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Addendum

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Table of contents

Page

List of tables iv
List of abbreviations v
1 Background 1
2 Assessment 2
2.1 Indirect comparison with the common comparator empagliflozin 25 mg 2
2.2 Indirect comparison with the common comparator linagliptin 5
2.3 Summary 5
3 References 6
Appendix A – Results of the studies 1245.28, 1245.23/31 and 1275.1 7
Appendix B – Indirect comparisons (common comparator empagliflozin 25 mg) under consideration of the total observation period of the individual studies 15

List of tables

Page

Table 1: Results mortality and morbidity – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) – results after 52 weeks 8

Table 2: Results adverse events – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) – results after 52 weeks 9

Table 3: Results continuous outcomes – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) – results after 52 weeks 12

Table 4: Results on dichotomous outcomes of Study 1245.23/31 (76 weeks) 13

Table 5: Results on continuous outcomes of Study 1245.23/31 (76 weeks)..... 14

Table 6: Results on indirect comparisons: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) under consideration of the total observation period of the individual studies 15

List of abbreviations

Abbreviation	Meaning
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class

1 Background

On 22 December 2014, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A14-26 (Empagliflozin – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In the dossier on empagliflozin, the pharmaceutical company (hereinafter referred to as "the company") had presented 2 indirect comparisons with 2 different common comparators on empagliflozin for the subindication "combination therapy with metformin", in which empagliflozin 10 mg daily was compared with glimepiride (each plus metformin) [2]. The dossier assessment on empagliflozin showed that the indirect comparison with the common comparator empagliflozin 25 mg (plus metformin) was incomplete because the company had not included the relevant study 1245.23 (plus extension study 1245.31) [1]. For the indirect comparison with the common comparator linagliptin (plus metformin), the company had included Study 1218.20 on linagliptin, in which different therapeutic strategies, and hence not only the drugs linagliptin and glimepiride, were compared.

The company presented further analyses and information on the indirect comparisons between empagliflozin 10 mg versus glimepiride (each plus metformin) with its comment [3]. The G-BA therefore commissioned IQWiG with the assessment of the indirect comparisons presented by the company in the dossier and in the commenting procedure.

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

The indirect comparisons presented by the company on the subindication "empagliflozin plus metformin" aimed to investigate the research question whether there is an added benefit of empagliflozin in the 10 mg dosage versus glimepiride (each in combination with metformin). These indirect comparisons are initially assessed separately in the following Sections 2.1 (common comparator empagliflozin 25 mg) and 2.2 (common comparator linagliptin). An overall conclusion on the added benefit can be found in Section 2.3.

2.1 Indirect comparison with the common comparator empagliflozin 25 mg

In its dossier, the company presented an indirect comparison between empagliflozin 10 mg versus glimepiride (each in combination with metformin) with the common comparator empagliflozin 25 mg (plus metformin) (referred to as "indirect comparison I" by the company). It had included Study 1245.28 (comparison empagliflozin 25 mg versus glimepiride) on one side, and Study 1275.1 (comparison empagliflozin 25 mg versus empagliflozin 10 mg) on the other side [2].

Although Study 1245.23 (comparison empagliflozin 25 mg versus empagliflozin 10 mg) also fulfilled the inclusion criteria for the indirect comparison described by the company in the dossier (both with and without consideration of the subsequent extension phase 1245.31), the company did not consider this study for the indirect comparison presented in the dossier. The indirect comparison I presented in the company's dossier was therefore incomplete [1].

With its comment, the company presented a new indirect comparison III, in which it also included Study 1245.23 including its extension phase 1245.31 (hereinafter referred to as "1245.23/31") [3]. No further relevant studies on these comparisons were identified in the check of the completeness of the study pool so that, with the presentation of the indirect comparison III, the company had considered all relevant studies.

Assessment of the comparability of the contents of the studies

A detailed description of the design and the patient characteristics of the 3 studies 1245.28, 1275.1 and 1245.23/31 can be found in dossier assessment A14-26 [1].

There were no relevant differences in the inclusion or exclusion criteria regarding the baseline data of the patients that would raise doubts about the comparability of the contents of the 3 studies. However, 2 other aspects had to be taken into account in the assessment of the similarity of the contents:

- In Study 1245.28, empagliflozin 25 mg (fixed dose) was compared with a target-level directed glimepiride treatment. It was explained in dossier assessment A14-26 that different treatment regimens were used in the study, but that the joint consideration of the time course of the HbA1c value and the hypoglycaemia suggested that the greater frequency of hypoglycaemia under glimepiride cannot be explained by the difference in

blood-glucose lowering alone. The overall substance-specific effect on hypoglycaemia (or its magnitude) was unclear, however [1].

- The duration differed between the 3 studies and was 1 year (52 weeks; Study 1275.1), 1.5 years (76 weeks; Study 1245.23/31) and 2 years (104 weeks; Study 1245.28) respectively. In the indirect comparison III, the company therefore used the data after 1 year for the studies 1245.23/31 and 1245.28. Such an analysis is initially meaningful and solves the problem of different observation periods, but it entails a loss of information, the relevance of which is to be evaluated on an individual basis. The loss of information was particularly important in the present case because the shortest study (1275.1) was also the one with the lowest number of patients included. Hence it would have been meaningful to present analyses after 76 weeks (duration of Study 1245.23/31; corresponding interim analysis required for Study 1245.28) and/or analyses under consideration of the respective overall duration of the studies, at least as additional information. In the present case, this also did not raise doubts about the similarity of the contents of the studies because the effects on patient-relevant outcomes, e.g. in Study 1245.28 after 52 weeks, were less precise, but largely consistent with those after 104 weeks (see Table 1 and Table 2 in Appendix A and analyses on Study 1245.28 after 104 weeks in dossier assessment A14-26 [1]).

Assessment of the indirect comparison

The results of the indirect comparison III presented by the company can be found in Table 1 to Table 3 in Appendix A.

Based on the results presented by the company with the indirect comparison III, there was no statistically significant result in favour of empagliflozin in any of the patient-relevant outcomes (the company calculated no indirect comparison for the outcome “symptomatic hypoglycaemia with a plasma glucose level under 54 mg/dL”), but there was a statistically significant result to the disadvantage of empagliflozin in the outcome “genital infection”.

However, the company did not present the indirect comparison for all relevant outcomes presented in dossier assessment A14-26 on Study 1245.28. There were no analyses on all-cause mortality, cardio- and cerebrovascular events, symptomatic hypoglycaemia (confirmed by a plasma glucose level between 54 and 70 mg/dL), discontinuations due to adverse events, reproductive system and breast disorders (System Organ Class [SOC]) and renal and urinary disorders (SOC). Since there were no results after 52 weeks for these outcomes for Study 1245.23/31 alone, it was not possible for the Institute to calculate the analyses. Moreover, results on severe hypoglycaemia were missing completely. The clinical study reports also did not contain these results in an adequate operationalization (see dossier assessment A14-26 [1] for reasons).

Under consideration of the available results on the 3 individual studies (on different observation periods) it can be assumed that the overall weighing of benefits and harms on the

added benefit may be influenced particularly by analyses on the outcomes “symptomatic hypoglycaemia (confirmed by a plasma glucose level between 54 and 70 mg/dL)”, “renal and urinary disorders” and “reproductive system and breast disorders”. Only few events occurred in the outcomes “all-cause mortality” and “cardio- and cerebrovascular events”, and there was no marked difference between the treatment groups in the individual studies.

Moreover, under consideration of the results in the individual studies and those of the indirect comparison III, particularly for the outcomes “serious adverse events” and “symptomatic hypoglycaemia (confirmed by a plasma glucose level under 54 mg/dL)”, it can be assumed that the loss of information from sole consideration of the 52-week data may have influence on the overall conclusion. In both outcomes, there was a statistically significant difference between the treatment groups in the largest study 1245.28 (once in favour [hypoglycaemia], once to the disadvantage [serious adverse events] of empagliflozin), whereas there was no statistically significant difference in the indirect comparison III (with imprecise results or missing calculation by the company).

Hence indirect comparisons under consideration of the total study duration of the 3 individual studies on the 5 outcomes mentioned were calculated by the Institute (analyses after 76 weeks could not be calculated because these data were not available for Study 1245.28). The results are presented in Appendix B.

There was a statistically significant result in favour of empagliflozin for the outcome “symptomatic hypoglycaemia”, both in the operationalization of plasma glucose < 54 mg/dL and in the operationalization of 54 mg/dL ≤ plasma glucose ≤ 70 mg/dL. The limitations due to the target-level directed therapeutic strategy in the glimepiride arm mentioned above apply to the interpretation of the results on hypoglycaemia. The positive results in hypoglycaemia are offset by statistically significant results to the disadvantage of empagliflozin regarding both renal and urinary disorders and genital infection. The result was not statistically significant with imprecise effect estimation for the outcomes “serious adverse events” and “reproductive system and breast disorders”.

The statistically significant results in favour and to the disadvantage of empagliflozin were limited to the area of non-serious adverse events. There were no statistically significant results in the area of serious adverse events. Only few data were available on serious late complications because the individual studies were not aimed at recording these outcomes.

Overall, there was neither proof of added benefit nor of lesser benefit of empagliflozin 10 mg versus glimepiride (each in combination with metformin) when comparing the lower rate of hypoglycaemia on the one hand with the higher rate of renal and urinary disorders and genital infection on the other hand.

2.2 Indirect comparison with the common comparator linagliptin

In its dossier, the company presented an indirect comparison between empagliflozin 10 mg versus glimepiride (each in combination with metformin) with the common comparator linagliptin (plus metformin) (referred to as "indirect comparison II" by the company). It had included Study 1275.1 (comparison empagliflozin 10 mg versus linagliptin) on one side, and Study 1218.20 (comparison linagliptin versus glimepiride) on the other side. No further studies on these 2 comparisons were identified from the check of the completeness of the study pool.

Assessment of the comparability of the contents of the studies

A detailed description of the design and the patient characteristics of Study 1275.1 can be found in dossier assessment A14-26 [1]; Study 1218.20 is described in detail in dossier assessment A12-11 (linagliptin) [6].

There were important differences between the 2 studies so that no sufficient similarity of contents can be assumed. Hence the indirect comparison II presented by the company is not interpretable.

Whereas patients with an HbA1c value of 7% or higher were included in Study 1275.1, patients with an HbA1c value as low as 6.5% or 6% (depending on the pretreatment) were included in Study 1218.20. Correspondingly, the mean baseline HbA1c value in Study 1218.20 was 7.7% and hence below the value in Study 1275.1 (8.0%) [2,6].

Moreover, the results of Study 1218.20, particularly the ones on hypoglycaemia and cerebrovascular events, were not interpretable, which is why no added benefit of linagliptin could be derived despite statistically significant differences in these outcomes [6,7]. Also in this study, not only drugs, but different therapeutic strategies were compared. In contrast to Study 1245.28 with empagliflozin described above, the results on these outcomes were not interpretable at all as substance-specific difference based on the joint consideration of the time course of the HbA1c value and hypoglycaemia or cerebrovascular events.

2.3 Summary

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 with the common comparator empagliflozin 25 mg.

The indirect comparison with the common comparator linagliptin was not interpretable.

Overall, the added benefit of empagliflozin 10 mg in the subindication "combination with metformin" versus the appropriate comparator therapy is not proven.

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Appendix A – Results of the studies 1245.28, 1245.23/31 and 1275.1

The results of the 3 individual studies that were included in the indirect comparison with the common comparator empagliflozin 25 mg are presented in this Appendix. The data extraction resulted in individual discrepancies between the data presented by the company in Module 4 B of the dossier or in its comment and the information provided in the clinical study reports of the respective studies. In these cases, the information in the respective study report was used.

Reasons for the choice of outcomes presented are given in dossier assessment A14-26 [1]. No doubts were raised about this choice by the company's rationale in its comment. Regarding the outcome "renal and urinary disorders", it should be noted that this outcome contained relevant events even though not all of these events are to be categorized as urinary tract infection (hence the outcome is not referred to as "urinary tract infection" in the present assessment). The company, in contrast, excluded relevant events in its consideration conducted post hoc in the comments, even though these may be symptoms of a urinary tract infection (e.g. dysuria, bladder symptoms, micturition symptoms). Regarding the outcome "reproductive system and breast disorders (SOC)" it should be noted that the observed difference cannot be solely explained by the argument of overlap with the outcome "genital infection" put forward by the company. The majority of the events recorded in the SOC were not comprised in the predefined outcome "genital infection". In the comments, the company post hoc excluded Preferred Terms (PTs) that are not comprised in the outcome "genital infection" (e.g. vulvovaginal pruritus, pruritus genital) to support its argument of overlapping. This actually contradicts its rationale, however, because markedly more events occurred under empagliflozin than under glimepiride in Study 1245.28 particularly in these PTs excluded post hoc.

The following tables Table 1, Table 2 and Table 3 show the results of the studies 1245.28, 1245.23/31 and 1275.1, in each case after an observation period of 52 weeks. The indirect comparisons conducted by the company are also shown in these tables; the company conducted such analyses for only 2 of the outcomes presented. Subsequently, the results of Study 1245.23/31 over the total duration of this study (76 weeks) are shown in Table 4 and Table 5. The results of Study 1245.28 over the total duration of this study (104 weeks) can be found in dossier assessment A14-26 [1].

Table 1: Results mortality and morbidity – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) – results after 52 weeks

Outcome category **outcome** comparison study	**Empa 10 mg + met or glimepiride + met**		**Common comparator empa 25 mg + met**		**Group difference**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
Mortality					
All-cause mortality					
Empa 10 mg + met vs. empa 25 mg + met					
1275.1	140	1 (0.7)	141	0 (0)	3.02 [0.12; 73.54][a]; 0.367[b]
1245.23/31		ND		ND	ND
Glimepiride + met vs. empa 25 mg + met					
1245.28	780	3 (0.4)	765	4 (0.5)	POR: 0.74 [0.17; 3.25]; 0.723[c]
Adjusted indirect comparison[d]:					
Empa 10 mg + met vs. glimepiride + met					
1275.1 and 1245.23/31 vs. 1245.28					**ND**
Morbidity					
MACE 3					
Empa 10 mg + met vs. empa 25 mg + met					
1275.1	140	1 (0.7)	141	0 (0)	3.02 [0.12; 73.54]; 0.367[b]
1245.23/31		ND		ND	ND
Glimepiride + met vs. empa 25 mg + met					
1245.28	780	8 (1.0)	765	7 (0.9)	POR: 1.12 [0.41; 3.10]; > 0.999[b]
Adjusted indirect comparison[d]:					
Empa 10 mg + met vs. glimepiride + met					
1275.1 and 1245.23/31 vs. 1245.28					**ND**

a: Institute's calculation, RR with correction factor 0.
b: Institute's calculation, unconditional exact test (CSZ method according to Andrés [4]).
c: Institute's calculation, Fisher's exact test.
d: Adjusted indirect comparison according to Bucher [5].

CI: confidence interval; CSZ: convexity, symmetry, z score; empa: empagliflozin; met: metformin; N: number of analysed patients; n: number of patients with at least one event; ND: no data; POR: Peto odds ratio; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 2: Results adverse events – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) – results after 52 weeks

Outcome category **outcome** comparison study	**Empa 10 mg + met or glimepiride + met**		**Common comparator empa 25 mg + met**		**Group difference**
	N	**Patients with at least one event n (%)**	**N**	**Patients with at least one event n (%)**	**RR [95% CI]; p-value**
Adverse events					
AEs					
Empa 10 mg + met vs. empa 25 mg + met					
1275.1	140	96 (68.6)	141	103 (73.0)	
1245.23/31	217	163 (75.1)	214	137 (64.0)	
Glimepiride + met vs. empa 25 mg + met					
1245.28	780	615 (78.8)	765	577 (75.4)	
SAEs					
Empa 10 mg + met vs. empa 25 mg + met					
1275.1	140	6 (4.3)	141	10 (7.1)	0.60 [0.23; 1.62]; 0.327[a]
1245.23/31	217	15 (6.9)	214	11 (5.1)	1.34 [0.63; 2.86]
Glimepiride + met vs. empa 25 mg + met					
1245.28	780	47 (6.0)	765	64 (8.4)	0.72 [0.50; 1.04]; 0.077[b]
Adjusted indirect comparison[c]:					
Empa 10 mg + met vs. glimepiride + met					
1275.1 and 1245.23/31 vs. 1245.28					**1.35 [0.68; 2.67][d]**
Discontinuation due to AEs					
Empa 10 mg + met vs. empa 25 mg + met					
1275.1	140	9 (6.4)	141	4 (2.8)	2.27 [0.71; 7.19]; 0.157[a]
1245.23/31	217	ND	214	ND	
Glimepiride + met vs. empa 25 mg + met					
1245.28	780	20 (2.6)	765	27 (3.5)	0.73 [0.41; 1.28]; 0.301[b]
Adjusted indirect comparison[c]:					
Empa 10 mg + met vs. glimepiride + met					
1275.1 and 1245.23/31 vs. 1245.28					**ND**
Symptomatic hypoglycaemia (PG < 54 mg/dL)					
Empa 10 mg + met vs. empa 25 mg + met					
1275.1	135	1 (0.7)	135	0 (0)	3.00 [0.12; 72.99][e]; 0.497[a]
1245.23/31	217	2 (0.9)	214	1 (0.5)	1.97 [0.18; 21.59]
Glimepiride + met vs. empa 25 mg + met					
1245.28	780	48 (6.2)	765	1 (0.1)	47.08 [6.51; 340.20]; < 0.001[b]
Adjusted indirect comparison[c]:					
Empa 10 mg + met vs. glimepiride + met					
1275.1 and 1245.23/31 vs. 1245.28					**ND**

(continued)

Table 2: Results adverse events – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) – results after 52 weeks (continued)

Outcome category outcome comparison study	Empa 10 mg + met or glimepiride + met N	 Patients with at least one event n (%)	Common comparator empa 25 mg + met N	 Patients with at least one event n (%)	Group difference RR [95% CI]; p-value
Symptomatic hypoglycaemia (54 mg/dL ≤ PG < 70 mg/dL)					
Empa 10 mg + met vs. empa 25 mg + met					
1275.1	135	1 (0.7)	135	1 (0.7)	POR 1.00 [0.06; 16.07]; > 0.999[a]
1245.23/31	217	ND	214	ND	
Glimepiride + met vs. empa 25 mg + met					
1245.28	780	93 (11.9)	765	6 (0.8)	15.20 [6.70; 34.50]; < 0.001[a]
Adjusted indirect comparison[c]:					
Empa 10 mg + met vs. glimepiride + met					
1275.1 and 1245.23/31 vs. 1245.28					**ND**
Renal and urinary disorders					
Empa 10 mg + met vs. empa 25 mg + met					
1275.1	140	9 (6.4)	141	14 (9.9)	0.65 [0.29; 1.45]; 0.294[a]
1245.23/31	217	ND	214	ND	
Glimepiride + met vs. empa 25 mg + met					
1245.28	780	34 (4.4)	765	77 (10.1)	0.43 [0.29; 0.64]; < 0.001[a]
Adjusted indirect comparison[c]:					
Empa 10 mg + met vs. glimepiride + met					
1275.1 and 1245.23/31 vs. 1245.28					**ND**
Reproductive system and breast disorders					
Empa 10 mg + met vs. empa 25 mg + met					
1275.1	140	6 (4.3)	141	10 (7.1)	0.60 [0.23; 1.62]; 0.327[a]
1245.23/31	217	ND	214	ND	
Glimepiride + met vs. empa 25 mg + met					
1245.28	780	27 (3.5)	765	64 (8.4)	0.41 [0.27; 0.64]; < 0.001[a]
Adjusted indirect comparison[c]:					
Empa 10 mg + met vs. glimepiride + met					
1275.1 and 1245.23/31 vs. 1245.28					**ND**

(continued)

Table 2: Results adverse events – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) – results after 52 weeks (continued)

Outcome category **outcome** comparison study	**Empa 10 mg + met or glimepiride + met**		**Common comparator empa 25 mg + met**		**Group difference**
	N	**Patients with at least one event n (%)**	**N**	**Patients with at least one event n (%)**	**RR [95% CI]; p-value**
Genital infection					
Empa 10 mg + met vs. empa 25 mg + met					
1275.1	140	11 (7.9)	141	12 (8.5)	0.92 [0.42; 2.02]; 0.891[a]
1245.23/31	217	15 (6.9)	214	13 (6.1)	1.14 [0.55; 2.33]
Total					
Glimepiride + met vs. empa 25 mg + met					
1245.28	780	13 (1.7)	765	71 (9.3)	0.18 [0.10; 0.32]; < 0.001[b]
Adjusted indirect comparison[c]:					
Empa 10 mg + met vs. glimepiride + met					
1275.1 and 1245.23/31 vs. 1245.28					**6.21 [2.78; 13.86][f]**

a: Institute's calculation, unconditional exact test (CSZ method according to Andrés [4]).
b: Institute's calculation, Fisher's exact test.
c: Adjusted indirect comparison according to Bucher [5].
d: The data provided by the company was based on deviating data for Study 1245.28; the deviations did not raise doubts about the overall conclusion (company's data: 50 vs. 69 patients with event instead of 47 vs. 64 patients with event).
e: Institute's calculation, RR with correction factor 0.5.
f: The data provided by the company was based on deviating data for Study 1245.28; the deviations did not raise doubts about the overall conclusion (company's data: 12 instead of 13 patients with event under glimepiride).
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; empa: empagliflozin; met: metformin; N: number of analysed patients; n: number of patients with at least one event; ND: no data; PG: plasma glucose; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 3: Results continuous outcomes – RCT, indirect comparison: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) – results after 52 weeks

Outcome comparison study	**Empa 10 mg + met or glimepiride + met**			**Common comparator empa 25 mg + met**			**Group difference**
	N	**Baseline values mean (SD)**	**Change at end of study mean (SD)**	**N**	**Baseline values mean (SD)**	**Change at end of study mean (SD)**	**Mean difference[a] [95% CI]; p-value**
Health status (EQ-5D VAS)							
Empa 10 mg + met vs. empa 25 mg + met							
1275.1	105	79.3 (17.1)	3.5 (17.8)	113	79.8 (17.1)	5.0 (18.4)	-1.5 [-6.3; 3.3]; 0.542[c]
1245.23/31	217	ND	ND	213	ND	ND	
Glimepiride + met vs. empa 25 mg + met							
1245.28	604	79.9 (13.7)	1.4 (13.7)	642	79.9 (13.6)	3.3 (11.8)	-1.9 [-3.3; -0.5]; 0.009[c]
Adjusted indirect comparison[c]:							
Empa 10 mg + met vs. glimepiride + met							
1275.1 and 1245.23/31 vs. 1245.28							**ND**
Supplementary outcome "body weight"							
Empa 10 mg + met vs. empa 25 mg + met							
1275.1	137	85.7 (1.6)	-2.9 (0.3)[a,b]	140	87.7 (1.5)	-2.8 (0.3)[a,b]	0.08 [-0.78; 0.94]; 0.852[a]
1245.23/31	217	81.6 (1.3)	-2.3 (0.2)[a,b]	213	82.2 (1.3)	-2.8 (0.2)[a,b]	0.50 [-0.06; 1.06]; 0.0781[c]
Glimepiride + met vs. empa 25 mg + met							
1245.28	780	83.0 (0.7)	1.6 (0.1)[a,b]	765	82.5 (0.7)	-3.2 (0.1)[a,b]	-4.81 [-5.12; -4.50][d]; < 0.001[a]
Adjusted indirect comparison[c]:							
Empa 10 mg + met vs. glimepiride + met							
1275.1 and 1245.23/31 vs. 1245.28							**ND**

a: Adjusted for baseline value, HbA1c, renal function (eGFR) and geographical region.
b: Standard error.
c: Institute's calculation, t-test.
d: Institute's calculation of 95% CI.

CI: confidence interval; eGFR: estimated glomerular filtration rate; empa; empagliflozin; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; met: metformin; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 4: Results on dichotomous outcomes of Study 1245.23/31 (76 weeks)

Study outcome category outcome	Empagliflozin 10 mg + metformin		Empagliflozin 25 mg + metformin		Group difference
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value[a]
1245.23/31					
Mortality					
All-cause mortality	217	0 (0)	214	0 (0)	
Morbidity					
MACE 3	217	0 (0)	214	2 (0.9)	0.20 [0.01; 4.08][b]; 0.159
Cardiovascular death	217	0 (0)	214	0 (0)	
Nonfatal MI	217	0 (0)	214	1 (0.5)	0.33 [0.01; 8.03][b]; 0.324
Nonfatal stroke	217	0 (0)	214	1 (0.5)	0.33 [0.01; 8.03][b]; 0.324
Adverse events					
AEs	217	174 (80.2)	214	154 (72.0)	
SAEs	217	19 (8.8)	214	17 (7.9)	1.10 [0.59; 2.06]; 0.824
Discontinuation due to AEs	217	7 (3.2)	214	12 (5.6)	0.58 [0.23; 1.43]; 0.246
Symptomatic hypoglycaemia (PG < 54 mg/dL)	217	2 (0.9)	214	2 (0.9)	POR: 0.99 [0.14; 7.05]; > 0.999
Symptomatic hypoglycaemia (54 mg/dL ≤ PG ≤ 70 mg/dL)	217	4 (1.8)	214	6 (2.8)	0.66 [0.19; 2.30]; 0.520
Renal and urinary disorders	217	17 (7.8)	214	15 (7.0)	1.12 [0.57; 2.18]; 0.795
Reproductive system and breast disorders	217	13 (6.0)	214	11 (5.1)	1.17 [0.53; 2.54]; 0.769
Genital infection	217	18 (8.3)	214	20 (9.3)	0.89 [0.48; 1.63]; 0.769

a: Institute's calculation, unconditional exact test (CSZ method according to Andrés [4]).
b: Institute's calculation, RR with correction factor 0.5.

AE: adverse event; CI: confidence interval; MACE: major adverse cardiovascular events; MI: myocardial infarction; N: number of analysed patients; n: number of patients with event; OR: odds ratio; PG: plasma glucose; POR: Peto odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 5: Results on continuous outcomes of Study 1245.23/31 (76 weeks)

Study outcome	Empagliflozin 10 mg + metformin			Empagliflozin 25 mg + metformin			Group difference
	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)	Mean difference[a] [95% CI]; p-value
1245.23/31							
Health status							
EQ 5D VAS	Outcome not recorded in Study 1245.23/31						
Supplementary outcome "body weight"							
Change in body weight at week 76	217	81.6 (1.3)	-2.4 (0.2)	213	82.2 (1.3)	-2.7 (0.2)	0.30 [-0.26; 0.86]; 0.290[b]

a: Results from LOCF analysis, adjusted for baseline value, HbA1c, renal function (eGFR) and geographical region.
b: Institute's calculation, t-test.

CI: confidence interval; eGFR: estimated glomerular filtration rate; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; N: number of analysed patients; RCT: randomized controlled trial; SE: standard error; vs.: versus

Appendix B – Indirect comparisons (common comparator empagliflozin 25 mg) under consideration of the total observation period of the individual studies

Table 6: Results on indirect comparisons: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) under consideration of the total observation period of the individual studies

Outcome comparison study	Empa 10 mg + met or glimepiride + met		Common comparator empa 25 mg + met		Group difference
	N	Patients with at least one event n (%)	N	Patients with at least one event n (%)	RR [95% CI]; p-value
SAEs					
Empa 10 mg + met vs. empa 25 mg + met					
1275.1 (52 W)	140	6 (4.3)	141	10 (7.1)	0.60 [0.23; 1.62]; 0.327[a]
1245.23/31 (76 W)	217	19 (8.8)	214	17 (7.9)	1.10 [0.59; 2.06]; 0.824[a]
Glimepiride + met vs. empa 25 mg + met					
1245.28 (104 W)	780	89 (11.4)	765	119 (15.6)	0.73 [0.57; 0.95]; 0.017[b]
Adjusted indirect comparison[c]:					
Empa 10 mg + met vs. glimepiride + met					
1275.1 and 1245.23/31 vs. 1245.28					**1.27 [0.70; 2.29]**
Symptomatic hypoglycaemia (PG < 54 mg/dL)					
Empa 10 mg + met vs. empa 25 mg + met					
1275.1 (52 W)	135	1 (0.7)	135	0 (0)	3.00 [0.12; 72.99][d]; 0.497[a]
1245.23/31 (76 W)	217	2 (0.9)	214	2 (0.9)	POR 0.99 [0.14; 7.05]; > 0.999[a]
Glimepiride + met vs. empa 25 mg + met					
1245.28 (104 W)	780	62 (7.9)	765	5 (0.7)	12.16 [4.92; 30.08]; < 0.001[b]
Adjusted indirect comparison[c]:					
Empa 10 mg + met vs. glimepiride + met					
1275.1 and 1245.23/31 vs. 1245.28					**0.11 [0.02; 0.73]**
Symptomatic hypoglycaemia (54 mg/dL ≤ PG < 70 mg/dL)					
Empa 10 mg + met vs. empa 25 mg + met					
1275.1 (52 W)	135	1 (0.7)	135	1 (0.7)	POR 1.00 [0.06; 16.07]; > 0.999[a]
1245.23/31 (76 W)	217	4 (1.8)	214	6 (2.8)	0.66 [0.19; 2.30]; 0.520[a]
Glimepiride + met vs. empa 25 mg + met					
1245.28 (104 W)	780	104 (13.3)	765	8 (1.0)	12.75 [6.25; 25.99]; < 0.001[b]
Adjusted indirect comparison[c]:					
Empa 10 mg + met vs. glimepiride + met					
1275.1 and 1245.23/31 vs. 1245.28					**0.06 [0.01; 0.21]**

(continued)

Table 6: Results on indirect comparisons: empagliflozin 10 mg vs. glimepiride with the common comparator empagliflozin 25 mg (each + metformin) under consideration of the total observation period of the individual studies (continued)

Outcome comparison study	**Empa 10 mg + met or glimepiride + met**		**Common comparator empa 25 mg + met**		**Group difference**
	N	**Patients with at least one event n (%)**	**N**	**Patients with at least one event n (%)**	**RR [95% CI]; p-value**
Renal and urinary disorders (SOC)					
Empa 10 mg + met vs. empa 25 mg + met					
1275.1 (52 W)	140	9 (6.4)	141	14 (9.9)	0.65 [0.29; 1.45]; 0.294[a]
1245.23/31 (76 W)	217	17 (7.8)	214	15 (7.0)	1.12 [0.57; 2.18]; 0.795[a]
Glimepiride + met vs. empa 25 mg + met					
1245.28 (104 W)	780	55 (7.1)	765	112 (14.6)	0.48 [0.35; 0.65]; < 0.001[b]
Adjusted indirect comparison[c]:					
Empa 10 mg + met vs. glimepiride + met					
1275.1 and 1245.23/31 vs. 1245.28					**1.86 [1.01; 3.42]**
Reproductive system and breast disorders (SOC)					
Empa 10 mg + met vs. empa 25 mg + met					
1275.1 (52 W)	140	6 (4.3)	141	10 (7.1)	0.60 [0.23; 1.62]; 0.327[a]
1245.23/31 (76 W)	217	13 (6.0)	214	11 (5.1)	1.17 [0.53; 2.54]; 0.769[a]
Glimepiride + met vs. empa 25 mg + met					
1245.28 (104 W)	780	46 (5.9)	765	91 (11.9)	0.51 [0.37; 0.71]; < 0.001[b]
Adjusted indirect comparison[c]:					
Empa 10 mg + met vs. glimepiride + met					
1275.1 and 1245.23/31 vs. 1245.28					**1.77 [0.87; 3.59]**

a: Institute's calculation, unconditional exact test (CSZ method according to Andrés [4]).
b: Institute's calculation, Fisher's exact test.
c: Institute's calculation, adjusted indirect comparison according to Bucher [5].
d: Institute's calculation, RR with correction factor 0.5.

CI: confidence interval; CSZ: convexity, symmetry, z score; empa: empagliflozin; met: metformin; N: number of analysed patients; n: number of patients with at least one event; PG: plasma glucose; POR: Peto odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus