Empagliflozin for the treatment of type 2 diabetes mellitus: An overview of safety and efficacy based on Phase 3 trials

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Abstract
In the treatment of type 2 diabetes mellitus (T2DM), a relatively new class of oral agents inhibits sodium–glucose cotransporter 2 (SGLT2), reducing reabsorption of filtered glucose and increasing urinary glucose excretion. Numerous SGLT2 inhibitors have been approved for the treatment of T2DM in adults, most recently empagliflozin, which was approved in Europe and the US in 2014. The Phase 3 program has enrolled >14,000 patients and has assessed the efficacy and safety of empagliflozin as monotherapy and in combination. These studies have demonstrated improvements in glycemic control, and modest reductions in body weight and blood pressure. Empagliflozin was generally well tolerated, with no increased risk of hypoglycemia versus placebo as monotherapy or as add-on therapy, except when given with sulfonylurea. The studies showed an increased risk of urinary tract and genital infections with empagliflozin, although most infections were mild to moderate in intensity. Furthermore, small (but clinically insignificant) increases in hematocrit and lipid levels have been observed for empagliflozin. Due to the mode of action of empagliflozin, care should be exercised when treating patients at risk of volume depletion. The risks and benefits must be weighed for each patient, but the data reviewed herein show promise for empagliflozin as a treatment for patients with T2DM.

Keywords: empagliflozin, sodium–glucose cotransporter 2, type 2 diabetes mellitus.

Introduction
In healthy individuals, the kidneys contribute to glucose homeostasis via glucose uptake and gluconeogenesis, generating approximately 180 L/day filtrate containing approximately 160 g glucose. Under normal conditions, virtually all this glucose is reabsorbed into the bloodstream through the actions of sodium–glucose cotransporters (SGLTs) and facilitative glucose transporters (GLUTs) as part of the maintenance of glucose homeostasis.

The SGLT2 transporter is a low-affinity, high-capacity transporter expressed in the convoluted segment of the proximal tubule. It mediates 80%–90% of renal glucose reabsorption and transports glucose into cells. The remaining glucose is reabsorbed by the high-affinity, low-capacity SGLT1 protein in the straight section of the proximal tubule. In addition, SGLT1 plays a role in the absorption of dietary glucose and galactose from the gastrointestinal tract, as well as in other tissues, such as the myocardium. Glucosuria occurs when plasma glucose concentrations exceed the maximal glucose reabsorptive threshold of SGLTs.

In healthy individuals, the glucose excretion threshold is approximately 180 mg/dL. In patients with diabetes, this threshold increases to approximately 220–250 mg/dL, so more glucose is reabsorbed before glucosuria occurs. Studies indicate that this is a result of increased renal glucose uptake, and that SGLT2/GLUT2 expression and activity are upregulated in type 2 diabetes mellitus (T2DM).
Introduction to SGLT2 inhibitors and empagliflozin

Individuals with familial renal glucosuria have alterations in the gene encoding SGLT2, and glucosuria varies from a few grams to >100 g/day. The condition is not known to be associated with clinically relevant consequences, suggesting that long-term urinary glucose excretion (UGE) induced by SGLT2 inhibition may be well tolerated.3

Pharmacological inhibition of SGLT2 in patients with T2DM results in reduced reabsorption of filtered glucose and increased UGE, thereby representing a strategy to reduce hyperglycemia independent of β-cell function and insulin resistance.1 Modest weight reduction is also expected through loss of calories via UGE.

Numerous SGLT2 inhibitors have been approved for the treatment of T2DM in adults, including canagliflozin, dapagliflozin, and empagliflozin in Europe and the US, and ipragliflozin in Japan. The present review provides an overview of available clinical data for empagliflozin, focusing on Phase 3 trials.

Empagliflozin, a potent and selective inhibitor of SGLT2, is rapidly absorbed after oral administration, reaching maximum plasma concentrations within 1–3 h.5,3 Phase 1 studies in patients with T2DM demonstrated that empagliflozin was well tolerated at doses up to 100 mg once daily for 4 weeks, with no increased risk of hypoglycemia.5–7 Phase 2 studies of 12 weeks’ duration, including active comparators as well as placebo control arms, demonstrated that empagliflozin improved glycemic control and weight loss as monotherapy, as well as add-on to other glucose-lowering treatments.8–10 A longer duration Phase 2 study (78 weeks) and a 78-week extension study to the 12-week trials also showed that empagliflozin provided sustained glycemic and weight control, and was well tolerated with a low risk of hypoglycemia.11,12

Empagliflozin has also been investigated in type 1 diabetes mellitus (T1DM): an 8-week open-label study (ClinicalTrials.gov identifier: NCT01392560) associated empagliflozin with a significant attenuation of renal hyperfiltration, improved glycemic control, and reduced hypoglycemic events, insulin doses, and weight in patients with T1DM.13,14 These results appear promising, although the study, at 8 weeks, was fairly short and it did not contain a control group.

As in clinical studies of other SGLT2 inhibitors,15–18 an increased incidence of genital infections (principally mycotic infections, and more common in women) was reported in Phase 2 studies, although these were mostly mild or moderate and rarely led to premature discontinuation of study medication.5,11,12 Treatment was generally well tolerated with a low risk of hypoglycemia. Data from Phase 2 empagliflozin studies provided a foundation for the Phase 3 trial program, which evaluated doses of 10 and 25 mg once daily.

Review methods

A search of the English language literature was performed using PubMed, without imposing any time limitations. Search terms included combinations of the following: “type 2 diabetes”, “SGLT-2 inhibitors”, and “empagliflozin”. Articles relevant to the subject were reviewed and bibliographies from retrieved articles were searched for further relevant articles. In addition, ClinicalTrials.gov was searched for empagliflozin studies. Additional references known to the author were included, and abstracts presented at annual meetings of the American Diabetes Association and European Association for the Study of Diabetes in 2011, 2012, and 2013 were searched.

Empagliflozin Phase 3 trials

The Phase 3 clinical trial program has enrolled over 14 000 patients and includes trials of empagliflozin as monotherapy, as add-on therapy to stable doses of other glucose-lowering treatments (including basal and multiple daily injection [MDI] insulin therapy), and in fixed-dose combination formulations (Table 1). Trials investigating empagliflozin in different patient populations are also included, as well as a cardiovascular (CV) outcome event study (EMPA-REG OUTCOMETM; ClinicalTrials.gov identifier: NCT01131676).

Empagliflozin as monotherapy (ClinicalTrials.gov identifier: NCT01177813)

A 24-week double-blind, randomized, placebo-controlled and active-controlled study investigated empagliflozin monotherapy in previously untreated patients with T2DM (NCT01177813).19 Patients received placebo, empagliflozin 10 mg, empagliflozin 25 mg, or sitagliptin 100 mg for 24 weeks. The study included an open-label empagliflozin 25 mg arm for eligible patients with HbA1c >10% at screening. Empagliflozin improved glycemic control in these patients (Table 2). In the double-blind groups, placebo-adjusted mean change (95% confidence interval [CI]) from baseline HbA1c at Week 24 was −0.74% (−0.88, −0.59; P < 0.0001) for empagliflozin 10 mg, −0.85% (−0.99, −0.71; P < 0.0001) for empagliflozin 25 mg, and −0.73% (−0.88, −0.59; P < 0.0001) for sitagliptin. In an exploratory comparison of patients with
| CT identifier (duration) | Short description | No. enrolled | Notable inclusion criteria and background therapy | Treatment arms | Primary endpoint | Key secondary endpoints |
|-------------------------|------------------|-------------|------------------------------------------------|----------------|----------------|------------------------|
| NCT01177813 (24 weeks) | Empa vs sitagliptin as monotherapy | 986 | Treatment naïve | Empa 10 mg q.d. Empa 25 mg q.d. Sitagliptin 100 mg q.d. Placebo | Change from BL in HbA1c at Week 24 | Change from BL at Week 2 in bodyweight, SBP and DBP |
| NCT01159600 (24 weeks) | Empa vs placebo as add-on to met | 707 | Mett | Empa 10 mg q.d. Empa 25 mg q.d. Placebo | Change from BL in HbA1c at Week 24 | Change from BL at Week 24 in bodyweight and weighted mean daily glucose using an eight-point blood glucose profile |
| NCT01210001 (24 weeks) | Empa as add on to pioglitazone ± met | 499 | Mett + SU ≤ half max recommended dose, or MTO, or max dose according to local label | Empa 10 mg q.d. Empa 25 mg q.d. Placebo | Change from BL in HbA1c at Week 24 | Change from BL at Week 24 in bodyweight and weighted mean daily glucose using an eight-point blood glucose profile |
| NCT01289990 (52 weeks) | 52-week extension of 24-week studies: NCT01177813, NCT01159600, NCT01210001 | 1869 | Patients continued previous treatment as randomized in 24-week trials | Safety | |
| NCT01422876 (24 weeks) | Empa with linagliptin as FDC | 1406 | Initial FDC in treatment naïve patients or FDC as add-on to met | Empa 10 mg + linagliptin 5 mg FDC q.d. Empa 25 mg + linagliptin 5 mg FDC q.d. Placebo | Change from BL in HbA1c at Week 24 | Change from BL at Week 24 in FPG and bodyweight |
| NCT01368081 (52 weeks) | Comprehensive add-on study in Japanese patients | 1162 | Any one OAD | Empa 10 mg q.d. Empa 25 mg q.d. Metformin | Safety | Change from BL in HbA1c at Week 52 |
| NCT01370005 (12 weeks) | Empa in hypertension | 825 | Patients with hypertension either treatment naïve (for T2DM) or pre-treated with any OAD therapy, GLP-1 analogue, or insulin for 12 weeks prior to randomization | Empa 10 mg q.d. Empa 25 mg q.d. Placebo | Change from BL in HbA1c and mean 24-h SBP (ABPM) at Week 12 | Change from BL in mean 24-h DBP (ABPM) at Week 12 |
| NCT01164501 (52 weeks) | Empa in renal impairment | 741 | Patients with renal impairment treated with any antidiabetes drugs (excluding SGLT2 inhibitors) | Empa 10 mg q.d. Empa 25 mg q.d. Placebo | Change from BL in HbA1c at Week 24 | Change from BL at Weeks 24 and 52 in FPG, bodyweight, SBP and DBP |
| NCT01306214 (52 weeks) | Empa as add-on to insulin in obese patients | 566 | Patients with BMI ≥30 and ≤45 kg/m² on insulin ± met | Empa 10 mg q.d. Empa 25 mg q.d. Placebo | Change from BL in HbA1c at Week 18 | Change from BL at Week 52 in insulin dose, bodyweight and HbA1c |
### Table 1 (Continued)

| CT identifier (duration) | Short description | No. enrolled | Notable inclusion criteria and background therapy | Treatment arms | Primary endpoint | Key secondary endpoints |
|--------------------------|-------------------|--------------|-------------------------------------------------|----------------|-----------------|-------------------------|
| **Active**               |                   |              |                                                 |                |                 |                         |
| NCT01167881 (2 years)    | Empa vs glimepiride as add-on to met | 1549 | Met                                              | Empa 25 mg q.d. | Change from BL in HbA1c at Weeks 52 and 104 | Change from BL at Weeks 52 and 104 in bodyweight, SBP and DBP; Occurrence of confirmed hypoglycemic AEs during 52 and 104 weeks of treatment. A microvascular composite (laser therapy for retinopathy, vitreous hemorrhage, blindness, new or worsening nephropathy). Changes from BL in HbA1c, FPG, bodyweight, waist circumference, and BP. Proportion of patients obtaining composite endpoint of HbA1c reduction ≥0.5%, SBP decrease >2 mmHg, bodyweight decrease >2% |
| NCT0131676 (endpoint driven; expected duration up to 5 years) | EMPA-REG OUTCOMETM | 7063 | Patients with high CV risk on any background therapy | Empa 10 mg q.d. + Empa 25 mg q.d. + Placebo | Time to first occurrence of CV death, non-fatal MI or non-fatal stroke |
| **Recruiting**           |                   |              |                                                 |                |                 |                         |
| NCT01719003 (24 weeks)   | Empa + met combination therapy | Estimated 1397 | Treatment naïve | Empa 10 mg q.d. + Met 500 mg b.i.d. + Met 500 mg b.i.d. + Met 1000 mg b.i.d. | Change from BL in HbA1c at Week 24 | Change from BL at Week 24 in FPG and bodyweight |
| NCT01734785 (24 weeks)   | Empa with linagliptin as FDC | Estimated 444 | Met and linagliptin 5 mg q.d. administered in 16-week run-in period | Empa 10 mg + linagliptin 5 mg FDC q.d. | Change from BL in HbA1c at Week 24 | Change from BL at Week 24 in FPG and bodyweight |
| NCT01778049 (24 weeks)   | Empa with linagliptin as FDC | Estimated 681 | Met and empagliflozin 10 or 25 mg, administered in 16-week run-in period | Empa 10 mg + linagliptin 5 mg FDC q.d. | Change from BL in HbA1c at Week 24 | Change from BL at Week 24 in FPG |

†Metformin dose unless specified: ≥1500 mg/day or maximum tolerated dose (MTD) or maximum dose according to local label.

CT, Clinicaltrials.gov; empagliflozin; BL, baseline; SBP, systolic blood pressure; DBP, diastolic blood pressure; met, metformin; SU, sulfonylureas; FDC, fixed-dose combination; OAD, oral antidiabetes drug; T2DM, type 2 diabetes mellitus; GLP-1, glucagon-like peptide-1; FPG, fasting plasma glucose; ABPM, ambulatory blood pressure monitoring; SGLT, sodium-glucose cotransporter; BP, blood pressure; BMI, body mass index; CV, cardiovascular; MI, myocardial infarction.
## Table 2

HbA1c, bodyweight (baseline and change from baseline), body mass index (baseline) and blood pressure (change from baseline) in key empagliflozin Phase 3 studies

| Study | Treatment arms | NCT01177813 vs sita monotherapy | NCT0115960020: Empa as add-on to met + SU | NCT01210001 | NCT01167881 | NCT01306214 add-on to met and glib | NCT01306214 as add-on to MDI and insulin |
|-------|----------------|----------------------------------|----------------------------------|--------------|--------------|------------------------------------|----------------------------------------|
|       | Study          | Empa 10 mg q.d. (n = 224)        | Empa 25 mg q.d. (n = 224)        | Empa 10 mg q.d. (n = 217) | Empa 10 mg q.d. (n = 225) | Empa 10 mg q.d. (n = 221) | Empa 10 mg q.d. (n = 186) |
|       |                | 7.87 ± 0.88                      | 7.86 ± 0.85                      | 7.94 ± 0.79  | 8.07 ± 0.81  | 8.10 ± 0.83                      | 8.39 ± 0.05                        |
|       |                | –0.66 (-0.76, –0.56)             | –0.78 (-0.88, –0.67)            | –0.70 (0.05) | –0.82 (0.09) | –0.77 (0.09)                      | –0.94 (0.05)                       |
|       |                | 78.4 ± 18.7                      | 77.8 ± 18.0                      | 81.6 ± 18.5  | 77.1 ± 18.3  | 77.5 ± 18.8                      | 95.7 ± 1.3                        |
|       |                | –2.26 (-2.60, –1.92)             | –2.48 (-2.82, –2.14)            | –2.08 ± 0.17 | –2.16 ± 0.15 | –2.39 ± 0.16                      | –0.97 ± 0.18                      |
|       |                | 28.3 (5.5)                       | 28.2 (5.5)                       | 29.1 (5.5)   | 28.3 (5.4)   | 28.3 (5.5)                       | 34.7 (3.8)                        |
|       |                | –2.9 (-4.5, –1.3)                | –3.7 (-5.3, –2.1)               | –4.5 ± 0.7   | –4.1 ± 0.7   | –3.5 ± 0.7                        | –3.6 ± 0.8                        |
|       |                | –1.0 (-2.0, –0.1)                | –1.9 (-2.9, –1.0)               | –2.0 ± 0.5   | –2.1 ± 0.4   | –1.6 ± 0.5                        | –2.2 ± 0.4                        |
|       |                | 78.2 ± 19.9                      | 78.2 ± 19.9                      | 79.7 ± 18.6  | 76.2 ± 16.9  | 76.2 ± 16.9                      | 30.0 (5.3)                        |
|       |                | –0.33 (-0.67, 0.00)              | –0.45 ± 0.17                     | –0.45 ± 0.17 | –0.39 ± 0.15 | –0.39 ± 0.15                      | –3.1 (-3.9, –2.2)                 |
|       |                | 28.7 (6.2)                       | 28.7 (6.2)                       | 28.7 (5.2)   | 27.9 (4.9)   | 27.9 (4.9)                       | 30.3 (5.3)                        |
|       |                | –0.3 (-1.9, 1.3)                 | –0.4 (-1.4, 0.5)                 | –0.4 ± 0.7   | –1.4 ± 0.7   | –1.4 ± 0.7                        | 2.5 (1.7, 3.4)                    |
|       |                | 78.0 ± 19.1                      | 78.0 ± 19.1                      | 78.1 ± 20.1  | 78.1 ± 20.1  | 78.1 ± 20.1                      | 0.9 (0.4, 1.4)                    |
|       |                | –1.62 ± 0.21                     | –1.52 ± 0.21                     | 0.34 ± 0.21  | 0.34 ± 0.21  | 0.34 ± 0.21                      | –1.8 (-2.3, –1.2)                 |
|       |                | 29.2 (5.6)                       | 29.2 (5.6)                       | 29.3 (5.4)   | 29.3 (5.4)   | 29.3 (5.4)                       | –1.8 (-2.3, –1.2)                 |
|       |                | –3.1 ± 0.9                       | –1.5 ± 0.5                       | 0.7 ± 0.9    | 0.7 ± 0.9    | 0.7 ± 0.9                        | –1.8 (-2.3, –1.2)                 |
|       |                | –1.5 ± 0.5                       | –2.2 ± 0.5                       | 0.3 ± 0.5    | 0.3 ± 0.5    | 0.3 ± 0.5                        | –1.8 (-2.3, –1.2)                 |
|       |                | 29.1 (5.5)                       | 29.1 (5.5)                       | 29.3 (5.4)   | 30.0 (5.3)   | 30.0 (5.3)                       | 2.5 (1.7, 3.4)                    |
|       |                | –4.0 ± 0.8                       | –2.2 ± 0.5                       | 0.7 ± 0.9    | –3.1 (-3.9, –2.2) | –1.8 (-2.3, –1.2) | 0.9 (0.4, 1.4) |
Empagliflozin as add-on therapy (ClinicalTrials.gov identifier: NCT01159600, NCT01210001, NCT01306214, NCT01167881)

The above comparison provides a clear indication of the efficacy and safety of empagliflozin. However, metformin is the recommended first-line therapy for most patients, and therefore a study of any new treatment as add-on to metformin is essential. A randomized, double-blind placebo-controlled study investigated the efficacy and safety of empagliflozin as add-on therapy to metformin (NCT01159600). Patients received placebo, empagliflozin 10 mg, or empagliflozin 25 mg for 24 weeks.20 Both doses of empagliflozin improved glycemic control (Table 2). Placebo-adjusted mean change (95% CI) from baseline HbA1c at Week 24 was −0.57% (−0.70, −0.43; P < 0.0001) for empagliflozin 10 mg and −0.64% (−0.77, −0.50; P < 0.0001) for empagliflozin 25 mg.20 Empagliflozin also reduced bodyweight and SBP (Table 2). This study included an open-label empagliflozin 25 mg arm for eligible patients with HbA1c >10% at screening. Mean HbA1c decreased from 11.1% at baseline to 7.9% at Week 24 in the open-label arm (mean change from baseline −3.2%). Events consistent with UTIs were reported in similar proportions of patients across groups (Table 3); most of these events were of mild intensity and were reported in more female than male patients (Table 3). Empagliflozin increased the incidence of genital infection compared with placebo (Table 3). Most of these events were mild in intensity; two events led to premature discontinuation of empagliflozin. Similar to UTIs, events consistent with genital infection were reported in more female than male patients (Table 3). The occurrence of hypoglycemia was low across groups (Table 3). Empagliflozin was associated with small increases from baseline in HDL-C versus placebo (Table 4; P ≤ 0.001 for both doses) and LDL-C (Table 4; P = 0.043 for empagliflozin 10 mg, P = 0.032 for empagliflozin 25 mg). No major differences in triglyceride levels were noted between treatment groups.20 Small increases in hematocrit (both empagliflozin groups) and a small decrease in eGFR (empagliflozin 25 mg) were noted compared with baseline (Table 4).20 Empagliflozin was also investigated as add-on therapy to metformin plus sulfonylurea in the same trial (NCT01159600), and efficacy results were consistent with those seen in metformin-treated patients (Table 2).21 The placebo-adjusted mean change (95% CI) from baseline HbA1c at Week 24 was −0.64% (−0.77, −0.51; P < 0.0001) for empagliflozin 10 mg and −0.59% (−0.73, −0.46; P < 0.0001) for empagliflozin 25 mg. In patients treated with open-label empagliflozin 25 mg, mean HbA1c was reduced from 11.2% at baseline to 8.2% at Week 24 (mean change from baseline −2.9%). The incidence of events consistent with UTIs was similar across groups (more frequent in females than males; Table 3). These events were mostly mild in intensity, with one event leading to study discontinuation. Events consistent with genital infections occurred more frequently with empagliflozin than placebo (and more frequently in females than males); although the overall proportion was low, most events were mild in intensity, and none led to discontinuation (Table 3). The incidence of hypoglycemia was very low, with one case reported in each treatment arm. The incidence of adverse events (AEs) was comparable in all groups (placebo, 61%; empagliflozin 10 mg, 55%; empagliflozin 25 mg, 61%; sitagliptin, 53%). However, events consistent with urinary tract infections (UTIs) occurred more frequently in female patients treated with empagliflozin than those treated with placebo or sitagliptin (Table 3); these events were mild or moderate in intensity and led to discontinuation in one patient. Events consistent with genital infection also occurred more frequently with empagliflozin 10 mg and empagliflozin 25 mg than with placebo (Table 3), but were also of mild or moderate intensity, with premature discontinuation in one patient. The incidence of hypoglycemia was very low, with one case reported in each treatment arm and none requiring assistance. High-density lipoprotein cholesterol (HDL-C; Table 4) increased significantly from baseline in both empagliflozin groups (P < 0.001 vs placebo for both groups). For low-density lipoprotein cholesterol (LDL-C) and triglycerides, small non-significant changes from baseline were recorded with both doses of empagliflozin (Table 4).19 No clinically meaningful changes in estimated glomerular filtration rate (eGFR) were noted across all groups, whereas small increases in hematocrit were observed in both empagliflozin groups (Table 4).19

HbA1c ≥8.5% at baseline, both doses of empagliflozin produced greater reductions in HbA1c than sitagliptin (−1.44% with empagliflozin 10 mg, −1.43% with empagliflozin 25 mg, −1.04% with sitagliptin). The authors proposed that the extent to which UGE is increased in patients taking an SGLT2 inhibitor depends, in part, on the degree of glycemia. In the open-label arm, mean HbA1c was reduced from 11.5% at baseline to 7.6% at Week 24 (mean change [95% CI] from baseline −3.7% [−4.1 to −3.3]).19 The reduction in diastolic blood pressure (DBP) from baseline at Week 24 with empagliflozin was comparable to that recorded with placebo, but greater than with sitagliptin. However, changes from baseline at Week 24 in systolic blood pressure (SBP) and bodyweight were greater with empagliflozin (both doses) than with placebo or sitagliptin (Table 2).19 Small increases in hematocrit (both empagliflozin groups) and a small decrease in eGFR (empagliflozin 25 mg arm for eligible patients with HbA1c ≥9% at baseline) were noted across all groups (placebo, 61%; empagliflozin 10 mg, 55%; empagliflozin 25 mg, 61%; sitagliptin, 53%). However, changes from baseline at Week 24 in systolic blood pressure (SBP) and bodyweight were greater with empagliflozin (both doses) than with placebo or sitagliptin (Table 2).19
**Table 3**  Adverse events (special interest categories) in key empagliflozin Phase 3 studies

| Study | Treatment arms | Hypoglycemia* (%) | No. hypoglycemic events requiring assistance | % UTI† | % Genital infection† |
|-------|----------------|-------------------|---------------------------------------------|--------|----------------------|
| NCT01177813: Empa vs sita as monotherapy | Empa 10 mg q.d. | <1                | 0                                           | 7 (M2.0, F15.0) | 3 (M3.0, F4.0) |
|       | Empa 25 mg q.d. | <1                | 0                                           | 5 (M1.0, F13.0) | 4 (M1.0, F9.0) |
|       | Sita 100 mg q.d.| <1                | 0                                           | 5 (M3.0, F9.0)  | 1 (M1.0, F1.0) |
|       | Placebo        | <1                | 0                                           | 5 (M2.0, F9.0)  | 0                  |
| NCT01159600: Empa as add-on to met | Empa 10 mg q.d. | 1.8               | 0                                           | 5.1 (M0.0, F12.0) | 3.7 (M0.8, F7.6) |
|       | Empa 25 mg q.d. | 1.4               | 0                                           | 5.6 (M0.8, F11.8) | 4.7 (M0.8, F9.7) |
|       | Placebo        | 0.5               | 0                                           | 4.9 (M2.6, F7.7)  | 0                  |
| NCT01159600: Empa as add-on to met + SU | Empa 10 mg q.d. | 15.1              | 0                                           | 16.3 (M2.7, F13.3) | 8.0 (M0.9, F9.0) |
|       | Empa 25 mg q.d. | 11.5              | 0                                           | 8.3 (M0.0, F17.5) | 2.3 (M0.9, F3.9) |
|       | Placebo        | 8.4               | 0                                           | 8.0 (M2.7, F13.3) | 0.9 (M0.9, F0.9) |
| NCT01210001: Empa as add-on to pioglitazone ± met | Empa 10 mg q.d. | 1.2               | 0                                           | 17.0 (M3.6, F30.5) | 8.5 (M7.2, F9.8) |
|       | Empa 25 mg q.d. | 2.4               | 0                                           | 11.9 (M2.4, F21.7) | 3.6 (M1.2, F6.0) |
|       | Placebo        | 1.8               | 0                                           | 16.4 (M8.2, F22.8) | 2.4 (M1.4, F3.3) |
| NCT01167881: Empa or glimepiride as add-on to met | Empa 25 mg q.d. | 4.0               | 2.0                                         | 14.0 (M7.0, F22.0) | 12.0 (M9.0, F15.0) |
|       | Glimepiride 1–4 mg q.d. | 25.0              | 24.0                                        | 13.0 (M5.0, F23.0) | 2.0 (M1.0, F3.0) |
| NCT01306214: Empa as add-on to MDI insulin | Empa 10 mg q.d. | 95 (51.1)          | 3 (1.6)                                     | 15.6 (M5.2, F27.0) | 4.3 (M1.0, F7.9) |
|       | Empa 25 mg q.d. | 109 (57.7)         | 1 (0.5)                                     | 15.3 (M3.6, F24.8) | 9.5 (M8.3, F10.5) |
|       | Placebo        | 109 (58.0)         | 3 (1.6)                                     | 15.4 (M0.0, F25.7) | 1.6 (M1.3, F1.8) |

*Events consistent with hypoglycemia, plasma glucose ≤3.9 mmol/L (≤70 mg/dL) and/or requiring assistance.
†Percentage of urinary tract infections (UTI) and genital infections as a whole, and in males (M) and females (F) separately, if stated.
Empa, empagliflozin; sita, sitagliptin; met, metformin; SU, sulfonylurea; MDI, multiple daily injection.
### Table 4: Laboratory measurements in key empagliflozin Phase 3 studies

| Study                  | Treatment arms              | HDL-C at BL (mmol/L) | HDL-C change from BL (mmol/L) | LDL-C at BL (mmol/L) | LDL-C change from BL (mmol/L) | TG at BL (mmol/L) | TG change from BL (mmol/L) | Mean ± SD Hct change from BL (%) | Mean ± SD eGFR* change from BL (%) |
|------------------------|-----------------------------|----------------------|--------------------------------|----------------------|--------------------------------|-------------------|--------------------------|----------------------------------|----------------------------------|
| NCT01177813[1]: Empa vs sita as monotherapy | Empa 10 mg q.d.             | 1.24 ± 0.02          | 0.11 ± 0.01                    | 2.96 ± 0.07          | 0.06 ± 0.04                    | 2.08 ± 0.12       | −0.30 ± 0.10                  | 43.6 ± 4.4                      | 2.1 ± 3.3                        |
|                        | Empa 25 mg q.d.             | 1.25 ± 0.02          | 0.13 ± 0.01                    | 2.75 ± 0.07          | 0.11 ± 0.04                    | 2.37 ± 0.20       | −0.18 ± 0.10                  | 43.8 ± 4.7                      | 2.1 ± 3.1                        |
|                        | Sita 100 mg q.d.            | 1.26 ± 0.02          | 0.02 ± 0.01                    | 2.74 ± 0.05          | 0.03 ± 0.04                    | 2.20 ± 0.13       | 0.06 ± 0.10                   | 43.5 ± 4.3                      | −0.8 ± 2.9                       |
|                        | Placebo                    | 1.26 ± 0.02          | 0.04 ± 0.01                    | 2.90 ± 0.06          | 0.04 ± 0.04                    | 2.01 ± 0.09       | −0.07 ± 0.10                  | 43.4 ± 4.7                      | −0.5 ± 3.1                       |
| NCT01159600[2]: Empa as add-on to met | Empa 10 mg q.d.             | 1.28 ± 0.02          | 0.08 ± 0.01                    | 2.40 ± 0.06          | 0.15 ± 0.04                    | 1.95 ± 0.09       | 0.00 ± 0.08                    | 42.4 ± 4.4                      | 2.4 ± 3.4                        |
|                        | Empa 25 mg q.d.             | 1.28 ± 0.02          | 0.06 ± 0.01                    | 2.48 ± 0.06          | 0.15 ± 0.04                    | 1.84 ± 0.08       | −0.04 ± 0.08                  | 41.9 ± 4.7                      | 2.7 ± 3.4                        |
|                        | Placebo                    | 1.22 ± 0.02          | 0.00 ± 0.01                    | 2.46 ± 0.06          | 0.03 ± 0.04                    | 1.96 ± 0.09       | 0.11 ± 0.08                   | 42.1 ± 4.3                      | −0.8 ± 3.0                       |
| NCT01159600[2]: Empa as add-on to met + SU | Empa 10 mg q.d.             | 1.26 ± 0.02          | 0.05 ± 0.01                    | 2.35 ± 0.06          | 0.04 ± 0.04                    | 1.87 ± 0.09       | 0.03 ± 0.09                   | 41.8 ± 5.0                      | 2.5 ± 3.4                        |
|                        | Empa 25 mg q.d.             | 1.27 ± 0.02          | 0.05 ± 0.01                    | 2.41 ± 0.06          | 0.10 ± 0.04                    | 1.92 ± 0.07       | 0.17 ± 0.09                   | 42.2 ± 4.1                      | 2.7 ± 3.4                        |
|                        | Placebo                    | 1.25 ± 0.02          | −0.02 ± 0.01                   | 2.39 ± 0.06          | 0.02 ± 0.04                    | 1.70 ± 0.09       | 0.08 ± 0.09                   | 41.7 ± 4.3                      | −0.8 ± 3.1                       |
| NCT01210001[2]: Empa as add-on to met | Empa 10 mg q.d.             | 1.28 ± 0.02          | 0.04 ± 0.02                    | 2.65 ± 0.08          | 0.09 ± 0.05                    | 1.86 ± 0.14       | −0.18 ± 0.06                  | 41.6 ± 5.0                      | 2.1 ± 4.4                        |
|                        | Empa 25 mg q.d.             | 1.31 ± 0.02          | 0.02 ± 0.02                    | 2.60 ± 0.07          | 0.04 ± 0.05                    | 1.76 ± 0.13       | 0.00 ± 0.06                   | 40.6 ± 5.2                      | 2.6 ± 3.4                        |
|                        | Pioglitazone ± met          | Placebo              | 1.31 ± 0.02                    | 0.01 ± 0.02          | 2.76 ± 0.08                    | 0.00 ± 0.05       | 1.73 ± 0.06                   | 40.6 ± 4.9                      | −0.6 ± 3.6                       |
| NCT01167881[2]: Empa or glimepiride as add-on to met | Empa 25 mg q.d.             | 1.26 ± 0.01          | 0.08 ± 0.01                    | 2.42 ± 0.03          | 0.19 ± 0.02                    | 1.87 ± 0.05       | 0.05 ± 0.04                   | 42.8 ± 4.8                      | 4.3 ± 4.4                        |
|                        | Glimepiride 1–4 mg q.d.     | 1.24 ± 0.01          | −0.01 ± 0.01                   | 2.41 ± 0.03          | 0.04 ± 0.02                    | 1.84 ± 0.04       | 0.12 ± 0.04                   | 42.6 ± 5.2                      | 0.6 ± 4.1                        |
| NCT01306214[2]: Empa as add on to MDI insulin | Empa 10 mg q.d.             | 1.19 ± 0.02          | 0.01 ± 0.01                    | 2.68 ± 0.08          | −0.06 ± 0.05                   | 1.94 ± 0.10       | 0.20 ± 0.10                   | 41.8 (5.3)                      | 4.8 (4.1)                        |
|                        | Empa 25 mg q.d.             | 1.20 ± 0.02          | 0.01 ± 0.01                    | 2.71 ± 0.07          | 0.06 ± 0.05                    | 1.92 ± 0.08       | −0.03 ± 0.10                  | 43.1 (5.4)                      | 4.4 (4.1)                        |
|                        | Placebo                    | 1.17 ± 0.02          | −0.02 ± 0.01                   | 2.73 ± 0.08          | 0.12 ± 0.05                    | 2.02 ± 0.14       | 0.01 ± 0.10                   | 42.6 (5.8)                      | 0.7 (4.1)                        |

Unless indicated otherwise, baseline (BL) data are given as the mean ± SE, whereas changes from BL data are given as the adjusted mean ± SE.

*Estimated glomerular filtration rate (eGFR) is given in mL/min per 1.73 m² (Modification of Diet in Renal Disease [MDRD] equation).

†For hematocrit (Hct), the change from BL is calculated using the last value on treatment; for eGFR, the change from BL is at Week 24 (or Week 104 for study NCT01167881). Note, the Hct was normalized to a standard reference range.

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; empa, empagliflozin; sita, sitagliptin; met, metformin; SU, sulfonylurea; MDI, multiple daily injection.
higher with empagliflozin than placebo (Table 3). This suggests an increased risk of hypoglycemia with empagliflozin in combination with sulfonylurea that may be based on the glucose-independent insulin-releasing effects of sulfonylureas. There was a small increase from baseline to Week 24 in HDL-C with both doses of empagliflozin ($P < 0.001$ for both doses vs placebo; Table 4). However, no major differences from baseline in LDL-C or triglycerides were reported (Table 4) and, for both these parameters and for both doses of empagliflozin, the differences compared with placebo were not statistically significant.

Similar improvements in glycemic control, as well as in weight and blood pressure (BP), were observed in a 24-week study of empagliflozin as add-on to pioglitazone ± metformin (NCT01210001; Table 2). The placebo-adjusted mean change (95% CI) from baseline HbA1c at Week 24 was $-0.48\%$ ($-0.66, -0.29$; $P < 0.001$) for empagliflozin 10 mg and $-0.61\%$ ($-0.79, -0.42$; $P < 0.001$) for empagliflozin 25 mg. The incidence of hypoglycemia across groups was low (Table 3). Empagliflozin did not increase the risk of events consistent with UTIs in that study, although the incidence was unexpectedly high in all groups (Table 3). The incidence of events consistent with genital infection was higher with empagliflozin than placebo (Table 3); however, none of these infections was severe or led to premature discontinuation. Importantly, there was no increase in the frequency of AEs typically associated with pioglitazone treatment, such as edema, heart failure, and bone fracture, in patients receiving empagliflozin compared with placebo. There was a significant increase from baseline in HDL-C with empagliflozin 10 mg (difference vs placebo 0.06 mmol/L; $P = 0.012$), but no clinically relevant changes in LDL-C or triglycerides with empagliflozin (Table 4).

Two-year data have been published from an ongoing head-to-head Phase 3 study comparing empagliflozin with the sulfonylurea glimepiride over 4 years in patients with T2DM inadequately controlled with metformin (NCT0167881). Patients were randomized to empagliflozin 25 mg q.d. or glimepiride 1–4 mg q.d. as add-on to metformin for 2 years, followed by a 2-year extension. The primary endpoint was change from baseline in HbA1c levels at Weeks 52 and 104. Differences in the primary endpoint were first tested for non-inferiority and, if demonstrated, were then tested for superiority at Week 104. Empagliflozin was non-inferior to glimepiride at both time points. Compared with glimepiride, the adjusted mean difference in change from baseline in HbA1c with empagliflozin at Week 104 was $-0.11\%$ (95% CI $-0.19, -0.02$; $P = 0.0153$ for superiority). Furthermore, empagliflozin provided greater reductions in weight and BP with a low risk of hypoglycemia compared with glimepiride. Over 104 weeks, the proportion of patients reporting at least one AE was similar in the two groups. Despite a greater reduction in HbA1c concentration at Week 104, fewer patients had confirmed hypoglycemic AEs with empagliflozin versus glimepiride (Table 3). The percentage of patients with events consistent with UTIs was similar in the two groups, although more patients treated with empagliflozin reported events consistent with genital infection than patients treated with glimepiride (Table 3). Small increases from baseline in hematocrit, HDL-C, and LDL-C were reported for empagliflozin versus glimepiride, but no major differences in triglycerides were noted between groups (Table 4).

Empagliflozin has also been studied as add-on therapy to MDI insulin for 52 weeks in obese, difficult-to-treat patients with T2DM who were inadequately controlled on high MDI insulin doses (NCT01306214; Table 2). Adjusted mean (± SE) changes from baseline to Week 18 in HbA1c were $-0.94 \pm 0.05\%$ and $-1.02 \pm 0.05\%$ for empagliflozin 10 mg and empagliflozin 25 mg, respectively, compared with $-0.50 \pm 0.05\%$ for placebo (i.e. insulin alone; $P < 0.001$ for both). Improvements in glycemic control with empagliflozin 10 mg and empagliflozin 25 mg were also seen at Week 52, together with a reduction in insulin requirements and weight, compared with placebo. The proportion of patients with confirmed hypoglycemic AEs, and with events consistent with UTIs, was similar across groups, whereas events consistent with genital infection were more frequent with empagliflozin than placebo (Table 3). There were no major differences between groups with regard to changes from baseline in HDL-C, LDL-C, or triglycerides. Small increases in hematocrit occurred with empagliflozin versus placebo (Table 4).

**Pooled analysis (ClinicalTrials.gov identifiers: NCT01177813, NCT01159600, NCT01210001)**

The Phase 3 trials summarized above have also been pooled for further analyses and preliminary results have been reported. The first pooled analysis evaluated the effect of empagliflozin on glycemic parameters, bodyweight, BP, lipid parameters, uric acid, and hypoglycemia in patients with T2DM. In that analysis, empagliflozin provided clinically meaningful improvements in glycemic parameters, bodyweight, and BP, with positive effects on uric acid. Small increases in HDL-C and LDL-C were also observed. Baseline mean (± SE) HDL-C values were $1.26 \pm 0.01, 1.26 \pm 0.01$, and $1.27 \pm 0.01$ mmol/L for placebo, empagliflozin 10 mg and empagliflozin 25 mg, respectively; the mean (± SE) change from baseline at
Week 24 was 0.00 ± 0.01 mmol/L for placebo and 0.07 ± 0.01 mmol/L for both empagliflozin groups (P < 0.001 vs placebo). For LDL-C, the corresponding baseline values were 2.62 ± 0.03 mmol/L (placebo) and 2.57 ± 0.03 mmol/L (empagliflozin 10 mg and 25 mg); the change from baseline at Week 24 in the placebo and empagliflozin 10 mg and 25 mg groups was 0.02 ± 0.02, 0.08 ± 0.02, and 0.10 ± 0.02 mmol/L, respectively (P < 0.01 for empagliflozin 25 mg vs placebo).28

A second pooled analysis of the above Phase 3 trials (n = 2477) further investigated the effect of empagliflozin treatment on the incidence of UTIs and genital infections.29 In that analysis, empagliflozin was not associated with an increased frequency of UTIs versus placebo, but was associated with more genital infections. Genital infections led to dose reduction or discontinuation by 0.1% and 0.2% of patients with empagliflozin 10 mg and 25 mg, respectively, and most events were mild in intensity.29

**Empagliflozin in special populations**

A Phase 3 study investigated the efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with T2DM and chronic kidney disease (CKD).24 Patients with Stage 2 CKD (eGFR ≥60 to <90 mL/min per 1.73 m²) received empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily for 52 weeks. Patients with Stage 3 CKD (eGFR ≥30 to <60 mL/min per 1.73 m²), and an exploratory group of patients with Stage 4 CKD (≥15 to <30 mL/min per 1.73 m²), received empagliflozin 25 mg or placebo for 52 weeks. The 25 mg dose was selected for patients with Stage 3 or 4 CKD because empagliflozin-mediated UGE is reduced in patients with increasing renal impairment,30 and empagliflozin 25 mg provides greater inhibition of glucose reabsorption than empagliflozin 10 mg.

Empagliflozin reduced HbA1c in patients with Stage 2 or 3 CKD.24 In patients with Stage 2 CKD, the change from baseline HbA1c (95% CI) at Week 24 was 0.06% (−0.08, 0.20) with placebo, −0.46% (−0.60, −0.32) with empagliflozin 10 mg, and −0.63% (−0.77, −0.49) with empagliflozin 25 mg. This effect was sustained at Week 52. The difference versus placebo was statistically significant for both empagliflozin doses at both Week 24 and Week 52 (all P < 0.0001).24 Empagliflozin produced significant reductions in bodyweight, SBP, and DBP at Week 24 compared with placebo, which were sustained at Week 52.24 In patients with Stage 3A CKD (eGFR ≥45 to <60 mL/min per 1.73 m²), the mean (± SE) change from baseline in HbA1c at Week 52 was 0.06 ± 0.07% for placebo and −0.48 ± 0.07% for empagliflozin 25 mg (P < 0.001 vs placebo). For Stage 3B CKD (eGFR ≥30 to <45 mL/min per 1.73 m²), the mean (± SE) change from baseline in HbA1c at Week 52 was 0.19 ± 0.08% and −0.18 ± 0.08% for placebo and empagliflozin 25 mg, respectively (P < 0.01 vs placebo).31

In patients with Stage 4 CKD, empagliflozin did not reduce HbA1c, although reductions in bodyweight and BP were reported24; the lack of effect on HbA1c is perhaps not unexpected because the mode of action of SGLT2 inhibitors depends on filtered glucose load and, hence, GFR; therefore their ability to reduce hyperglycemia is anticipated to decrease with increasing renal impairment.31 Inclusion of a control arm (normal renal function) would have allowed direct comparison of glucose-lowering efficacy across subgroups with increasing degrees of renal impairment.

The incidence of AEs and rates of hypoglycemia were comparable across treatment arms in the Stage 2 CKD subgroup. Two cases of confirmed hypoglycemic events needing assistance were reported, one in each empagliflozin group. The incidence of events consistent with UTIs was also comparable across groups, with more events reported in females than males. One such event in the empagliflozin 25 mg group led to premature discontinuation of treatment. The incidence of events consistent with genital infection was comparable across groups. A similar profile of AEs was observed in the Stage 3 CKD subgroup. In patients with Stage 4 CKD, the proportion of patients reporting AEs was higher with empagliflozin (91.9%) than placebo (83.8%), including the proportion with hypoglycemia (14/37 [37.8%] vs 12/37 [32.4%], respectively). The significance of this difference is unclear and, because the number of patients in this subgroup was relatively small, it may simply be due to chance.24

Although several Phase 3 studies demonstrated BP reductions, the analyses were limited by a lack of adjustment for changes in antihypertensive medication. However, a Phase 3 trial that specifically investigated empagliflozin in patients with T2DM and hypertension (mean seated office SBP 130–159 mmHg and DBP 80–99 mmHg) has been reported (NCT01370005).25 The primary endpoints included changes from baseline in mean HbA1c and 24-h SBP (using 24-h ambulatory BP measurements [ABPM]). Patients were randomized to empagliflozin 10 mg, empagliflozin 25 mg, or placebo, once daily for 12 weeks. Both doses of empagliflozin significantly reduced HbA1c versus placebo at Week 12. Placebo-adjusted mean (95% CI) change from baseline in HbA1c was −0.62% (−0.72, −0.52; P < 0.001) with empagliflozin 10 mg and −0.65% (−0.75, −0.55; P < 0.001) with empagliflozin 25 mg. Both doses of empagliflozin resulted in significant and clinically meaningful reductions in SBP and DBP. Placebo-adjusted mean (95% CI)
change from baseline in 24-h SBP (ABPM) at Week 12 was −3.4 mmHg (−4.8, −2.1; \(P < 0.001\)) with empagliflozin 10 mg, and −4.2 mmHg (−5.5, −2.8; \(P < 0.001\)) with empagliflozin 25 mg. Placebo-adjusted mean (95% CI) change from baseline in 24-h DBP (ABPM) at Week 12 was −1.4 mmHg (−2.2, −0.6; \(P < 0.001\)) with empagliflozin 10 mg and −1.7 mmHg (−2.5, −0.9; \(P < 0.001\)) with empagliflozin 25 mg. Empagliflozin was well tolerated with a similar AE profile to placebo, except for an increased incidence of events consistent with genital infection.25

Recently completed and ongoing Phase 3 studies
Numerous Phase 3 clinical studies are completed but the findings have not yet been published. These include investigations of empagliflozin in a comprehensive add-on study in Japanese patients (NCT01368081), in a fixed-dose combination formulation with linagliptin (NCT01422876), and in a 52-week extension of three 24-week trials as monotherapy or with different background therapies (NCT01289990).

An ongoing head-to-head Phase 3 study is comparing glycemic control with empagliflozin versus glimepiride over 4 years in patients with T2DM inadequately controlled with metformin (NCT01167881).32 The study will also investigate effects on \(\beta\)-cell function, CV risk factors, and markers of renal function/damage.

Empagliflozin is associated with beneficial changes in a number of CV risk factors, such as lowering BP, bodyweight, and uric acid, in addition to decreasing HbA1c; however, current data on clinical outcomes, such as stroke, myocardial infarction, and CV death are limited and, furthermore, small increases in LDL-C and HDL-C have been observed. The empagliflozin CV outcome trial (EMPA-REG OUTCOMETM; NCT01131676) is an ongoing multicenter, randomized, double-blind, placebo-controlled trial designed to assess the impact of empagliflozin 10 or 25 mg versus placebo on CV events. This event-driven trial includes approximately 7000 patients with T2DM at elevated CV risk. The primary endpoint is time to first occurrence of CV death, non-fatal myocardial infarction, or non-fatal stroke. The study is designed to evaluate CV safety with the option to test for CV superiority for empagliflozin compared with current standard of care.25

Discussion
Good glycemic control is the cornerstone of diabetes management, although managing modifiable CV disease risk factors, including hypertension and overweight/obesity, is also key in patients with T2DM. Several studies have demonstrated that improving BP control in patients with hypertension and diabetes reduces the risk of CV events.33–39 Nevertheless, hypertension is frequently uncontrolled in the diabetes population, with an incidence of approximately 80%.40 Similarly, over 80% of patients with T2DM are overweight or obese,41 which can worsen insulin resistance and glucose intolerance, complicating the management of T2DM. Furthermore, losing weight may be difficult for patients with T2DM,41 and many existing glucose-lowering treatments are associated with weight gain.42 All clinical practice guidelines for T2DM advocate good glycemic and BP control, as well as weight loss for patients who are overweight or obese.43,44 In addition to their effects on glucose lowering, SGLT2 inhibitors exhibit weight-loss and BP-lowering activity.

The Phase 3 studies of empagliflozin as monotherapy or add-on to other glucose-lowering treatments have demonstrated improvements in glycemic control, as well as modest reductions in bodyweight and BP. Data from a Phase 2 study also suggests that \(\beta\)-cell glucose sensitivity was enhanced and insulin sensitivity improved, following empagliflozin therapy.35 The weight reduction associated with empagliflozin is likely due to UGE, leading to mild osmotic diuresis and calorie loss in urine.46 Osmotic diuresis associated with UGE may also underlie the reductions in SBP associated with empagliflozin treatment,46 although other mechanisms may be involved, such as weight reduction and improvement in arterial stiffness reported with empagliflozin.47 Notably, these reductions in BP were not associated with an overall increase in pulse rate.

The risk of hypoglycemia is an important consideration for T2DM management because it is associated with decreased treatment satisfaction and health-related quality of life, as well as increased mortality risk. Data from Phase 3 trials demonstrate that empagliflozin is generally well tolerated, with no increased risk of hypoglycemia compared with placebo when used as monotherapy or as add-on therapy except when given with sulfonylurea.

Patients with T2DM are predisposed to genital infections and UTIs, and the tendency to develop genital infections may be exacerbated by the UGE induced by SGLT2 inhibitors.48 Indeed, data from clinical trials investigating various SGLT2 inhibitors have shown an increased risk of developing genital infections and, to a lesser extent, UTIs.49 In the empagliflozin Phase 3 studies published to date, there was an increased incidence of events consistent with UTIs in female patients treated with empagliflozin compared with placebo. Consistent with data from studies of other SGLT2 inhibitors, empagliflozin was also associated with an increased incidence of mild-to-moderate genital infections.
Practical considerations: Dosing and administration

Empagliflozin is recommended in the US and Europe for the treatment of adult patients with T2DM. In the US, empagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control, whereas in Europe empagliflozin may be used as monotherapy in patients with inadequate glycemic control despite diet and exercise alone and in whom metformin is considered inappropriate due to intolerance. In Europe, empagliflozin may be used in combination with other antihyperglycemic agents when these, together with diet and exercise, do not provide adequate glycemic control. The recommended starting dosage is 10 mg once daily as monotherapy or in combination with other antihyperglycemic agents, including insulin. In patients tolerating this dose (who have an eGFR ≥60 mL/min/1.73 m²) and who require tighter glycemic control, the dose may be increased to 25 mg once daily maximum. When empagliflozin is used in combination with a sulfonylurea or with insulin, a lower dose of the sulfonylurea or insulin may be considered to reduce the risk of hypoglycemia.

Empagliflozin should not be initiated in individuals with an eGFR of <60 mL/min per 1.73 m² or a creatinine clearance (CCr) of <60 mL/min (in Europe) or <45 mL/min per 1.73 m² (in the US). In Europe, in patients who are tolerating empagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m² or a CCr of <60 mL/min, the dose should be adjusted to, or maintained at, 10 mg once daily, with empagliflozin discontinued when the eGFR is persistently <45 mL/min/1.73 m² or CCr persistently below 45 mL/min. Empagliflozin should not be used in patients with end-stage renal disease or on dialysis.

Caution should be exercised when treating patients at risk of volume depletion, including patients with renal impairment, the elderly, and patients receiving antihypertensive therapy with a history of hypotension. Volume status should be assessed and, if necessary, corrected prior to treatment, and monitoring for hypotension should continue.

Conclusions

Experts have recommended SGLT2 inhibitors for use as monotherapy in T2DM where appropriate (i.e. in patients for whom metformin is not tolerated or is contraindicated), as well as a component of dual and triple therapy (including with basal insulin) in patients who would benefit from weight loss. Caution is recommended because longer-term experience with SGLT2 inhibitors is limited until the long-term CV outcome studies report. Nevertheless, SGLT2 inhibitors have the potential to make an important contribution to the treatment of T2DM, and their non-insulin-dependent mechanism of action makes them suitable for use in combination with any background glucose-lowering agent, including insulin. Because the glycemic effects of SGLT2 inhibitors are not dependent on insulin production, they may be considered for use at any stage of T2DM. Completion of Phase 3 programs and post-marketing studies will provide further data regarding the specific properties of each SGLT2 inhibitor, perhaps identifying differences between individual agents that may have implications for physicians and patients alike. The ongoing outcome studies for SGLT2 inhibitors (i.e. CANVAS, canagliflozin, NCT01032629; DECLARE-TIMI 58, dapagliflozin, NCT01730534; EMPA-REG OUTCOME, empagliflozin, NCT01131676; ertugliflozin, NCT01986881) will jointly provide CV safety data for over 30,000 patients, with the first data expected later in 2015. Based on the Phase 3 data available, empagliflozin appears to be a promising option for the treatment of patients with T2DM.

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