July 23rd

# ERG addendum: empagliflozin for the treatment of type 2 diabetes: a single technology assessment

Produced by Warwick Evidence

# 1 The EMPA-REG Pioglitazone trial

## 1.1 Overview of the trial

The EMPA-REG PIO trial assessed the efficacy, safety and tolerability of empagliflozin 10 mg or 25 mg once daily against placebo as an add-on therapy to pioglitazone alone or pioglitazone plus metformin in patients with type 2 diabetes mellitus (T2DM). The study is also published in full (Kovacs et al 2014 *Diabetes, Obesity and Metabolism* 16: 147–158, 2014). For convenience, we will refer this trial by an abbreviation ER Pio.

The baseline characteristics table relating to this trial has been reproduced below (Table 1).

**Table 1. Characteristics of patients in the ER Pio trial.**

| **Baseline characteristic** | **Treatment group** | | |
|---|---|---|---|
| **EMPA-REG PIO (N=498)** | **Placebo (n =165)** | **Empagliflozin 10mg (n=165)** | **Empagliflozin 25mg (n=168)** |
| ***Demographic data*** | | | |
| Age, mean (SD) [years] | 54.6 (10.5) | 54.7 (9.9) | 54.2 (8.9) |
| *Gender, (%* | | | |
| Male | (44.2 | 50.3 | 50.6 |
| Female | 55.8 | 49.7 | 49.4 |
| *Race, N (%)* | | | |
| Asian | 62.4% | 55.2% | 56.0% |
| Black/African American | 0.6% | 2.4% | 3.6% |
| White | 36.4% | 41.8% | 40.5% |
| eGFR (MDRD), mean (SD) [mL/min/1.73m$^2$] | 85.49 (20.07) | 84.26 (20.91) | 87.43 (24.36) |
| ***Baseline efficacy variables*** | | | |
| $HbA_{1C}$ [%], mean (SD) | 8.16 (0.92) | 8.07 (0.89) | 8.06 (0.82) |
| *Time since diagnosis of T2DM, %* | | | |
| ≤1 year | 11.5% | 17.6% | 10.1% |
| >1 to 5 years | 47.3 | 36.4 | 45.2 |
| >5 to 10 years | 25.5 | 27.3 | 28.6 |
| >10 years | 15.8 | 18.8 | 16.1 |
| Weight, mean (SD) [kg] | 78.1 (20.1) | 78.0 (19.1) | 78.9 (19.9) |
| BMI, mean (SD), [kg/m$^2$] | 29.32 (5.39) | 29.15 (5.59) | 29.08 (5.54) |
| SBP, mean (SD) [mmHg] | 125.7 (12.1) | 126.5 (13.7) | 125.9 (13.9) |

*Settings*

The trial was conducted in 69 centres in eight countries (Canada, China, Greece, India, Philippines, Thailand, Ukraine and USA). The mean number of patients in each centre was 7.2.

*Baseline characteristics*

The mean age of participants was about 54 years. Proportions of male and female participants were similar. Over half the participants were from the Asian countries (55.2% to 62.4%). Baseline

characteristics such as mean HbA1c level, weight, BMI, eGFR, SBP and FPG appeared to be well balanced across groups.

*Background treatments*

Patients continued their treatment of pioglitazone or pioglitazone + metformin throughout the trial. In addition, patient received diet and exercise advice according to local recommendations.

*Intervention and comparators*

Patients were randomised to empagliflozin 10 mg (n=165), or empagliflozin 25 mg (n=168) or placebo (n=165) as add-ons to background treatments.

*Outcomes*

The primary outcome measure of the trial was mean change in HbA1c at 24 weeks. Other outcome measures included mean change in FPG and body weight at 24 weeks.

## 1.2 Results

The ERG has summarised results reported in the MS, and where necessary from the full-text published paper.

### 1.2.1 Proportion of patients achieving HbA1c level of <7%

The findings for this outcome were not reported in the Boehringer submission. The ERG obtained the data from the published paper.

The proportion of patients achieving an HbA1c level of <7% was greater in the empagliflozin 25 mg (30%) group than in the empagliflozin 10 mg (23.8%) and placebo (7.7%) ($p<0.001$ for both empa groups). (Figure 1).

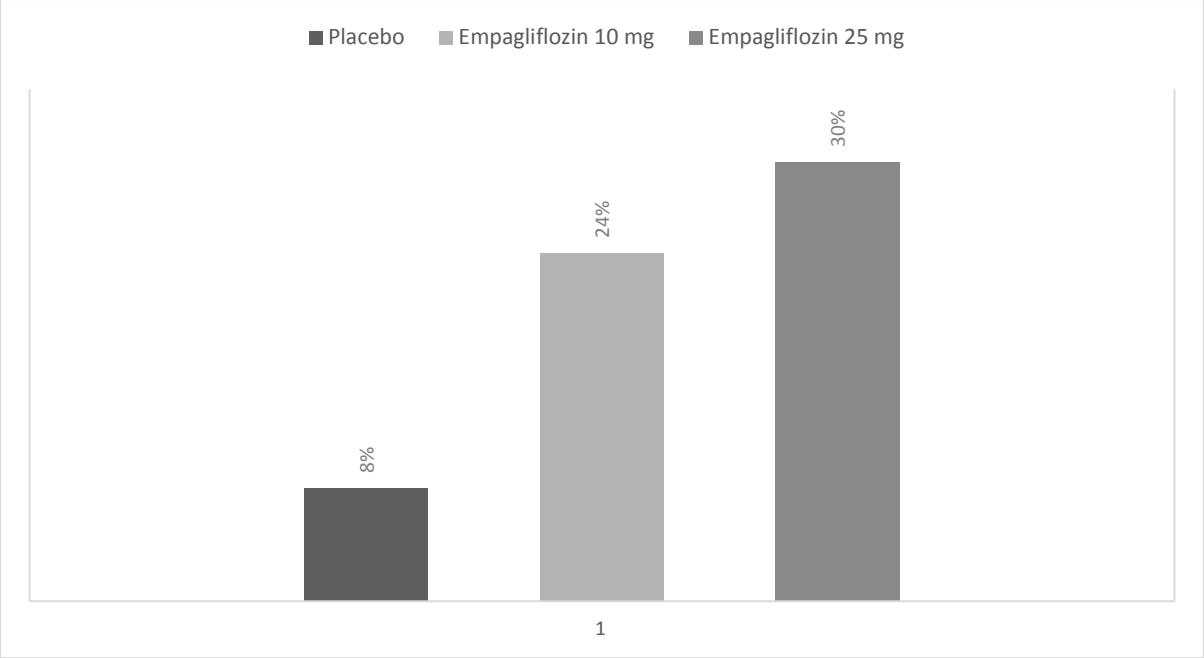



**Figure 1. Proportion of patients achieving an HbA1c level of <7%**

### 1.2.2 Mean change in HbA1c

Mean changes in HbA1c are reported in section 6.5 (table 16 and figure 14) of the MS. For convenience, the results are presented below (Table 2).

The adjusted mean reduction in HbA1c from baseline to week 24 was slightly greater with empagliflozin 25 mg (-0.72%) than with empagliflozin 10 mg (-0.59%). There was a small reduction on placebo (-0.11%).

**Table 2. Mean change in HbA1c (%)**

| Empagliflozin 10 mg | Empagliflozin 25 m | Placebo | Difference between groups |
|---|---|---|---|
| -0.59% SE 0.07 | -0.72 SE 0.07 | -0.11 SE 0.07 | **Empa 10 mg vs. placebo:** -0.48 SE 0.09% (95% CI: -0.66, -0.29; p<0.0001)<br>**Empa 25 mg vs. placebo:** -0.61 SE 0.09% (95% CI: -0.79 to -0.42; p<0.0001) |

### 1.2.3 Mean change in body weight

The results are reported in section 6.5 (table 16) of the MS.

At week 24, patients in the empagliflozin 10 mg group (-1.62 kg) lost slightly more weight than those in the empagliflozin 25 mg group (-1.47 kg), whereas in placebo group (+0.34 kg), patients gained weight (Table 3).

**Table 3. Mean change in body weight (kg)**

| Empagliflozin 10 mg | Empagliflozin 25 m | Placebo | Difference between groups |
|---|---|---|---|
| −1.62 SE 0.21 | −1.47 SE 0.21 | 0.34 SE 0.21 | **Empa 10 mg vs. placebo:** -−1.95 SE 0.30 (95% CI −2.64, −1.27; p<0.0001)<br>**Empa 25 mg vs. placebo:** -−1.81 SE 0.30 (95% CI −2.49, −1.13; p<0.0001) |

### 1.2.4 Mean change in systolic blood pressure (SBP)

At week 24, mean change in SBP was slightly greater with the higher dose of empagliflozin (-4.00 mmHg) than with the lower dose of empagliflozin (-3.14 mmHg) (Table 4). The SBP in the placebo group increased by a mean of 0.72 SE 0.85 mm Hg.

**Table 4. Mean change in SBP (mmHg)**

| Empagliflozin 10 mg | Empagliflozin 25 m | Placebo | Difference between groups |
|---|---|---|---|
| −3.14 SE 0.85 | −4.00 SE 0.84 | 0.72 SE 0.85 | **Empa 10 mg vs. placebo:** −3.86 SE 1.20 (95% CI −6.23, −1.50; p<0.0014)<br>**Empa 25 mg vs. placebo:** −4.73 SE 1.20 (95% CI −7.08, −2.37; p<0.0001 |

### 1.2.5 Changes in lipids

The changes in lipids were not reported in the MS but are given in the published paper, and summarised by the ERG in Table 5.

**Table 5. Changes in lipids (Source: Kovacs et al 2014)**

| | Empagliflozin 10 mg | Empagliflozin 25 m | Placebo | Difference between groups |
|---|---|---|---|---|
| **Total cholesterol, mmol/l** | 0.06 SD 0.06 | 0.06 SD 0.06 | 0.00 SD 0.06 | **Empa 10 mg vs. placebo:** 0.06 SD 0.09; p=0.489)<br>**Empa 25 mg vs. placebo:** 0.06 SD 0.09; p=0.480 |
| **HDL-cholesterol, mmol/l** | 0.04 SD 0.02 | 0.02 SD 0.02 | -0.01 SD 0 02 | **Empa 10 mg vs. placebo:** 0.06 SD 0.02; p=0.012<br>**Empa 25 mg vs. placebo:** 0.03 SD 0.02; p=0.186 |
| **LDL-cholesterol, mmol/l** | 0.09 SD 0.05 | 0.04 SD 0.05 | 0.00 SD 0.05 | **Empa 10 mg vs. placebo:** 0.09 SD 0.07; p=0.234<br>**Empa 25 mg vs. placebo:** 0.04 SD 0.07; p=0.576 |

| | | | | |
|---|---|---|---|---|
| **Triglycerides, mmol/l** | -0.18 SD 0.06 | 0.00 SD 0.06 | -0.01 SD 0.06 | **Empa 10 mg vs. placebo:** -0.17 SD 0.09; p=0.070<br>**Empa 25 mg vs. placebo:** 0.02 SD 0.09; p=0.842 |

## 1.3 Network meta-analysis (NMA) results

In the absence of head-to-head comparisons, Boehringer compared the efficacy of empagliflozin against other flozins and gliptins in patients failing pioglitazone monotherapy (24 ± 4 weeks) or pioglitazone plus metformin therapy (at 24 ± 4 weeks and 52 ± 4 weeks) using indirect comparison methods. Outcomes such as mean change in HbA1c, weight, SBP, hypoglycaemia and UTIs were compared.

The network diagrams (reported as figure 30 and 31 in the MS) for this analysis have been reproduced below (Figure 2 ).

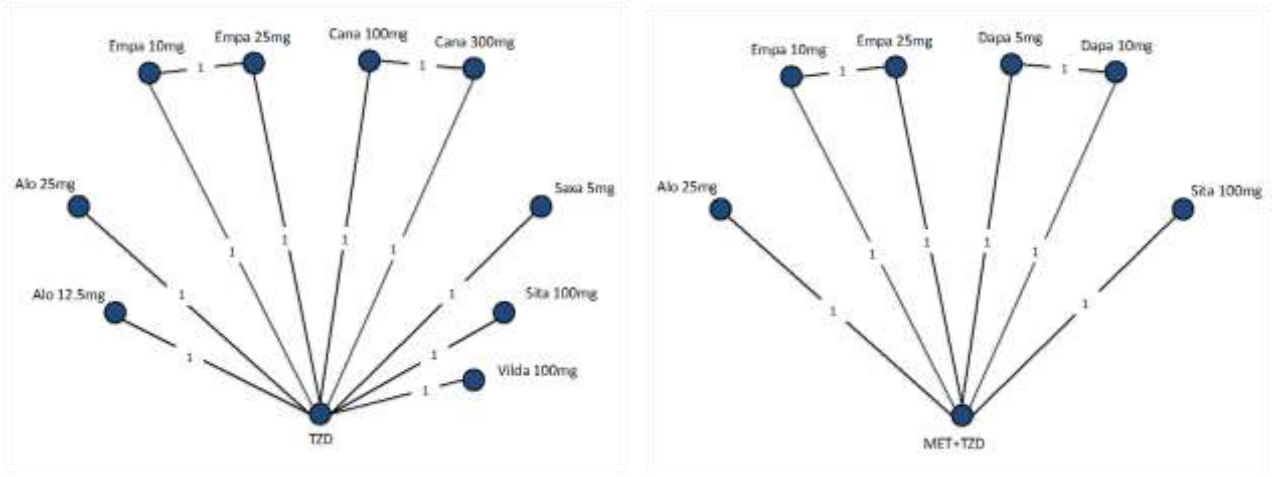



**Figure 2. MS NMA diagrams; left labelled as those failing TZDs monotherapy, right labelled as those failing TZD plus metformin therapy**

Table 30 of the MS gives details of studies included in the NMA.

These diagrams appear to be mislabelled, do not conform with the list of relevant studies (MS Table 30) and have errors. For those failing TZD monotherapy the diagram depicts a canagliflozin study but there are no canagliflozin trials in patients failing TZD monotherapy. Furthermore a sitagliptin study is indicated in both diagrams, but only a single dual arm study (Derosa et al 2010) is listed in Table 30.

In clarification some of these deficiencies were addressed. Figures 3 and 4 show the new NMA diagrams.

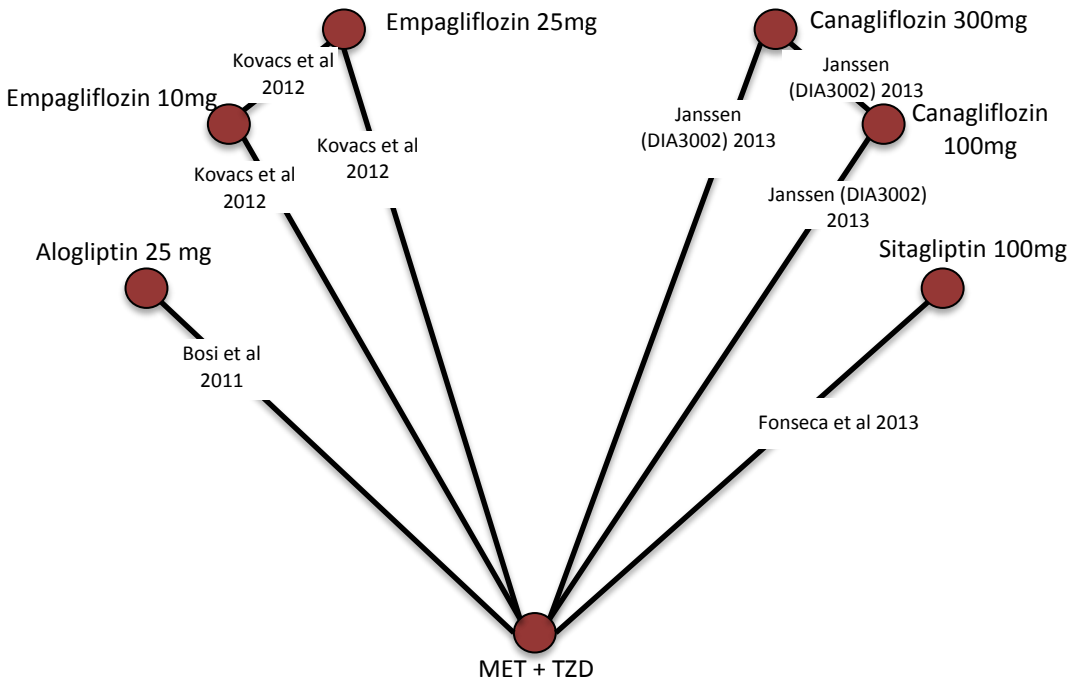



**Figure 3 clarification NMA diagram for add on therapy to TZD + metformin (note the Janssen DIA 3002 study has been mislabelled and should be labelled DIA 3012).**

In Figure 3, a new sitagliptin study has been introduced, namely Fonseca et al 2013. In this study patients on a background of metformin + TZD were randomised to placebo or sitagliptin; therefore this trial is appropriate for the NMA.

In Figure 4 below showing the new NMA diagram for flozins or gliptins used as add-on to TZD monotherapy the sitagliptin study is represented by Derosa et al 2010. This trial compared effectiveness of TZD + metformin with TZD + sitagliptin. Thus, in the control arm the patients received TZD and metformin, rather than TZD alone. The ERG do not agree that this trial is appropriate for this NMA and therefore believe that the sitagliptin results from this NMA are likely unreliable and should be disregarded.

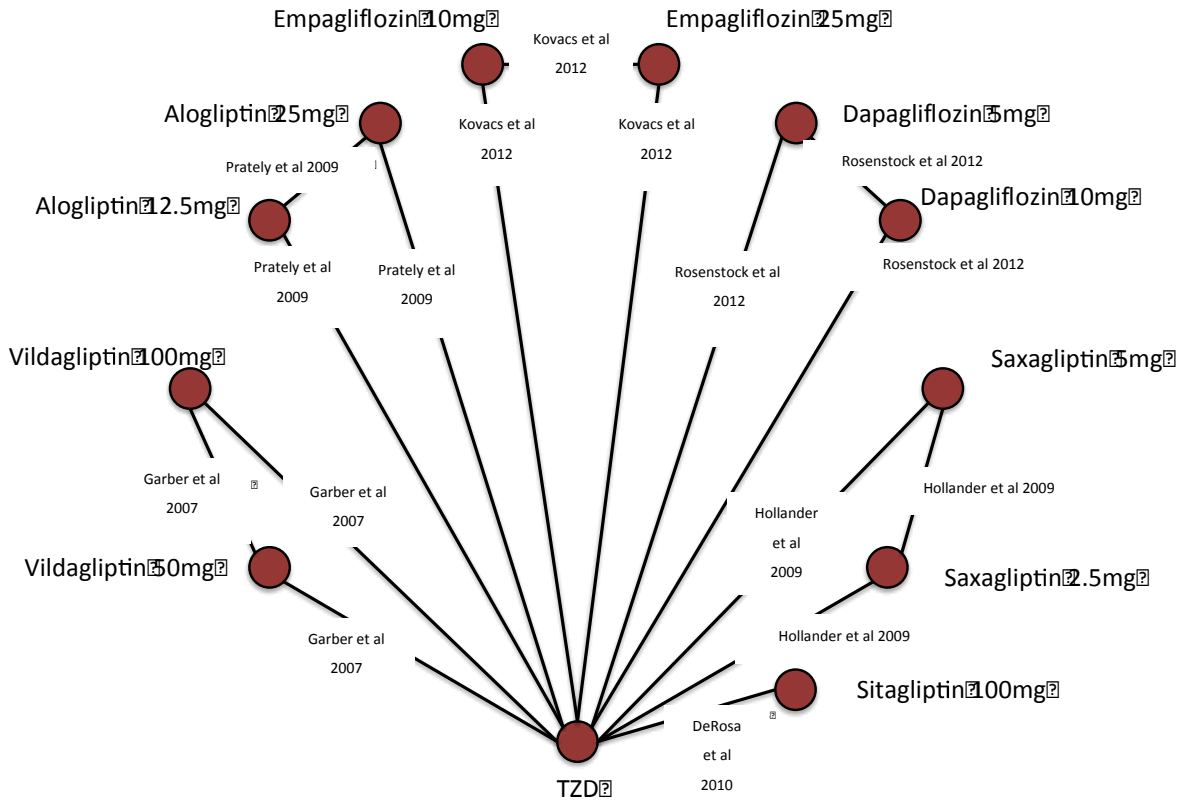
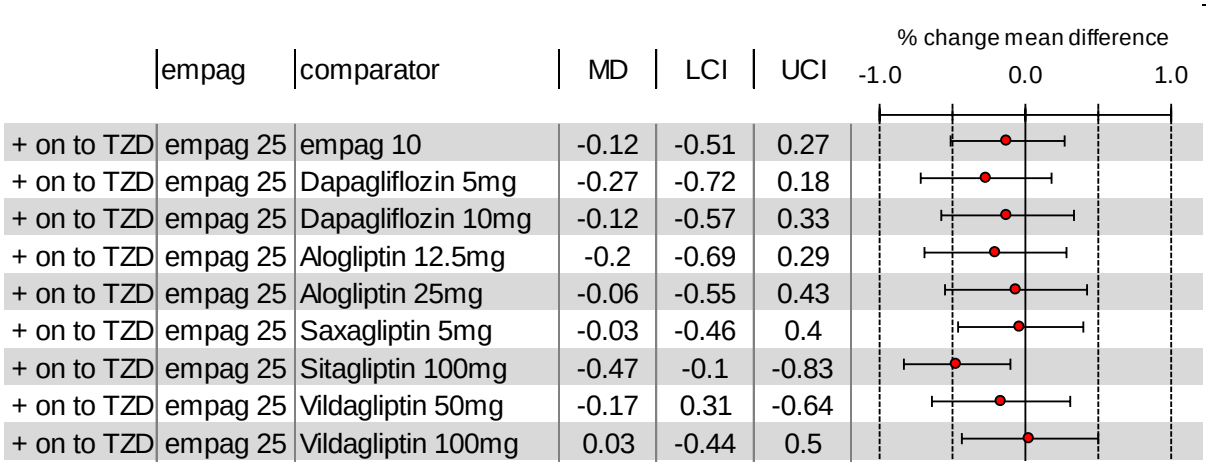



**Figure 4, clarification NMA diagram for add on therapy to TZD**

The NMA results are reported in clarification Appendix 2 tables 21 and 22. For convenience, the results against other flozins and sitagliptin have been reproduced below. Please note ERG did not have enough time to check the WinBUGS codes provided by the manufacturer with the original MS and codes were not supplied with clarifications.

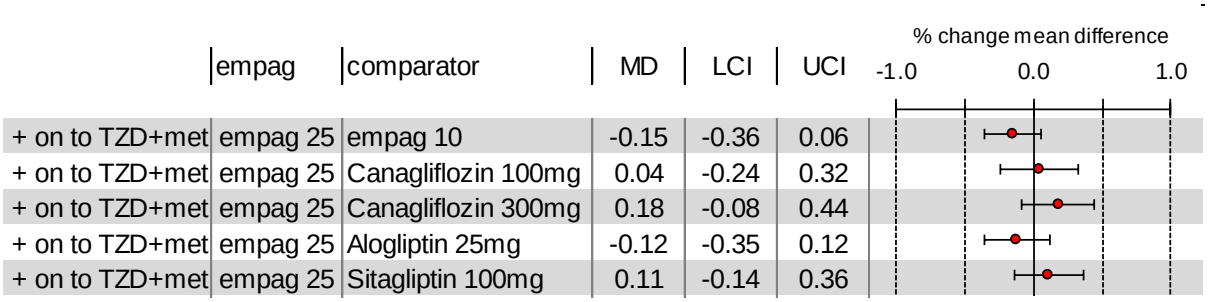



| | empag | comparator | MD | LCI | UCI |
|---|---|---|---|---|---|
| + on to TZD | empag 25 | empag 10 | -0.12 | -0.51 | 0.27 |
| + on to TZD | empag 25 | Dapagliflozin 5mg | -0.27 | -0.72 | 0.18 |
| + on to TZD | empag 25 | Dapagliflozin 10mg | -0.12 | -0.57 | 0.33 |
| + on to TZD | empag 25 | Alogliptin 12.5mg | -0.2 | -0.69 | 0.29 |
| + on to TZD | empag 25 | Alogliptin 25mg | -0.06 | -0.55 | 0.43 |
| + on to TZD | empag 25 | Saxagliptin 5mg | -0.03 | -0.46 | 0.4 |
| + on to TZD | empag 25 | Sitagliptin 100mg | -0.47 | -0.1 | -0.83 |
| + on to TZD | empag 25 | Vildagliptin 50mg | -0.17 | 0.31 | -0.64 |
| + on to TZD | empag 25 | Vildagliptin 100mg | 0.03 | -0.44 | 0.5 |

**Figure 5, NMA results for change in HbA1c (24 ±4 weeks data) in add on therapy to TZD**

Figure 5 summarises results for percent change in HbA1c at 24 weeks comparing the relative effect of empagliflozin 25 mg versus other therapies as add on to TZD. Differences are marginal except for the

comparison with sitagliptin, where empagliflozin appears significantly superior to 100mg sitagliptin in reducing HbA1c. However this depends on inclusion of the Derosa et al 2010 study which ERG considers to be inappropriate.




| | empag | comparator | MD | LCI | UCI |
|---|---|---|---|---|---|
| + on to TZD+met | empag 25 | empag 10 | -0.15 | -0.36 | 0.06 |
| + on to TZD+met | empag 25 | Canagliflozin 100mg | 0.04 | -0.24 | 0.32 |
| + on to TZD+met | empag 25 | Canagliflozin 300mg | 0.18 | -0.08 | 0.44 |
| + on to TZD+met | empag 25 | Alogliptin 25mg | -0.12 | -0.35 | 0.12 |
| + on to TZD+met | empag 25 | Sitagliptin 100mg | 0.11 | -0.14 | 0.36 |

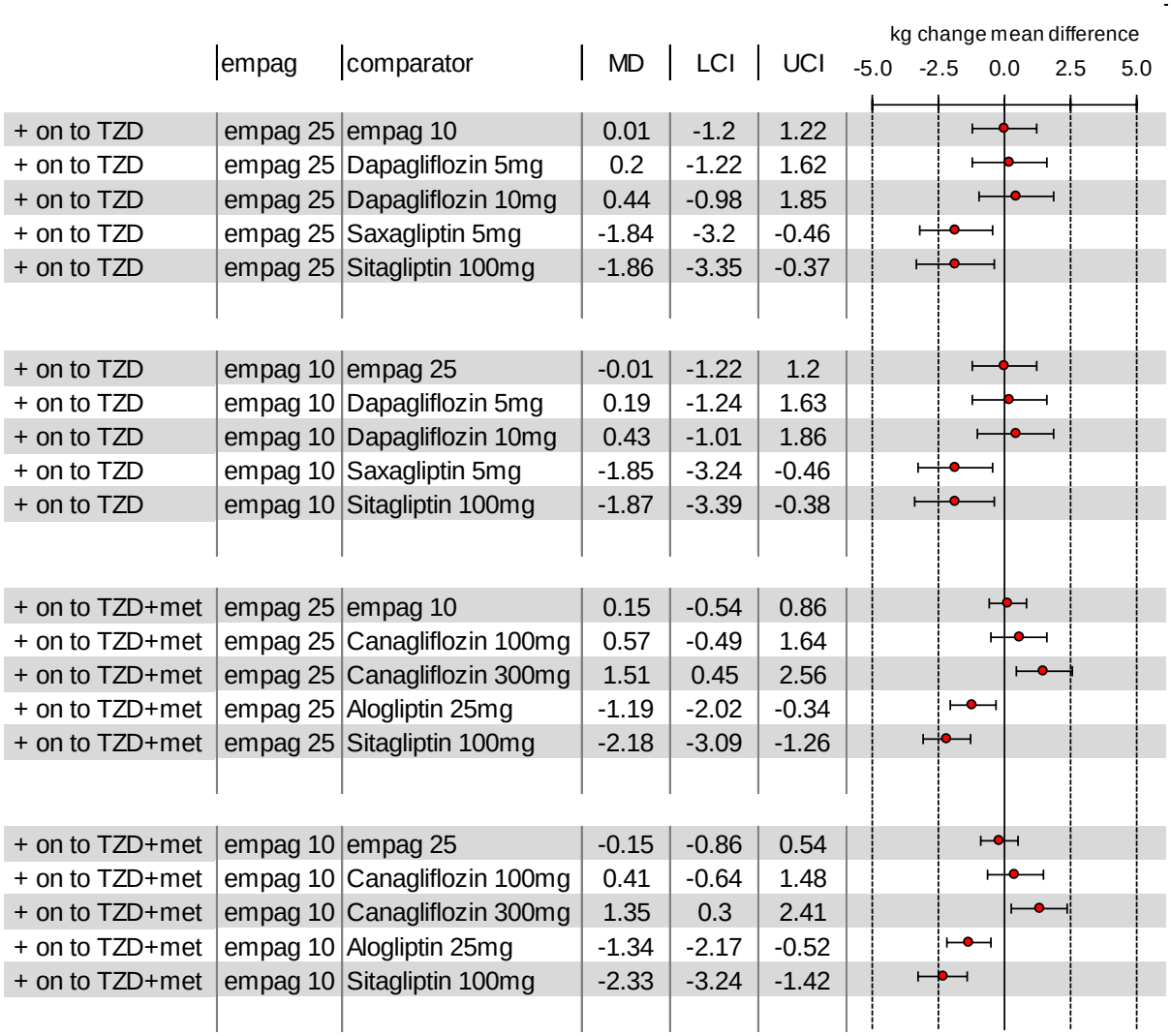
**Figure 6. NMA results for add on therapy to TZD + metformin for change in HbA1c (24 ±4 weeks data)**

**Error! Reference source not found.**Figure 6 summarises results for percent change in HbA1c at 24 weeks comparing the relative effect of empagliflozin 25 mg versus other therapies as add on to TZD and metformin. In all comparisons there is little difference between treatments.

The sitagliptin trial in this NMA is by Fonseca and colleagues. Their results for weight change are a little unusual because the sitagliptin group gained weight, and almost as much as the placebo arm (1.1 kg and 1.3 kg).

Both the Cochrane review of the gliptins and the HTA monograph that underpinned CG87 reported no weight gain with sitagliptin. Those reviews do not include recent trials. The ERG notes that in the DIA3006 trial of dual therapy with canagliflozin versus sitagliptin, those on sitagliptin lost 1.2 kg in weight (SHTAC ERG report table 23). The differences between canagliflozin 100 mg and 300 mg and sitagliptin were 2.5 kg and 3.0 kg.

In the triple therapy trial, DIA3015, patients on sitagliptin lost 0.3 kg, giving a difference from canagliflozin 300 mg of 2.8 kg. (SHTAC ERG report table 28). In the 52 week trial of sitagliptin versus canagliflozin reported by Schernthaner et al (Diabetes Care 2013), the sitagliptin group lost 0.1 kg. Several systematic reviews have reported weight change on the gliptins, and have reported no significant change (McIntosh 2011, Deacon 2012) or weight loss (Aroda 2012; Zhang 2014).




| | empag | comparator | MD | LCI | UCI |
|---|---|---|---|---|---|
| + on to TZD | empag 25 | empag 10 | 0.01 | -1.2 | 1.22 |
| + on to TZD | empag 25 | Dapagliflozin 5mg | 0.2 | -1.22 | 1.62 |
| + on to TZD | empag 25 | Dapagliflozin 10mg | 0.44 | -0.98 | 1.85 |
| + on to TZD | empag 25 | Saxagliptin 5mg | -1.84 | -3.2 | -0.46 |
| + on to TZD | empag 25 | Sitagliptin 100mg | -1.86 | -3.35 | -0.37 |
| + on to TZD | empag 10 | empag 25 | -0.01 | -1.22 | 1.2 |
| + on to TZD | empag 10 | Dapagliflozin 5mg | 0.19 | -1.24 | 1.63 |
| + on to TZD | empag 10 | Dapagliflozin 10mg | 0.43 | -1.01 | 1.86 |
| + on to TZD | empag 10 | Saxagliptin 5mg | -1.85 | -3.24 | -0.46 |
| + on to TZD | empag 10 | Sitagliptin 100mg | -1.87 | -3.39 | -0.38 |
| + on to TZD+met | empag 25 | empag 10 | 0.15 | -0.54 | 0.86 |
| + on to TZD+met | empag 25 | Canagliflozin 100mg | 0.57 | -0.49 | 1.64 |
| + on to TZD+met | empag 25 | Canagliflozin 300mg | 1.51 | 0.45 | 2.56 |
| + on to TZD+met | empag 25 | Alogliptin 25mg | -1.19 | -2.02 | -0.34 |
| + on to TZD+met | empag 25 | Sitagliptin 100mg | -2.18 | -3.09 | -1.26 |
| + on to TZD+met | empag 10 | empag 25 | -0.15 | -0.86 | 0.54 |
| + on to TZD+met | empag 10 | Canagliflozin 100mg | 0.41 | -0.64 | 1.48 |
| + on to TZD+met | empag 10 | Canagliflozin 300mg | 1.35 | 0.3 | 2.41 |
| + on to TZD+met | empag 10 | Alogliptin 25mg | -1.34 | -2.17 | -0.52 |
| + on to TZD+met | empag 10 | Sitagliptin 100mg | -2.33 | -3.24 | -1.42 |

**Figure 7. NMA results for mean difference in change in body weight at 24 weeks**

Figure 7 summarises body weight changes comparing empagliflozin 25mg versus other therapies. In dual therapy (add on to TZD) there is no difference between flozins and empagliflozin is significantly superior relative to the two gliptins (saxagliptin and sitagliptin). In triple therapy (add on to TZD + metformin), empagliflozin is significantly inferior to canagliflozin 300mg but significantly superior to both gliptins. NMA results relative to empagliflozin at 10 mg were very similar since there was almost no difference between 10 mg and 25 mg doses

| | empag | comparator | MD | LCI | UCI |
|---|---|---|---|---|---|
| + on to TZD | empag 25 | Empagliflozin 10mg | -4.32 | -9.08 | 0.55 |
| + on to TZD | empag 25 | Dapagliflozin 5mg | -4.85 | -10.65 | 1.08 |
| + on to TZD | empag 25 | Dapagliflozin 10mg | -2.24 | -8.05 | 3.71 |
| | | | | | |
| + on to TZD+met | empag 25 | Empagliflozin 10mg | 0.18 | -2.54 | 2.82 |
| + on to TZD+met | empag 25 | Canagliflozin 100mg | 0.05 | -3.93 | 4.02 |
| + on to TZD+met | empag 25 | Canagliflozin 300mg | -0.5 | -4.53 | 3.48 |

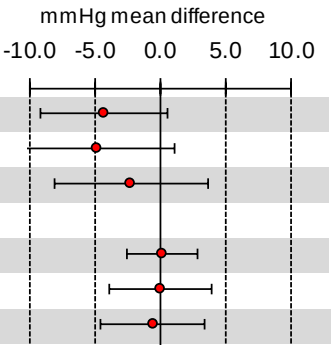



**Figure 8, NMA results for mean difference in change in SBP at 24 weeks**

Figure 8 summarises NMA results reported for change in blood pressure. In add on to TZD + metformin there were no differences between empagliflozin and canagliflozin. In add on to TZD alone empagliflozin appeared more effective at 25 mg than 10 mg and superior to a low dose of dapagliflozin, but all CIs overlapped with no difference, and evidence from only two studies was available.

## 1.4 Adverse events

The summary of adverse events in the ER Pio trial was reported in table 40 of the MS, which has been reproduced below (Table 6).

Slightly more patients in the placebo (19%) and empagliflozin 25 mg (18.5%) had drug related AEs than in the empagliflozin 10 mg group (14.5%). Few patients in all treatment groups discontinued the study due to AEs (2.4% placebo; 1.2% empa 10 mg and 3.0% empa 25 mg). Serious events (details not given in the MS) were similar across groups (~4%). The frequencies of urinary tract infections (UTIs) were similar in placebo (16.4%) and empagliflozin 10 mg (17%) and slightly lower in the empagliflozin 25 mg group (12%). There are no other details in the MS however the published paper reported that UTIs were more common in female patients and were mild to moderate in intensity in almost 97% of cases. There were two serious UTIs (one in each of placebo and empagliflozin 10 mg group), which led to discontinuation of those patients from the study. More patients in the empagliflozin 10 mg (8.5%) than in the empagliflozin 25 mg (3.6%) and placebo (2.4%) group were diagnosed with genital tract infection (GTI). GTIs were more common in females and most were mild to moderate in intensity. There were no discontinuations from the trial due to GTIs.

In the trial, few patients developed AEs specific to pioglitazone such as oedema, heart failure and fractures. Four patients on placebo, two on empagliflozin 10 mg and one on empagliflozin 25 mg had fractures.

Note that in the empagliflozin trials, hypoglycaemia was defined as <3.9mmol/l as per the ADA which excludes some of the normal range of plasma glucose.

**Table 6. Summary of adverse events in ER Pio trial**

| | Placebo (n=165) | Empagliflozin 10mg (n=165) | Empagliflozin 25mg (n=168) |
|---|---|---|---|
| One or more drug-related AE(s), n (%) | 31 (18.8) | 24 (14.5) | 31 (18.5) |
| AEs leading to discontinuation, n (%) | 4 (2.4) | 2 (1.2) | 5 (3.0) |
| One or more serious AE(s), n (%) | 7 (4.2) | 7 (4.2) | 6 (3.6) |
| Deaths, n (%) | 1 (0.6) | 0 (0.0) | 2 (1.2) |
| ***AEs with frequency of ≥5% in any randomised group*** | | | |
| UTI, n (%) | 18 (10.9) | 24 (14.5) | 18 (10.7) |
| Hyperglycaemia, n (%) | 26 (15.8) | 8 (4.8) | 4 (2.4) |
| Dyslipidemia, n (%) | 17 (10.3) | 18 (10.9) | 12 (7.1) |
| Hypertension, n (%) | 9 (5.5) | 3 (1.8) | 2 (1.2) |
| | | | |
| Hypoglycaemia, n (%) | 3 (1.8) | 2 (1.2) | 4 (2.4) |
| Events requiring assistance, n (%) | 0 | 0 | 0 |
| Genital infection, n (%) | 4 (2.4) | 14 (8.5) | 6 (3.6) |
| Fractures, n (%) | 4 ( 2.4) | 2 (1.2) | 1 (0.6) |

**NMA results reported for adverse events in add on therapies to TZD + metformin**

With regard to safety outcomes no results were reported for GTIs. Relative to TZD + placebo, empagliflozin at 10 and 25 mg increased UTI risk by about 6.6 and 9 fold respectively (6.57, credible CI 0.88 to 66.34, and 9.0, credible CI 1.37 to 75.85). Relative risk results (empagliflozin 25mg versus other treatments) reported for UTIs at 24 weeks are summarised in Table 7.

**Table 7 RR of UTIs at 24 weeks**

| NMA | Treatment | | Comparator | RR | LCI | UCI |
|---|---|---|---|---|---|---|
| + on toTZD | Empagliflozin 25mg | v. | Empagliflozin 10mg | 6.570 | 0.880 | 66.340 |
| + on toTZD | Empagliflozin 25mg | v. | Dapagliflozin 5mg | 9.091 | 0.083 | >100 |
| + on toTZD | Empagliflozin 25mg | v. | Dapagliflozin 10mg | 10.000 | 0.085 | >100 |
| + on toTZD | Empagliflozin 25mg | v. | Alogliptin 12.5mg | 10.000 | 0.082 | >100 |
| + on toTZD | Empagliflozin 25mg | v. | Alogliptin 25mg | 10.000 | 0.086 | >100 |
| + on toTZD | Empagliflozin 25mg | v. | Saxagliptin 5mg | 9.091 | 1.190 | 100.000 |
| + on toTZD | Empagliflozin 25mg | v. | Sitagliptin 100mg | 9.091 | 0.084 | >100 |
| + on toTZD | Empagliflozin 25mg | v. | Vildagliptin 50mg | 5.263 | 0.377 | 100.000 |

| | | | | | | |
|---|---|---|---|---|---|---|
| + on toTZD | Empagliflozin 25mg | v. | Vildagliptin 100mg | 2.000 | 0.189 | 25.000 |
| | | | | | | |
| + on toTZD +metformin | Empagliflozin 25mg | v. | Empagliflozin 10mg | 0.600 | 0.280 | 1.110 |
| + on toTZD +metformin | Empagliflozin 25mg | v. | Canagliflozin 100mg | 5.556 | 0.046 | >100 |
| + on toTZD +metformin | Empagliflozin 25mg | v. | Canagliflozin 300mg | 5.263 | 0.043 | >100 |
| + on toTZD +metformin | Empagliflozin 25mg | v. | Alogliptin 25mg | 0.441 | 0.171 | 0.980 |

The RR credible intervals for all comparisons were wide. In add on to TZD treatments the risk of UTI was about ten times greater for empagliflozin than for all other treatments, however the only comparison for which credible intervals did not traverse unity was from the comparison with saxagliptin 5mg. In add on to TZD plus metformin empagliflozin incurred greater risk of UTI than canagliflozin but, surprisingly, less than alogliptin.

Few results were reported for the risk of hypoglycaemia in add on to TZD. The lack of events during follow up resulted in very wide credible intervals. Relative to TZD + placebo, empagliflozin at 10 and 25mg both increased hypoglycaemia risk by ~ 2 to 3 fold (1.9, credible CI <0.01 to 0.88 to 44.93, and 1.87, credible CI <0.01 to 43.89); relative to vildagliptin empagliflozin at each dosage increased risk of hypoglycaemia about 25 times but with very wide credible intervals (e.g. RR 25, CI 0.036 to >100). Very similar results were reported for non-severe hypoglycaemic risk. These results are inconclusive. In add on to TZD+ metformin empagliflozin at 10mg reduced risk of hypoglycaemia and empagliflozin at 25mg increased risk of hypoglycaemia relative to TZD + metformin (RR 0.63, CI 0.11 to 2.63, and 1.51, CI 0.44 to 5.85 respectively). Again these results have little meaning because of the sparcity of events and much longer follow up or larger cohorts are required. Similar inconclusive results were reported for non-severe hypoglycaemia. The reported results comparing empagliflozin verus other treatments in add on to TZD + metformin are summarised in Table 8.

**Table 8 relative risk of hypoglycaemia in add on therapy to TZD + metformin**

| **Hypoglycaemia, RR (95% credible interval)** | | | | | |
|---|---|---|---|---|---|
| Intervention | | Comparator | RR | LCI | UCI |
| Empagliflozin 25mg | v. | Empagliflozin 10mg | 2.40 | 0.74 | 13.10 |
| Empagliflozin 25mg | v. | Canagliflozin 100mg | 14.29 | 0.05 | >100 |
| Empagliflozin 25mg | v. | Canagliflozin 300mg | 14.29 | 0.05 | >100 |
| Empagliflozin 25mg | v. | Alogliptin 25mg | 0.66 | 0.19 | 2.27 |
| Empagliflozin 25mg | v. | Sitagliptin 100mg | 1.11 | 0.32 | 5.00 |
| Empagliflozin 10mg | v. | Alogliptin 25mg | 0.27 | 0.04 | 1.15 |
| **Hypoglycaemia (non-severe), RR (95% credible interval)** | | | | | |
| Intervention | | Comparator | RR | LCI | UCI |
| Empagliflozin 25mg | v. | Empagliflozin 10mg | 3.18 | 0.75 | 23.82 |
| Empagliflozin 25mg | v. | Canagliflozin 100mg | 20.00 | 0.02 | >100 |

| | | | | | |
|---|---|---|---|---|---|
| Empagliflozin 25mg | v. | Canagliflozin 300mg | 20.00 | 0.02 | >100 |
| Empagliflozin 25mg | v. | Alogliptin 25mg | 0.61 | 0.14 | 2.78 |
| Empagliflozin 10mg | v. | Alogliptin 25mg | 1.14 | 0.02 | >100 |

In general empagliflozin tends to be associated with increased risk of hypoglycaemia relative to other flozins and gliptins for which there was any evidence in this indication. The 95% credible intervals are far too wide to draw firm conclusions.

### 1.5 Cost-effectiveness

The ERG does not regard the results from the ECEM model as reliable, but for completeness we reproduce some of the Boehringer results here.

In triple therapy, empagliflozin 10 mg was compared with sitagliptin 100mg, both in combination with metformin and pioglitazone. Lifetime difference in QALYs was 0.016 more with empagliflozin and lifetime difference in costs was £540 more with empagliflozin, giving an ICER of £41,538. However with such trivial differences in costs and QALYs, any such ICER would have very wide confidence intervals.

When the 25 mg doses of empagliflozin was compared with sitagliptin, the cost difference was £183 and the QALY difference 0.032, giving an ICER of £5719.
The caveat about the weight gain with sitagliptin reported by the NMA should be borne in mind.

## 2 EMPA-REG H2H SU trial: empagliflozin 25mg versus glimepiride

In the ERG, we excluded the ER-SU trial because we regard sulphonylureas as precursors to flozins, not comparators. The SUs are old cheap drugs with decades of experience in millions of patients, and so have known safety records. The flozins are new and about 35 times the price of sulphonylureas (see ERG report figure 2). They may have adverse effects not yet known. These could be class effects or idiosyncratic effects of individual drugs. There are examples of serious adverse effects that only occur with one drug in a class: sclerosing peritonitis was only seen with one beta-blocker, practolol, and liver problems with only one TZD, troglitazone.

However, NICE requested that it be included and an account of the SU trial follows.

## 2.1 Overview of the study

ER SU was a two year RCT assessing the efficacy, safety and tolerability of empagliflozin 25 mg once daily against glimepiride 1 to 4 mg once daily in patients with T2DM inadequately controlled with metformin. Patients completing the initial two year phase of the trial were eligible to participate in a 2 year double-blind extension study. A protocol of the study is available as a full-text article (Ridderstale et al 2013; Cardiovascular Diabetology 2013;12:129). A peer-reviewed paper has been published very recently but we have not yet been able to access this article (Ridderstale et al 2014; The Lancet Diabetes and Endocrinology 2014; Jun 16. [Epub ahead of print]. For convenience, the trial has been referred as 'ER SU' throughout this section.

The baseline characteristics of the study were given in table 11 of the MS, and reproduced below in Table 9.

**Table 9. Baseline characteristics of ER SU trial**

| **Baseline characteristic** | **Treatment group** | |
|---|---|---|
| **1245.28 (EMPA-REG H2H-SU) (N=1,545)** | **Empagliflozin 25mg (n=765)** | **Glimepiride 1-4mg (n=780)** |
| ***Demographic data*** | | |
| Age, mean (SD) [years] | 56.2 (10.3) | 55.7 (10.4) |
| *Gender, N (%)* | | |
| Male | 432 (56.5) | 421 (54.0) |
| Female | 333 (43.5) | 359 (46.0) |
| *Race, N (%)* | | |
| American Indian/Alaska native | 0 | 0 |
| Asian | 254 (33.2) | 253 (32.4) |
| Black/African American | 12 (1.6) | 8 (1.0) |
| Hawaiian/pacific Islander | 1 (0.1) | 0 |
| White | 498 (65.1) | 519 (66.5) |
| eGFR (MDRD), mean (SD) [mL/min/1.73m$^2$] | 87.94 (16.82) | 88.11 (17.85) |
| ***Baseline efficacy variables*** | | |
| $HbA_{1C}$, mean (SD) [%] | 7.92 (0.81) | 7.92 (0.86) |
| *Time since diagnosis of T2DM, N (%)* | | |
| ≤1 year | 79 (10.3) | 93 (11.9) |
| >1 to 5 years | 341 (44.6) | 336 (43.1) |
| >5 to 10 years | 214 (28.0) | 211 (27.1) |
| >10 years | 131 (17.1) | 140 (17.9) |
| Weight, mean (SD) [kg] | 82.52 (19.16) | 83.03 (19.22) |
| BMI, mean (SD), [kg/m$^2$] | 29.95 (5.28) | 30.27 (5.3) |

| Baseline characteristic | Treatment group | |
|---|---|---|
| SBP, mean (SD) [mmHg] | 133.4 (15.9) | 133.5 (16.0) |
| DBP, mean (SD) [mmHg] | 79.5 (9.6) | 79.4 (9.2) |

*Settings*

The trial was conducted in 181 centres in 23 countries across Africa, Asia, Europe and North America (details of countries not given in the MS). Mean number of patients per centre 8.5.

*Baseline characteristics*

All the baseline characteristics appeared to be similar across treatment groups.

*Background treatments*

All patients were also receiving metformin.

*Interventions and comparators*

A total of 1549 patients were randomised to empagliflozin 25 mg (n=769) or glimepiride (n=780).

*Outcomes*

The primary outcome was change in HbA1c level from baseline to 104 weeks. Other outcomes included change in body weight, confirmed hypoglycaemic events, and change in systolic and diastolic blood pressure at 104 weeks.

## 2.2 Results

The results are reported in section 6.5 (pages 118 to 122) in the MS. The manufacturer did not report the proportions of patients achieving an HbA1c level target of <7% in the MS.

### 2.2.1 Mean change in HbA1c

The mean changes in HbA1c are reported in table 19 and figure 17. The figure demonstrating mean change in HbA1c over time has been reproduced below (Figure 9). At 104 weeks, both empagliflozin (-0.66%) and glimepiride (-0.55%) led to reductions in HbA1c. The difference between the two was statistically significant (-0.11, 97.5% CI -0.20 to -0.01, p<0.0001) but clinically unimportant. The reduction in HbA1c was initially greater with glimepiride but over time empagliflozin produced a slightly lower HbA1c level than glimepiride. The long-term "drift" upwards of HbA1c varies amongst drugs, including amongst SUs.

**Table 10. Mean change in HbA1c (%)**

| Empagliflozin 25 mg | Glimepiride | Difference between groups |
|---|---|---|
| -0.66 SE 0.03% | -0.55 SE 0.03% | -0.11 SE 0.04% (97.5% CI: -0.20 to -0.01; p<0.0001 for non-inferiority |

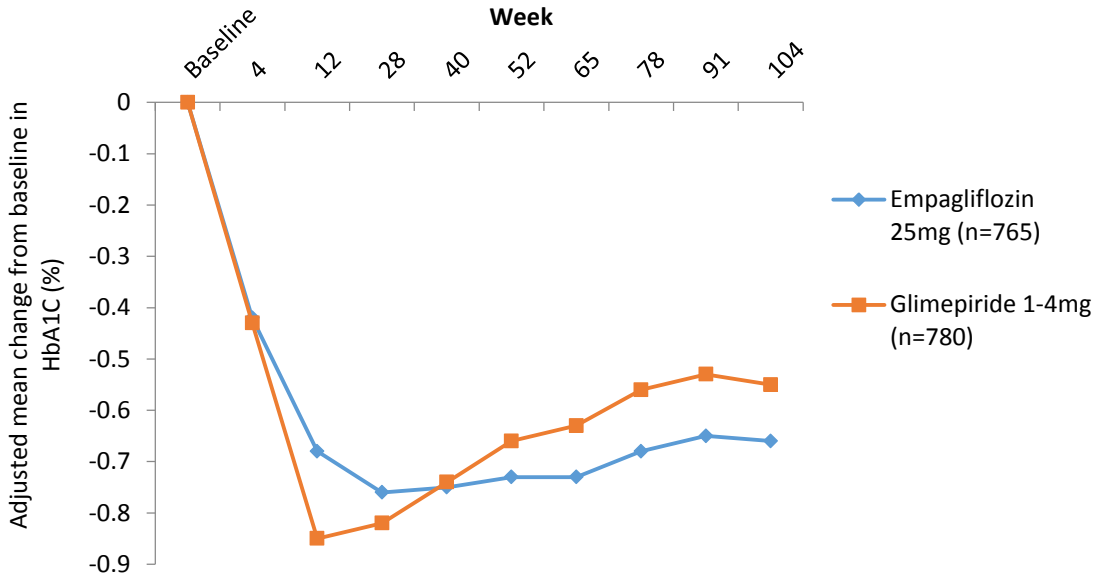



**Figure 9. Adjusted mean change from baseline in HbA1c (%) results overtime in ER SU trial**

### 2.2.2 Mean change in body weight

At 104 weeks, patients in empagliflozin had lost up to 3 kg weight while those in the glimepiride group had gained up to 1.3 kg. The difference between the two was statistically significant – see table.

**Table 11. Mean change in body weight (kg)**

| Empagliflozin 25 mg | Glimepiride | Difference between groups |
|---|---|---|
| -3.12 SE 0.13kg | 1.34 SE 0.13kg | -4.46 SE 0.18kg (97.5% CI: -4.87 to -4.05; p<0.0001) |

### 2.2.3 Mean change in SBP

At 104 weeks, SBP of patients in the empagliflozin group had decreased by 3 mmHg but had increased by 2.5mmHg in the glimepiride group, a difference that was statistically significant (Table 12).

**Table 12. Mean change in SBP (mmHg)**

| Empagliflozin 25 mg | Glimepiride | Difference between groups |
|---|---|---|
| -3.1 SE 0.4mmHg | 2.5 SE 0.4mmHg | -5.6 SE 0.6 (97.5% CI: -7.04 to -4.2; p<0.0001) |

### 2.2.4 Adverse events

The summary of AEs was given in table 43 of the MS. For convenience, some data from the table has been reproduced below. (In the table in the MS, the glimepiride group has been labelled as 'placebo'.)

**Table 13 Adverse events based on MS table 43**

| | Empagliflozin 25mg (n=765) | Glimepiride (n=780) |
|---|---|---|
| One or more drug-related AE(s), n (%) | 190 (24.8) | 252 (32.3) |
| AEs leading to discontinuation, n (%) | 39 (5.1) | 34 (4.4) |
| One or more serious AE(s), n (%) | 119 (15.6) | 89 (11.4) |
| Deaths, n (%) | 5 (0.7) | 5 (0.6) |
| UTI, n (%) | 95 (12.4) | 99 (12.7) |
| Hypoglycaemia, n (%) | 32 (4.2) | 197 (25.3) |
| Dyslipidemia, n (%) | 41 (5.4) | 39 (5.0) |
| Hypertension, n (%) | 41 (5.4) | 77 (9.9) |
| Genital infections n (%) | 90 (11.8) | 17 (2.2) |

More patients in the glimepiride group reported drug-related AEs (32.3% vs. 24.8%). The numbers of patients discontinuing the study were similar (5.1% in empa; 4.4% in glim). Serious events (details of events not given – only reported that 10 cases were fatal, five in each group) were reported by more patients in the empagliflozin group (15.6% vs. 11.4%).

As expected, more patients in the glimepiride group reported hypoglycaemia (24.2% vs. 2.5%). The intensity of hypoglycaemia was not reported. UTIs appeared to be similar in the two groups (13.7% in empa vs. 13.1% in glim). Other details of UTIs for e.g. by gender, intensity, need for discontinuation were not provided. More patients in the empagliflozin group reported genital tract infection (GTI) (11.8% vs. 2.2%).

The sulphonylurea used was glimepiride. There have been reports that hypoglycaemia is less frequent with gliclazide, and that time to secondary SU failure is longer with gliclazide than with glimepiride (Satoh et al 2005).

Hypoglycaemia is common with SUs, but the risk should not be over-estimated. A recent very large meta-analysis (Monami et al 2014) of hypoglycaemia risk with SUs (69 RCTs, over 40,000 patients, mean duration 70 weeks) found that severe hypos occurred in 1.2%, and at least one hypo occurred in 17% of patients. However in 45 of the 69 trials, there were no severe hypos.