**EMPAGLIFLOZIN IN COMBINATION WITH ORAL AGENTS IN YOUNG AND OVERWEIGHT/OBESE TYPE 2 DIABETES MELLITUS PATIENTS: A POOLED ANALYSIS OF THREE RANDOMISED TRIALS.**

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**ABSTRACT**

**Aims:** This analysis aimed to evaluate the efficacy and safety of empagliflozin in combination therapy in patients <65, overweight/obese, and with uncontrolled T2DM.

**Methods:** Pooled analysis from three randomised phase III trials, in patients aged <65 years, with BMI 25-35 kg/m2, and HbA1c ≥8% at baseline. Patients (N=439) were randomized to placebo (n=138), empagliflozin 10 mg (n=160), or empagliflozin 25 mg (n=141) once daily for 24 weeks as add-on to metformin, to metformin plus sulfonylurea, or to pioglitazone ± metformin.

**Results:** At week 24, adjusted mean (SE) changes from baseline in HbA1c were -0.19% (0.07) for placebo vs. -1.10% (0.07) and -1.10% (0.07) for empagliflozin 10 and 25 mg, respectively (both p<0.001). Adjusted mean (SE) changes from baseline in weight were -0.33 kg (0.21) for placebo vs. -1.94 kg (0.19) and -2.14 kg (0.20) for empagliflozin 10 and 25 mg, respectively (both p<0.001). Adverse events (AEs) were reported in 57.2% on placebo, 64.4% on empagliflozin 10 mg and 59.6% on empagliflozin 25 mg. Genital infection AEs were reported in 1.4% on placebo, 3.8% on empagliflozin 10 mg, and 5.0% on empagliflozin 25 mg.

**Conclusions:** In this specific population empagliflozin in combination therapy with other oral agents, significantly reduced HbA1c and body weight and was well tolerated.

**Keywords**: Oral agents, Type 2 diabetes, Obesity, Therapy, Glycemic control, Hba1c.

**1. INTRODUCTION**

The rise in the prevalence of type 2 diabetes mellitus (T2DM) observed over the last few decades has been accompanied by an increasingly frequent occurrence of this condition in younger adults (Hillier and Pedula 2001, 2003; Pettitt et al. 2014). Moreover, studies have found that T2DM patients under 65 have poorer blood glucose control than older patients.(Berkowitz et al. 2013; Vinagre et al. 2012) As a consequence of the earlier onset of the condition, they may be more exposed to hyperglycaemic states (Constantino et al. 2013) and proper control through early diagnosis and treatment is, therefore, crucial in reducing potential long-term complications (Holman et al. 2008).

Obesity is a risk factor that plays an important role in the development of T2DM (ADA 2015). In a study evaluating the prevalence of overweight/obesity in patients with T2DM, over 85% had a body mass index (BMI) greater than 25 kg/m2. These patients also had poorer blood glucose control (Daousi et al. 2006). In view of the benefits of modest weight reductions on the control of T2DM, it is essential to focus the treatment of T2DM and obesity under the same premise (Klein et al. 2004), although reducing weight can be difficult in these patients because of comorbidities, the difficulty of making lifestyle changes or even the glucose-lowering treatment itself; which is frequently associated with weight gain (Pi-Sunyer 2005). Similarly, an inverse linear relationship has been reported between BMI and the age at T2DM diagnosis(Hillier and Pedula 2001, 2003; Pettitt et al. 2014), indicating the importance of weight control in younger patients.

Empagliflozin and other sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new therapeutic option for T2DM treatment, particularly in overweight/obese patients. Their unique mechanism of action, independent of beta-cell function and insulin resistance, inhibits renal glucose reabsorption, thus, eliminating excess glucose in the urine, resulting in significant HbA1c reductions (DeFronzo et al. 2012). Moreover, treatment with empagliflozin is associated with moderate and sustained reductions in body weight and systolic blood pressure (SBP), possibly due to osmotic diuresis caused by glucose and loss of calories resulting from its elimination (Kovacs et al. 2014).

This analysis was carried out in response to the increasingly early onset of T2DM and its strong relationship with overweight and obesity (Hillier and Pedula 2001, 2003; Pettitt et al. 2014). The objective was to study the efficacy and safety of empagliflozin in participants younger than 65 years, with overweight or class I obesity (BMI 25-35 kg/m2), and with poorly controlled T2DM (HbA1c ≥64 mmol/mol (8%)) at baseline.

**2. Subjects**

The patients included in this analysis met all the inclusion and exclusion criteria previously reported in the respective clinical trials.(Haring et al. 2014; Haring et al. 2013; Kovacs et al. 2014) In general terms, the inclusion criteria stipulated patients aged 18 or over, with uncontrolled T2DM (HbA1c 7-10% (53-86 mmol/mol)); despite diet, exercise, and a stable regimen (more than 12 weeks) of anti-diabetes treatment, and a BMI of 45 kg/m2 or less. The main exclusion criteria were the presence of uncontrolled fasting hyperglycaemia (fasting blood glucose > 239.6 mg/dl (13.3 mmol/L), confirmed by a second measurement), acute coronary syndrome or transient ischaemic attack in the three months prior to consent, and renal or hepatic failure.

For this analysis, patients who met the following criteria at baseline were selected: uncontrolled T2DM (baseline HbA1c of 8% (64 mmol/mol) or higher); overweight or class I obesity (25-35 kg/m2); and aged under 65.

**3. MATERIALS and METHODS**

3.1 Design

This is a pooled post hoc analysis of three multicentre, phase III, randomised, double-blind, placebo-controlled clinical trials [EMPA-REG PIO (NCT01289990), EMPA-REG MET (NCT01159600), EMPA-REG METSU (NCT01159600)]. Patients enrolled in the three trials had been treated with a stable regimen of 1) pioglitazone ± metformin, 2) metformin or 3) metformin + sulfonylurea for at least 12 weeks prior to randomization. These trials examined the efficacy and safety of empagliflozin (10 and 25 mg once daily) vs. placebo (1:1:1) as part of a combined treatment in patients with T2DM after 24 weeks of follow-up.(Haring et al. 2014; Haring et al. 2013; Kovacs et al. 2014) The design and methodology are described in detail in the original studies.(Haring et al. 2014; Haring et al. 2013; Kovacs et al. 2014) All three trials were conducted according to the ethical principles set out in the Declaration of Helsinki and in compliance with GCP and the applicable regulatory requirements. They had all been approved by the regulatory authorities and independent ethics committees. All patients were properly and adequately informed, were free to ask questions, and signed the informed consent form enabling them to take part in the trials.

3.2 Endpoints and assessments

The primary endpoint of the studies included in this analysis was to evaluate the changes in HbA1c from baseline to week 24 of treatment. Secondary and exploratory endpoints included changes in body weight, systolic (SBP) and diastolic blood pressure (DBP) from baseline to 24 weeks of treatment, and the percentage of participants whose HbA1c fell below 7% ( 53 mmol/mol) after 24 weeks of therapy.

Safety and tolerability were assessed from adverse events (AEs) reported on treatment and for 7 days after the last dose (coded according to the Medical Dictionary for Drug Regulatory Activities, MedDRA, version 15.0), laboratory tests, electrocardiograms and vital signs. The incidence of AEs of special interest was assessed, including confirmed hypoglycaemia AEs (plasma glucose ≤ 70 mg/dl (3.9 mmol/l) and/or requiring assistance) and AEs consistent with urinary tract infections (UTI) and genital infections (GI). Events consistent with UTI and GI were identified from AEs reported spontaneously by the investigator using prospectively defined search categories based on 67 and 87 preferred terms, respectively.

3.3 Statistical analysis

All patients who had been randomised, received one or more doses of study medication, and had a baseline HbA1c measurement, were considered evaluable for the statistical analyses of efficacy (FAS, full analysis set). Data following the initiation of anti-diabetes rescue therapy were set to missing; the last observation carried forward (LOCF) approach was used to impute missing data. The primary analysis of efficacy, defined as the change in HbA1c at 24 weeks of treatment, was performed by analysis of covariance (ANCOVA) in the FAS (LOCF) using baseline HbA1c as a linear covariate. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation; geographic location, the study to which the participant belonged, and the treatment, were considered as fixed effects in the model. For other continuous efficacy endpoints, the same model was used, considering the baseline value of the variable in question as an additional linear covariate. Categorical changes in HbA1c levels were analysed using logistic regression in the FAS and non-completers considered failure (NCF) imputation.

The safety analysis used the population that took, at least, one dose of study medication (TS, Treated Set). The analysis was descriptive and results were expressed in absolute values and frequency of occurrence.

**4. RESULTS**

4.1. Patients characteristics

In this analysis, a total of 439 patients were included (empagliflozin 10 mg, n=160 (148 completed); empagliflozin 25 mg, n=141 (135 completed); placebo n=138 (122 completed), with overall completion of 405 participants (92.3%)). The demographic characteristics and baseline condition of the included patients were similar across treatment groups (Table 1). The mean age ± SD (range) of the population was 52.5 ± 7.7 (27-64) years and 56.3% were men. Mean HbA1c ± SD was 8.7% ± 2.8 (72 mmol/mol ± 7). The vast majority of patients were receiving metformin as background therapy, either alone (34.2%, n=150), in combination with a sulfonylurea (34.9%, n=153) or in combination with pioglitazone (23.9%; n=105).

4.2. Efficacy

From baseline to week 24 of treatment, there was a statistically significant reduction in HbA1c levels with both doses of empagliflozin (10 and 25 mg) compared to placebo (Fig. 1). The difference in adjusted mean change from baseline between empagliflozin 10 mg and placebo was -0.91% ([95% CI: -1.11; -0.71]; p<0.001), and between empagliflozin 25 mg and placebo was -0.91% ([95% CI: -1.12; -0.70]; p<0.001). Regardless of the study (pioglitazone +/- metformin, metformin; metformin and sulfonylurea), the reduction in the adjusted mean change from baseline HbA1c in participants treated with either dose of empagliflozin was significantly higher than in the placebo participants. Likewise, the percentage of participants with baseline HbA1c of 64 mmol/mol (8%) or above achieving a value below 53 mmol/mol (7%) at 24 weeks was greater in the empagliflozin 10 and 25 mg treatment arms compared to those receiving placebo (23.8% and 19.9% vs. 3.6% respectively; odds ratio for empagliflozin 10 mg vs. placebo was 8.69 (95% CI: 3.23; 23.47) and for empagliflozin 25 mg vs. placebo was 7.65 (95% CI: 2.77; 21.11), p<0.001 for both).

There was a statistically significant reduction from baseline in body weight with both doses of empagliflozin compared to placebo at week 24 (Fig. 2). The differences in the adjusted mean change from baseline were -1.61 kg ([95% CI: -2.16; -1.05]; p<0.001) between empagliflozin 10 mg and placebo, and -1.81 kg ([95% CI: -2.38; -1.24]; p<0.001) between empagliflozin 25 mg and placebo. Body weight was analysed for each individual study (pioglitazone +/- metformin, metformin; metformin and sulfonylurea) and in all cases, reductions were found with empagliflozin (Fig. 2).

There were no statistically significant differences between patients treated with empagliflozin and those who received placebo in the changes in SBP at 24 weeks (Fig. 3). The difference in adjusted mean change from baseline SBP between empagliflozin 10 mg and placebo was -1.7 mmHg ([95% CI: -4.1; 0.8]; p=0.1909) and it was -2.0 mmHg ([95% CI: -4.5; 0.6]; p=0.131) between empagliflozin 25 mg and placebo. The difference in adjusted mean change from baseline DBP between empagliflozin 10 mg and placebo was also not statistically significant: -1.3 mmHg ([95% CI: -2.9; 0.2]; p=0.098). Empagliflozin 25 mg, however, was associated with a statistically significant reduction in DBP at 24 weeks of treatment compared with placebo; the difference in the adjusted mean change from baseline was -2.0 mmHg ([95% CI: -3.6; -0.4]; p=0.015).

4.3. Safety

In this analysis, the percentage of patients treated with empagliflozin who had one or more AEs was similar to placebo (64.4%, 59.6%, 57.2%; empagliflozin 10 mg, 25 mg, and placebo, respectively) (Table 2). The proportion of patients who discontinued treatment due to an AE was lower among those treated with empagliflozin (0.6% and 1.4% with empagliflozin 10 mg and 25 mg respectively) than in those treated with placebo (4.3%).

The proportion of patients with confirmed hypoglycaemia AEs was higher with empagliflozin (5.6 and 5.0% for empagliflozin 10 and 25 mg respectively) than with placebo (3.6%), although there were no severe hypoglycaemia episodes or episodes requiring hospital care in none of the treatment arms.

The incidence of UTI was similar between the placebo group and the group treated with empagliflozin 25 mg (6.5% and 5.0%, respectively) and slightly higher in participants treated with empagliflozin 10 mg (8.8%). More UTIs were reported among women than in men, regardless of treatment arm. The majority of UTIs reported were mild with no reported cases of pyelonephritis. None of the cases of UTI required hospitalisation, nor reduction or discontinuation of the anti-diabetes treatment. The proportion of patients with a history of chronic or recurring UTI who developed UTI during the studies was 42.9% in the placebo arm (3 of the 7 participants with previous history) and 28.6% (2 out of 7) and 25% (2 out of 8) in the empagliflozin 10 and 25 mg arms, respectively.

Genital infections were reported in 2 patients treated with placebo (1.4%), 6 treated with empagliflozin 10 mg (3.8%) and 7 treated with empagliflozin 25 mg (5.0%). The rate of genital infections was higher in women than in men and higher in patients treated with empagliflozin 10 mg (6.8% vs. 1.2%) and empagliflozin 25 mg (10.7% vs. 1.2%) compared to placebo. There were no severe genital infections; they were generally mild or moderate, and only one patient treated with empagliflozin 25 mg discontinued the anti-diabetes treatment.

There were no statistically significant differences between patients treated with empagliflozin and those who received placebo in change from baseline in total cholesterol, LDL cholesterol, triglycerides or the LDL/HDL ratio at week 24. In contrast, there was a statistically significant increase from baseline in HDL cholesterol in patients treated with empagliflozin compared to placebo. The HDL adjusted mean change from baseline vs. placebo for empagliflozin 10 mg was 0.08 mmol/l ([95% CI: 0.04; 0.11]; p=0.0001) and for empagliflozin 25 mg was 0.06 mmol/l ([95% CI: 0.02; 0.10]; p=0.0041).

**5. DISCUSSION**

This post hoc analysis of three randomised trials shows that empagliflozin is associated with a clinically and statistically significant reduction in HbA1c in overweight or obese patients under the age of 65 with poorly controlled T2DM. Empagliflozin also produces a consistent decrease in body weight and has demonstrated a good safety and tolerability profile.

When comparing HbA1c reductions in this patient profile to the general population of the parent studies, empagliflozin was found to have a greater blood glucose-lowering effect in this profile, since the reduction of HbA1c in the parent studies was about 0.6%. Therefore, the results of the current analysis show that this specific population may gain greater benefit in terms of glycaemic control, consequently, optimising its use. As described in the literature, empagliflozin’s efficacy depends on circulating plasma glucose levels, thus, patients with higher concentrations of blood glucose will excrete more glucose in their urine (Roden et al. 2013). As a result, the most poorly controlled patients may experience steeper reductions in HbA1c. Furthermore, approximately 60% of participants in the analysis had T2DM for 5 years or more, and this would be associated with greater degeneration of pancreatic β-cell function (Campbell 2009). Therefore, even in this population, diabetes duration did not seem to affect the blood glucose-lowering effect of empagliflozin, probably because of its insulin-independent mechanism of action, which is a clear differentiating factor from other classes of anti-diabetes drugs.

Weight loss is usually associated with improvement in blood glucose control and cardiovascular risk factors (Fujioka et al. 2000; Lavie et al. 2009; Williams and Kelley 2000). In this analysis, the greater reduction in HbA1c experienced by patients treated with empagliflozin was accompanied by significant decreases in body weight, regardless of the patients’ background therapy. In the light of the results shown above, empagliflozin is presented as a new therapeutic option for T2DM, allowing a multifactorial approach in poorly controlled patients with diabetes who are overweight or obese and have problems losing weight.

Treatment with empagliflozin was also associated with reductions in SBP and DBP, although it was only statistically significant for DBP with the 25 mg dose.

From the safety point of view, empagliflozin was well tolerated in the studied population; the rate of AEs was similar for placebo, empagliflozin 10 and 25 mg arms. Episodes of confirmed hypoglycaemia AEs were uncommon, with an increased risk in the empagliflozin arms versus placebo; although no serious cases or cases requiring assistance were reported. The incidence of UTI was similar between the participants treated with empagliflozin 25 mg and those who received placebo, but slightly higher with empagliflozin 10 mg. Events consisting of genital infections were mild to moderate, with a higher rate in the empagliflozin 10 and 25 mg treatment arms (3.8 to 5.0% vs. 1.4%). There were no reports of diabetes-related ketoacidosis or AEs consistent with volume depletion in participants treated with empagliflozin, indicating a favourable profile in these patients.

The additional value of the efficacy of empagliflozin in a poorly controlled, younger than 65 years, adult population who are overweight/obese at baseline, serves to generate further evidence on this specific population which may help in clinical decision-making and to individualise anti-diabetes treatment.

The limitations of this analysis include the fact that it is post hoc and the relatively short duration of the included studies. It would be also important to evaluate the long-term effects of empagliflozin in this type of patients. Although this analysis found a non-significant result on SBP with both empagliflozin doses and DBP with empagliflozin 10 mg, in a trial specifically designed to assess the effects of empagliflozin on blood pressure in hypertensive patients with T2DM, empagliflozin resulted in significant and sustained reductions in blood pressure (Tikkanen et al. 2015). Lastly, it is important to highlight the inherent limitation of clinical trials which, despite having a high degree of internal validity, have less external validity than other types of study.

We present an analysis of a subgroup of patients, from three phase III trials, younger than 65 years with overweight or class I obesity (BMI 25-35 kg/m2) and poorly controlled T2DM (HbA1c >64 mmol/mol (8%)) at baseline treated with empagliflozin. To conclude, the results show that in this specific population, adding empagliflozin to oral background therapies was associated with a clinically and statistically significant reduction in HbA1c compared to placebo, with a favourable safety profile. Furthermore, the reduction in HbA1c was proved to be considerably higher than that found in the general population included in the parent studies. That fact, accompanied by the significant decrease in body weight, provides us with a profile of patients who could obtain a relevant clinical benefit in terms of glycaemic and weight control from empagliflozin treatment.

**6. ACKNOWLEDGEMENTS**

We thank the participants who contributed in the trials and BCNscience for their assistance in medical writing.

**Funding sources:** This study was funded by Boehringer Ingelheim and Eli Lilly.

**Conflict of interest:** Irene Romera, Sanja Giljanovic Kis and Ebrahim Naderali are full-time employees of Eli Lilly. Susanne Crowe and Arantxa García are full-time employees of Boehringer Ingelheim. Unai Aranda was an employee of Boehringer Ingelheim during the development of the manuscript. Pedro de Pablos-Velasco has received speaker and consulting fees from AstraZeneca, Boehringer Ingelheim, Lilly, Novo Nordisk, and Sanofi-aventis. All remaining authors have none declared.

**Submission declaration and verification:** The work described here has not been published previously nor it is under consideration for publication elsewhere. This manuscript is approved by all authors and, if accepted, it will not be published elsewhere without the consent of the copyright-holder.

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**TABLES**

**Table 1. Demographic and Baseline Characteristics of the study population**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** | Placebo(n = 138) | EMPA 10 mg(n = 160) | EMPA 25 mg(n = 141) | Total(n = 439) |
| **Age (years), M ±SD** | 52.4 ± 7.7 | 52.3 ± 7.7 | 52.7 ± 7.6 | 52.5 ± 7.7 |
| **Gender, n (%)** |  |  |  |  |
| Men | 76 (55.1) | 86 (53.8) | 85 (60.3) | 247 (56.3) |
| Women | 62 (44.9) | 74 (46.3) | 56 (39.7) | 192 (43.7) |
| **Ethnicity, n (%)** |  |  |  |  |
| Native American | 3 (2.2) | 2 (1.3) | 0 | 5 (1.1) |
| Asian | 73 (52.9) | 85 (53.1) | 76 (53.9) | 234 (53.3) |
| African American | 1 (0.7) | 1 (0.6) | 0 | 2 (0.5) |
| Hawaiian / Pacific Islander | 0 | 0 | 0 | 0 |
| Caucasian | 61 (44.2) | 72 (45.0) | 65 (46.1) | 198 (45.1) |
| **Region, n (%)** |  |  |  |  |
| Europe | 34 (24.6) | 28 (17.5) | 28 (19.9) | 90 (20.5) |
| North America | 24 (17.4) | 37 (23.1) | 35 (24.8) | 96 (21.9) |
| Latin America | 9 (6.5) | 16 (10.0) | 7 (5.0) | 32 (7.3) |
| Asia | 71 (51.4) | 79 (49.4) | 71 (50.4) | 221 (50.3) |
| **Treatment for T2DM, n (%)** |  |  |  |  |
| Glitazone monotherapy | 11 (8.0) | 11 (6.9) | 8 (5.7) | 30 (6.8) |
| Metformin + glitazone | 31 (22.5) | 37 (23.1) | 37 (26.2) | 105 (23.9) |
| Metformin + sulfonylurea + insulin | 0 | 1 (0.6) | 0 | 1 (0.2) |
| Metformin + sulfonylurea | 50 (36.2) | 57 (35.6) | 46 (32.6) | 153 (34.9) |
| Metformin monotherapy | 46 (33.3) | 54 (33.8) | 50 (35.5) | 150 (34.2) |
| **HbA1c**mmol/mol; M ±SD | 73 ± 8 | 71 ± 6 | 72 ± 7 | 72 ± 7 |
| %; M ±SD | 8.8 ± 2.9 | 8.7 ± 2.7 | 8.7 ± 2.8 | 8.7 ± 2.8 |
| **Fasting blood glucose** mg/dl; M ±SDmmol/mol; M ±SD | 167.0 ± 43.29.27 ± 2.4 | 166.4 ± 35.39.24 ± 1.96 | 166.0 ± 37.59.21 ± 2.08 | 166.5 ± 38.59.24 ± 2.14 |
| **Time to T2DM diagnosis (years), n (%)** |  |  |  |  |
| 1 year or less | 5 (3.6) | 13 (8.1) | 4 (2.8) | 22 (5.0) |
| 1-5 years | 52 (37.7) | 57 (35.6) | 47 (33.3) | 156 (35.5) |
| 5-10 years | 52 (37.7) | 49 (30.6) | 53 (37.6) | 154 (35.1) |
| Over 10 years | 29 (21.0) | 41 (25.6) | 37 (26.2) | 107 (24.4) |
| **Weight (kg), M ±SD** | 79.41 ± 12.61 | 78.79 ± 13.41 | 79.13 ± 10.82 | 79.10 ± 12.35 |
| **Waist circumference (cm), M ±SD** | 99.0 ± 9.3 | 99.3 ± 9.5 | 98.8 ± 8.1 | 99.0 ± 9.0 |
| **BMI (kg/m2), M ±SD** | 29.09 ± 2.86 | 28.79 ± 2.66 | 28.96 ± 2.67 | 28.94 ± 2.72 |
| **eGFR (ml/min/1.73m2), M ±SD\*** | 92.88 ± 20.38 | 91.77 ± 21.55 | 90.53 ± 19.73 | 91.72 ± 20.58 |
| **CrCl (ml/min), M ±SD** | 115.02 ± 27.68 | 112.89 ± 28.15 | 111.39 ± 24.82 | 113.08 ± 26.95 |
| **SBP (mmHg), M ±SD** | 128.1 ± 14.4 | 128.7 ± 13.7 | 126.9 ± 13.4 | 127.9 ± 13.8 |
| **DBP (mmHg), M ±SD** | 79.2 ± 7.7 | 79.8 ± 9.2 | 78.6 ± 8.1 | 79.2 ± 8.4 |

Data for the FAS population (Full Analysis Set).

\*Calculated using the Modification of Diet in Renal Disease (MDRD) equation

*SD: Standard Deviation; M: Mean value; T2DM: Diabetes Mellitus Type 2; eGFR:* Estimated glomerular filtration rate; CrCl: *Creatinine Clearance; SBP:* Systolic blood pressure; DBPDiastolic blood pressure; HDL: *High Density Lipoprotein; LDL: Low Density Lipoprotein*

**Table 2. Summary of side effects**

|  |  |  |  |
| --- | --- | --- | --- |
| **Participants, n (%)** | **Placebo****(n = 138)** | **EMPA 10 mg****(n = 160)** | **EMPA 25 mg****(n = 141)** |
| **1 or more AE** | **79 (57.2)** | **103 (64.4)** | **84 (59.6)** |
| **1 or more AE related to the study medication\***  | **20 (14.5)** | **21 (13.1)** | **18 (12.8)** |
| **AE leading to discontinuation of treatment** | **6 (4.3)** | **1 (0.6)** | **2 (1.4)** |
| **Serious AE** | **5 (3.6)** | **5 (3.1)** | **3 (2.1)** |
| Deaths | 0 (0.0) | 1 (0.6) | 0 (0.0) |
| **AE with rate of 5% or above in any of the groups** |  |  |  |
| UTI | 7 (5.1) | 12 (7.5) | 4 (2.8) |
| Nasopharyngitis | 8 (5.8) | 7 (4.4) | 10 (7.1) |
| Hyperglycaemia | 25 (18.1) | 9 (5.6) | 8 (5.7) |
| Hypoglycaemia | 6 (4.3) | 9 (5.6) | 10 (7.1) |
| Dyslipidaemia | 5 (3.6) | 8 (5.0) | 3 (2.1) |
| **Categories of special interest** |  |  |  |
| Confirmed hypoglycaemia AE\*\* | 5 (3.6) | 9 (5.6) | 7 (5.0) |
| Hypoglycaemia requiring assistance | 0 | 0 | 0 |
| **Volume depletion** | **0** | **0** | **0** |
| **Events consisting of UTI** | **9 (6.5)** | **14 (8.8)** | **7 (5.0)** |
| Men | 2 (2.6) | 1 (1.2) | 0 |
| Women | 7 (11.3) | 13 (17.6) | 56 (12.5) |
| **Events consisting of genital infections** | **2 (1.4)** | **6 (3.8)** | **7 (5.0)** |
| Men | 1 (1.3) | 1 (1.2) | 1 (1.2) |
| Women | 1 (1.6) | 5 (6.8) | 6 (10.7) |

Data for the TS population (Treated Set).

\* as defined by investigator, \*\*plasma glucose ≤ 70 mg/dl (3.9 mmol/l) and/or requiring assistance

AE: Adverse effect; UTI: Urinary tract infections

**FIGURE CAPTIONS**

**Figure 1.** Adjusted mean change in blood glucose (HbA1c) at week 24 compared to baseline in participants treated with pioglitazone with or without metformin, metformin, metformin plus sulfonylureas at baseline and for all participants included in the analysis. FAS (LOCF).

**Figure 2.** Adjusted mean change in body weight at week 24 compared to baseline in participants treated with pioglitazone with or without metformin, metformin, metformin plus sulfonylureas at baseline and for all participants included in the analysis. FAS (LOCF).

**Figure 3.** Adjusted mean change in blood pressure at week 24 compared to baseline for all participants included in the analysis. FAS (LOCF).