IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Empagliflozin (type 2 diabetes mellitus) –

Addendum to Commission A16-12[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CSR	clinical study report
eGFR	estimated glomerular filtration rate
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MACE	major adverse cardiovascular events
PG	plasma glucose
SAE	serious adverse events
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

1 Background

On 11 July 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-12 (Empagliflozin – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In Module 4 B [2] of its dossier on empagliflozin, the pharmaceutical company (hereinafter referred to as "the company") had presented a study of direct comparison and 2 indirect comparisons for research question B (empagliflozin plus another blood-glucose lowering drug except insulin in comparison with metformin plus sulfonylurea). All studies used for this were already known from the first assessment A14-26 [3]. The data presented by the company were incomplete, however. In addition, there were noticeable discrepancies between the company's analyses in Module 4 B and the corresponding clinical study reports (CSRs).

Furthermore, the company had presented the study EMPA-REG-Outcome (hereinafter abbreviated as "EMPA-REG") in Module 4 D of its dossier [4]. This study was comprehensively assessed in dossier assessment A16-12 with the result that it was unsuitable for the benefit assessment. On the one hand, the company had presented no analyses that would have allowed a comparison with the appropriate comparator therapy (ACT). On the other, there were substantial deviations between the conduct of the study and the "standard treatment" mandated in the study protocol so that the results of the study were not interpretable.

With its written comments [5] and after the oral hearing [6], the company subsequently submitted data on the studies mentioned above. The G-BA commissioned IQWiG to assess study 1245.28, the indirect comparison under consideration of the studies 1245.28, 1275.1 and 1245.23/1245.31, and to analyse the results of the EMPA-REG study.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Research question B: empagliflozin plus another blood-glucose lowering drug except insulin

In accordance with the commission, the direct comparison based on study 1245.28 and the indirect comparison based on the studies 1245.28, 1275.1 and 1245.23/1245.31 are assessed in the following Section. The company used these studies for answering the following research question in its dossier [2]: assessment of the added benefit of empagliflozin in combination with another blood-glucose lowering drug except insulin in comparison with metformin in combination with a sulfonylurea (glibenclamide, glimepiride) in patients with type 2 diabetes mellitus. According to the G-BA decision on the first assessment of empagliflozin, these studies provided data on a subquestion B1 (combination with metformin) of research question B [7].

2.1.1 Underlying data

For the direct comparison based on study 1245.28, the results of the data cut-off after 208 weeks are presented below. These differ from the ones of the first assessment of empagliflozin because only results at the data cut-off after 104 weeks were available at that time.

For the indirect comparison, the data cut-off after 104 weeks was used for study 1245.28, the data cut-off after 52 weeks was used for study 1275.1, and the data cut-off after 76 weeks was used for study 1245.23/1245.31. Hence the underlying data did not differ regarding the studies, but the present assessment analysed further outcomes for which no indirect comparisons were available in the first assessment.

Module 4 B [2] of the dossier does not contain results on several patient-relevant outcomes. In particular, these are the following outcomes: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, severe hypoglycaemia, renal and urinary disorders (System Organ Class [SOC]), and reproductive system and breast disorders (SOC).

In addition, some of the results presented by the company in Module 4 B [2] deviated substantially from the information provided in Module 5. For example, the CSR of study 1245.28 contained the following data for the outcome “symptomatic hypoglycaemia” (54 mg/dL ≤ plasma glucose [PG] ≤ 70 mg/dL) after 208 weeks: 13 events in the empagliflozin arm versus 104 events in the glimepiride arm. Module 4 B, in contrast, cited 17 events in the empagliflozin arm versus 171 events in the glimepiride arm. In the present report, the information provided in the respective CSRs is presented in case of such discrepancies.

There were also discrepancies within Module 5. For example, in the additional analyses of study 1245.28 [8] at the data cut-off 104 weeks, 12 events in the empagliflozin arm versus 16 events in the glimepiride arm were cited for the outcome “major adverse cardiovascular

events-3 (MACE-3)". The corresponding CSR [9] cited 12 events in the empagliflozin arm versus 19 events in the glimepiride arm. In the present report, the information provided in the CSRs is presented.

With its comments [5] and after the oral hearing [6], the company subsequently submitted analyses on the outcomes "renal and urinary disorders" and "reproductive system and breast disorders". Data on the outcome "severe hypoglycaemia" were still not available and could also not be inferred from the further documents. Results on the outcomes "MACE-3", "cardiovascular death", "nonfatal myocardial infarction", and "nonfatal stroke" were extracted from the CSRs.

2.1.2 Direct comparison of empagliflozin 25 mg versus glimepiride

The company presented study 1245.28 for the comparison of empagliflozin in combination with another blood-glucose lowering drug except insulin in comparison with metformin in combination with a sulfonylurea (glibenclamide, glimepiride).

2.1.2.1 Study design and study characteristics

A detailed description of study 1245.28, its limitations, as well as tables presenting the study characteristics, the interventions, and the study population can be found in the first benefit assessment of empagliflozin [3].

2.1.2.2 Results

Table 1 and Table 2 show the results of study 1245.28 after 208 weeks.

Table 1: Results (mortality, morbidity, side effects) – RCT, direct comparison: empagliflozin 25 mg vs. glimepiride (each + metformin) (208 weeks)

Study Outcome category Outcome	Empagliflozin + metformin N	 Patients with event n (%)	Glimepiride + metformin N	 Patients with event n (%)	Empagliflozin + metformin vs. glimepiride + metformin RR [95% CI]; p-value
1245.28					
Mortality					
All-cause mortality	765	8 (1.0)	780	8 (1.0)	1.02 [0.38; 2.70]; > 0.999[a]
Morbidity					
MACE-3	765	15 (2.0)	780	25 (3.2)	0.61 [0.33; 1.15]; 0.132[a]
Cardiovascular death	765	2 (0.3)	780	4 (0.5)	0.51 [0.09; 2.78]; 0.533[a]
Nonfatal myocardial infarction	765	4 (0.5)	780	13 (1.7)	0.31 [0.10; 0.96]; 0.032[a]
Nonfatal stroke	765	10 (1.3)	780	8 (1.0)	1.27 [0.51; 3.21]; 0.683[a]
Side effects					
AEs (supplementary information)	765	706 (92.3)	780	713 (91.4)	–
SAEs	765	161 (21.0)	780	153 (19.6)	1.07 [0.88; 1.31]; 0.533[a]
Discontinuation due to AEs	765	48 (6.3)	780	52 (6.7)	0.94 [0.64; 1.38]; 0.809[a]
Severe hypoglycaemia	No relevant analysis was available for this outcome.				
Symptomatic hypoglycaemia (PG < 54 mg/dL)	765	5 (0.7)	780	84 (10.8)[b]	0.06 [0.02; 0.15]; < 0.001[a]
Symptomatic hypoglycaemia (54 mg/dL ≤ PG ≤ 70 mg/dL)	765	13 (1.7)[b]	780	104 (13.3)[b]	0.13 [0.07; 0.22]; < 0.001[a]
Renal and urinary disorders[c]	765	146 (19.1)	780	91 (11.7)	1.64 [1.28; 2.08]; < 0.001[a]
Reproductive system and breast disorders[c]	765	117 (15.3)	780	66 (8.5)	1.81 [1.36; 2.40]; < 0.001[a]
Genital infection[d]	765	104 (13.6)	780	30 (3.8)	3.54 [2.38; 5.24]; < 0.001[a]

a: Institute's calculation, unconditional exact test (CSZ method according to Andrés [10]).
b: The information provided in the CSR partly deviates substantially from the information in Module 4.
c: Analysis by MedDRA SOC.
d: Analysis (pre)planned according to MedDRA query developed by the company.
AE: adverse event; CI: confidence interval; MACE: major adverse cardiovascular events: MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; PG: plasma glucose; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 2: Results (morbidity) – RCT, direct comparison: empagliflozin 25 mg vs. glimepiride (each + metformin) (208 weeks)

Study Outcome category Outcome	Empagliflozin + met			Glimepiride + met			Empagliflozin + met vs. glimepiride + met
	N	Baseline values mean (SE)	Change at end of study mean[a] (SE)	N	Baseline values mean (SE)	Change at end of study mean[a] (SE)	MD[a] [95% CI]; p-value
1245.28							
Morbidity							
Health status (EQ-5D VAS)	No usable data[b]						
Supplementary outcomes							
Body weight	765	82.52 (0.69)	-3.44 (0.14)	780	83.03 (0.69)	1.21 (0.14)	-4.64 [-5.04; -4.25]; < 0.001
HbA1c	765	7.92 (0.03)	-0.41 (0.03)	780	7.92 (0.03)	-0.34 (0.03)	-0.07 [-0.17; 0.03]; 0.151

a: Adjusted for geographical region and treatment as well as baseline values of weight, HbA1c, and eGFR.
b: Only analysis without imputation of missing values available. The data are not presented because the proportion of the patients who were not considered in the analysis was > 30% or the difference of the proportions of patients who were not considered was more than 15 percentage points between the groups.
CI: confidence interval; eGFR: estimated glomerular filtration rate; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; HbA1c: glycosylated haemoglobin A1c; MD: mean difference; met: metformin; N: number of analysed patients; RCT: randomized controlled trial; SE: standard error; vs.: versus

Mortality/morbidity

All-cause mortality

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality".

MACE-3

There was no statistically significant difference between the treatment groups for the outcome "MACE-3". This also applied to the individual components "cardiovascular death" and "nonfatal stroke". A statistically significant effect in favour of empagliflozin was shown for the component "nonfatal myocardial infarction", however.

Health status (EQ-5D VAS)

There were no usable data for the outcome "European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS)".

Health-related quality of life

There were no data for the outcome "health-related quality of life".

Side effects

Severe adverse events and discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcomes "serious adverse events (SAEs)" and "discontinuation due to adverse events (AEs)".

Hypoglycaemia

There were no relevant analyses for the outcome "severe hypoglycaemia" (see also dossier assessment A14-26 on the first assessment of empagliflozin [3]).

A statistically significant effect in favour of empagliflozin was shown for the outcome "symptomatic hypoglycaemia" for each of both operationalizations (PG < 54 mg/dL and 54 mg/dL ≤ PG ≤ 70 mg/dL).

Specific adverse events

A statistically significant effect to the disadvantage of empagliflozin was shown for each of the outcomes "renal and urinary disorders", "reproductive system and breast disorders", and "genital infection".

2.1.2.3 Summary of the direct comparison

Table 3 summarizes the positive and negative effects of empagliflozin on the basis of the study of direct comparison 1245.28.

Table 3: Positive and negative effects of empagliflozin 25 mg vs. glimepiride (each + metformin)

Positive effects	**Negative effects**
Morbidity ▪ Nonfatal myocardial infarction Side effects ▪ Symptomatic hypoglycaemia	Side effects ▪ Renal and urinary disorders ▪ Reproductive system and breast disorders ▪ Genital infection
vs.: versus	

In the overall consideration, this resulted in an advantage of empagliflozin 25 mg versus glimepiride (each in combination with metformin).

2.1.3 Indirect comparison of empagliflozin 10 mg versus glimepiride using the common comparator empagliflozin 25 mg

The company presented the studies 1245.28, 1275.1, and 1245.23/1245.31 for the comparison of empagliflozin 10 mg versus glimepiride using the common comparator empagliflozin 25 mg (each in combination with metformin).

2.1.3.1 Study design and study characteristics

The first benefit assessment of empagliflozin [3] and the corresponding addendum [11] contain descriptions of the studies 1245.28, 1275.1, and 1245.23/1245.31 as well as tables presenting the study characteristics, the interventions, and the study population.

2.1.3.2 Results

Table 4 and Table 5 show the results of the indirect comparison of the studies 1245.28, 1275.1, and 1245.23/1245.31. These were partly already presented in the addendum to the first assessment of empagliflozin [11]. The results on the following outcomes were additionally available for the present assessment: mortality, MACE-3, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, discontinuation due to AEs, and genital infection.

Table 4: Results (mortality, morbidity, side effects) – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin)

Outcome category Outcome Comparison Study	Empa 10 mg + met or glimepiride + met N	 Patients with event n (%)	Empa 25 mg + met N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
Mortality					
All-cause mortality					
Intervention vs. common comparator					
1245.23/31 (76 W)	217	0 (0)	214	0 (0)	NC
1275.1 (52 W)	140	1 (0.7)	141	0 (0)	3.02 [0.12; 73.54]; 0.369[a]
Total					
Comparator therapy vs. common comparator					
1245.28 (104 W)	780	5 (0.6)	765	5 (0.7)	POR 1.00 [0.29; 3.47] > 0.999
Adjusted indirect comparison[b]:					
Intervention vs. comparator therapy					
1245.23/31 and 1275.1 vs. 1245.28					3.08 [0.10; 94.44]; 0,519[c]
Morbidity					
MACE-3					
Intervention vs. common comparator					
1245.23/31 (76 W)	217	0 (0)	214	2 (0.9)	0.20 [0.01; 4.08]; 0.159[a]
1275.1 (52 W)	140	1 (0.7)	141	0 (0)	3.02 [0.12; 73.54]; 0.367[a]
Total					0.74 [0.05; 10.71]; 0.822[d]
Comparator therapy vs. common comparator					
1245.28 (104 W)	780	19 (2.4)	765	12 (1.6)	1.55 [0.76; 3.18]; 0.249[a]
Adjusted indirect comparison[b]:					
Intervention vs. comparator therapy					
1245.23/31 and 1275.1 vs. 1245.28					0.47 [0.03; 7.57]; 0.597[d]

(continued)

Table 4: Results (mortality, morbidity, side effects) – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) (continued)

Outcome category Outcome Comparison Study	Empa 10 mg + met or glimepiride + met N	 Patients with event n (%)	Empa 25 mg + met N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
Cardiovascular death					
Intervention vs. common comparator					
1245.23/31 (76 W)	217	0 (0)	214	0 (0)	NC
1275.1 (52 W)	140	0 (0)	141	0 (0)	NC
Total					NC
Comparator therapy vs. common comparator					
1245.28 (104 W)	780	5 (0.6)	765	1 (0.1)	4.90 [0.57; 41.88]; 0.129[a]
Adjusted indirect comparison[b]:					
Intervention vs. comparator therapy					
1245.23/31 and 1275.1 vs. 1245.28					NC
Nonfatal myocardial infarction					
Intervention vs. common comparator					
1245.23/31 (76 W)	217	0 (0)	214	1 (0.5)	0.33 [0.01; 8.03]; 0.369[a]
1275.1 (52 W)	140	1 (0.7)	141	0 (0)	3.02 [0.12; 73.54]; 0.369[a]
Total					1.00 [0.10; 9.54]; 0.998[d]
Comparator therapy vs. common comparator					
1245.28 (104 W)	780	9 (1.2)	765	3 (0.4)	2.94 [0.80; 10.83]; 0.097[a]
Adjusted indirect comparison[b]:					
Intervention vs. comparator therapy					
1245.23/31 and 1275.1 vs. 1245.28					0.34 [0.03; 4.6]; 0.416[d]

(continued)

Table 4: Results (mortality, morbidity, side effects) – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) (continued)

Outcome category Outcome Comparison Study	Empa 10 mg + met or glimepiride + met N	 Patients with event n (%)	Empa 25 mg + met N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
Nonfatal stroke					
Intervention vs. common comparator					
1245.23/31 (76 W)	217	0 (0)	214	1 (0.4)	0.33 [0.01; 8.03]; 0.369[a]
1275.1 (52 W)	140	0 (0)	141	0 (0)	NC
Total					
Comparator therapy vs. common comparator					
1245.28 (104 W)	780	5 (0.6)[d]	765	8 (1.0)[d]	0.61 [0.20; 1.87]; 0.530[a]
Adjusted indirect comparison[b]:					
Intervention vs. comparator therapy					
1245.23/31 and 1275.1 vs. 1245.28					0.54 [0.02; 15.8]; 0.718[d]
Side effects					
AEs (supplementary information)					
Intervention vs. common comparator					
1245.23/31 (76 W)	217	174 (80.2)	214	154 (72.0)	–
1275.1 (52 W)	140	96 (68.6)	141	103 (73.0)	–
Comparator therapy vs. common comparator					
1245.28 (104 W)	780	673 (86.3)	765	661 (86.4)	–

(continued)

Table 4: Results (mortality, morbidity, side effects) – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) (continued)

Outcome category Outcome Comparison Study	Empa 10 mg + met or glimepiride + met N	 Patients with event n (%)	Empa 25 mg + met N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
SAEs					
Intervention vs. common comparator					
1245.23/31 (76 W)	217	19 (8.8)	214	17 (7.9)	1.10 [0.59; 2.06]; 0.824[a]
1275.1 (52 W)	140	6 (4.3)	141	10 (7.1)	0.60 [0.23; 1.62]; 0.327[a]
Total					0.92 [0.54; 1.58]; 0.775
Comparator therapy vs. common comparator					
1245.28 (104 W)	780	89 (11.4)	765	119 (15.6)	0.73 [0.57; 0.95]; 0.018[a]
Adjusted indirect comparison[b]:					
Intervention vs. comparator therapy					
1245.23/31 and 1275.1 vs. 1245.28					1.27 [0.70; 2.29]; 0.445[d]
Discontinuation due to AEs					
Intervention vs. common comparator					
1245.23/31 (76 W)	217	7 (3.2)	214	12 (5.6)	0.58 [0.23; 1.43]; 0.247[a]
1275.1 (52 W)	140	9 (6.4)	141	4 (2.8)	2.27 [0.71; 7.19]; 0.157[a]
Total					Heterogeneity: p = 0.068; I^2 = 70.0 %
Comparator therapy vs. common comparator					
1245.28 (104 W)	780	34 (4.4)	765	39 (5.1)	0.86 [0.55; 1.34]; 0.533[a]
Adjusted indirect comparison[b]:					
Intervention vs. comparator therapy					
1245.23/31 vs. 1245.28					0.67 [0.24; 1.86]; 0.445[d]
1275.1 vs. 1245.28					2.65 [0.77; 9.15]; 0.123[d]

(continued)

Table 4: Results (mortality, morbidity, side effects) – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) (continued)

Outcome category Outcome Comparison Study	Empa 10 mg + met or glimepiride + met N	 Patients with event n (%)	Empa 25 mg + met N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
Severe hypoglycaemia					
Intervention vs. common comparator					
1245.23/31 (76 W)	No relevant analysis was available for this outcome.				
1275.1 (52 W)	No relevant analysis was available for this outcome.				
Total					NC
Comparator therapy vs. common comparator					
1245.28 (104 W)	No relevant analysis was available for this outcome.				
Adjusted indirect comparison[b]:					
Intervention vs. comparator therapy					
1245.23/31 and 1275.1 vs. 1245.28					NC
Symptomatic hypoglycaemia (PG < 54 mg/dL)					
Intervention vs. common comparator					
1245.23/31 (76 W)	217	2 (0.9)	214	2 (0.9)	POR 0.99 [0.14; 7.05]; > 0.999[a]
1275.1 (52 W)	135	1 (0.7)	135	0 (0)	3.00 [0.12; 72.99][e]; 0.497[a]
Total					1.33 [0.25; 7.05]; 0.734[c]
Comparator therapy vs. common comparator					
1245.28 (104 W)	780	62 (7.9)	765	5 (0.7)	12.16 [4.92; 30.08]; < 0.001[a]
Adjusted indirect comparison[b]:					
Intervention vs. comparator therapy					
1245.23/31 and 1275.1 vs. 1245.28					0.11 [0.02; 0.73]; 0.022[d]

(continued)

Table 4: Results (mortality, morbidity, side effects) – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) (continued)

Outcome category Outcome Comparison Study	Empa 10 mg + met or glimepiride + met N	 Patients with event n (%)	Empa 25 mg + met N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
Symptomatic hypoglycaemia (54 mg/dL ≤ PG < 70 mg/dL)					
Intervention vs. common comparator					
1245.23/31 (76 W)	217	4 (1.8)	214	6 (2.8)	0.66 [0.19; 2.30]; 0.520[a]
1275.1 (52 W)	135	1 (0.7)	135	1 (0.7)	POR 1.00 [0.06; 16.07]; > 0.999[a]
Total					0.71 [0.23; 2.21]; 0.549[c]
Comparator therapy vs. common comparator					
1245.28 (104 W)	780	104 (13.3)	765	8 (1.0)	12.75 [6.25; 25.99]; < 0.001[a]
Adjusted indirect comparison[b]:					
Intervention vs. comparator therapy					
1245.23/31 and 1275.1 vs. 1245.28					0.06 [0.01; 0.21]; < 0.001
Renal and urinary disorders[f]					
Intervention vs. common comparator					
1245.23/31 (76 W)	217	17 (7.8)	214	15 (7.0)	1.12 [0.57; 2.18]; 0.808[a]
1275.1 (52 W)	140	9 (6.4)	141	14 (9.9)	0.65 [0.29; 1.45]; 0.294[a]
Total					0.89 [0.53; 1.51]; 0.671[d]
Comparator therapy vs. common comparator					
1245.28 (104 W)	780	55 (7.1)	765	112 (14.6)	0.48 [0.35; 0.65]; < 0.001[a]
Adjusted indirect comparison[b]:					
Intervention vs. comparator therapy					
1245.23/31 and 1275.1 vs. 1245.28					1.86 [1.01; 3.42]; 0.047[d]

(continued)

Table 4: Results (mortality, morbidity, side effects) – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) (continued)

Outcome category Outcome Comparison Study	Empa 10 mg + met or glimepiride + met N	 Patients with event n (%)	Empa 25 mg + met N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
Reproductive system and breast disorders[f]					
Intervention vs. common comparator					
1245.23/31 (76 W)	217	13 (6.0)	214	11 (5.1)	1.17 [0.53; 2.54]; 0.769[a]
1275.1 (52 W)	140	6 (4.3)	141	10 (7.1)	0.60 [0.23; 1.62]; 0.327[a]
Total					0.90 [0.48; 1.69]; 0.746[d]
Comparator therapy vs. common comparator					
1245.28 (104 W)	780	46 (5.9)	765	91 (11.9)	0.50 [0.35; 0.70]; < 0.001[a]
Adjusted indirect comparison[b]**:**					
Intervention vs. comparator therapy					
1245.23/31 and 1275.1 vs. 1245.28					1.82 [0.89; 3.71]; 0.101[d]
Genital infection[g]					
Intervention vs. common comparator					
1245.23/31 (76 W)	217	18 (8.3)	214	20 (9.3)	0.89 [0.48; 1.63]; 0.769[a]
1275.1 (52 W)	140	11 (7.9)	141	12 (8.5)	0.92 [0.42; 2.02]; 0.896[a]
Total					0.90 [0.56; 1.46]; 0.670[d]
Comparator therapy vs. common comparator					
1245.28 (104 W)	780	17 (2.2)	765	90 (11.8)	0.19 [0.11; 0.31]; < 0.001[a]
Adjusted indirect comparison[b]**:**					
Intervention vs. comparator therapy					
1245.23/31 and 1275.1 vs. 1245.28					4.86 [2.42; 9.79]; < 0,001[d]

(continued)

Table 4: Results (mortality, morbidity, side effects) – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) (continued)

a: Institute's calculation, unconditional exact test (CSZ method according to Andrés [10]).
b: Adjusted indirect comparison according to Bucher [12].
c: Based on RRs in all studies.
d: Institute's calculation.
e: Institute's calculation, RR with correction factor 0.5.
f: Analysis by MedDRA SOC.
g: Boehringer Ingelheim customized MedDRA query.

AE: adverse event; CI: confidence interval; empa: empagliflozin; MACE: major adverse cardiovascular events; MedDRA: Medical Dictionary for Regulatory Activities; met: metformin; n: number of patients with (at least one) event; N: number of analysed patients NC: not calculable; ND: no data; PG: plasma glucose; POR: Peto odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus; W: weeks

Table 5: Results (morbidity) – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin)

Outcome category / Outcome / Study	Empa 10 mg + met or glimepiride + met			Empa 25 mg + met			Group difference
	N	Baseline values mean (SE)	Change at end of study mean[a, b] (SE)	N	Baseline values mean (SE)	Change at end of study mean[a, b] (SE)	Mean difference[b] [95% CI]; p-value
Morbidity							
Health status (EQ-5D VAS)							
Intervention vs. common comparator							
1245.23/ 31 (76 W)	Outcome not recorded in Study 1245.23/31						
1275.1 (52 W)	105	79.3 (17.1[c])	3.5 (17.8[c])	113	79.8 (17.1[c])	5.0 (18.4[c])	ND
Total							ND
Comparator therapy vs. common comparator							
1245.28 (104 W)	No usable data[d]						
Adjusted indirect comparison[e]:							
Intervention vs. comparator therapy							
1245.23/31 and 1275.1 vs. 1245.28							ND
Supplementary outcomes							
Body weight							
Intervention vs. common comparator							
1245.23/ 31 (76 W)	217	81.59 (1.26)	-2.39 (0.21)	213	82.21 (1.32)	-2.65 (0.21)	ND
1275.1 (52 W)	137	85.69 (1.57)	-2.93 (0.32)	140	87.68 (1.49)	-2.80 (0.32)	ND
Total							ND
Comparator therapy vs. common comparator							
1245.28 (104 W)	780	83.03 (0.69)	1.34 (0.13)	765	82.52 (0.69)	-3.12 (0.13)	-4.46 [-4.81; -4.10]; < 0.001
Adjusted indirect comparison[e]:							
Intervention vs. comparator therapy							
1245.23/31 and 1275.1 vs. 1245.28							ND

(continued)

Table 5: Results (morbidity) – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) (continued)

Outcome category	Empa 10 mg + met or glimepiride + met			Empa 25 mg + met			Group difference
Outcome Study	N	Baseline values mean (SE)	Change at end of study mean[a, b] (SE)	N	Baseline values mean (SE)	Change at end of study mean[a, b] (SE)	Mean difference[b] [95% CI]; p-value
HbA1c							
Intervention vs. common comparator							
1245.23/31 (76 W)	217	7.94 (0.05)	-0.62 (0.05)	213	7.86 (0.06)	-0.74 (0.05)	0.12 [-0.02; 0.27]; ND
1275.1 (52 W)	137	8.00 (0.08)	-0.69 (0.07)	140	8.02 (0.07)	-0.64 (0.07)	-0.04 [-0.25; 0.17]; ND
Total							Heterogeneous, p = 0.19; I^2 = 47%
Comparator therapy vs. common comparator							
1245.28 (104 W)	780	7.92 (0.03)	-0.55 (0.03)	765	7.92 (0.03)	-0.66 (0.03)	0.11 [-0.02; 0.19]; ND
Adjusted indirect comparison[e]:							
Intervention vs. comparator therapy							
1245.23/31 vs. 1245.28							0.01 [-0.15; 0.17]; ND
1275.1 vs. 1245.28							-0.15 [-0.38; 0.08]; ND

a: Unless stated otherwise, LOCF analysis of the ITT population.
b: Adjusted for baseline values of HbA1c and eGFR, geographical region, and treatment.
c: Standard deviation.
d: Only analysis without imputation of missing values available. The data are not presented because the proportion of the patients who were not considered in the analysis was > 30% or the difference of the proportions of patients who were not considered was more than 15 percentage points between the groups.
e: Adjusted indirect comparison according to Bucher [12].

CI: confidence interval; eGFR: estimated glomerular filtration rate; empa: empagliflozin; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; HbA1c: glycosylated haemoglobin A1c; ITT: intention to treat; LOCF: last observation carried forward; MD: mean difference; met: metformin; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SE: standard error; vs.: versus; W: weeks

Mortality/morbidity

All-cause mortality

The adjusted indirect comparison showed no statistically significant difference between the treatment groups for the outcome “all-cause mortality”.

MACE-3

The adjusted indirect comparison showed no statistically significant difference between the treatment groups for the outcome "MACE-3". This also applied to the individual components "cardiovascular death", nonfatal myocardial infarction, and "nonfatal stroke".

Health status (EQ-5D VAS)

There were no usable data for the outcome "EQ-5D VAS".

Health-related quality of life

There were no data for the outcome "health-related quality of life".

Side effects

Severe adverse events and discontinuation due to adverse events

The adjusted indirect comparison showed no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs".

Hypoglycaemia

There were no relevant analyses for the outcome "severe hypoglycaemia".

The adjusted indirect comparison showed a statistically significant effect in favour of empagliflozin for the outcome "symptomatic hypoglycaemia" for each of both operationalizations (PG < 54 mg/dL and 54 mg/dL ≤ PG ≤ 70 mg/dL).

Specific adverse events

The adjusted indirect comparison showed no statistically significant difference between the treatment groups for the outcome "reproductive system and breast disorders".

The adjusted indirect comparison showed a statistically significant effect to the disadvantage of empagliflozin for each of the outcomes "renal and urinary disorders" and "genital infection".

2.1.3.3 Summary of the indirect comparison

Table 6 summarizes the positive and negative effects of empagliflozin 10 mg.

Table 6: Positive and negative effects of empagliflozin 10 mg, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin)

Positive effects	**Negative effects**
Side effects ▪ Symptomatic hypoglycaemia	Side effects ▪ Renal and urinary disorders ▪ Genital infection
vs.: versus	

Overall, neither an advantage nor a disadvantage of empagliflozin 10 mg versus glimepiride (each in combination with metformin) could be derived from the indirect comparison.

2.2 Study EMPA-REG

The EMPA-REG study was already comprehensively assessed in dossier assessment A16-12. The assessment concluded that, on the basis of the information provided in the company's dossier, the EMPA-REG study was unsuitable for a comparison with the G-BA's ACT or for a comparison with "standard treatment".

- A comparison with the G-BA's ACT was impossible because treatment in the comparator group in the EMPA-REG study was not conducted according to the G-BA's specifications. For example, patients in whom combination therapy with metformin and a sulfonylurea was inadequate were not switched to the ACT (human) insulin with or without metformin. Instead, the ongoing treatment was continued, and after 3 months, any treatment adjustment was possible. In addition, the company itself did not assess the EMPA-REG study in the context of the G-BA's ACT in the dossier[3].
- The EMPA-REG study was also unsuitable for the comparison with "standard treatment". On the one hand, "standard treatment" was only defined insofar as treatment was to follow local guidelines. Since the study was conducted at a multinational and multicontinental level, no uniform "standard" could therefore be assumed. There was no specific information on the recommendations contained in the respective local guidelines or on their commonalities and differences. On the other hand, no guideline-oriented treatment was recognizable in the EMPA-REG study despite the respective requirement. Although, according to the inclusion criteria, only patients with inadequate glycaemic control who would have required treatment escalation were enrolled in the EMPA-REG study, such treatment escalation was neither visible in the blood glucose levels in the course of the EMPA-REG study nor in relevant adjustments of blood-glucose lowering treatment.

Dossier assessment A16-12 [1] contains a detailed description of the design of the EMPA-REG study, the baseline characteristics of the patients included and of the aspects mentioned above. In compliance with the commission, the present addendum additionally contains a presentation of the results of the EMPA-REG study.

Results of the EMPA-REG study

In its dossier, the company primarily used the total population of the EMPA-REG study for its assessment. In addition, it presented subgroup analyses on selected (not all prespecified, see below) subgroups, but derived no conclusions deviating from the assessment in the total population from them.

[3] With its comments, the company had presented data on a selected subpopulation (patients treated with insulin plus metformin), which constituted a subgroup of research question C of dossier assessment A16-12. These data were also unsuitable for a comparison with the ACT, however, because apparently no treatment escalation concurring with an ACT was conducted in this subpopulation either. This could be inferred from the information on treatment escalation in the total population. In its comments, the company presented no specific information on the treatment escalation for the subpopulation mentioned.

The results on the total population of the EMPA-REG study can be found in Appendix A of the present assessment. Both the results for the pooled empagliflozin arms versus placebo and, separately, the results of both dose arms of empagliflozin (10 mg and 25 mg daily) are presented.

Advantage of empagliflozin versus non-guideline-compliant treatment in the study population, no approval-compliant assessment possible

Results in the study population

The results presented in Appendix A show a statistically significant result in favour of empagliflozin for some of the relevant outcomes (pooled analysis for both dose arms; results on individual dose arms largely consistent).

This particularly applied to all-cause mortality (mainly caused by a difference in cardiovascular mortality[4]), to outcomes on cardiac failure, and to the outcome "renal failure". The result was not statistically significant for nonfatal myocardial infarction and the joint consideration of fatal and nonfatal myocardial infarction. A direction of effect to the disadvantage of empagliflozin was shown for stroke; the result was also not statistically significant. No statistically significant result was shown for the outcomes on diabetes-related eye disorders.

The results on overall AE rates (SAEs and discontinuations due to AEs) were not usable because late complications that are already represented by the outcomes mentioned above were also recorded under these outcomes (see Table 9 in Appendix A on the most common SAEs for illustration). The company did not present analyses on overall AE rates without recording of the late complications. Regarding specific AEs, no noticeable difference was shown in the occurrence of hypoglycaemia, with no usable analyses being available on the outcome "severe hypoglycaemia". There was a statistically significant result to the disadvantage of empagliflozin for the outcomes "reproductive system and breast disorders" (SOC) and "genital infection", whereas the result was not statistically significant for the SOC "renal and urinary disorders".

Particularly due to the result on all-cause mortality, the advantages of empagliflozin versus placebo (in addition to non-guideline-compliant treatment) observed in the EMPA-REG study outweighed the disadvantages. It is unclear, however, whether this also applied to patients who received approval-compliant treatment in the EMPA-REG study because no such analyses were available.

[4] 309 of 463 deaths had cardiovascular causes (67%). 124 of these deaths were evaluated as "cardiovascular", although they were "non-assessable" [13]. This potentially incorrect allocation did not influence the conclusion on all-cause mortality.

No approval-compliant treatment in a relevant proportion of the EMPA-REG study

According to the Summary of Product Characteristics (SPC), empagliflozin is not approved for initiating treatment in patients with an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 [14]. The company used an inconsistent approach regarding this aspect: It considered this in the research questions A to D (Module A to C, assessments versus the ACT, see dossier assessment A16-12), but not in the assessment of the EMPA-REG study. In the EMPA-REG study, the eGFR was below 60 mL/min/1.73 m^2 in 26% of the patients. Regarding the treatment arm of the patients with 25 mg daily (and therefore also regarding the analysis of the pooled empagliflozin arms), the proportion of the patients who were not treated in compliance with the approval was presumably even larger. In patients with an eGFR above 60 mL/min/1.73 m^2 that falls below this level in the course of treatment with 25 mg empagliflozin, the dose of empagliflozin should be reduced to 10 mg daily [14]. This was not mandated in the EMPA-REG study. The proportion of those patients in the 25 mg arm with an eGFR level above 60 mL/min/1.73 m^2 at the start of the study who were affected by this is unclear.

Overall, no conclusion on the approval-compliant use of empagliflozin could therefore be drawn on the basis of the total population.

The use of empagliflozin monotherapy without proving metformin intolerance constituted a further deviation from the SPC in the EMPA-REG study. This was irrelevant for the informative value of the EMPA-REG study, however, because fewer than 2% of the study population were treated with empagliflozin monotherapy. As a result, the EMPA-REG study can provide no conclusion for empagliflozin monotherapy also irrespective of further deficits.

Selective subgroup analyses of the company, inadequate analyses on regional influences

Subgroup analyses were not available for all prespecified characteristics

The company used different subgroup analyses in its dossier and presented them in Module 4. Contrary to the requirements in the G-BA's dossier templates, the company did not describe all subgroup characteristics prespecified in the study, but only a selection of them in Module 4. The company justified this with the availability of analyses on individual outcomes. This was incomprehensible on the one hand because it had the individual data of the study and also conducted additional analyses to a major extent for the present benefit assessment [15]. On the other, these additional analyses in Module 5 partly contain subgroup analyses, which the company did not use for its assessment in Module 4.

Regional effects could not be finally clarified

Indications or proof of an effect modification for some characteristics resulted from the analyses available in Module 4 of the dossier. This also applied to those characteristics that may be associated with the health care of the patients, e.g. region.

It was described in dossier assessment A16-12 that the effects observed in the regions Asia and Latin America were partly not visible in Europe in the same way (i.e. that there were

either qualitative or quantitative differences). For example, there was an indication of an effect modification by the characteristic "region" both for the primary outcome "MACE-3" of the EMPA-REG study and for its individual components "cardiovascular mortality", which the company used as an important outcome to justify an added benefit of empagliflozin, and "nonfatal stroke" (p = 0.128 and p = 0.145 and p = 0.083). There were 5 categories (regions) to this characteristic: Europe, North America, Latin America, Asia, and Africa. As already presented in dossier assessment A16-12, the effect estimates of the regions Latin America and Asia differed notably from those of other regions regarding the outcome "cardiovascular mortality". Accordingly, a corresponding subgroup analysis of the regions Latin America and Asia on one side versus the other 3 regions on the other side showed proof of an interaction between these 2 groups (p = 0.01; see Figure 1 in Appendix A). The result was statistically significant also for the group of regions including Europe, but the effect was smaller than in the group of Latin America/Asia. There was a similar picture for the outcome "MACE-3", where the result of the group of regions including Europe was not statistically significant (see Figure 2 in Appendix A), however. The picture was different for the outcome "nonfatal stroke", where there was also an indication of interaction for the characteristic "region" (p = 0.083). There was a disadvantage of empagliflozin in the region Europe (HR 2.06 [1.23; 3.46]; p = 0.006; see Figure 17 in dossier assessment A16-12), whereas there was no noticeable difference between the treatment groups in the other regions (Figures 18 to 21 in dossier assessment A16-12).

As mentioned in dossier assessment A16-12, the results mentioned give reason to further analyses on the influence of the regions beyond these subgroup analyses. In particular, analyses by region on the courses of blood glucose and blood pressure as well as on blood-glucose and blood-pressure lowering treatment would be required. The company did not present such analyses in the commenting procedure either. Similarly, analyses that consider the health care situation in Europe in a differentiated way would be meaningful in the present case because of their potential heterogeneity: The region Europe created by the company contained centres from East European countries to a major extent (a total of about 46% of the patients allocated to the region Europe were treated in these countries).

Analyses subsequently submitted by the company confirmed inadequate "standard treatment"

In the oral hearing, the company referred to different sensitivity analyses, which it considered to show the robustness of the results of the EMPA-REG study. Most of these sensitivity analyses did not address the problem that, contrary to the requirements stipulated in the study protocol, "standard treatment" was inadequate and were therefore unsuitable to refute this argument. As described above, among other things, there were no analyses on a more detailed analysis of regional differences, regarding both "standard treatment" and the results of the EMPA-REG study.

One of the analyses subsequently submitted by the company addressed the quality of both the antihypertensive and the lipid-lowering treatment, which, according to the study protocol,

were also to be conducted in compliance with the guidelines as part of the standard treatment. This analysis did not show that "standard treatment" was adequate, however, but rather showed its inadequacy.

The company's analysis considered 2 subgroups of patients: patients with and patients without adequate blood-pressure and lipid-lowering treatment. Adequate treatment was defined as a systolic blood pressure below 140 mmHg and a diastolic blood pressure below 90 mmHg as well as an LDL cholesterol level below 100 mg/dL. The values for these 3 parameters were calculated for each patient as a mean value over the course of the study. According to this, the characteristic was influenced by the treatment itself and therefore unsuitable for subgroup analyses as conducted by the company because randomized allocation to the respective groups was no longer guaranteed. The number of the patients allocated to both groups described the quality of the blood-pressure and lipid-lowering treatment, however: The analysis determined inadequate blood pressure and lipid control in 3400 of 7020 patients (48%), although blood pressure and lipid control was an explicit treatment goal of the "standard treatment". The proportion of patients with inadequate treatment was higher in the comparator group (51%) than in the empagliflozin group (pooled dose arms, 47%). The difference was statistically significant ($p = 0.002$).

In summary, the quality of treatment in the EMPA-REG study failed to meet the requirements placed on such treatment in Germany, as formulated in the appropriate disease management programmes, for example, not only regarding blood glucose treatment, but also regarding blood pressure treatment. It therefore remains unclear what the results of the EMPA-REG study mean for Germany.

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Appendix A – Results of the EMPA-REG study

Table 7: Results of the EMPA-REG study: empagliflozin (pooled dose arms) vs. placebo

Study Outcome category Outcome	Empagliflozin		Placebo		Empagliflozin vs. placebo
	N	Patients with event n (%)	N	Patients with event n (%)	HR [95% CI]; p-value
EMPA-REG					
Mortality/morbidity					
All-cause mortality	4687	269 (5.7)	2333	194 (8.3)	0.68 [0.57; 0.82]; < 0.001
MACE-3	4687	490 (10.5)	2333	282 (12.1)	0.86 [0.74; 0.99]; 0.038
Cardiovascular death	4687	172 (3.7)	2333	137 (5.9)	0.62 [0.49; 0.77]; < 0.001
Nonfatal myocardial infarction	4687	213 (4.5)	2333	121 (5.2)	0.87 [0.70; 1.09]; 0.219
Nonfatal stroke	4687	150 (3.2)	2333	60 (2.6)	1.24 [0.92; 1.67]; 0.164
Myocardial infarction (fatal and nonfatal)	4687	223 (4.8)	2333	126 (5.4)	0.87 [0.70; 1.09]; 0.230
Stroke (fatal and nonfatal)	4687	164 (3.5)	2333	69 (3.0)	1.18 [0.89; 1.56]; 0.257
TIA	4687	39 (0.8)	2333	23 (1.0)	0.85 [0.51; 1.42]; 0.537
Cardiac failure					
Hospitalization due to cardiac failure	4687	126 (2.7)	2333	95 (4.1)	0.65 [0.50; 0.85]; 0.002
Severe cardiac failure (SMQ)	4687	192 (4.1)	2333	136 (5.8)	0.69 [0.55; 0.86]; 0.001
Retinal photocoagulation	4687	41 (0.9)	2333	29 (1.2)	0.69 [0.43; 1.12]; 0.134
Vitreous haemorrhage	4687	30 (0.6)	2333	16 (0.7)	0.93 [0.51; 1.71]; 0.815
Diabetes-related blindness	4687	4 (0.1)	2333	2 (0.1)	NC
Renal failure[a]	4645	70 (1.5)	2323	60 (2.6)	0.56 [0.39; 0.79]; < 0.001
Side effects					**RR [95% CI]; p-value**
AEs (supplementary information)	4687	4230 (90.2)	2333	2139 (91.7)	–
SAEs	4687	1789 (38.2)	2333	988 (42.3)	Not usable[b]
Discontinuation due to AEs	4687	813 (17.3)	2333	453 (19.4)	Not usable[b]
Severe hypoglycaemia	No relevant analysis was available for this outcome.				
Symptomatic hypoglycaemia (PG < 54 mg/dL)	4687	522 (11.1)	2333	259 (11.1)	1.00 [0.87; 1.15]; 0.973[c]
Symptomatic hypoglycaemia (54 mg/dL ≤ PG ≤ 70 mg/dL)	4687	460 (9.8)	2333	231 (9.9)	0.99 [0.85; 1.15]; 0.940[c]
Renal and urinary disorders[d]	4687	912 (19.5)	2333	492 (21.1)	0.92 [0.84; 1.02]; 0.111[c]
Reproductive system and breast disorders[d]	4687	438 (9.3)	2333	136 (5.8)	1.60 [1.33; 1.93]; < 0.001[c]
Genital infection[e]	4687	301 (6.4)	2333	42 (1.8)	3.57 [2.59; 4.91]; < 0.001[f]

(continued)

Table 7: Results of the EMPA-REG study: empagliflozin (pooled dose arms) vs. placebo (continued)

a: Time to doubling of serum creatinine level accompanied by an eGFR ≤ 45 mL/min/1.73m^2. Results on the outcome "initiation of continuous renal replacement therapy" are consistent with this with an imprecise effect estimation (HR: 0.45 [0.21; 0.97]; p = 0.041).
b: Overall rates not usable due to the recording of late complications.
c: Institute's calculation of effect, 95% CI (asymptotic) and p-value (unconditional exact test; CSZ method according to Andrés [10]).
d: Analysis by MedDRA SOC.
e: Analysis (pre)planned according to MedDRA query developed by the company.
f: Institute's calculation of the p-value, unconditional exact test (CSZ method according to Andrés [10]).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; empa: empagliflozin; HR: hazard ratio; MACE: major adverse cardiovascular events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; ND: no data; RCT: randomized controlled trial; PG: plasma glucose; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; TIA: transient ischaemic attack; vs.: versus

Table 8: Results of the EMPA-REG study: empagliflozin (separate dose arms: 10 mg or 25 mg daily) vs. placebo

Study Outcome category Outcome	Empa 10 mg		Empa 25 mg		Placebo		Empa 10 mg vs placebo	Empa 25 mg vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)	HR [95% CI]; p-value	HR [95% CI]; p-value
EMPA-REG								
Mortality/morbidity								
All-cause mortality	2345	137 (5.8)	2342	132 (5.6)	2333	194 (8.3)	0.70 [0.56; 0.87]; 0.001	0.67 [0.54; 0.83]; < 0.001
MACE-3	2345	243 (10.4)	2342	247 (10.5)	2333	282 (12.1)	0.85 [0.72; 1.01]; 0.067	0.86 [0.73; 1.02]; 0.087
Cardiovascular death	2345	90 (3.8)	2342	82 (3.5)	2333	137 (5.9)	0.65 [0.50; 0.85]; 0.002	0.59 [0.45; 0.77]; < 0.001
Nonfatal myocardial infarction	2345	96 (4.1)	2342	117 (5.0)	2333	121 (5.2)	0.79 [0.60; 1.03]; 0.077	0.95 [0.74; 1.23]; 0.711
Nonfatal stroke	2345	77 (3.3)	2342	73 (3.1)	2333	60 (2.6)	1.27 [0.91; 1.79]; 0.159	1.20 [0.85; 1.69]; 0.295
Myocardial infarction (fatal and nonfatal)	2345	101 (4.3)	2342	122 (5.2)	2333	126 (5.4)	0.79 [0.61; 1.03]; 0.085	0.95 [0.74; 1.22]; 0.714
Stroke (fatal and nonfatal)	2345	85 (3.6)	2342	79 (3.4)	2333	69 (3.0)	1.22 [0.89; 1.68]; 0.212	1.13 [0.82; 1.56]; 0.459
TIA	2345	19 (0.8)	2342	20 (0.9)	2333	23 (1.0)	0.83 [0.45; 1.53]; 0.560	0.87 [0.48; 1.58]; 0.636
Cardiac failure (CF)								
Hospitalization due to CF	2345	60 (2.6)	2342	66 (2.8)	2333	95 (4.1)	0.62 [0.45; 0.86]; 0.004	0.68 [0.50; 0.93]; 0.017
Severe CF (SMQ)	2345	99 (4.2)	2342	93 (4.0)	2333	136 (5.8)	0.72 [0.55; 0.93]; 0.012	0.67 [0.51; 0.87]; 0.003
Retinal photocoagulation	2345	20 (0.9)	2342	21 (0.9)	2333	29 (1.2)	0.68 [0.38; 1.20]; 0.183	0.71 [0.41; 1.25]; 0.233
Vitreous haemorrhage	2345	17 (0.7)	2342	13 (0.6)	2333	16 (0.7)	1.06 [0.54; 2.10]; 0.866	0.80 [0.39; 1.67]; 0.553
Diabetes-related blindness	2345	1 (< 0.1)	2342	3 (0.1)	2333	2 (0.1)	NC	NC
Renal failure[a]	2323	42 (1.8)	2322	28 (1.2)	2323	60 (2.6)	0.67 [0.45; 1.00]; 0.048	0.44 [0.28; 0.69]; < 0.001

(continued)

Table 8: Results of the EMPA-REG study: empagliflozin (separate dose arms: 10 mg or 25 mg daily) vs. placebo (continued)

Study Outcome category Outcome	Empa 10 mg		Empa 25 mg		Placebo		Empa 10 mg vs placebo	Empa 25 mg vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value	RR [95% CI]; p-value
Side effects								
AEs (supplementary information)	2345	2112 (90.1)	2342	2118 (90.4)	2333	2139 (91.7)	–	–
SAEs	2345	876 (37.4)	2342	913 (39.0)	2333	988 (42.3)	Not usable[b]	Not usable[b]
Discontinuation due to AEs	2345	416 (17.7)	2342	397 (17.0)	2333	453 (19.4)	Not usable[b]	Not usable[b]
Severe hypoglycaemia	No relevant analysis was available for this outcome.							
Symptomatic hypoglycaemia								
PG < 54 mg/dL	2345	257 (11.0)	2342	265 (11.3)	2333	259 (11.1)	0.99 [0.84; 1.16]; 0.917[c]	1.02 [0.87; 1.20]; 0.878[c]
54 ≤ PG ≤ 70 mg/dL	2345	240 (10.2)	2342	220 (9.4)	2333	231 (9.9)	1.03 [0.87; 1.23]; 0.770[c]	0.95 [0.80; 1.13]; 0.574[c]
Renal and urinary disorders[d]	2345	454 (19.4)	2342	458 (19.6)	2333	492 (21.1)	0.92 [0.82; 1.03]; 0.147[c]	0.93 [0.83; 1.04]; 0.248[c]
Reproductive system and breast disorders[d]	2345	218 (9.3)	2342	220 (9.4)	2333	136 (5.8)	1.59 [1.30; 1.96]; < 0.001[c]	1.61 [1.31; 1.98]; < 0.001[c]
Genital infection[e]	2345	153 (6.5)	2342	148 (6.3)	2333	42 (1.8)	3.62 [2.59; 5.07]; < 0.001[f]	3.51 [2.50; 4.92]; < 0.001[f]

a: Time to doubling of serum creatinine level accompanied by an eGFR ≤ 45 mL/min/1.73m^2. Results on the outcome "initiation of continuous renal replacement therapy" are consistent with this with an imprecise effect estimation (empagliflozin 10 mg: HR 0.21 [0.06; 0.74], p = 0.015; empagliflozin 25 mg: HR: 0.70 [0.31; 1.57]; p = 0.381).
b: Overall rates not usable due to the recording of late complications.
c: Institute's calculation of effect, 95% CI (asymptotic) and p-value (unconditional exact test; CSZ method according to Andrés [10]).
d: Analysis by MedDRA SOC.
e: Analysis (pre)planned according to MedDRA query developed by the company.
f: Institute's calculation of the p-value, unconditional exact test (CSZ method according to Andrés [10]).

AE: adverse event; CI: confidence interval; CF: cardiac failure; CSZ: convexity, symmetry, z score; empa: empagliflozin; HR: hazard ratio; MACE: major adverse cardiovascular events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; PG: plasma glucose; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; TIA: transient ischaemic attack; vs.: versus

Table 9: Results of the EMPA-REG study: common SAEs (≥ 1% in at least one study arm)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Empagliflozin** **N = 4687**	**Placebo** **N = 2333**
EMPA-REG		
Overall rate of SAEs	1789 (38.2)	988 (42.3)
Infections and infestations	360 (7.7)	213 (9.1)
Pneumonia	79 (1.7)	53 (2.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	219 (4.7)	87 (3.7)
Metabolism and nutrition disorders	79 (1.7)	61 (2.6)
Nervous system disorders	306 (6.5)	159 (6.8)
Cerebrovascular accident	83 (1.8)	31 (1.3)
Transient ischaemic attack	53 (1.1)	23 (1.0)
Cardiac disorders	652 (13.9)	398 (17.1)
Angina unstable	155 (3.3)	87 (3.7)
Cardiac failure	66 (1.4)	55 (2.4)
Myocardial infarction	94 (2.0)	47 (2.0)
Acute myocardial infarction	80 (1.7)	42 (1.8)
Coronary artery disease	50 (1.1)	46 (2.0)
Cardiac failure congestive	65 (1.4)	45 (1.9)
Angina pectoris	78 (1.7)	32 (1.4)
Vascular disorders	191 (4.1)	116 (5.0)
Peripheral arterial occlusive disease	58 (1.2)	23 (1.0)
Respiratory, thoracic and mediastinal disorders	101 (2.2)	75 (3.2)
Gastrointestinal disorders	169 (3.6)	85 (3.6)
Hepatobiliary disorders	51 (1.1)	19 (0.8)
Skin and subcutaneous tissue disorders	48 (1.0)	29 (1.2)
Musculoskeletal and connective tissue disorders	135 (2.9)	78 (3.3)
Renal and urinary disorders	112 (2.4)	73 (3.1)
Acute kidney injury	45 (1.0)	32 (1.4)
General disorders and administration site conditions	154 (3.3)	94 (4.0)
Chest pain	65 (1.4)	28 (1.2)
Investigations	33 (0.7)	29 (1.2)
Injury, poisoning and procedural complications	129 (2.8)	77 (3.3)

a: MedDRA version 18.0.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

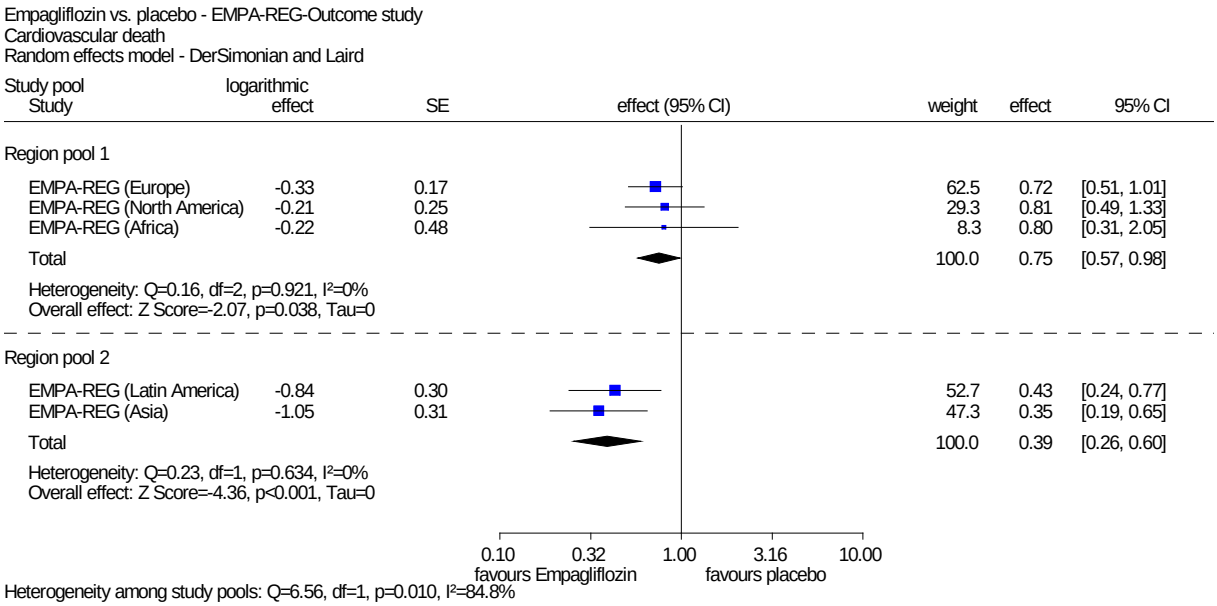

Figure 1: Subgroup analyses by region for the outcome “cardiovascular death” – Europe/North America/Africa (pool 1) vs. Latin America/Asia (pool 2)

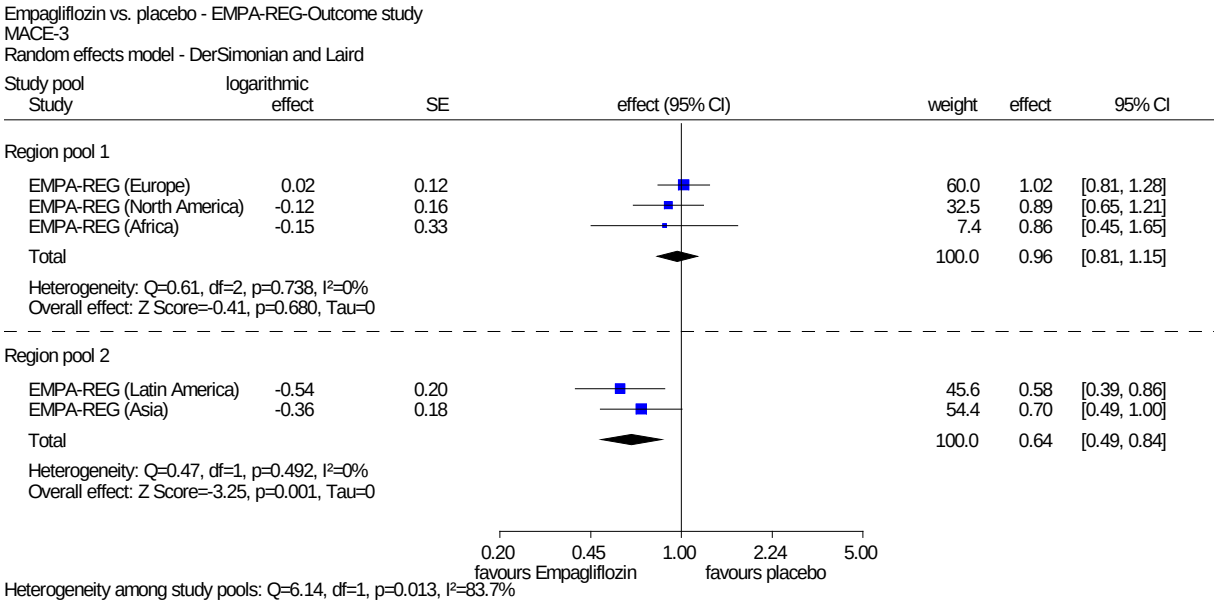

Figure 2: Subgroup analyses by region for the outcome “MACE-3” – Europe/North America/Africa (pool 1) vs. Latin America/Asia (pool 2)