CLINICAL INVESTIGATION

Sodium–glucose cotransporter 2 inhibitors in the treatment of Type 2 diabetes: a review of Phase II and III trials

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As a result of the progressive nature of Type 2 diabetes, novel, insulin-independent therapies are needed to reduce blood glucose, without increasing body weight. A new class of investigational drugs, sodium–glucose cotransporter 2 (SGLT2) inhibitors, remove glucose from circulation via the kidney. Several SGLT2 inhibitors in development (dapagliflozin, canagliflozin, ASP1941, BI10773 and LX4211) have demonstrated improvement in glycemic control and weight loss. Because renal glucose reabsorption is independent of insulin action or secretion, SGLT2 inhibition may be a versatile mechanism with utility as monotherapy and in combination with oral antidiabetics and/or insulin, and has a low potential for hypoglycemia. Heightened concern over the long-term cardiovascular risks posed by hypoglycemia as well as obesity may eventually drive the use of this class earlier in the treatment paradigm.

Keywords: insulin-independent glucose removal • renal glucose reabsorption • SGLT2 inhibitor • Type 2 diabetes • weight loss

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by rising hyperglycemia, increased peripheral insulin resistance and declining insulin secretion [1,2]. Most current therapies reduce hyperglycemia by either directly or indirectly improving insulin sensitivity or increasing insulin levels [3]. Due to the progressive nature of the disease, therapies that rely on insulin-dependent mechanisms must eventually be escalated or supplemented with add-on antidiabetic therapies [3]. In addition, most patients with T2DM are overweight [4,5]. Weight loss is difficult in the T2DM population, especially for patients on therapies, including insulin, that are associated with weight gain [3]. Thus, there is an unmet need for new insulin-independent therapies that will help to achieve glycemic targets and which help, or at least do not hinder, weight loss.

In normal individuals, glucose is filtered at the glomerulus of the kidney and almost entirely reabsorbed in the proximal tubules so that virtually no glucose appears in the urine [6]. In humans, the renal sodium–glucose cotransporter 2 (SGLT2) is predominantly expressed in the kidney proximal tubules and is responsible for the majority of glucose reabsorption [7–9]. Inhibition of SGLT2 has been shown to increase urinary glucose excretion (UGE) and reduce hyperglycemia in animal models of diabetes and obesity [10–13]. Inhibition of SGLT2 may represent a rational insulin-independent approach to treating T2DM. Several highly selective SGLT2 inhibitors are currently in clinical development for the treatment of T2DM (Table 1). This article will review those SGLT2 inhibitors that have reached Phase II and/or III of their clinical development. Key outcomes of Phase II and III studies are summarized in Tables 2 & 3, respectively.

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Table 1. Sodium–glucose cotransporter 2 inhibitors in clinical development.

Drug	Alternate name	Sponsor	Development phase
Dapagliflozin	BMS512148	Bristol-Myers Squibb/AstraZeneca	III
Dapagliflozin/metformin	BMS512148/metformin	Bristol-Myers Squibb/AstraZeneca	III (USA)
Canagliflozin	JNJ28431754; TA-7284	Johnson & Johnson	III
ASP1941		Astellas Pharma	III (Japan)
BI10773		Boehringer Ingelheim	II
LX4211		Lexicon Pharmaceuticals	II (USA)
RG 7201	CSG452; R7201	Chugai Pharmaceuticals	II (Japan, World)
TS 071		Taisho Pharmaceuticals	II (Japan)
BI44847		Boehringer Ingelheim	I
ISIS 388626	ISIS-SGLT2Rx	Isis Pharmaceuticals	I

Dapagliflozin

The selective SGLT2 inhibitor dapagliflozin is currently in Phase III development. Proof-of-concept was demonstrated in a Phase IIa, multicenter, double-blind study in 47 patients with T2DM receiving daily oral doses of dapagliflozin (5, 25 or 100 mg) or placebo (Table 2) [14]. Dapagliflozin produced dose-dependent UGE and clinically meaningful, dose-dependent improvement in fasting serum glucose and oral glucose tolerance [14].

In an international, randomized, double-blind, placebo-controlled, dose-ranging study in 389 drug-naive patients with T2DM, dapagliflozin (2.5, 5, 10, 20 and 50 mg/day) induced UGE (52–85 g urinary glucose/day) and, compared with placebo, demonstrated significant improvements in hemoglobin A1C (A1c) of -0.55 to -0.90% (baseline: 7.6–8%) and in fasting plasma glucose (FPG) of -16 to -31 mg/dl [15]. Relative to placebo, dapagliflozin-treated patients lost 1.3–2.0 kg. Although renal function did not change, dapagliflozin treatment was associated with a decrease in serum uric acid, an increase in serum magnesium, an increase in serum phosphate at higher doses, and dose-related increases in 24 h urine volume and hematocrit; all deviations were of small magnitude. Small increases in mean parathyroid hormone (0.6–7.0 pg/ml above the baseline of 31.1–35.0 pg/ml) were also observed compared with placebo (0.8 pg/ml).

These Phase II studies established a dose range of 2.5–50 mg/day as being effective and well tolerated.

A multicenter, randomized, placebo-controlled, Phase II trial examined the efficacy of dapagliflozin for lowering blood glucose in 71 patients with T2DM who had not responded adequately to high-dose insulin combined with stable-dose oral insulin sensitizer therapy (Table 3) [16]. Patients received 12 weeks of double-blind treatment with dapagliflozin (10 or 20 mg/day) or placebo in addition to open-label therapy with 50% of their usual daily insulin dose and their oral antihyperglycemic drugs (OADs). Compared with placebo, dapagliflozin 10 and 20 mg significantly reduced A1c (-0.70 and -0.78%, respectively) and increased the proportion of patients who achieved a decrease from baseline in A1c by at least 0.5% (65.2% for both dose groups vs 15.8% for placebo). In addition, patients given dapagliflozin showed dose-dependent reductions in FPG (+2.4 to -9.6 mg/dl) when compared with placebo (+17.8 mg/dl) over 12 weeks. Postprandial glucose was also reduced with dapagliflozin (-34.3 to -42.9 mg/dl) compared with placebo (+18.7 mg/dl). Body weight decreased to a greater degree with dapagliflozin (-4.5 to -4.3 kg) versus placebo (-1.9 kg). The most common adverse events (AEs) observed with dapagliflozin that occurred at a greater rate than with placebo were nausea, vomiting and vulvovaginal mycotic infection; these AEs occurred at higher rates with the 20-mg than with the 10-mg dose of dapagliflozin. Thus, based on the results of this study, the investigators concluded that SGLT2 inhibition can improve glycemic control despite a 50% reduction in baseline insulin dose and reduce weight in patients with T2DM poorly controlled with high doses of insulin and insulin sensitizers. These results also suggest that this approach may help to prevent or reduce the weight gain that otherwise may occur when insulin therapy is intensified in patients with T2DM.

Phase III studies have been reported with dapagliflozin as monotherapy and add-on therapy in patients with T2DM. In a randomized, double-blind, placebo-controlled trial, dapagliflozin monotherapy (2.5–10 mg/day) produced clinically meaningful decreases in A1c (-0.58 to -0.89% vs -0.23% with placebo) and FPG (-15.2 to -28.8 mg/dl vs -4.1 mg/dl with placebo) at 24 weeks and appeared to be generally safe and well tolerated in treatment-naive patients with T2DM [17]. Dapagliflozin-treated patients with A1c 7.0–10.0% at enrollment showed mean reductions from baseline in A1c and FPG that were

Table 2. Phase II trials of sodium–glucose cotransporter 2 inhibitors.

Study design	Study length	ΔA1c (%)	ΔFPG (mg/dl, unless otherwise defined)	ΔWeight (kg, unless otherwise defined)	Adverse events	Ref.
Dapagliflozin						
■ T2DM patients (n = 47) ■ 18–70 years old ■ Unimpaired renal function ■ Stable dose of MET or diet alone	14 days	NA	5 mg: -18.8† 25 mg: -28.8† 100 mg: -38.7‡ PBO: 0.0	NA	■ Proportion of patients with ≥ 1 AE: ■ 5 mg: 72.7% ■ 25 mg: 33.3% ■ 100 mg: 50.0% ■ PBO: 87.5% ■ No serious AEs or discontinuations due to AEs	[14]
■ T2DM patients (n = 389) ■ Drug-naive ■ 18–79 years old ■ A1c 7–10%	12 weeks	Baseline A1c 7.6 to 8% 2.5 mg: -0.71‡ 5 mg: -0.72‡ 10 mg:-0.85‡ 20 mg:-0.55‡ 50 mg: -0.90‡ PBO: -0.18 MET: -0.73	2.5 mg: -16† 5 mg: -19§ 10 mg:-21§ 20 mg:-24‡ 50 mg:-31‡ PBO: -6 MET: -18	% body weight reduction: 2.5 mg: -2.7 5 mg : -2.5 10 mg: -2.7 20 mg: -3.4 50 mg:-3.4 PBO:-1.2 MET: -1.7	■ AE rates similar across groups ■ No deaths or drug-related serious AEs	[15]
■ T2DM patients (n = 71) ■ 18–75 years old ■ BMI ≤ 45 kg/m² ■ A1c 7.5–10% ■ High-dose INS and stable-dose INS-sensitizer therapy	12 weeks	Baseline A1c 8.3 to 8.5% 10 mg: -0.61 20 mg: -0.69 PBO: 0.09	10 mg: 2.4 20 mg: -9.6 PBO + INS: 17.8	10mg: -4.5 20 mg: -4.3 PBO + INS: -1.9	■ AEs balanced across treatment groups ■ Genital infections: ■ 20 mg: 20.8% ■ 10 mg: 0 ■ PBO + INS: 4.3%	[16]
Canagliflozin						
■ T2DM (n = 116)	2 weeks	NA	30 mg:-20 100 mg: -54§ 200 mg: -65§ 400 mg: -60§ 300 mg b.i.d.: -66‡	NA	■ AEs balanced across all groups, transient and mild-to-moderate in nature ■ 1 episode of vaginal candidiasis	[23]
■ T2DM (n = 451) ■ Inadequate glycemic control on MET	12 weeks	Baseline A1c 7.6 to 8.0% 50 mg: -0.45‡ 100 mg: -0.51‡ 200 mg: -0.54‡ 400 mg: -0.71‡ 300 mg b.i.d.: -0.73‡ SITA: -0.56‡	50 mg: -16.2‡ 100 mg: -25.2‡ 200 mg: -32.4‡ 400 mg: -32.4‡ 300 mg b.i.d.: -30.6‡ SITA: -18.0‡	50 mg: -1.3§ 100 mg: -1.5§ 200 mg: -1.6‡ 400 mg: -2.3‡ 300 mg b.i.d.: -2.3‡ SITA 0.4	■ AEs balanced across all groups	[24]

†p < 0.05 vs placebo; ‡p ≤ 0.001 vs placebo; §p < 0.01 vs placebo.

AE: Adverse event; ASP: ASP1941; BI: BI10773; b.i.d.: Twice daily; BMI: Body mass index; CANA: Canagliflozin; DAPA: Dapagliflozin; FPG: Fasting plasma glucose; FSG: Fasting serum glucose; INS: Insulin; LX: LX4211; MET: Metformin; NA: Not applicable; OAD: Oral antihyperglycemic drug; PBO: Placebo; q.i.d.: Once daily; RE: Remogliflozin etabonate; SER: Sergliflozin; SITA: Sitagliptin; T2DM: Type 2 diabetes mellitus; UTI: Urinary tract infection(s).

Table 2. Phase II trials of sodium–glucose cotransporter 2 inhibitors (cont.).

Study design	Study length	ΔA1c (%)	ΔFPG (mg/dl, unless otherwise defined)	ΔWeight (kg, unless otherwise defined)	Adverse events	Ref.
Canagliflozin (cont.)						
■ T2DM (n = 29) ■ Inadequate glycemic control on stable doses of insulin	28 days	Baseline A1c 8.27 to 8.42% 100 mg q.i.d.:-0.73 300 mg b.i.d.: -0.92 PBO: -0.19	100 mg q.i.d.:-38.1 300 mg b.i.d.: -42.4 PBO: 8.7	100 mg q.i.d.:-0.7 300 mg b.i.d.: -1.2 PBO: 0		[25]
ASP1941						
■ T2DM patients (n = 361) ■ Japanese	12 weeks	Baseline A1c ~8% ASP 50 mg: -0.80%‡ PBO: 0.5 Drug-naive patients ASP: 50 and 100 mg -0.9%‡ PBO: 0.1%	NA	Body weight decreased by up to 2 kg with ASP 100-mg ASP. Weight reduction was not different in obese vs nonobese subjects	■ Five cases of UTI and five cases of genital infection	[27]
ASP1941 ■ T2DM patients (n = 61) ■ 18–74 years ■ Diagnosed with T2DM for ≥2 months ■ Drug-naive, on monotherapy or low-dose combination therapy	4 weeks	NA	mMol/l ASP 50 mg: -3.35‡ 100 mg:-2.72¶ 200 mg:-3.92‡ 300 mg:-3.61‡ PBO: -0.58	Reductions in body weight were greater with ASP (3.2–4.2 kg) than with PBO (1.8 kg)	■ AEs balanced across all groups	[28]
BI10773						
BI10773 ■ T2DM (n = 78) ■ 18–70 (55–70 for postmenopausal women) ■ A1c ≤ 8.5% and treated with diet or exercise or 1 OAD except glitazones	4 weeks	NA	BI 10 mg: -43.7 25 mg: -34.2 100 mg: -28.7 PBO: -4.1	BI 10 mg:-2.61 25 mg: -1.56 100 mg: -1.49 PBO: -0.42	■ AEs balanced across all groups; most mild or moderate in intensity ■ Balanitis, pruritis: 1 case each in 10-mg group	[29]
LX4211						
■ T2DM (n = 36)	4 weeks	150 mg: -1.15† 300 mg: -1.25† PBO: -0.49	150 mg: -53.4‡ 300 mg: -65.9‡ PBO: -15.1	Both doses decreased weight relative to PBO	■ AEs generally mild and balanced across all groups	[30]
Sergliflozin						
■ T2DM (n = 8)	24 h	NA	Over 4 h with oral glucose tolerance test. SER: 500 mg -7.1 mmol*h/l	NA	■ Most common AEs: headache, dyspepsia	[31]

Table 2. Phase II trials of sodium–glucose cotransporter 2 inhibitors (cont.).

Study design	Study length	ΔA1c (%)	ΔFPG (mg/dl, unless otherwise defined)	ΔWeight (kg, unless otherwise defined)	Adverse events	Ref.
Remogliflozin						
■ T2DM (n = 35) ■ A1c 7.0–9.3% ■ Drug-naive or in whom MET was discontinued	12 days	NA	mMol/l RE: 100 mg b.i.d.: -1.3† RE: 1000 mg q.i.d.: -0.3 RE: 1000 mg b.i.d.: -2.3‡	100 mg b.i.d.: -0.5 1000 mg q.i.d.: -2.6‡ 1000 mg b.i.d.: -0.7	■ Most common AEs: headache, flatulence ■ Mean blood pressure decreased by 6.1–9.3 mmHg	[32]
■ T2DM (n = 13) ■ A1c < 10% with MET (n = 10) or diet/exercise (n = 3)	3 days	NA	(mMol/l) MET 500 mg b.i.d.: 0.004 RE 500 mg b.i.d.: -0.594 MET 500 mg b.i.d. + RE 500 mg b.i.d.: -0.559	NA	■ Only drug-related AEs were mild hypoglycemic symptoms in two patients (1 MET, 1 MET + RE)	[33]

†p < 0.05 vs placebo; ‡p ≤ 0.001 vs placebo; ¶p < 0.01 vs placebo; ¶p < 0.005 vs placebo.

AE: Adverse event; ASP: ASP1941; BI: BI10773; b.i.d.: Twice daily; BMI: Body mass index; CANA: Canagliflozin; DAPA: Dapagliflozin; FPG: Fasting plasma glucose; FSG: Fasting serum glucose; INS: Insulin; LX: LX4211; MET: Metformin; NA: Not applicable; OAD: Oral antihyperglycemic drug; PBO: Placebo; q.i.d.: Once daily; RE: Remogliflozin etabonate; SER: Sergliflozin; SITA: Sitagliptin; T2DM: Type 2 diabetes mellitus; UTI: Urinary tract infection(s).

statistically significant with 5- and 10-mg doses (Table 3). Mean reductions in weight were greater with dapagliflozin than placebo, although differences did not reach statistical significance. For an exploratory cohort of patients with A1c 10.1–12.0% at enrollment, dapagliflozin 5 and 10 mg also demonstrated mean reductions from baseline in A1c, FPG and weight (Table 3). Similar rates of hypoglycemia and hypotension/dehydration/hypovolemia were observed among placebo and dapagliflozin arms. Although there were no clinically relevant mean changes from baseline in electrolytes or creatinine, dapagliflozin treatment was associated with small, dose-related increases in hematocrit. The incidences of urinary tract infections and genital infections were higher with dapagliflozin than with placebo.

A second Phase III study randomized 546 patients with T2DM with inadequate glycemic control on metformin (>1500 mg/day) to add-on therapy with dapagliflozin (2.5, 5.0 or 10.0 mg) or placebo, administered once daily over 24 weeks [18]. As shown in Table 3, all doses of dapagliflozin significantly reduced A1c (-0.67 to -0.84% vs -0.3% with placebo), FPG (-0.99 to -1.3 mmol/l vs -0.33 mmol/l with placebo), and body weight (-2.2 to -3.0 kg vs -0.9 kg with placebo). A therapeutic response (A1c < 7.0%) was achieved by a significantly greater percentage of patients in the dapagliflozin 5 mg (37.5%) and 10 mg (40.6%) groups compared with the placebo group (25.9%). Hypoglycemia symptoms were infrequent and mild and occurred in similar proportions of patients in the dapagliflozin and placebo groups. The most commonly observed side effects were headache, back pain and diarrhea. Dapagliflozin was well tolerated, although signs, symptoms and other reports suggestive of genital infections were reported more commonly for patients receiving dapagliflozin

Table 3. Phase III trials of sodium–glucose cotransporter 2 inhibitors.

Study population	Study length	ΔA1c (%)	ΔFPG (mg/dl)	ΔWeight (kg, unless otherwise defined)	Adverse events	Ref.
■ T2DM ■ A1c 7.0–10.0% (n = 274) ■ A1c 10.1–12% (n = 74) ■ 18–77 years old ■ Inadequate glycemic control by diet and exercise	24 week	Patients with A1c 7.0–10.0%: Baseline A1c 7.92–8.1% 2.5 mg: -0.58 5 mg: -0.77‡ 10 mg: -0.89‡ PBO:-0.23 Patients with A1c 10.1–12%: Baseline A1c 10.73–10.82% 5 mg: -2.88 10 mg: -2.66	Patients with A1c 7.0–10.0%: 2.5 mg: -15 5 mg: -24‡ 10 mg: -29‡ PBO: -4 Patients with A1c 10.1%–12%: DAPA 5 mg: -77 DAPA 10 mg: -84	Patients with A1c 7.0%–10.0%: 2.5 mg: -3.3 5 mg: -2.8 10 mg: -3.2 PBO: -2.2 Patients with A1c 10.1–12%: 5 mg: -2.1 10 mg: -1.9	■ AEs balanced across groups ■ No drug-related deaths or drug-related serious AEs ■ UTI: DAPA 2.5 mg, 4.6%; 5 mg, 12.5%; 10 mg, 5.7%; PBO, 4.0% ■ Genital infection: DAPA 2.5 mg, 7.7%; 5 mg, 7.8%; 10 mg, 12.9% PBO, 1.3%	[17]
■ T2DM patients (n = 546) ■ 18–77 years old ■ Inadequate glycemic control on MET ■ A1c 7–10%	24 week	Baseline A1c 7.92 to 8.17% DAPA 2.5 mg + MET: -0.67† DAPA 5 mg + MET: -0.70‡ DAPA 10 mg + MET: -0.84‡ PBO + MET: -0.30	DAPA 2.5 mg + MET: -0.99‡ DAPA 5 mg + MET: -1.19‡ DAPA 10 mg + MET: -1.30‡ PBO + MET: -0.33	DAPA 2.5 mg + MET: -2.2‡ DAPA 5 mg + MET: -3.0‡ DAPA 10 mg + MET: -2.9‡ PBO + MET: -0.9	■ AEs and serious AEs balanced across groups ■ Signs/symptoms suggestive of genital infections: DAPA, 8–13.1%; PBO, 5.1%	[18]
■ T2DM patients (n = 807) ■ 18–80 years old ■ Inadequate glycemic control on ≥ 30 IU/day insulin for ≥ 8 week ± up to 2 OADs ■ A1c 7.5–10.5%	24 week	Baseline A1c mean: 8.5% DAPA 2.5 mg + INS: -0.75§ DAPA 5 mg + INS: -0.82§ DAPA 10 mg + INS: -0.90§ PBO + INS: -0.30	DAPA 2.5 mg + INS: -12.5‡ DAPA 5 mg + INS: -18.8‡ DAPA 10 mg + INS: -21.7‡ PBO + INS: 3.3¶	DAPA 2.5 mg + INS: -0.98§¶ DAPA 5 mg + INS: -0.98§¶ DAPA 10 mg + INS: -1.67§¶ PBO + INS: 0.002¶	■ AEs and serious AEs balanced across groups ■ Signs/symptoms suggestive of UTI: DAPA, 8.4%; PBO, 4.1% ■ Suggestive of genital infection: DAPA, 7.2%; PBO, 2.0%	[19]
■ T2DM patients (n = 808) ■ 18–80 years old ■ Inadequate glycemic control on ≥ 30 IU/day INS for min. week ± up to 2 OADs ■ A1c 7.5–10.5%	48 week	Baseline A1c mean: 8.35% DAPA + INS 2.5 mg: -0.74 5 mg: -0.94 10 mg: -0.93 PBO + INS: -0.43	NA	DAPA + INS 2.5 mg: -1.11¶ 5 mg: -1.21¶ 10 mg: -1.79¶ PBO + INS: -0.18¶	■ AEs, serious AEs balanced across groups ■ Signs/symptoms suggestive of UTI: DAPA, 7.9–10.8%; PBO, 5.1% ■ Suggestive of genital infection: DAPA, 6.4–10.7%; PBO, 2.5%	[20]

†p < 0.01 vs placebo; ‡p ≤ 0.001 vs placebo; §p ≤ 0.0001 vs placebo; ¶Excluding data after insulin up-titration.

AE: Adverse event; BMI: Body mass index; DAPA: Dapagliflozin; FPG: Fasting plasma glucose; GLI: Glipizide; GLM: Glimepiride; INS: Insulin; MET: Metformin; PBO: Placebo; T2DM: Type 2 diabetes mellitus; Min: Minimum; NA: Not available; UTI: Urinary tract infection(s).

Table 3. Phase III Trials of sodium–glucose cotransporter 2 inhibitors (cont.).

Study population	Study length	ΔA1c (%)	ΔFPG (mg/dl)	ΔWeight (kg, unless otherwise defined)	Adverse events	Ref.
■ T2DM patients (n = 597) ■ A1c 7.5–10% ■ On at least half the maximum recommended dose of sulfonylurea (GLM) alone	24 week	Baseline A1c 8.07 to 8.15% 2.5 mg: -0.58[§] 5 mg: -0.63[§] 10 mg: -0.82[§] PBO: -0.13		2.5 mg: -1.18 5 mg: -1.56[‡] 10 mg: -2.26 PBO: -0.72	■ AEs balanced across groups ■ Signs/symptoms suggestive of UTI: DAPA, 3.9–6.9%; PBO, 5.3% ■ Signs/symptoms suggestive of UTI: DAPA, 3.9–6.9%; PBO, 5.3% ■ Suggestive of genital infection: DAPA, 3.9–6.6%; PBO, 0.7%	[21]
■ T2DM patients (n = 814) ■ A1c 7.5–10% ■ Inadequately controlled on MET	52 week	Baseline A1c 7.72% ≤10 mg: -0.52 GLI ≤20 mg: -0.52		≤10 mg: -3.2 GLI ≤20 mg: +1.4	■ AEs balanced across groups ■ Serious AEs: DAPA, 8.6%; GLIP, 11.3% ■ Signs/symptoms suggestive of UTI: DAPA, 10.8%; GLIP, 6.4% ■ Suggestive of genital infection: DAPA, 12.3%; GLIP, 2.7%	[22]

[‡]$p < 0.01$ vs placebo; [§]$p \leq 0.001$ vs placebo; [¶]$p \leq 0.0001$ vs placebo; [¶]Excluding data after insulin up-titration.

AE: Adverse event; BMI: Body-mass index; DAPA: Dapagliflozin; FPG: Fasting plasma glucose; GLI: Glipizide; GLM: Glimepiride; INS: Insulin; MET: Metformin; PBO: Placebo; T2DM: Type 2 diabetes mellitus; Min: Minimum; NA: Not available; UTI: Urinary tract infection(s).

than placebo. Mean increases in high-density lipoprotein (HDL) cholesterol (1.8–4.4% vs 0.4% for placebo) and low-density lipoprotein cholesterol (5.0–9.5% vs 3.5% for placebo) and decreases in triglycerides (-2.4% to -6.2% vs 2.1% for placebo) were observed in patients who took dapagliflozin over 24 weeks [18].

A recent Phase III multicenter, double-blind, placebo-controlled, parallel-group trial evaluated the efficacy and safety of dapagliflozin in 807 patients with T2DM poorly controlled on insulin therapy (A1c: 7.5–10.5%) [19]. Patients in the 24-week trial were treated with dapagliflozin (2.5, 5 or 10 mg) or placebo while continuing on background insulin therapy (≥30 IU/day) with or without concomitant OADs (Table 3). At study end (24 weeks), there were no clinically relevant increases in hypoglycemia and highly significant reductions in A1c, FPG, bodyweight and insulin dose across all dapagliflozin-treated groups ($p \leq 0.0008$). Additionally, a trend towards small mean decreases in systolic blood pressure without orthostatic hypotension was observed in dapagliflozin-treated patients. Continuation of the study demonstrated that A1c and body weight reductions from baseline were maintained over 48 weeks [20]. Although this was not a treat-to-target study, insulin doses were adjusted for the management of hypoglycemia or hyperglycemia. The mean insulin dose rose over the course of the study in those receiving placebo, but remained stable in patients receiving dapagliflozin. Major hypoglycemic events occurred infrequently (1%) and were similar in both groups. For both the initial study and study continuation, AE occurrence, type and severity were similar between all groups, with the exception that more patients in the dapagliflozin group reported symptoms of urinary and genital infections.

In a 24-week, randomized, double-blind, placebo-controlled, parallel-group multicenter trial, the efficacy and safety of dapagliflozin were assessed in patients with T2DM with inadequate glycemic control on the sulfonylurea glimepiride [21]. Significant reductions in A1c (-0.58 to -0.82%) and in body weight (-0.46 to -1.54 kg) were observed with dapagliflozin. Furthermore, significantly more dapagliflozin- (5 and 10 mg) treated patients achieved an A1c of under 7.0% at week 24 compared with placebo.

In a 52-week, randomized, double-blind, active-controlled, parallel-group, multicenter trial in T2DM patients inadequately controlled with metformin, the efficacy, safety and

tolerability of dapagliflozin was compared with glipizide [22]. The adjusted mean change from baseline in A1c was -0.52% with dapagliflozin (titrated to ≤10 mg once daily) and -0.52% with glipizide (titrated to ≤20 mg once daily). Significant weight loss was observed at 52 weeks in patients administered dapagliflozin (-3.2 kg) compared with glipizide (+1.4 kg). In addition, significantly more patients achieved ≥5% weight loss from baseline with dapagliflozin (33.3%) compared with glipizide (2.5%). Greater reductions in blood pressure and improvements in HDL were observed in the dapagliflozin versus glipizide treatment groups. The overall frequency of AEs was similar between the dapagliflozin and glipizide groups although hypoglycemic episodes were more frequent in those patients receiving glipizide (40.8%) compared with dapagliflozin (3.5%). Actively solicited events suggestive of urinary tract and genital infections were higher in the dapagliflozin group.

Ongoing trials are investigating the efficacy and safety of dapagliflozin in patients with T2DM as monotherapy and in combination with other treatments. Two Phase III studies are examining the safety and efficacy of dapagliflozin, added to existing medications, in T2DM patients with cardiovascular (CV) disease. Ongoing mechanistic studies are evaluating the glycemic efficacy, renal safety, pharmacokinetics and pharmacodynamics of dapagliflozin in patients with T2DM and moderate renal impairment; the effects of dapagliflozin monotherapy on insulin resistance and acute insulin secretion; and the effects of dapagliflozin versus hydrochlorothiazide (active comparator) on glomerular filtration rate in patients with inadequate control of glycemia and blood pressure.

Canagliflozin

Canagliflozin has been found to be well tolerated and efficacious in comparison to both placebo and antidiabetic treatments, and also as additional therapy to insulin, in several Phase II studies. In a dose-escalation study, canagliflozin 30, 100, 200 and 400 mg once daily, canagliflozin 300 mg twice daily, and placebo were compared in 97 patients who maintained an isocaloric diet [23]. Treatment with canagliflozin resulted in a decreased renal threshold for glucose secretion and a concomitant increase in glucose excretion (69–113 g urinary glucose/day). Similar results were found when comparing canagliflozin and sitagliptin in a Phase II double-blind, dose-escalation study in which 451 subjects were randomized into groups that received canagliflozin 50, 100, 200 and 300 mg doses once daily, canagliflozin 300 mg twice daily, sitagliptin 100 mg once daily, or placebo [24]. After 12 weeks, placebo-adjusted decreases from baseline for FPG and A1c were statistically significant for all canagliflozin arms (-25.2 to -32.4 mg/dl and -0.51 to -0.73%, respectively) and for sitagliptin (-18 mg/dl and -0.56%, respectively). Significant decreases in weight were observed at 12 weeks in all groups treated with canagliflozin (-1.3 to -2.3 kg), but not in the sitagliptin-treated group (+0.4 kg). In both studies, AEs were similar in frequency and severity across all groups, with the exception of symptomatic genital infections reported in the canagliflozin-treated groups (8 vs 2% in both placebo and sitagliptin groups).

Similarly in patients not optimally controlled with stable doses of insulin who were administered canagliflozin 100 mg once daily or 300 mg twice daily, reductions were observed in A1c (-0.73 to -0.92 vs -0.19% for placebo), FPG (-38.1 to -42.4 vs +8.7 mg/dl for placebo), and body weight (-0.7 to -1.2 vs 0 kg for placebo) over 28 days [25].

Results from two of these clinical trials were used to indirectly evaluate whether canagliflozin treatment improves β-cell function in T2DM patients [26]. Plasma glucose and C-peptide concentrations were used to calculate the insulin secretion rate at specified glucose concentrations in a 16-day trial of various doses of canagliflozin (30–400 mg once daily and 300 mg twice daily) compared with placebo. Statistically significant increases of the insulin secretion rate were found at both 10 and 12 mM glucose for the majority of doses over 30 mg, with the exception of the insulin secretion rate at 12 mM glucose seen with the 200 mg once daily dose. β-cell function was assayed in the second study, a 12-week Phase II clinical study comparing several doses of canagliflozin (50–300 mg once daily and 300 mg twice daily) with both sitagliptin (100 mg once daily) and placebo using HOMA2-B%. Significant increases were observed for doses of canagliflozin greater than 100 mg and sitagliptin in comparison to placebo.

Ongoing Phase III studies to investigate the efficacy, safety, and tolerability of canagliflozin in patients with T2DM include trials of:

- Monotherapy in patients uncontrolled by diet and exercise;
- Add-on therapy to metformin plus sulfonylurea;
- Add-on therapy with metformin versus glimepiride;
- Add-on therapy to metformin compared with placebo plus metformin (first 26 weeks) or sitagliptin plus metformin;
- Add-on therapy to metformin plus pioglitazone compared with placebo plus metformin (first 26 weeks) or sitagliptin plus metformin (subsequent 26 weeks) in patients with inadequate glycemic control on metformin plus pioglitazone;
- Monotherapy in patients with T2DM and moderate renal impairment.

A long-term (up to 4 years) Phase III study will assess the CV risk for major adverse cardiac events when canagliflozin is added to standard therapy for T2DM. In addition, a Phase III study of canagliflozin as add-on therapy in older patients (aged 55–80 years) with T2DM has been registered, but this trial is not yet recruiting patients.

ASP1941

Proof of concept with ASP1941 has been demonstrated in a Phase II study in Japan and a Phase IIa study in the USA (Table 2). In the Japanese study, four doses of ASP1941 (12.5, 25, 50 and 100 mg) were compared with placebo in a 12-week double-blind, randomized study of 361 T2DM patients [27]. ASP1941 dose-dependently reduced A1c (baseline ~8%) after 12 weeks, with statistical significance compared with placebo across all groups. The maximum change in A1c was achieved at the 50-mg dose, with a change from baseline of -0.8% compared with +0.5% for placebo. Furthermore, dose-dependent reduction in A1c was greater in patients with an A1c ≥ 8% than in those with an A1c < 8%. In the US study, ASP1941 was administered to 61 T2DM patients in a double-blind, randomized, placebo-controlled, dose-escalation study [28]. FPG levels were significantly decreased for all doses of ASP1941 (50, 100, 200 and 300 mg) compared with placebo ($p < 0.005$ for all). UGE was dose-dependently increased at all doses of ASP1941 administered. Body weight decreases were observed in patients receiving ASP1941 in both studies and the drug appeared to be safe and well tolerated, with only one AE (mild hypoglycemia) in each of the studies.

Two ongoing Phase III studies are assessing the efficacy, safety and tolerability of ASP1941 in Japanese patients with T2DM. These include a 52-week open-label, uncontrolled monotherapy study and a 16-week, double-blind, placebo-controlled monotherapy study. In addition, an ongoing Phase II study is evaluating the efficacy, safety and tolerability of multiple doses of ASP1941 compared with placebo and metformin (active comparator) in patients with T2DM.

BI10773

A 4-week, randomized, double-blind, parallel-group Phase IIa study was conducted in 80 T2DM patients to determine the safety and efficacy of BI10773 10, 25, or 100 mg once daily [29]. At 28 days, decreases in FPG and mean daily glucose levels were observed at all doses in comparison to placebo. Mean UGE was increased from baseline in all groups that received BI10773 (64.4–72.6 g/24 h) in comparison to a decrease in mean UGE observed in the placebo group (-0.7 g/24 h). In general, the study drug was well tolerated, with similar frequencies of AEs in the treatment and placebo group and no study discontinuations as a result of AEs.

Ongoing Phase II studies of BI10773 include a 78-week, placebo-controlled efficacy and safety trial of BI10773 in combination with basal insulin in patients with T2DM who have inadequate glycemic control and a 78-week, open-label extension study comparing BI10733 with metformin or sitagliptin in patients with T2DM.

LX4211

LX4211 is a dual SGLT1/SGLT2 inhibitor with approximately 20-fold selectivity for SGLT2 over SGLT1 [30]. LX4211 has been evaluated in a single Phase II study in which 36 patients with T2DM were randomized to receive either placebo or LX4211 (150 or 300 mg) once daily for 28 days (Table 2) [30]. Patients were sequestered and given a controlled diet. Consistent with the mechanism of action, treatment produced a significant, dose-dependent increase in 24 h UGE throughout the study period relative to placebo. Average baseline A1c levels were in the range 8.20–8.55% and both doses of LX4211 significantly reduced mean A1c (-1.15 to -1.25%) relative to placebo (-0.49%). In the LX4211 arms, A1c was reduced by up to 1.25% over the 4 weeks of treatment (Table 2), while the placebo group experienced a 0.49% decrease in A1c. In both LX4211 dose groups, A1c levels were reduced to 7% or less for half of the patients. Decreases in FPG (-53.4 to -65.9 mg/dl) were observed throughout the treatment period in both dose groups compared with placebo (-15.1 mg/dl). Furthermore, 42% of patients randomized to LX4211 300 mg achieved FPG levels of less than 105 mg/dl at week 4 as compared with placebo ($p = 0.037$). In both dose groups, patients exhibited improved oral glucose tolerance as compared with patients receiving placebo ($p < 0.001$ for both dose groups). Patients in both dose groups also demonstrated reductions in weight and decreases in blood pressure and triglycerides relative to placebo. LX4211 exhibited a favorable safety profile, with no dose-limiting toxicities. No additional Phase II or III studies are registered at this time.

Other SGLT2 inhibitors

Other SGLT2 inhibitors include sergliflozin, remogliflozin etabonate, AVE2268, RG 7201, TS 071, BI44847 and ISIS 388626. The SGLT2 inhibitors sergliflozin and remogliflozin etabonate have shown promising initial results (Table 2) [31–33], but the development of these drugs has been discontinued for a variety of possible reasons, including lack of SGLT2 selectivity over SGLT1, unfavorable pharmaceutical properties, or development of replacement SGLT2 compounds.

No Phase II or III trials have been registered for RG7201, TS 071, GSK 1614235, BI44847 or ISIS 388626. A Phase II study with AVE2268 recruited 317 patients with T2DM not adequately controlled by metformin to assess the effects of several doses of AVE2268, added to metformin, on glycemic control and to assess safety and tolerability. Results of this study have not yet been published.

Future perspective

SGLT2 inhibitors offer a novel insulin independent approach to treating T2DM and there is growing evidence that this class of drugs can effectively reduce hyperglycemia as evidenced by the reductions in plasma glucose and A1c levels with dapagliflozin, canagliflozin and ASP1941 over 12–24 weeks. The change in A1c with LX4211 over 4 weeks is difficult to interpret as A1c is an indicator of average glycemic control over longer periods, typically at least 12 weeks.

Several of the clinical responses seen with this class of medication in addition to blood glucose lowering may be beneficial to patients. The majority of patients with T2DM are overweight, and a greater number of treatment options that are associated with weight loss are needed. In addition, the relatively low risk for hypoglycemia with this class of drugs when used alone, or in combination with other medications that do not cause hypoglycemia, is encouraging. Several recent large-scale diabetes CV outcome studies have raised concerns that hypoglycemia and weight gain may reduce the overall benefit of intensive diabetes control [34–36]. In view of these studies, SGLT2 inhibitors might become an earlier option in the treatment paradigm of treating T2DM. The slight reduction in blood pressure seen in some of the trials may be seen as a benefit, although the theoretic concern of orthostasis in patients with autonomic neuropathy may necessitate added blood pressure monitoring in these patients.

High-density lipoprotein levels are inversely related to coronary heart disease [37]. The slight increases in HDL cholesterol and decreases in triglycerides seen with dapagliflozin in the 24-week study of patients with T2DM concurrently taking metformin also warrant further investigation to fully understand the potential clinical implications.

Whether there is any clinical significance to the small increases observed in parathyroid hormone in the 24-week studies with dapagliflozin in drug-naive T2DM patients is also unknown.

As T2DM progresses over time, β-cell function usually diminishes. Evidence from studies with canagliflozin would suggest, albeit indirectly, that there is a potential for improvement of β-cell function in patients with T2DM. Dapagliflozin has been shown to prevent the continued decline in β-cell function in obese rats using hyperglycemic clamping methods [38]. Direct measurement with clamping techniques in human subjects will be necessary in order to definitively confirm these findings.

Another consequence of the distinct mechanism of action of SGLT2 inhibitors is their potential to be used not only as monotherapy, but also in combination with other oral agents or insulin, as has been demonstrated in several of the aforementioned trials.

In general, the SGLT2-inhibitor class has been well tolerated, with no major safety signals; however, an increase in genitourinary infections seems to run through many of the trials. The increased incidence of vulvovaginitis would not be surprising, given the mechanism of action of these drugs. More worrisome would be urinary tract infections, which also might be predicted from the mechanism of action. Longer-term trials with monitoring of urinalysis and urine culture in double-blind designs might be helpful to accurately allow us to evaluate the true incidence of urinary tract infections. It is possible that patients with history of frequent urinary tract infections or autonomic neuropathy and neurogenic bladder would not be good candidates for this class of medication.

While mean increases in urine volume, serum magnesium, serum phosphate and hematocrit, as well as decreases in serum uric acid, have been reported with dapagliflozin, these were all still within normal physiological parameters. Available data reveal no propensity to cause clinically significant electrolyte imbalance. Mean changes in hematocrit probably reflect slight volume depletion as a result of mechanism-based osmotic diuresis, and the importance of hydration would be an essential part of patient education with this medication class. The implications of decreased serum uric acid are unknown.

Theoretic concerns over loss of magnesium and possible effects on metabolic bone status might require further evaluation. Also, future studies are warranted to determine the level of renal function necessary for these drugs to be effective. Other studies, given the present FDA climate, include CV outcome studies. Lastly, studies in Type 1 diabetes mellitus (T1DM) patients have been considered, as the mechanism of action of this class of drugs might improve postprandial hyperglycemia. The potential option of an oral agent for T1DM added to insulin therapy is intriguing, although the eventual place in therapy for such an agent remains unclear.

Differentiating features in terms of efficacy and side effects are not yet apparent in the early trials, with the exception of a dual SGLT1/SGLT2 inhibitor that has been evaluated in a Phase II trial. Theoretically, the addition of a modest SGLT1 inhibitor could decrease gastrointestinal (GI) absorption of glucose and add to the glycemic effect. Too much SGLT1 inhibition could result in treatment-limiting GI symptoms, although these were not observed in the small Phase II trial [30].

How this and other within-class differences in chemical and pharmacologic properties may ultimately affect the clinical profiles of these drugs remains to be determined.

In summary, this class of drugs may have many advantageous features and could be a welcome addition to our armamentarium for the treatment of diabetes. Several different compounds of this class are being developed. Further studies are needed, but the future of this class of medications seems bright.

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