enrolling by invitation	Phase III	99050
NCT01969747	Empagliflozin add-on to Insulin in Type 1 Diabetes Mellitus Over 28 Days	Active, not recruiting	Phase II	1245.78|2011-004354-25
NCT01984606	Efficacy and Safety of Empagliflozin Versus Sitagliptin in Patients With Type 2 Diabetes	Not yet recruiting	Phase III	1245.22|2013-000060-29
	Ipragliflozin Phase II and III studies			
NCT01505426	A Study to Assess the Efficacy and Safety of ASP1941 in Combination With Metformin in Asian Diabetes Patients	Completed	Phase III	1941-CL-2004
NCT01514838	A Study to Assess the Efficacy and Safety of ASP1941 in Asian Subjects With Type 2 Diabetes Mellitus	Terminated	Phase III	1941-CL-2003
NCT01672762	A Study to Evaluate Long-term Safety and Efficacy of ASP1941 in Diabetes Patients	Completed	Phase III	1941-CL-0122
NCT01054092	A Study to Assess the Long-term Safety and Efficacy of ASP1941 in Japanese Diabetic Patients	Completed	Phase III	1941-CL-0121
NCT00790660	A Study to Assess the Safety and Tolerability of ASP1941 in Adults With Type 2 Diabetes Mellitus	Completed	Phase II	1941-CL-0016
NCT01071850	A Study to Evaluate the Effect of ASP1941 in Adult Patients With Type 2 Diabetes Mellitus	Completed	Phase II	1941-CL-0004
NCT01117584	A Study to Evaluate the Effect of ASP1941 in Combination With Metformin in Adult Patients With Type 2 Diabetes Mellitus	Completed	Phase II	1941-CL-0005|2009-013881-25
NCT01316094	A Study to Assess Efficacy and Safety of ASP1941 in Diabetic Patients With Renal Impairment	Completed	Phase III	1941-CL-0072
NCT01057628	A Study to Assess the Efficacy and Safety of ASP1941 in Japanese Type 2 Diabetes Patients	Completed	Phase III	1941-CL-0105
NCT01242215	A Study to Assess the Efficacy and Safety of ASP1941 in Combination With Sulfonylurea in Type 2 Diabetic Patients	Completed	Phase III	1941-CL-0109
NCT01135433	A Study to Assess the Efficacy and Safety of ASP1941 in Combination With Metformin in Type 2 Diabetic Patients	Completed	Phase III	1941-CL-0106
NCT01225081	A Study to Assess the Efficacy and Safety of ASP1941 in Combination With Pioglitazone in Type 2 Diabetic Patients	Completed	Phase III	1941-CL-0107

(*Continued*)

Table S1 (*Continued*)

Trial ID	Title	Status	Phase	Other trial ID numbers
NCT01316107	A Study to Assess Safety and Efficacy of ASP1941 in Combination With Nateglinide in Type 2 Diabetic Patients	Completed	Phase III	1941-CL-0111
NCT01242202	A Study to Assess the Safety and Efficacy of ASP1941 in Combination With α-glucosidase Inhibitor in Type 2 Diabetic Patients	Completed	Phase III	1941-CL-0108
NCT01242228	A Study to Assess the Safety and Efficacy of ASP1941 in Combination With Dipeptidyl Peptidase-4 (DPP-4) Inhibitor in Type 2 Diabetic Patients	Completed	Phase III	1941-CL-0110
NCT00621868	A Phase II Study of ASP1941 in Japanese Patients With Type 2 Diabetes Mellitus	Completed	Phase II	1941-CL-0103
	Ertugliflozin Phase II and III studies			
NCT02099110	Ertugliflozin and Sitagliptin Co-administration Factorial Study (MK-8835-005)	Not yet recruiting	Phase III	8835-005
NCT02036515	Safety and Efficacy of Ertugliflozin in the Treatment of Participants With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin and Sitagliptin (MK-8835-006)	Not yet recruiting	Phase III	8835-006|2013-003697-26|B1521015
NCT01986855	A Study of the Efficacy and Safety of Ertugliflozin in Participants With Type 2 Diabetes Mellitus With Stage 3 Chronic Kidney Disease Who Have Inadequate Glycemic Control on Antihyperglycemic Therapy (MK-8835-001)	Recruiting	Phase III	8835-001|2013-003587-31|B1521016
NCT01999218	MK-8835/PF-04971729 vs Glimepiride in Type 2 Diabetes Mellitus (T2DM) Participants on Metformin (MK-8835-002)	Recruiting	Phase III	8835-002|2013-003582-34
NCT01958671	A Study of the Efficacy and Safety of Ertugliflozin Monotherapy in the Treatment of Participants With Type 2 Diabetes Mellitus and Inadequate Glycemic Control Despite Diet and Exercise (MK-8835-003)	Recruiting	Phase III	8835-003|2013-002519-90|B1521022
NCT01986881	Cardiovascular Outcomes Following Treatment With Ertugliflozin in Participants With Type 2 Diabetes Mellitus and Established Vascular Disease (MK-8835-004)	Recruiting	Phase III	8835-004|2013-002518-11
NCT02033889	A Study To Evaluate The Efficacy And Safety Of Ertugliflozin In Participants With Type 2 Diabetes Mellitus And Inadequate Glycemic Control On Metformin Monotherapy (MK-8835-007)	Recruiting	Phase III	8835-007|2013-003290-95|B1521017
NCT01059825	Study Of Safety And Efficacy Of PF-04971729 In Patients With Type 2 Diabetes	Completed	Phase II	B1521006
NCT01096667	Study of Safety and Efficacy Of PF-04971729 In Patients With Type 2 Diabetes And Hypertension	Completed	Phase II	B1521004
	LX4211 Phase II studies			
NCT01742208	Safety and Efficacy of LX4211 in Patients With Inadequately Controlled Type 1 Diabetes Mellitus	Completed	Phase II	LX4211.1-203-T1DM|LX4211.203
NCT00962065	Study of LX4211 in Subjects With Type 2 Diabetes Mellitus	Completed	Phase II	LX4211.1-201-DM|LX4211.201
NCT01376557	Safety and Efficacy of LX4211 With Metformin in Type 2 Diabetes Patients With Inadequate Glycemic Control on Metformin	Completed	Phase II	LX4211.1-202-DM|LX4211.202
	EGT0001442 Phase II studies			
NCT01029704	Safety and Efficacy Study of EGT0001442 in Subjects With Type 2 Diabetes Mellitus	Completed	Phase II	THR-1442-C-402
NCT01377844	Efficacy and Safety of EGT0001442 in Patients With Type 2 Diabetes Mellitus	Active, not recruiting	Phase II	THR-1442-C-418
–	Luseogliflozin (TS-071) – no trials registered	–	–	–
–	Tofogliflozin (CSG452) – no trials registered	–	–	–

Abbreviations: XR, extended release formulation; SGLT, sodium glucose co-transporter.

Table S2 SGLT2 and SGLT1 inhibitors currently in the development pipeline

Compound	Sponsor	Status	Details	Reference
SBM-TFC-039	Sirona Biochem	Preclinical	SBM-TFC-039 is a novel SGLT-2 inhibitor, under development for the treatment of Type 2 diabetes and obesity using GlycoMim Technology: an IND application is expected in 2013. It has been investigated in monkeys, where it triggered glucosuria in a dose-dependent manner, and in obese diabetic rats, where it normalized diabetes and reduced blood glucose by 48% compared to the non-treated group.	http://www.sironabiochem.com/sirona-biochem-announces-preclinical-results-of-diabetes-compound-2/
N-glucoside 9d	Mitsubishi Tanabe	Preclinical	A series of N-glucosides was synthesized for biological evaluation as human SGLT2 (hSGLT2) inhibitors. Among these compounds, N-glucoside 9d possessing an indole core structure showed good in vitro activity (IC50=7.1 nM against hSGLT2). Furthermore, 9d exhibited favorable in vivo potency with regard to UGE in rats based on good pharmacokinetic profiles.	Yamamoto et al[33]
LX2761	Lexicon	Preclinical	LX2761, an SGLT1 inhibitor restricted to the intestine, improves glycemic control in mice.	Powell et al[34]
KGA2727	GlaxoSmithKline	Preclinical	Synergistic glucose-lowering effects of SGLT1- and apical sodium-dependent bile acid transporter-inhibitor (GSK2299027) combinations in Zucker-fatty diabetic rats.	Young et al[35]
6-Deoxydapagliflozin	None stated	Preclinical	Systematic mono-deoxylation of the four hydroxyl groups in the glucose moiety in dapagliflozin led to the discovery of 6-deoxydapagliflozin 1 as a more active sodium-dependent glucose co-transporter 2 (SGLT2) inhibitor (IC50=0.67 nM against human SGLT2 (hSGLT2) versus 1.16 nM for dapagliflozin). It exhibited more potent blood glucose inhibitory activity in rat oral glucose tolerance test and induced more urinary glucose in rat urinary glucose excretion test than its parent compound dapagliflozin.	Zhang et al[36]

Abbreviations: SGLT, sodium glucose co-transporter; IND, investigational new drug; IC50, half minimal inhibitory concentration; UGE, urinary glucose excretion.

Table S3 Efficacy data from pivotal clinical trials of SGLT2 inhibitors[a]

Reference & NCT ID (Study number or acronym)	Study details	Regimen	N	Treatment and dose, mg/day	Change in HbA_{1c} from baseline, %	
					Mean	SD or (95% CI) or [SEM]
Dapagliflozin						
List *Diabetes Care* 2009[1] NCT00263276 (MB102008)	Phase II, 12 week	Drug naïve, diet/exercise	389			
			54	Pbo	–0.2	0.1
			59	2.5	–0.7	0.1
			58	5	–0.7	0.1
			47	10	–0.9	0.1
			59	20	–0.6	0.1
			56	50	–0.9	0.1
			56	MET XR	–0.7	0.1
Wilding *Diabetes Care* 2009[2] NCT00357370 (MB102009)	Phase II, 12 week	OADs + INS	71			
			23	Pbo	0.1	(–0.2, 0.4)
			24	10	–0.6	(–0.9, –0.4)
			24	20	–0.7	(–0.9, –0.4)
Ferrannini *Diabetes Care* 2010[3] NCT00528372 (MB102013)	Phase III, 24 week	Drug naïve, diet/exercise	485			
			75	Pbo	–0.2	[0.1]
			65	2.5 AM	–0.6	[0.1]
			64	5 AM	–0.8	[0.1]
			70	10 AM	–0.9	[0.1]
			67	2.5 PM	–0.8	[0.1]
			68	5 PM	–0.8	[0.1]
			76	10 PM	–0.8	[0.1]
			34	5 ($A_{1c} \geq 10.1$)	–2.9	1.4
			39	10 ($A_{1c} \geq 10.1$)	–2.7	1.3
Bailey *Diabetes Obes Metab* 2012[4] NCT00736879 (MB102032)	Phase III, 24 week	Drug naïve, diet/exercise	282			
			68	Pbo	0.0	(–0.2, 0.3)
			72	1	–0.7	(–1.0, –0.5)
			74	2.5	–0.7	(–1.0, –0.5)
			68	5	–0.8	(–1.1, –0.6)
Bailey *Lancet* 2010[5] NCT00528879 (MB102014)	Phase III, 24 week	MET	546			
			137	Pbo	–0.3	(–0.4, –0.2)
			137	2.5	–0.7	(–0.9, –0.6)
			137	5	–0.7	(–0.8, –0.5)
			135	10	–0.8	(–1.0, –0.7)
Bolinder *J Clin Endocrinol Metab* 2012[6] NCT00855166 (D1690C00012)	Phase III, 24 week, BMI ≥25	MET	182			
			91	Pbo	–0.1	–
			91	10	–0.4	–
Henry *Int J Clin Pract* 2012[7]	Phase III, 24 week (both)	MET XR				
NCT00643851 (MB102021)			201	Pbo + MET	–1.4	(–1.5, –1.2)
			194	5 + MET	–2.1	(–2.2, –1.9)
			203	5 + Pbo	–1.2	(–1.4, –1.0)
NCT00859898 (MB102034)			208	Pbo + MET	–1.4	(–1.6, –1.3)
			211	10 + MET	–2.0	(–2.1, –1.8)
			219	10 + Pbo	–1.5	(–1.6, –1.3)

Change in FPG from baseline, mg/dL		Change in body weight from baseline, kg		Change in SBP from baseline, mmHg	
Mean	**SD or (95% CI) or [SEM]**	**Mean**	**SD or (95% CI) or [SEM]**	**Mean**	**SD or (95% CI) or [SEM]**
				Supine	
–6	3	–1.1	(–1.8, –0.4)	2	11
–16	3	–2.4	(–3.1, –1.7)	–3	11
–19	3	–2.2	(–2.9, –1.6)	–3	13
–21	4	–2.3	(–3.0, –1.5)	–6	11
–24	3	–3.0	(–3.6, –2.3)	–4	12
–31	3	–3.1	(–3.8, –2.4)	–3	13
–18	3	–1.5	(–2.1, –0.8)	–0	12
18	(1, 34)	–1.9	(–2.9, –0.9)	2	[6]
2	(–14, 18)	–4.5	(–5.5, –3.5)	–1	[3]
–10	(–26, 6)	–4.3	(–5.3, –3.3)	–6	[2]
				Seated	
–4	[4]	–2.2	[0.4]	–1	[2]
–15	[4]	–3.3	[0.5]	–5	[2]
–24	[4]	–2.8	[0.5]	–2	[2]
–29	[4]	–3.2	[0.5]	–4	[2]
–26	[4]	–3.8	[0.5]	–4	[2]
–27	[4]	–3.6	[0.5]	–5	[2]
–30	[4]	–3.1	[0.4]	–2	[1]
–77	53	–2.1	3.4	–6	[2]
–84	61	–1.9	3.5	–3	[2]
				Seated	
4	(–4, 12)	–1.0	(–1.7, –0.2)	1	[1]
–11	(–19, –3)	–2.7	(–3.4, –1.9)	–4	[1]
–22	(–30, –14)	–2.6	(–3.4, –1.9)	–3	[2]
–28	(–37, –20)	–2.7	(–3.5, –1.9)	–5	[2]
				Seated	
–6	(–11, –1)	–0.9	(–1.4, –0.4)	0	[1]
–18	(–23, –12)	–2.2	(–2.7, –1.8)	–2	[1]
–21	(–29, –16)	–3.0	(–3.5, –2.6)	–4	[1]
–23	(–29, –18)	–2.9	(–3.3, –2.4)	–5	[1]
				Seated	
2	–	–0.9	(–1.4, –0.3)	0	–
–15	–	–3.0	(–3.5, –2.4)	–3	–
–34	(–39, –28)	–1.3	(–1.8, –0.8)	–2	[1]
–61	(–66, –56)	–2.7	(–3.1, –2.2)	–3	[1]
–42	(–47, –37)	–2.6	(–3.1, –2.2)	–4	[1]
–35	(–40, –30)	–1.4	(–1.8, –0.9)	–1	[1]
–60	(–65, –55)	–3.3	(–3.8, –2.9)	–3	[1]
–46	(–51, –41)	–2.7	(–3.2, –2.3)	–4	[1]

(*Continued*)

Table S3 (*Continued*)

Reference & NCT ID (Study number or acronym)	Study details	Regimen	N	Treatment and dose, mg/day	Change in HbA_{1c} from baseline, %	
					Mean	SD or (95% CI) or [SEM]
Strojek *Diabetes Obes Metab* 2011[8] NCT00680745 (D1690C00005)	Phase III, 24 week	SU (GLIM)	597			
			145	Pbo	–0.1	–
			154	2.5	–0.6	–
			142	5	–0.6	–
			151	10	–0.8	–
Nauck *Diabetes Care* 2011[9] NCT00660907 (D1690C00004)	Phase III, 52 week	MET				
			406	DAPA 2.5–10	–0.5	(–0.6, 0.4)
			408	GLIP 5–20	–0.5	(–0.6, 0.4)
Rosenstock *Diabetes Care* 2012[10] NCT00683878 (MB102030)	Phase III, 48 week	TZD (PIO)	420			
			139	Pbo	–0.5	[0.1]
			141	5	–1.0	[0.1]
			140	10	–1.2	[0.1]
Wilding *Ann Intern Med* 2012[11] NCT00673231 (D1690C00006)	Phase III, 48 week	INS ≥30 units/day ± OADs	800			
			193	Pbo	–0.5	–
			202	2.5	–0.8	–
			211	5	–1.0	–
			194	10	–1.0	–
Kohan *Kidney Int* 2013[12] NCT00663260 (MB102029)	Phase III, 104 week Renal impairment	AHAs including INS				
		24 week data	50	Pbo	–0.3	[0.1]
		24 week data	63	5	–0.4	[0.1]
		24 week data	65	10	–0.4	[0.1]
Jabbour *Diabetes Care* 2013[13] NCT00984867 (D1690C00010)	Phase III, 24 week	DDP4 inhibitor (SITA) ± MET				
			224	Pbo	0.0	(–0.1, 0.1)
			223	10	–0.5	(–0.6, 0.4)
		Stratum 1	111	Pbo + SITA	0.1	(–0.1, 0.3)
		Stratum 1	110	10 + SITA	–0.5	(–0.6, –0.3)
		Stratum 2	113	Pbo + SITA + MET	–0.0	(–0.2, 0.1)
		Stratum 2	113	10 + SITA + MET	–0.4	(–0.6, –0.3)
Canagliflozin						
Stenlöf *Diabetes Obes Metab* 2013[14] NCT01081834 (CANTATA-M)	Phase III, 26 week	Drug naïve, diet/exercise	584			
			192	Pbo	0.1	–
			195	100	–0.8	–
			197	300	–1.0	–
Cefalu *Lancet* 2013[15] NCT00968812 (CANTATA-SU)	Phase III, 52 week	MET	1,450			
			483	100	–0.8	[0.0]
			485	300	–0.9	[0.0]
			482	GLIM 1–8	–0.8	[0.0]

Change in FPG from baseline, mg/dL		Change in body weight from baseline, kg		Change in SBP from baseline, mmHg	
Mean	**SD or (95% CI) or [SEM]**	**Mean**	**SD or (95% CI) or [SEM]**	**Mean**	**SD or (95% CI) or [SEM]**
				Seated	
–2	–	–0.7	–	–1	–
–17	–	–1.2	–	–5	–
–21	–	–1.6	–	–4	–
–28	–	–2.3	–	–5	–
–22	(–26, –19)	–3.2	(–3.6, –2.9)	–4	–
–19	(–22, –18)	1.4	(1.1, 1.8)	1	–
				Seated	
–13	[4]	3.0	[0.4]	2	[1]
–23	[3]	1.4	[0.4]	–1	[1]
–33	[3]	0.7	[0.4]	–2	[1]
Not reported				Seated	
–	–	0.8	–	–1	(–4, 1)
–	–	–1.0	–	–5	(–7, –3)
–	–	–1.0	–	–4	(–6, –2)
–	–	–1.6	–	–4	(–6, –2)
3	[7]	0.7	[0.5]	–	–
–10	[6]	–1.3	[0.4]	–	–
–9	[6]	–1.7	[0.4]	–	–
				Seated SBP at week 8 in patients with seated baseline SBP ≥130 mmHg	
4	(–1, 8)	–0.3	(–0.6, 0.1)	–5	(–7, –3)
–24	(–28, –20)	–2.1	(–2.5, –1.8)	–6	(–8, –4)
5	(–2, 12)	–0.1	(–0.5, 0.4)	–4	(–7, –1)
–22	(–29, –15)	–1.9	(–2.4, –1.5)	–7	(–10, –4)
3	(–3, 9)	–0.5	(–1.0, 0.1)	–6	(–8, –3)
–26	(–32, –20)	–2.4	(–2.9, –1.8)	–5	(–8, –2)
9	–	–0.5	–	0	[1]
–27		–2.5		–3	[1]
–34		–3.4		–5	[1]
–25	[2]	–3.7	[0.2]	–3	[1]
–27	[2]	–4.0	[0.2]	–5	[1]
–18	[2]	0.7	[0.2]	0	[1]

(*Continued*)

Table S3 (*Continued*)

Reference & NCT ID (Study number or acronym)	Study details	Regimen	N	Treatment and dose, mg/day	Change in HbA_{1c} from baseline, %	
					Mean	SD or (95% CI) or [SEM]
Lavalle-González *Diabetologia* 2013[16] NCT01106677 (CANTATA-D)	Phase III, 52 week	MET	–			
			368	100	–0.7	[0.1]
			367	300	–0.9	[0.1]
			366	SITA 100	–0.7	[0.1]
Schernthaner *Diabetes Care* 2013[17] NCT01137812 (CANTATA-D2)	Phase III, 52 week	MET + SU	755			
			377	300	–1.0	–
			378	SITA 100	–0.7	–
Wilding *Int J Clin Pract* 2013[18] NCT01106625 (CANTATA-MSU)	Phase III, 26 week (+26 week extension)	MET + SU	469			
		26 week	156	Pbo	–0.1	–
		26 week	157	100	–0.9	–
		26 week	156	300	–1.1	–
		52 week	119	Pbo	0.0	–
		52 week	127	100	–0.7	–
		52 week	128	300	–1.0	–
Forst *Diabetes Obes Metab* 2014[19] NCT01106690 (CANTATA–MP)	Phase III, 26 week (+26 week extension)	MET + TZD (PIO)	342			
			115	Pbo	–0.3	–
			113	100	–0.9	–
			114	300	–1.0	–
Matthews *Diabetologia* 2012[20] NCT01032629 (CANVAS, INS sub-study)	Phase III, Sub-study efficacy duration 18 week	INS ≥20 units/day	1,708			
			565	Pbo	Δ vs Pbo	–
			566	100	–0.7	(–0.7, –0.6)
			587	300	–0.7	(–0.8, –0.7)
Rosenstock *Diabetes Care* 2012[21] NCT00642278	Phase II, 12 week	MET	451			
			65	Pbo	–0.2	[SEM shown graphically; no data reported]
			64	50	–0.8	–
			64	100	–0.8	–
			65	200	–0.7	–
			64	300	–0.9	–
			64	300 BD	–1.0	–
			65	SITA 100	–0.7	–
Yale *Diabetes Obes Metab* 2013[22] NCT01064414	Phase III, 26 week, CKD	AHAs	269			
			90	Pbo	–0.0	Difference vs Pbo
			90	100	–0.3	(–0.5, –0.1)
			89	300	–0.4	(–0.6, –0.2)

Change in FPG from baseline, mg/dL		Change in body weight from baseline, kg		Change in SBP from baseline, mmHg	
Mean	**SD or (95% CI) or [SEM]**	**Mean**	**SD or (95% CI) or [SEM]**	**Mean**	**SD or (95% CI) or [SEM]**
–26	[2]	–3.3	[0.2]	–4	[1]
–36	[2]	–3.7	[0.2]	–5	[1]
–18	[2]	–1.2	[0.2]	–1	[1]
–29	–	–2.3	–	–5	[1]
–2	–	0.1	–	1	[1]
4	–	–0.8	–	–3	[1]
–18	–	–1.9	–	–5	[1]
–31	–	–2.5	–	–4	[1]
11	–	–1.0	–	0	[1]
–20	–	–2.0	–	–4	[1]
–27	–	–3.1	–	–3	[1]
3	–	–0.2	–	–1	[1]
–27	–	–2.6	–	–5	[1]
–33	–	–3.8	–	–5	[1]
Δ vs Pbo	–	Δ vs Pbo	–	Δ vs Pbo	–
–23	(–28, –17)	–1.9%	(–2.2, –1.6)	–3	(–4, –1)
–29	(–34, –24)	–2.4%	(–2.7, –2.1)	–4	(–6, –3)
4	[SEM shown graphically; no data reported]	–1.1	[SEM shown graphically; no data reported]	–1	2
–16	–	–2.3	–	–1	2
–25	–	–2.6	–	1	1
–27	–	–2.7	–	–2	2
–25	–	–3.4	–	–5	2
–23	–	–3.4	–	–4	1
–13	–	–0.6	–	–1	1
1	Difference vs Pbo	0.2	Difference vs Pbo	0	[2]
–15	(–29, –2)	–1.2	(–2.1, –0.7)	–6	[2]
–12	(–25, 1)	–1.4	(–2.3, –0.9)	–6	[2]

(*Continued*)

Table S3 (*Continued*)

Reference & NCT ID (Study number or acronym)	Study details	Regimen	N	Treatment and dose, mg/day	Change in HbA_{1c} from baseline, %	
					Mean	SD or (95% CI) or [SEM]
Bode *Hosp Pract* 2013[23] NCT01106651	Phase III, 26 week Elderly	AHAs	714			[SEM shown graphically; no data reported]
			237	Pbo	–0.0	–
			241	100	–0.6	–
			236	300	–0.7	–
Empagliflozin						
Roden *Lancet Diab Endo* 2013[24] NCT01177813 (1245.20)	Phase III, 24 week	Drug naïve	899			
			228	Pbo	0.1	(–0.0, 0.2)
			224	10	–0.7	(–0.8, –0.6)
			224	25	–0.8	(–0.9, –0.7)
			223	SITA 100	–0.7	(–0.8, –0.6)
Häring *Diabetes* 2013[25] NCT01159600 (1245.23)	Phase III, 24 week	MET	637			
			207	Pbo	–0.1	[0.1]
			217	10	–0.7	[0.1]
			213	25	–0.8	[0.1]
Ferrannini *Diabetes Care* 2013[26] NCT00881530 (1245.24)	Phase IIb, 78 week	Monotherapy or MET monotherapy or MET + SITA				
			80	10	–0.3	(–0.5, –0.1)
			88	25	–0.5	(–0.7, –0.3)
			56	MET	–0.6	(–0.8, –0.3)
			137	10 + MET	–0.3	(–0.5, –0.2)
			139	25 + MET	–0.6	(–0.8, –0.5)
			56	SITA 100 + MET	–0.4	(–0.6, –0.2)
Häring *Diabetes Care* 2013[27] NCT01159600 (1245.23)	Phase III, 24 week	MET + SU	666			
			225	Pbo	–0.2	[0.1]
			225	10	–0.8	[0.1]
			216	25	–0.8	[0.1]
Kovacs *Diabetes Obes Metab* 2013[28] NCT01210001 (1245.19)	Phase III, 24 week	TZD (PIO) ± MET	498			
			165	Pbo	–0.1	[0.1]
			165	10	–0.6	[0.1]
			168	*25*	–0.7	[0.1]
Rosenstock *Diabetes* 2013[29] NCT01011868 (1245.33)	Phase IIb, 78 week	INS (dose not stated)	494			
			170	Pbo	0.0	[0.1]
			169	10	–0.5	[0.1]
			155	25	–0.6	[0.1]
Ferrannini *Diabetes Obes Metab* 2013[30] NCT00789035 (1245.9)	Phase IIb, 12 week	Drug naïve or 4-week washout	406			
			82	Pbo	0.1	(–0.09, 0.27)
			81	5	–0.4	(–0.61, –0.25)
			81	10	–0.5	(–0.66, –0.30)
			82	25	–0.6	(–0.81, –0.45)
			80	MET(O/L)	–0.7	(–0.92, –0.57)

Change in FPG from baseline, mg/dL		Change in body weight from baseline, kg		Change in SBP from baseline, mmHg	
Mean	**SD or (95% CI) or [SEM]**	**Mean**	**SD or (95% CI) or [SEM]**	**Mean**	**SD or (95% CI) or [SEM]**
	[SEM shown graphically; no data reported]		[SEM shown graphically; no data reported]		
7	–	–0.1	–	1	[1]
–18	–	–2.2	–	–4	[1]
–20	–	–2.8	–	–7	[1]
12	(8, 16)	–0.3	(–0.7, 0.0)	0	(–2, 1)
–20	(–23, –16)	–2.3	(–2.6, –1.9)	–3	(–5, –1)
–25	(–28, –21)	–2.5	(–2.8, –2.1)	–4	(–5, –2)
–7	(–11, –3)	0.2	(–0.2, 0.5)	1	(–1, 2)
6	[2]	–0.5	[0.2]	0	[1]
–20	[2]	–2.1	[0.2]	–5	[1]
–22	[2]	–2.5	[0.2]	–5	[1]
–30	(–37, –24)	–2.2	(–3.1, –1.4)	0	(–3, 3)
–28	(–34, –21)	–2.6	(–3.5, –1.8)	–2	(–5, 2)
–26	(–34, –18)	–1.3	(–2.3, –0.3)	2	(–2, 6)
–21	(–26, –16)	–3.1	(–3.9, –2.4)	–3	(–6, –1)
–32	(–37, –27)	–4.0	(–4.8, –3.3)	–3	(–5, –1)
–16	(–24, –8)	–0.4	(–1.5, 0.7)	2	(–2, 5)
6	[2]	–0.4	[0.2]	–1	[1]
–23	[2]	–2.2	[0.2]	–4	[1]
–23	[2]	–2.4	[0.2]	–4	[1]
6	[3]	0.3	[0.2]	1	[1]
–17	[3]	–1.6	[0.2]	–3	[1]
–22	[3]	–1.5	[0.2]	–4	[1]
3	[3]	0.7	[0.5]	0	[1]
–10	[3]	–2.2	[0.5]	–4	[1]
–15	[3]	–2.0	[0.5]	–2	[1]
				Not reported	
1	(–6, –8)	–0.8	(–1.3, –0.2)	–	–
–23	(–30, –16)	–1.8	(–2.3, –1.3)	–	–
–29	(–36, –22)	–2.3	(–2.8, –1.8)	–	–
–31	(–38, –24)	–2.0	(–2.5, –1.5)	–	–
–30	(–38, –22)	–1.3	(–1.8, –0.8)	–	–

(*Continued*)

Table S3 (*Continued*)

Reference & NCT ID (Study number or acronym)	Study details	Regimen	N	Treatment and dose, mg/day	Change in HbA_{1c} from baseline, %	
					Mean	SD or (95% CI) or [SEM]
Rosenstock *Diabetes Obes Metab* 2013[31] NCT00749190 (1245.10)	Phase IIb, 12 week	MET	495			
			71	Pbo	0.2	(0.0, 0.3)
			71	1	–0.1	(–0.2, 0.1)
			71	5	–0.2	(–0.4, –0.1)
			71	10	–0.6	(–0.7, –0.4)
			70	25	–0.6	(–0.7, –0.4)
			70	50	–0.5	(–0.6, –0.3)
			71	SITA 100 (O/L)	–0.5	(–0.7, –0.3)
Barnett *Lancet Diab Endo* 2014[32] NCT01164501 (1245.36)	Phase III, 52 week, CKD	AHAs		(Efficacy data reported at week 24)		
		Stage 2 CKD	95	Pbo	0.1	(–0.1, 0.2)
			98	10	–0.5	(–0.6, –0.3)
			97	25	–0.6	(–0.8, –0.5)
		Stage 3 CKD	187	Pbo	0.1	(–0.5, 0.2)
			187	25	–0.4	(–0.5, –0.3)
		Stage 4 CKD	37	Pbo	–0.2	0.8
			37	25	0.0	1.6

Notes: [a]Data are presented as published (from randomized double-blind arms of each trial unless otherwise stated).

Abbreviations: AHA, anti-hyperglycemic agent; AM, ante meridiem (in the morning); BD, bis in die (twice per day); BMI, body mass index; CANTATA, canagliflozin treatment and trial analysis; CANTATA-D2, dipeptidyl peptidase 4 inhibitor second comparator; CANTATA-M, metformin; CANTATA-MSU, metformin + sulfonylurea; CANTATA-SU, sulfonylurea; CANVAS, canagliflozin cardiovascular assessment study; CI, confidence interval; CKD, chronic kidney disease; DAPA, dapagliflozin; DPP4, dipeptidyl peptidase 4; FPG, fasting plasma glucose; GLIM, glimepiride; GLIP, glipizide; HbA_{1c} (or A_{1c}), glycated hemoglobin; INS, insulin; MET, metformin; NCT ID, National Clinical Trials (US) identification (number); OAD, oral anti-diabetes drug; O/L, open label; Pbo, placebo; PIO, pioglitazone; PM, post meridiem (in the afternoon); SBP, systolic blood pressure; SD, standard deviation; SEM, standard error of the mean; SGLT2, sodium glucose co-transporter type 2; SITA, sitagliptin; SU, sulfonylurea; TZD, thiazolidinedione; XR, extended release formulation; vs, versus.

Change in FPG from baseline, mg/dL		Change in body weight from baseline, kg		Change in SBP from baseline, mmHg	
Mean	**SD or (95% CI) or [SEM]**	**Mean**	**SD or (95% CI) or [SEM]**	**Mean**	**SD or (95% CI) or [SEM]**
5	(–2, 12)	–1.2	(–1.8, –0.5)	–2	15
–2	(–9, 5)	–1.6	(–2.2, –0.9)	–2	12
–16	(–23, –9)	–2.3	(–2.9, –1.7)	–3	15
–22	(–29, –16)	–2.7	(–3.4, –2.1)	–4	13
–27	(–34, –20)	–2.6	(–3.2, –2.0)	–9	13
–28	(–35, –21)	–2.9	(–3.5, –2.2)	–3	15
–13	(–22, –3)	–0.8	(–1.5, –0.2)	–2	12
6	(–1, 12)	–0.33	(–0.80, 0.14)	1	(–2, 3)
–14	(–21, –7)	–1.76	(–2.21, –1.31)	–3	(–5, 1)
–18	(–25, –11)	–2.33	(–2.78, –1.88)	–5	(–7, –2)
11	(4, 18)	–0.08	(–0.43, 0.27)	0	(–1, 2)
–9	(–16, –2)	–0.98	(–1.33, –0.63)	–4	(–6, –2)
11	11	–0.1	1.9	1	16
4	108	–1.4	5.0	–7	17

Table S4 Safety data from pivotal clinical trials of SGLT2 inhibitors[a]

Reference & NCT ID (Study number or acronym)	Study detail	Regimen	N	Treatment and dose, mg/day	Adverse events		Serious adverse events	
					Total	%	Total	%
Dapagliflozin								
List *Diabetes Care* 2009[1] NCT00263276 (MB102008)	Phase II 12 week	Drug naïve, diet/exercise	389					
			54	Pbo	29	54	0	0
			59	2.5	35	59	1	2
			58	5	35	60	0	0
			47	10	32	68	1	2
			59	20	40	68	1	2
			56	50	35	63	1	2
			56	MET XR	38	68	1	2
Wilding *Diabetes Care* 2009[2] NCT00357370 (MB102009)	Phase II, 12 week	OADs + INS	71					
			23	Pbo	15	65.2	1	4.3
			24	10	18	75.0	0	0
			24	20	16	66.7	1	4.2
Ferrannini *Diabetes Care* 2010[3] NCT00528372 (MB102013)	Phase III, 24 week	Drug naïve, diet/exercise	485					
			75	Pbo	45	60.0	3	4.0
			65	2.5 AM	41	63.1	0	0
			64	5 AM	37	57.8	1	1.6
			70	10 AM	48	68.6	1	1.4
			67	2.5 PM	45	67.2	1	1.5
			68	5 PM	44	64.7	1	1.5
			76	10 PM	45	59.2	1	1.3
			34	5 (A_{1c} ≥10.1)	27	79.4	0	0
			39	10 (A_{1c} ≥10.1)	28	71.8	0	0
Bailey *Diabetes Obes Metab* 2012[4] NCT00736879 (MB102032)	Phase III, 24 week	Drug naïve, diet/exercise	282					
			68	Pbo	41	60.3	0	0
			72	1	42	58.3	2	2.8
			74	2.5	43	58.1	2	2.7
			68	5	39	57.4	0	0
Bailey *Lancet* 2010[5] NCT00528879 (MB102014)	Phase III, 24 week	MET	546					
			137	Pbo	88	64	5	4
			137	2.5	89	65	4	3
			137	5	95	69	4	3
			135	10	98	73	4	3
Bolinder *J Clin Endocrinol Metab* 2012[6] NCT00855166 (D1690C00012)	Phase III, 24 week, BMI ≥25	MET	182					
			91	Pbo	36	39.6	1	1.1
			91	10	39	42.9	6	6.6

Number of patients with an adverse event of special interest

Hypoglycemia		Urinary tract infection		Genital infection	
Total	%	Total (males and females, if stated)	% (males and females, if stated)	Total (males and females, if stated)	% (males and females, if stated)
(Not defined)		(MedDRA PTs)		(MedDRA PTs)	
2	4	3	6	0	0
4	7	3	5	2	3
6	10	5	9	1	2
3	6	5	11	1	2
4	7	7	12	4	7
4	7	5	9	4	7
5	9	5	9	1	2
(Not defined; no major episodes reported with dapagliflozin)		(Not defined)		(Not defined)	
3	13.0	0	0	1	4.3
7	29.2	0	0	0	0
6	25.0	1	4.2	5	20.8
(MedDRA PTs; no major episodes reported, no discontinuations reported)		(Reports based on predefined list of signs, symptoms and other events suggestive of UTI)		(Reports based on predefined list of signs, symptoms, and other events suggestive of GenI)	
2	2.7	3	4.0	1	1.3
1	1.5	3	4.6	5	7.7
0	0	8	12.5	5	7.8
2	2.9	4	5.7	9	12.9
1	1.5	5	7.5	6	9.0
0	0	8	11.8	3	4.4
1	1.3	5	6.6	2	2.6
1	2.9	3	8.8	2	5.9
0	0	6	15.4	7	17.9
0	0	1 (M1/37, F0/31)	1.5 (M2.7%, F0%)	2 (M1/37, F1/31)	2.9 (M2.7%, F3.2%)
0	0	3 (M1/38, F2/34)	4.2 (M2.6%, F5.9%)	1 (M1/38, F0/34)	1.4 (M2.6%, F0%)
1	1.4	1 (M0/34, F1/40)	1.4 (M0%, F2.5%)	5 (M2/34, F3/40)	6.8 (M5.9%, F7.5%)
1	1.5	2 (M1/32, F1/36)	2.9 (M3.1%, F2.8%)	2 (M0/32, F2/36)	2.9 (M0%, F5.6%)
(Not stated; no major episodes were reported, no discontinuations were reported)		(Reports based on PTs for upper UTI [20] and lower UTI [44])		(Reports based on 49 PTs for GenI)	
4	3	11	8	7	5
3	2	6	4	11	8
5	4	10	7	18	13
5	4	11	8	12	9
(Major/minor/other episodes defined per BG/PG levels ± need for assistance ± symptoms)		(MedDRA PTs plus active questioning)		(MedDRA PTs plus active questioning)	
3	3.3	2	2.2	0	0
2	2.2	6	6.6	3	3.3

(*Continued*)

Table S4 (*Continued*)

Reference & NCT ID (Study number or acronym)	Study detail	Regimen	N	Treatment and dose, mg/day	Adverse events		Serious adverse events	
					Total	%	Total	%
Henry *Int J Clin Pract* 2012[7]	Phase III, 24 week (both)	MET XR						
NCT00643851 (MB102021)			201	Pbo + MET	119	59.2	7	3.5
			194	5 + MET	133	68.6	6	3.1
			203	5 + Pbo	107	52.7	9	4.4
NCT00859898 (MB102034)			208	Pbo + MET	118	56.7	4	1.9
			211	10 + MET	126	59.7	3	1.4
			291	10 + Pbo	132	60.3	5	2.3
Strojek *Diabetes Obes Metab* 2011[8] NCT00680745 (D1690C00005)	Phase III, 24 week	SU (GLIM)	597					
			145	Pbo	69	47.3	7	4.8
			154	2.5	80	51.9	11	7.1
			142	5	70	48.3	10	6.9
			151	10	76	50.3	9	6.0
Nauck *Diabetes Care* 2011[9] NCT00660907 (D1690C00004)	Phase III, 52 week	MET						
			406	DAPA 2.5–10	318	78.3	35	8.6
			408	GLIP 5–20	318	77.9	46	11.3
Rosenstock *Diabetes Care* 2012[10] NCT00683878 (MB102030)	Phase III, 48 week	TZD (PIO)	420					
			139	Pbo	93	66.9	4	2.9
			141	5	96	68.1	6	4.3
			140	10	99	70.7	2	1.4
Wilding *Ann Intern Med* 2012[11] NCT00673231 (D1690C00006)	Phase III, 48 week	INS ≥30 units/day ± OADs	800					
			193	Pbo	144	73.1	26	13.2
			202	2.5	153	75.7	27	13.4
			211	5	153	72.2	19	9.0
			194	10	145	74.0	23	11.7

Number of patients with an adverse event of special interest

Hypoglycemia		Urinary tract infection		Genital infection	
Total	**%**	**Total (Males and females, if stated)**	**% (Males and females, if stated)**	**Total (Males and females, if stated)**	**% (Males and females, if stated)**
(MedDRA PTs; no discontinuations were reported)		(Reports based on predefined list of signs, symptoms, and other events suggestive of UTI)		(Reports based on predefined list of signs, symptoms, and other events suggestive of GenI)	
0	0	15 (M3, F12)	7.5 (M3.2%, F11.3%)	4 (M0, F4)	2.0 (M0%, F3.8%)
5	2.6	15 (M2, F13)	7.7 (M2.6%, F11.2%)	13 (M4, F9)	6.7 (M5.1%, F7.8%)
0	0	16 (M4, F12)	7.9 (M4.3%, F10.8%)	14 (M1, F13)	6.9 (M1.1%, F11.7%)
6	2.9	9 (M3, F6)	4.3 (M3.1%, F5.4%)	5 (M2, F3)	2.4 (M2.1%, F2.7%)
7	3.3	16 (M6, F10)	7.6 (M5.7%, F9.5%)	18 (M6, F12)	8.5 (M5.7%, F11.4%)
2	0.9	24 (M6, F18)	11.0 (M5.7%, F15.8%)	28 (M7, F21)	12.8 (M6.7%, F18.4%)
(MedDRA PTs; no discontinuations were reported)		(Reports based on signs, symptoms, and other events suggestive of UTI)		(Reports based on signs, symptoms, and other events suggestive of GenI)	
7	4.8	9 (M0, F9/75)	6.2 (M0%, F12.0%)	1 (M0, F1/75)	0.7 (M0%, F1.3%)
11	7.1	6 (M0, F6/77)	3.9 (M0%, F7.8%)	6 (M0, F6/77)	3.9 (M0%, F7.8%)
10	6.9	10 (M4/72, F6/73)	6.9 (M5.6%, F8.2%)	9 (M2/72, F7/73)	6.2 (M2.8%, F9.6%)
12	7.9	8 (M2/66, F6/85)	5.3 (M3.0%, F7.1%)	10 (M4/66, F6/85)	6.6 (M6.1%, F7.1%)
(Minor: BG <63 mg/dL [3.5 mmol/L], major: BG <54 mg/dL [3.0 mmol/L] requiring assistance, or other episode suggestive of hypoglycemia)		(Reports based on signs, symptoms, and other events suggestive of UTI)		(Reports based on signs, symptoms, and other events suggestive of GenI)	
14	3.4	44 (M18/226, F26/180) (positive culture M6, F14)	10.8 (M8.0%, F14.4%)	50 (M12/226, F38/180) (positive culture M0, F4)	12.3 (M5.3%, F21.1%)
162	39.7	26 (M9/223, F17/185) (positive culture M2, F4)	6.4 (M4.0%, F9.2%)	11 (M1/223, F10/185) (positive culture M0, F0)	2.7 (M0.4%, F5.4%)
(Minor: BG <63 mg/dL [3.5 mmol/L], major: BG <54 mg/dL [3.0 mmol/L] requiring assistance, or other episode reported by investigator; no major episodes were reported)		(Reports based on signs, symptoms, and other events suggestive of UTI)		(Reports based on signs, symptoms and other events suggestive of GenI)	
1	0.7	11	7.9	4	2.9
3	2.1	12	8.5	13	9.2
0	0	7	5.0	12	8.6
(Minor: BG <63 mg/dL [3.5 mmol/L], major: BG <54 mg/dL [3.0 mmol/L] requiring assistance, or other episode suggestive of hypoglycemia)		(Reports based on signs, symptoms, and other events suggestive of UTI)		(Reports based on signs, symptoms, and other events suggestive of GenI)	
102	51.8	10 (M3, F7)	5.1 (M3.1%, F7.1%)	5 (M0, F5)	2.5 (M0%, F5.1%)
122	60.4	16 (M6, F10)	7.9 (M6.0%, F9.8%)	13 (M5, F8)	6.4 (M5.0%, F7.8%)
118	55.7	23 (M5, F18)	10.8 (M5.0%, F16.1%)	21 (M2, F19)	9.9 (M2.0%, F17.0%)
105	53.6	20 (M5, F15)	10.2 (M5.7%, F13.9%)	21 (M8, F13)	10.7 (M9.1%, F12.0%)

(*Continued*)

Table S4 (*Continued*)

Reference & NCT ID (Study number or acronym)	Study detail	Regimen	N	Treatment and dose, mg/day	Adverse events		Serious adverse events	
					Total	%	Total	%
Kohan *Kidney Int* 2013[12] NCT00663260 (MB102029)	Phase III, 104 week Renal impairment	AHAs including INS						
			84	Pbo	77	91.7	26	31.0
			83	5	80	96.4	16	19.3
			85	10	77	90.6	11	2.9
Jabbour *Diabetes Care* 2013[13] NCT00984867 (D1690C00010)	Phase III, 24 week	DDP4 inhibitor (SITA) ± MET						
		24 week	226	Pbo	109	48.2	9	4.0
		24 week	225	DAPA	119	52.9	10	4.4
Canagliflozin								
Stenlöf *Diabetes Obes Metab* 2013[14] NCT01081834 (CANTATA-M)	Phase III, 26 week	Drug naïve, diet/exercise	584					
			192	Pbo	101	52.6	4	2.1
			195	100	119	61.0	8	4.1
			197	300	118	59.9	2	1.0
Cefalu *Lancet* 2013[15] NCT00968812 (CANTATA-SU)	Phase III, 52 week	MET	1,450					
			483	100	311	64	24	5
			485	300	332	69	26	5
			482	GLIM 1–8	330	69	39	8
Lavalle-González *Diabetologia* 2013[16] NCT01106677 (CANTATA-D)	Phase III, 52 week	MET	1,284					
			183	Pbo/SITA	122	66.7	7	3.8
			368	100	266	72.3	15	4.1
			367	300	230	62.7	12	3.3
			366	SITA 100	236	64.5	18	4.9
Schernthaner *Diabetes Care* 2013[17] NCT01137812 (CANTATA-D2)	Phase III, 52 week	MET + SU	755					
			377	300	289	76.7	24	6.4
			378	SITA 100	293	77.5	21	5.6

Number of patients with an adverse event of special interest					
Hypoglycemia		**Urinary tract infection**		**Genital infection**	
Total	**%**	**Total (Males and females, if stated)**	**% (Males and females, if stated)**	**Total (Males and females, if stated)**	**% (Males and females, if stated)**
43	51.2	12	14.3	3	3.6
38	45.8	11	13.3	8	9.6
33	38.8	12 (Reports based on adverse events reporting)	14.1	7 (Reports based on adverse events reporting)	8.2
4	1.8	9	4.0	19	8.4
6	2.7	11	4.9	1	0.4
(Biochemically confirmed, BG ≤70 mg/dL [≤3.9 mmol/L], and severe episodes requiring assistance, etc; no severe episodes were reported)		(Reports based on adverse events reporting)		Genital mycotic infection reported (Reports based on adverse events reporting)	
5	2.6	8	4.2	4 (M0/88, F4/104)	2.1 (M0%, F3.8%)
7	3.6	14	7.2	12 (M2/81, F10/114)	6.2 (M2.5%, F8.8%)
6 (Biochemically confirmed, BG ≤70 mg/dL [≤3.9 mmol/L], and severe episodes requiring assistance, etc)	3.0	10	5.1 (Reports based on adverse events reporting)	13 (M5/89, F8/108) Genital mycotic infection reported (Reports based on adverse events reporting)	6.6 (M5.6%, F7.4%)
27	6	31	6	43 (M17/252, F26/231)	8.9 (M7%, F11%)
24	5	31	6	54 (M20/241, F34/244)	11.1 (M8%, F14%)
165 (Biochemically confirmed, BG ≤70 mg/dL [≤3.9 mmol/L], and/or severe episodes requiring assistance, etc)	34	22	5	8 (M3/263, F5/219) Genital mycotic infection reported	1.7 (M1%, F2%)
5	2.7	12	6.6	2 (M1/94, F1/89)	1.1 (M1.1%, F1.1%)
25	6.8	29	7.9	31 (M9/174, F22/194)	8.4 (M5.2%, F11.3%)
25	6.8	18	4.9	24 (M4/165, F20/202)	6.5 (M2.4%, F9.9%)
15 (Biochemically confirmed, BG ≤70 mg/dL [≤3.9 mmol/L], and severe episodes requiring assistance, etc)	4.1	23 (Reports based on adverse events reporting)	6.3	7 (M2/172, F5/194) Genital mycotic infection reported (Reports based on adverse events reporting)	1.9 (M1.2%, F2.6%)
163	43.2	15	4.0	45 (M19/207, F26/170)	11.9 (M9.2%, F15.3%)
154	40.7	21	5.6	8 (M1/215, F7/163)	2.1 (M0.5%, F4.3%)

(*Continued*)

Table S4 (*Continued*)

Reference & NCT ID (Study number or acronym)	Study detail	Regimen	N	Treatment and dose, mg/day	Adverse events		Serious adverse events	
					Total	%	Total	%
Wilding *Int J Clin Pract* 2013[18] NCT01106625 (CANTATA-MSU)	Phase III, 26 week (+26 week extension)	MET + SU	469					
		52 week	156	Pbo	111	71.2	13	8.3
		52 week	157	100	106	67.5	7	4.5
		52 week	156	300	114	73.1	8	5.1
Forst *Diabetes Obes Metab* 2014[19] NCT01106690 (CANTATA-MP)	Phase III, 26 week (+26 week extension)	MET + TZD (PIO) (Pbo group switched to SITA during 26 week extension)	342	(Safety data reported at week 52)				
			115	Pbo/SITA	88	76.5	6	5.2
			113	100	79	69.9	8	7.1
			114	300	87	76.3	7	6.1
Matthews *Diabetologia*[20] NCT01032629 (CANVAS, INS sub-study)	Phase III, Sub-study efficacy duration 18 week	INS ≥20 units/day	1,708					
			565	Pbo	–	59	–	6.4
			566	100	–	63	–	5.5
			587	300	–	65	–	4.9
Rosenstock *Diabetes Care* 2012[21] NCT00642278	Phase II, 12 week	MET	451					
			65	Pbo	26	40	1	2
			64	50	32	50	1	2
			64	100	30	47	1	2
			65	200	26	40	1	2
			64	300	26	41	1	2
			64	300 BD	36	56	1	2
			65	SITA 100	23	35	0	0
Yale *Diabetes Obes Metab* 2013[22] NCT01064414	Phase III, 26 week, CKD	AHAs	269					
			90	Pbo	67	74.4	16	17.8
			90	100	71	78.9	10	11.1
			89	300	66	74.2	10	11.2
Bode *Hosp Pract* 2013[23] NCT01106651	Phase III, 26 week Elderly	AHAs	714					
			237	Pbo	174	73.4	12	5.1
			241	100	174	71.8	10	4.1
			236	300	184	78.0	8	3.4

Number of patients with an adverse event of special interest

Hypoglycemia		Urinary tract infection		Genital infection	
Total	**%**	**Total (Males and females, if stated)**	**% (Males and females, if stated)**	**Total (Males and females, if stated)**	**% (Males and females, if stated)**
(Biochemically documented, BG ≤70 mg/dL [≤3.9 mmol/L] ± symptoms, and/or severe episodes requiring assistance, etc)				Genital mycotic infection reported	
28	17.9	12	7.7	5 (M1/76; F4/80)	3.2 (M1.3%; F5.0%)
53	33.8	13	8.3	21 (M6/76; F15/81)	13.3 (M7.9%; F18.5%)
57	36.5	13	8.3	18 (M5/87; F13/69)	11.5 (M5.7%; F18.8%)
(Biochemically documented, BG ≤70 mg/dL [≤3.9 mmol/L] ± symptoms, and/or severe episodes requiring assistance, etc)				Genital mycotic infection reported	
5	4.4	9	7.8	3 (M0/76;F3/39)	2.6 (M0; F7.7%)
7	6.1	6	5.3	9 (M3/77; F6/36)	8.0 (M3.9%; F16.7%)
7	6.1	9	7.9	14 (M3/63; F11/51) Genital mycotic infection reported	12.3 (M4.8%; F21.6%)
–	37	–	2.1	–	(M0.5%, F2.2%)
–	49	–	2.3	–	(M4.0%, F11.8%)
–	48	–	3.4	–	(M8.3%, F9.9%)
(Symptomatic hypoglycemia)		(Not defined)		(Symptomatic GenI [VVAE in females reported separately])	
1	2	5	8	1 (VVAE 1/34)	2 (VVAE 3%)
0	0	6	9	5 (VVAE 6/30)	8 (VVAE 20%)
1	2	6	9	4 (VVAE 7/28)	6 (VVAE 25%)
4	6	8	12	2 (VVAE 4/32)	3 (VVAE 13%)
0	0	6	9	2 (VVAE 4/28)	3 (VVAE 14%)
2	3	5	8	4 (VVAE 7/36)	6 (VVAE 19%)
3	5	4	6	1 (VVAE 2/27)	2 (VVAE 7%)
34	36.4	5	5.6	0	0
48	52.9	5	5.6	2 (M1/58, F1/32)	2.2 (M1.7%, F3.1%)
46	51.2	7	7.9	2 (M1/48, F1/41)	2.2 (M2.1%, F2.4%)
a = AHAs associated with hypoglycemia; b = AHAs not associated with hypoglycemia				Genital mycotic infection	
a 66/175 b 2/62	a 37.7 b 3.2	12	5.1	2 (M0/143, F2/94)	0.8 (M0%, F2.1%)
a 78/181 b 4/60	a 43.1 b 6.7	14	5.8	22 (M4/124, F18/117)	9.1 (M3.2%, F15.4%)
a 82/173 b 3/63	a 47.4 b 4.8	19	8.1	20 (M8/129, F12/107)	8.5 (M6.2%, F11.2%)

(*Continued*)

Table S4 (*Continued*)

Reference & NCT ID (Study number or acronym)	Study detail	Regimen	N	Treatment and dose, mg/day	Adverse events		Serious adverse events	
					Total	%	Total	%
Empagliflozin								
Roden *Lancet Diab Endo* 2013[24] NCT01177813 (1245.20)	Phase III, 24 week	Drug naïve						
			229	Pbo	140	61	6	3
			224	10	123	55	8	4
			223	25	135	61	5	2
			223	SITA 100	119	53	6	3
Häring *Diabetes* 2013[25] NCT01159600 (1245.23)	Phase III, 24 week	MET	637					
			207	Pbo	–	58.7	–	–
			217	10	–	57.1	–	–
			213	25	–	49.5	–	–
Ferrannini *Diabetes Care* 2013[26] NCT00881530 (1245.24)	Phase IIb, 78 week	Monotherapy or MET monotherapy or + MET + SITA						
			106	10	67	63.2	10	9.4
			109	25	75	68.8	7	6.4
			56	MET	39	69.6	3	5.4
			166	10 + MET	112	67.5	10	6.0
			166	25 + MET	123	74.1	13	7.8
			56	SITA 100 + MET	39	69.6	9	16.1
Häring *Diabetes Care* 2013[27] NCT01159600 (1245.23)	Phase III, 24 week	MET + SU	666					
			225	Pbo	141	62.7	14	6.2
			225	10	152	67.9	11	4.9
			216	25	139	64.1	1	0.5
Kovacs *Diabetes Obes Metab* 2013[28] NCT01210001 (1245.19)	Phase III, 24 week	TZD (PIO) ± MET						
			165	Pbo	120	72.7	7	4.2
			165	10	111	67.3	7	4.2
			168	25	120	71.4	6	3.6
Rosenstock *Diabetes*[29] NCT01011868 (1245.33)	Phase IIb, 78 week	INS (dose not stated)	494					
			170	Pbo	–	–	–	–
			169	10	–	–	–	–
			155	25	–	–	–	–

Number of patients with an adverse event of special interest

Hypoglycemia		Urinary tract infection		Genital infection	
Total	%	Total (Males and females, if stated)	% (Males and females, if stated)	Total (Males and females, if stated)	% (Males and females, if stated)
(Plasma glucose ≤70 mg/dL [≤3.9 mmol/L] ± requiring assistance; no events required assistance)		(MedDRA PTs consistent with UTIs)		(MedDRA PTs consistent with GenIs)	(MedDRA PTs consistent with UTIs)
1	<1	12 (M3/124, F9/105)	5 (M2%, F9%)	0 (M0/124, F0/105)	0
1	<1	15 (M3/142, F12/82)	7 (M2%, F15%)	7 (M4/142, F3/82)	3 (M3%, F4%)
1	<1	12 (M2/144, F10/79)	5 (M1%, F13%)	9 (M2/144, F7/79)	4 (M1%, F9%)
1	<1	11 (M4/141, F7/82)	5 (M3%, F9%)	2 (M1/141, F1/82)	1 (M1%, F1%)
(Plasma glucose ≤70 mg/dL [≤3.9 mmol/L] ± requiring assistance; no events required assistance)					
–	0.5	–	4.9	–	0
–	1.8	–	5.1	–	3.7
–	1.4	–	5.6	–	4.7
(Plasma glucose ≤70 mg/dL [≤3.9 mmol/L])		(MedDRA PTs consistent with UTIs)		(MedDRA PTs consistent with GenIs)	
1	0.9	4 (M0, F4)	3.8 (M0%, F7.0%)	5 (M2, F3)	4.7 (M4.1%, F5.3%)
2	1.8	7 (M4, F3)	6.4 (M7.0%, F5.8%)	6 (M3, F3)	5.5 (M5.3%, F5.8%)
2	3.6	2 (M0, F2)	3.6 (M0%, F7.1%)	1 (M0, F1)	1.8 (M0%, F3.6%)
3	1.8	15 (M2, F13)	9.0 (M2.4%, F15.7%)	5 (M2, F3)	3.0 (M2.4%, F3.6%)
4	2.4	21 (M3, F18)	12.7 (M3.4%, F23.1%)	6 (M3, F3)	3.6 (M3.4%, F3.8%)
2	3.6	7 (M3, F4)	12.5 (M10.3%, F14.8%)	0	0
(Plasma glucose ≤70 mg/dL [≤3.9 mmol/L] ± requiring assistance; no events required assistance)		(MedDRA PTs consistent with UTIs)		(MedDRA PTs consistent with GenIs)	
19	8.4	18 (M3, F15)	8.0 (M2.7%, F13.3%)	2 (M1, F1)	0.9 (M0.9%, F0.9%)
36	16.1	23 (M3, F20)	10.3 (M2.7%, F18.0%)	6 (M1, F5)	2.7 (M0.9%, F4.5%)
25	11.5	18 (M0, F18)	8.3 (M0%, F17.5%)	5 (M1, F4)	2.3 (M0.9%, F3.9%)
(Plasma glucose ≤70 mg/dL [≤3.9 mmol/L] ± requiring assistance; no events required assistance)		(MedDRA PTs consistent with UTIs)		(MedDRA PTs consistent with GenIs)	
3	1.8	27 (M6, F21)	16.4 (M8.2%, F22.8%)	4 (M1, F3)	2.4 (M1.4%, F3.3%)
2	1.2	28 (M3, F25)	17.0 (M3.6%, F30.5%)	14 (M6, F8)	8.5 (M7.2%, F9.8%)
4	2.4	20 (M2, F18)	11.9 (M2.4%, F21.7%)	6 (M1, F5)	3.6 (M1.2%, F6.0%)
(Plasma glucose ≤70 mg/dL [≤3.9 mmol/L] ± requiring assistance; 2 cases [EMPA 25 mg] required assistance)					
–	35.3	–	8.8	–	1.8
–	36.1 (dose groups pooled)	–	14.8	–	7.7
–	–	–	11.6	–	5.2

(*Continued*)

Table S4 (*Continued*)

Reference & NCT ID (Study number or acronym)	Study detail	Regimen	N	Treatment and dose, mg/day	Adverse events		Serious adverse events	
					Total	%	Total	%
Ferrannini *Diabetes Obes Metab* 2013[30] NCT00789035 (1245.9)	Phase IIb, 12 week	Drug naïve or 4-week washout	406					
			82	Pbo	27	33	0	0
			81	5	26	32	2	2.5
			81	10	22	27	0	0
			82	25	23	28	1	1.2
			80	MET (O/L)	31	39	3	3.8
Rosenstock *Diabetes Obes Metab* 2013[31] NCT00749190 (1245.10)	Phase IIb, 12 week	MET	495					
			71	Pbo	26	36.6	2	2.8
			71	1	21	29.6	0	0
			71	5	26	36.6	3	4.2
			71	10	30	42.3	1	1.4
			70	25	25	42.3	2	2.9
			70	50	34	48.6	3	4.3
			71	SITA 100 (O/L)	25	35.2	0	0
Barnett *Lancet Diab Endo* 2014[32] NCT01164501 (1245.36)	Phase III, 52 week, CKD	AHAs	741	(Safety data reported at week 52)				
		Stage 2 CKD	97	Pbo	83	87.4	11	11.6
			98	10	86	87.8	6	6.1
			97	25	78	80.4	7	7.2
		Stage 3 CKD	187	Pbo	156	83.4	23	12.3
			188	25	156	83.4	22	11.8
		Stage 4 CKD	37	Pbo	31	83.8	10	27.0
			37	25	34	91.9	11	29.7

Notes: [a]Data are presented as published (from randomized double-blind arms of each trial unless otherwise stated).

Abbreviations: AHA, anti-hyperglycemic agent; AM, ante meridiem (in the morning); BD, bis in die (twice per day); BG, blood glucose; BMI, body mass index; CANTATA, canagliflozin treatment and trial analysis; CANTATA-D2, dipeptidyl peptidase 4 inhibitor second comparator; CANTATA-M, metformin; CANTATA-MSU, metformin + sulfonylurea; CANTATA-SU, sulfonylurea; CANVAS, canagliflozin cardiovascular assessment study; CKD, chronic kidney disease; DAPA, dapagliflozin; DDP4, dipeptidyl peptidase 4; EMPA, empagliflozin; F, female; GenI, genital infection; GLIM, glimepiride; GLIP, glipizide; HbA_{1c} (or A_{1c}), glycated hemoglobin; INS, insulin; M, male; MedDRA PT, Medical Dictionary for Regulatory Activities Preferred Terms; MET, metformin; NCT ID, National Clinical Trials (US) identification (number); OAD, oral anti-diabetes drug; O/L, open label; Pbo, placebo; PG, plasma glucose; PIO, pioglitazone; PM, post meridiem (in the afternoon); SGLT2, sodium glucose co-transporter type 2; SITA, sitagliptin; SU, sulfonylurea; TZD, thiazolidinedione; UTI, urinary tract infection; VVAE, vulvovaginal adverse event; XR, extended release formulation.

Number of patients with an adverse event of special interest

Hypoglycemia		Urinary tract infection		Genital infection	
Total	%	Total (Males and females, if stated)	% (Males and females, if stated)	Total (Males and females, if stated)	% (Males and females, if stated)
(Symptomatic or laboratory-defined)		(MedDRA PTs consistent with UTIs)		(MedDRA PTs consistent with GenIs)	
1	1.2	1	1.2	0	0
0	0	2	2.5	0	0
0	0	1	1.2	3	3.7
0	0	1	1.2	2	2.4
1	1.2	2	2.5	0	0
(Defined by MedDRA PTs)		(MedDRA PTs consistent with UTIs)		(MedDRA PTs consistent with GenIs)	
0	0	2	2.8	0	0
0	0	2	2.8	1	1.4
3	4.2	2	2.8	4	5.6
0	0	3	4.2	7	9.9
0	0	4	5.7	0	0
1	1.4	3	4.3	2	2.9
2	2.8	3	4.2	2	2.8
23	24.2	15 (M5; F10)	15.8 (M8.9%; F25.6%)	6 (M2; F4)	6.3 (M3.6%; F10.3%)
26	26.5	14 (M5; F9)	14.3 (M8.3%; F23.7%)	7 (M6; F1)	7.1 (M10.0%; F2.6%)
22	22.7	9 (M2; F7)	9.3 (M3.3%; F19.4%)	5 (M0; F5)	5.2 (M0; F13.9%)
53	28.3	29 (M4; F25)	15.5 (M3.8%; F30.9%)	2 (M1; F1)	1.1 (M0.9%; F1.2%)
52	27.8	31 (M6; F25)	16.6 (M5.6%; F31.3%)	5 (M2; F3)	2.7 (M1.9%; F3.8%)
12	32.4	3 (M0; F3)	8.1 (M0; F16.7%)	0 (M0; F0)	0 (M0; F0)
14	37.8	7 (M2; F5)	18.9 (M9.5%; F31.3%)	1 (M0; F1)	2.7 (M0; F6.3%)

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