**Efficacy and safety of empagliflozin in combination with other oral hypoglycaemic agents in patients with type 2 diabetes mellitus**

Irene Romera,1 Francisco Javier Ampudia-Blasco,2 Antonio Pérez Pérez,3 Bernat Ariño,4 Egon Pfarr,5 Sanja Giljanovic Kis,6 Ebrahim Naderali.7

1. Eli Lilly and Company, Spain

2. Hospital Clínic Universitari de València, Valencia, Spain

3. Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

4. Boehringer Ingelheim Pharma GmbH & Co., Spain

5. Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany

6. Eli Lilly (Suisse) SA Representative Office, Zagreb, Croatia

7. Eli Lilly and Company, Basingstoke, UK; Faculty of Science, Liverpool Hope University, Liverpool, UK

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**Corresponding author details:**

Irene Romera

Telephone: 91 623 36 32; Email: [romerai@lilly.com](mailto:romerai@lilly.com);

Address: Av. de la Industria 30, 28108 Alcobendas, Madrid, Spain

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**Abstract and keywords**

**Objective:** To analyse the efficacy and safety of empagliflozin in combination with other oral hypoglycaemic agents in patients with type 2 diabetes mellitus (T2DM).  
**Methods:** Pooled analysis of three phase III trials in patients with T2DM (n = 1,801) who received placebo, empagliflozin 10 mg or empagliflozin 25 mg once daily for 24 weeks, in combination with metformin, metformin + sulphonylurea or pioglitazone ± metformin.  
**Results:** Empagliflozin significantly reduced HbA1c (adjusted mean reduction vs placebo: with empagliflozin 10 mg, –0.58% [95% CI: –0.66; –0.49]; p < 0.0001 and with empagliflozin 25mg, –0.62% [95% CI: –0.70; –0.53], p < 0.0001), weight (adjusted mean reduction vs placebo: with empagliflozin 10 mg, –1.77 kg [95% CI: –2.05; –1.48]; p < 0.0001 and with empagliflozin 25 mg, –1.96 kg [95% CI: –2.24; –1.67], p < 0.0001), systolic blood pressure (SBP) and diastolic blood pressure (DBP). The frequency of adverse effects (AEs) was 64% with placebo, 63.9% with empagliflozin 10 mg and 60.9% with empagliflozin 25 mg. Confirmed episodes of hypoglycaemia (≤ 70 mg/dl and/or requiring care) occurred in 3.9% of patients with placebo, 6.9% of patients with empagliflozin 10 mg and 5.3% of patients with empagliflozin 25 mg. Urinary tract infections were reported in 9.4% of patients with placebo, 10.2% of patients with empagliflozin 10 mg and 8.3% of patients with empagliflozin 25 mg. Genital infections were reported in 1.0% of patients with placebo, 4.6% of patients with empagliflozin 10 mg and 3.5% of patients with empagliflozin 25 mg. **Conclusions:** Empagliflozin in combination with other oral treatments versus placebo significantly decreased HbA1c, body weight and SBP/DBP with an overall good safety and tolerability profile.  
**Keywords**

Empagliflozin, combination treatment, type 2 diabetes mellitus, SGLT2 inhibitors

**Abstract and keywords**

**Introduction**

To achieve suitable blood glucose management, metformin is a first-line drug treatment in patients with type 2 diabetes mellitus (T2DM), in combination with nutrition therapy and increased physical activity.1 However, with time this treatment becomes inadequate owing to a progressive decline in insulin secretion by pancreatic beta-cells. The UKPDS study demonstrated that 40%-50% of patients did not achieve therapeutic objectives after 2 years of treatment with metformin.2,3 This figure rose to 70% after 3 years.4 The current recommendations specify using dual or even triple therapy when metformin does not achieve or maintain therapeutic objectives.1 Although there are several drug options with similar efficacy, they have certain limitations such as risk of hypoglycaemia, increased weight, oedema, gastrointestinal effects, etc. and/or specific contraindications.5 In addition, insulin secretion-stimulating agents lose their efficacy when insulin secretion is limited or non-existent owing to a loss of pancreatic β-cell function with the progression of the disease.6,7 As a result, there is a need to develop effective glucose lowering agents with novel mechanism of action that is independent of insulin secretion, and that are not associated with weight gain and increased risk of hypoglycaemia “per se”

. These are some of the factors that contribute to a substantial proportion of patients with type 2 diabetes mellitus not achieving or maintaining blood glucose management objectives.8

Sodium-glucose cotransporter-2 (SGLT2) inhibitors represent a new family of antihyperglycaemic drugs in the treatment of T2DM. Their mechanism of action consists of inhibiting glucose reabsorption in the kidneys, thereby promoting urinary elimination of glucose, and is independent of insulin secretion. These drugs have low risk of hypoglycaemia and are associated with reductions in body weight and blood pressure.9

Empagliflozin is a highly selective SGLT2 inhibitor10 with demonstrated efficacy in reducing HbA1c by decreasing fasting and postprandial plasma glucose, and with significantly decreased body weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP). Empagliflozin is effective both in monotherapy and in combination with other hypoglycaemic medicines, including insulin.9,11-13

The objective of this post-hoc analysis was to evaluate the efficacy and safety of empagliflozin in combination with other oral agents in patients with T2DM and inadequate blood glucose management in monotherapy or dual therapy.

**Patients and methods**

*Design:* A post-hoc analysis of 3 placebo-controlled, double-blind, randomised, multi-centre, phase III clinical trials.9,12,13 All of them compared the efficacy and safety of empagliflozin (10 mg/day or 25 mg/day) versus placebo in patients with T2DM in combination therapy for 24 weeks. The design and methodology of the studies were described in the original manuscripts.9,12,13 The patients enrolled in the different studies received treatment prior to enrolment with metformin,12 metformin + sulphonylurea13 or pioglitazone ± metformin9 for at least the 12 weeks prior to randomisation. The patients maintained their starting treatment and were randomly assigned to a daily dose of placebo, 10 mg of empagliflozin or 25 mg of empagliflozin.

All of the clinical trials were conducted in accordance with the ethical principles of the Declaration of Helsinki and complied with Good Clinical Practice guidelines and the applicable regulatory requirements. All received the approval of the relevant regulatory institutions and independent ethics committees. The patients enrolled were duly informed, asked questions freely and signed the informed consent form prior to participating in the trials.

*Study population:* The patients included in this analysis met all of the inclusion criteria and none of the exclusion criteria, as specified in each clinical trial.9,12,13 The patients recruited were ≥ 18 years of age, with uncontrolled T2DM (HbA1c = 7%-10%), despite diet, exercise and a stable regimen of hypoglycaemic treatment for more than 12 weeks, and a BMI ≤ 45 kg/m2. The main exclusion criteria were uncontrolled hyperglycaemia (fasting blood glucose > 240 mg/dl confirmed by a second measurement), acute coronary syndrome, infarction or transient ischaemic attack in the 3 months prior to granting consent and kidney or liver failure.

*Study endpoints:* The primary endpoint of all the studies was the change observed in HbA1c levels, from the baseline visit up to week 24 of treatment. In addition, changes in body weight, systolic blood pressure and diastolic blood pressure, from the start of the study up to 24 weeks of treatment, were evaluated. The percentage of patients who achieved an HbA1c level below 7% after 24 weeks of treatment was also evaluated.

The safety and tolerability of empagliflozin were analysed based on the adverse events reported during the study and up to 7 days after the final dose (according to the MedDRA — Medical Dictionary for Drug Regulatory Activities, version 15.0). Various laboratory tests, electrocardiograms and vital signs were also recorded. In addition, the incidence of certain adverse effects of interest, such as confirmed episodes of hypoglycaemia (plasma glucose ≤ 70 mg/dl and/or requiring care), urinary tract infections (UTIs) and genital infections, was evaluated.

*Statistical analysis:* The statistical analysis of efficacy was performed on patients who had received one or more doses of the study medication and who had a baseline measurement of HbA1c (FAS — full analysis set). The primary analysis of efficacy, defined as the change in HbA1c levels after 24 weeks of treatment, was performed by means of analysis of covariance (ANCOVA), using baseline HbA1c as a linear covariate. Estimated glomerular filtration rate (eGFR), calculated according to the Modification of Diet in Renal Disease (MDMR) equation, geographic region and treatment were considered fixed effects in the model. The same model was used for all other continuous variables, considering the baseline value of each variable as an additional linear covariate. In the comparison between the empagliflozin treatment groups (10 and 25 mg) and the placebo group, the 95% confidence intervals and p values were calculated. The analysis of categorical change in HbA1c was performed by means of logistic regression on the FAS, patients who did not complete the study were considered as therapeutic failure.

The safety analysis included all the patients who took at least one dose of the study medication, and the results were expressed in absolute values and frequency of occurrence.

**Results**

*Patient characteristics:*

The number of patients included in the post-hoc analysis was 1,801 (596 with placebo, 606 with empagliflozin 10 mg and 599 with empagliflozin 25 mg). Among these, 1,656 completed the study.

The demographic and clinical characteristics of the patients enrolled were similar in all of the treatment groups (Table 1). Regarding the total population, 52.2% were males, the mean age was 55.9 ± 9.7 years (mean ± SD; range: 19-85) and the mean baseline HbA1c was 8.03 ± 0.85%. The majority of patients received metformin as baseline therapy, in monotherapy (35.1%; n = 632), in combination with a sulphonylurea (37.3%, n = 671) or in combination with pioglitazone (20.9%; n = 376). A total of 60.2% of the patients (n = 1,084) had been diagnosed with T2DM at least 5 years before enrolling in the study.

*Efficacy:*

Between the baseline visit and 24 weeks of treatment, a statistically significant reduction in HbA1c levels was observed in both treatment arms with empagliflozin (10 mg and 25 mg) versus placebo (Figure 1A). The difference in the adjusted mean value between placebo and empagliflozin 10 mg was –0.58% ([95% CI: –0.66; –0.49], p< 0.0001) and –0.62% ([95% CI: –0.70; –0.53], p < 0.0001) with the 25 mg dose of empagliflozin. Among the patients with baseline HbA1c equal to or greater than 7%, the percentage who managed to bring it below 7% was greater with empagliflozin 10 mg and 25 mg (27.3% and 31.3%, respectively) than with placebo (9.2%) (Figure 2). Calculation of p-value and SDs missing

When both doses of empagliflozin were compared with placebo, statistically significant reductions in body weight (Figure 1B) as well as SBP and DBP (Figure 1C) were observed. The difference in the adjusted mean value for weight compared with placebo was –1.77 kg ([95% CI: –2.05; –1.48], p < 0.0001) with empagliflozin 10 mg and –1.96 kg ([95% CI: –2.24; –1.67], p < 0.0001) with empagliflozin 25 mg. The reduction in adjusted mean value for SBP versus placebo was 3.5 mmHg with 10 mg of empagliflozin ([95% CI: –4.7; –2.3], p < 0.0001) and 3.8 mmHg ([95% CI: –5.0; –2.6], p < 0.0001) with 25 mg of empagliflozin. As for the reduction in mean value for DBP versus placebo, this was 1.3 mmHg with 10 mg of empagliflozin ([95% CI: –2.1; –0.5], p < 0.001) and 1.4 mmHg with 25 mg of empagliflozin ([95% CI: –2.1; –0.6], p < 0.001).

*Safety:*

In this study, the incidence of one or more adverse effects was similar in the three treatment arms (Table 2). The percentage of patients who discontinued the treatment owing to the occurrence of an adverse event was slightly lower with empagliflozin 10 mg (1.7%) than with empagliflozin 25 mg (2.8%) or placebo (3.2%).

The incidence of UTIs was similar between placebo and 25 mg of empagliflozin (6.9% and 7.0%, respectively), although it was higher in the patients treated with 10 mg of empagliflozin (8.9%). In the three treatment arms, the proportion of UTIs was higher in women than in men and also higher in patients with chronic or recurrent UTIs versus those who had not reported a previous UTI. The vast majority of the UTIs recorded were mild. Only 2 patients with placebo and 1 with empagliflozin 10 mg reported serious UTIs.

The percentage of patients who had genital infections was higher with empagliflozin 10 mg and 25 mg than with placebo (4.6% and 3.5% vs 1%). More females patients treated with empagliflozin reported genital infections in comparison with males (7.0% and 2.5% for empagliflozin 10 mg respectively; 6.5% and 0.9% for empagliflozin 25 mg respectively). All of the events were of mild or moderate intensity. In most of the cases study drug was not discontinued.The frequency of confirmed episodes of hypoglycaemia was greater in the patients treated with empagliflozin than in those who received placebo (6.9%, 5.3% and 3.9% with empagliflozin 10 mg, 25 mg and placebo, respectively). These episodes occurred predominantly in patients treated with sulphonylureas. No serious episodes or episodes requiring care were recorded.

Table 3 summarises the effects on the lipid profile. For HDL cholesterol, adjusted mean percentage changes from starting values were + 5.57% with empagliflozin 10 mg, + 4.35% with empagliflozin 25 mg and + 0.11% with placebo (p < 0.0001), while for LDL cholesterol they were + 6.75% and + 7.76%, with empagliflozin 10 mg and 25 mg, respectively, versus + 4.21% with placebo (p = 0.031 for empagliflozin 25 mg vs placebo). No significant changes were observed in adjusted mean values versus placebo for LDL/HDL cholesterol ratio or level of triglycerides.

**Discussion**

This post-hoc analysis based on 3 phase III studies demonstrated that empagliflozin, in combination with other oral hypoglycaemic agents, is effective in reducing HbA1c in patients with T2DM previously treated with monotherapy or dual therapy and inadequate blood glucose management. Likewise, treatment with empagliflozin was associated with reductions in body weight and blood pressure, and all with a good safety and tolerability profile. These facts establish empagliflozin as a suitable second- or third-line therapeutic option in the treatment of T2DM.

In this analysis, treatment with empagliflozin reduced HbA1c by 0.57%-0.61% and body weight by 1.77-1.96 kg. These findings are consistent with those reported previously with SGLT2 inhibitors 14-17.

The mechanism of action of Empagliflozin depends on levels of hyperglycaemia, which causes greater urinary glucose excretion in patients with higher plasma glucose levels.18 This explains why the most pronounced HbA1c reductions are observed in the most poorly controlled patients.11 In addition, in 60% of patients who had a time of evolution of T2DM of ≥ 5 years and therefore greater pancreatic β-cell dysfunction,6 the efficacy of empagliflozin did not decrease. Its mechanism of action, which is independent of insulin secretion, would explain the persistent hypoglycaemic efficacy of empagliflozin in more advanced stages of T2DM. This sets it apart from other families of hypoglycaemic drugs.

The safety profile and tolerance of empagliflozin were good, confirming the data from other studies. The frequency of adverse effects was similar among the treatment arms with placebo, empagliflozin 10 mg and empagliflozin 25 mg. As expected, genital infections were more common in patients treated with empagliflozin. They were more prevalent in women and in patients with a prior history of recurrent candidiasis.19,20 The majority of the UTIs recorded were mild. Their incidence was only slightly greater with treatment with empagliflozin 10 mg, and similar among the patients treated with empagliflozin 25 mg and placebo. Although SGLT2 inhibitors do not intrinsically cause hypoglycaemia,9,16,17 the incidence of episodes of hypoglycaemia increases, as this analysis has shown, when they are combined with sulphonylureas or other hypoglycaemia-inducing drugs.21-23 However, this analysis did not record episodes of hypoglycaemia that were serious or required care. Finally, the increases in HDL cholesterol and, to a lesser extent, LDL cholesterol observed with treatment with empagliflozin were consistent with those reported in previous studies with SGLT2 inhibitors.24,25 The pathophysiology of these modifications is unknown and their clinical significance also has yet to be determined, but they do not change the atherogenic index of LDL/HDL cholesterol.

The limitations of this study include the fact that it is a post hoc analysis. In addition, the applicability of the results is confined to the characteristics of the population of patients enrolled in the trials on which it is based. In this regard, it would be interesting to corroborate the effects related to adding empagliflozin to treatment in T2DM patients with fewer restrictions. It should be noted that the large sample size of this analysis strengthens its conclusions.

Currently, in the majority of patients with T2DM, failure of monotherapy with metformin2-4 requires therapeutic progression to dual or even triple therapy.1 Depending on the agent selected, this may result in an additional risk of hypoglycaemia or be associated with increased body weight.5 In this regard, the results reported in this study have confirmed the efficacy of treatment with empagliflozin in combination with other oral hypoglycaemic agents in reducing HbA1c, body weight and blood pressure, with an overall good safety and tolerability profile.

**Table 1: Demographic and baseline characteristics of the included population (FAS)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** | **Placebo**  **(n = 597)** | **EMPA 10 mg**  **(n = 607)** | **EMPA 25 mg**  **(n = 597)** | **Total**  **(n = 1,801)** |
| **Age (years), M (± SD)** | 56.0 (± 9.8) | 55.8 (± 9.7) | 55.9 (± 9.6) | 55.9 (± 9.7) |
| **Gender, n (%)** |  |  |  |  |
| Male | 301 (50.4) | 321 (52.9) | 319 (53.4) | 941 (52.2) |
| Female | 296 (49.6) | 286 (47.1) | 278 (46.6) | 860 (47.8) |
| **Ethnicity, n (%)** |  |  |  |  |
| Native American | 4 (0.7) | 7 (1.2) | 5 (0.8) | 16 (0.9) |
| Asian | 322 (53.9) | 319 (52.6) | 317 (53.1) | 958 (53.2) |
| African American | 10 (1.7) | 11 (1.8) | 9 (1.5) | 30 (1.7) |
| Hawaiian / Pacific Islander | 0 | 0 | 0 | 0 |
| Caucasian | 261 (43.7) | 270 (44.5) | 266 (44.6) | 797 (44.3) |
| **Region, n (%)** |  |  |  |  |
| Europe | 135 (22.6) | 142 (23.4) | 139 (23.3) | 416 (23.1) |
| North America | 131 (21.9) | 135 (22.2) | 137 (22.9) | 403 (22.4) |
| Latin America | 23 (3.9) | 25 (4.1) | 23 (3.9) | 71 (3.9) |
| Asia | 308 (51.6) | 305 (50.2) | 298 (49.9) | 911 (50.6) |
| **Treatment for T2DM, n (%)** |  |  |  |  |
| Glitazone ± insulin | 41 (6.9) | 40 (6.6) | 41 (6.9) | 122 (6.8) |
| Metformin + glitazone | 124 (20.8) | 125 (20.6) | 127 (21.3) | 376 (20.9) |
| Metformin + sulphonylurea + insulin | 0 | 1 (0.2) | 0 | 1 (0.1) |
| Metformin + sulphonylurea | 227 (38.0) | 227 (37.4) | 216 (36.2) | 670 (37.2) |
| Metformin monotherapy | 205 (34.3) | 214 (35.3) | 213 (35.7) | 632 (35.1) |
| **HbA1c (%), M (± SD)** | 8.07 (± 0.88) | 8.02 (± 0.83) | 8.00 (± 0.85) | 8.03 (± 0.85) |
| **Fasting blood glucose (mg/dl), M (± SD)** | 153.3 (36.0) | 152.6 (35.2) | 152.7 (33.8) | 152.8 (35.0) |
| **Time to diagnosis of T2DM (years), n (%)** |  |  |  |  |
| One year or less | 40 (6.7) | 52 (8.6) | 43 (7.2) | 135 (7.5) |
| 1-5 years | 197 (33.0) | 197 (32.5) | 188 (31.5) | 582 (32.3) |
| 5-10 years | 201 (37.7) | 187 (30.8) | 201 (33.7) | 589 (32.7) |
| Over 10 years | 159 (26.6) | 171 (28.2) | 165 (27.6) | 495 (27.5) |
| **Weight (kg), M (± SD)** | 77.96 (± 18.43) | 78.93 (± 18.70) | 79.58 (± 19.38) | 78.83 (± 18.84) |
| **Waist circumference (cm), M (± SD)** | 98.1 (± 13.5) | 98.2 (± 13.2) | 98.7 (± 14.0) | 98.3 (± 13.6) |
| **eGFR (ml/min/1.73m2)a, M (± SD)** | 87.48 (± 20.59) | 86.95 (± 20.87) | 87.86 (± 21.98) | 87.43 (± 21.15) |
| **SBP (mmHg), M (± SD)** | 127.9 (± 13.9) | 128.4 (± 13.9) | 128.6 (± 14.5) | 128.3 (± 14.1) |
| **DBP (mmHg), M (± SD)** | 77.7 (± 8.4) | 78.5 (± 8.8) | 78.3 (± 8.3) | 78.2 (± 8.5) |
| **HDL cholesterol (mmol/l)\*, M (± SD)** | 1.26 (± 0.31) | 1.27 (± 0.32) | 1.28 (± 0.33) | 1.27 (± 0.32) |
| **LDL cholesterol (mmol/l)\*\*, M (± SD)** | 2.52 (± 0.90) | 2.45 (± 0.86) | 2.50 (± 0.87) | 2.49 (± 0.88) |
| **Triglycerides (mmol/l)\*, M (± SD)** | 1.79 (± 1.19) | 1.90 (± 1.44) | 1.81 (± 1.32) | 1.84 (± 1.32) |

Data from the FAS population.

aCalculated by means of the Modification of Diet in Renal Disease (MDRD) equation.

EMPA: empagliflozin; SD: standard deviation; M: mean; T2DM: type 2 diabetes mellitus; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein

**Table 2: Summary of adverse effects (TS)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Patients, n (%)** | **Placebo**  **(n = 596)** | **EMPA 10 mg**  **(n = 606)** | **EMPA 25 mg**  **(n = 599)** |
| **1 or more AEs** | **382 (64.1)** | **387 (63.9)** | **365 (60.9)** |
| **1 or more AEs related to the study medicinea** | **90 (15.1)** | **113 (18.6)** | **101 (16.9)** |
| **AEs leading to discontinuation of treatment** | **19 (3.2)** | **10 (1.7)** | **17 (2.8)** |
| **Severe AEs** | **28 (4.7)** | **25 (4.1)** | **12 (2.0)** |
| Deaths | 1 (0.2) | 1 (0.2) | 2 (0.3) |
| **AEs with a frequency ≥ 5% in any of the treatment arms** |  |  |  |
| UTI | 41 (6.9) | 54 (8.9) | 42 (7.0) |
| Nasopharyngitis | 33 (5.5) | 36 (5.9) | 32 (5.3) |
| Hyperglycaemia | 77 (12.9) | 19 (3.1) | 11 (1.8) |
| Hypoglycaemia | 27 (4.5) | 45 (7.4) | 39 (6.5) |
| **Categories of special interest** |  |  |  |
| Confirmed episode of hypoglycaemia**b** | 23 (3.9) | 42 (6.9) | 32 (5.3) |
| Episode of hypoglycaemia requiring care | 0 | 0 | 0 |
| **Volume depletion** | **1 (0.2)** | **3 (0.5)** | **0** |
| **Events consisting of UTIs** | **56 (9.4)** | **62 (10.2)** | **50 (8.3)** |
| Male | 13 (4.3) | 6 (1.9) | 3 (0.9) |
| Female  Chronic or recurrent UTIs (UTI/total chronic UTIs [%]) No previous UTIs (UTIs/total previous UTIs [%])  Serious UTI | 43 (14.5)  9/40 (22.5) 47/556 (8.5)  2 (0.3) | 56 (19.6)  9/32 (28.1) 53/574 (9.2)  1 (0.2) | 47 (16.8)  11/32 (34.4) 39/567 (6.9)  0 |
| **Events consisting of genital infections** | **6 (1.0)** | **28 (4.6)** | **21 (3.5)** |
| Male | 2 (0.7) | 8 (2.5) | 3 (0.9) |
| Female | 4 (1.4) | 20 (7.0) | 18 (6.5) |

**a**As defined by investigator; **b**Plasma glucose ≤ 70 mg/dl (≤ 3.9 mmol/l) and/or requiring care

EMPA: empagliflozin; AE: Adverse effect; UTIs: Urinary tract infections

**Table 3: Changes in lipid parameters with empagliflozin versus placebo.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Treatment** | **Change from starting value**  **(Difference versus placebo)** | | **% change from starting value**  **(Difference versus placebo)** | |
| **Adjusted mean (SD)** | **CI (95%)** | **Adjusted mean (SD)** | **CI (95%)** |
| **HDL cholesterol (mmol/l)**  EMPA 10 mg  EMPA 25 mg | 0.07 (0.01)b  0.05 (0.01)b | (0.05-0.09)  (0.03-0.08) | 5.46 (0.87)b  4.24 (0.87)b | (3.75-7.17)  (2.53-5.94) |
| **LDL cholesterol (mmol/l)**  EMPA 10 mg  EMPA 25 mg | 0.07 (0.03)a  0.08 (0.03)a | (0.00-0.14)  (0.01-0.15) | 2.54 (1.65)  3.56 (1.65)a | (–0.70 - 5.78)  (0.32 - 6.79) |
| **LDL/HDL cholesterol ratio**  EMPA 10 mg  EMPA 25 mg | –0.04 (0.03)  –0.01 (0.03) | (–0.10 - 0.02)  (–0.07 - 0.05) | --  -- | --  -- |
| **Triglycerides (mmol/l)**  EMPA 10 mg  EMPA 25 mg | –0.11 (0.07)  –0.02 (0.07) | (–0.24 - 0.02)  (–0.15 - 0.11) | –6.18 (2.78)a  –1.83 (2.78) | (–11.63, -0.72)  (–7.28, 3.62) |

EMPA: empagliflozin*;* SD: standard deviation*;* CI: confidence interval; a*p-value < 0.05;* b*p-value < 0.0001*

**Figure 1**

**A**

**B**

**C**

\*

\*

EMPA: empagliflozin; DBP: diastolic blood pressure; SBP: systolic blood pressure. ,\* p-value < 0.0001

**Figure 2**

EMPA: Empagliflozin

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**Figure 1:** Change in percentage of HbA1c (A) and weight (B) as well as SBP and DBP (C) after 24 weeks versus the start of the study and in the entire population. The results are shown as the change in the adjusted mean (ANCOVA) along with standard deviation and calculation of the p-value. \*p < 0.001 (difference vs placebo)

**Figure 2:** Percentage of patients with a baseline HbA1c ≥ 7.0% who managed to achieve an HbA1c < 7.0% after 24 weeks of treatment. SD and p calculation missing