

IQWiG Reports – Commission No. A14-26

Empagliflozin – Benefit assessment according to §35a Social Code Book V¹

Extract

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ANCOVA	analysis of covariance
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycosylated haemoglobin A1c
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug empagliflozin. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as “the company”). The dossier was sent to IQWiG on 15 August 2014.

Research question

The aim of this report was to assess the added benefit of empagliflozin for the treatment of adults with type 2 diabetes mellitus in the following approved subindications:

- **monotherapy:** when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance
- **add-on combination therapy:** in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control

Following the G-BA’s subdivision of the therapeutic indication, the assessment was conducted for 5 research questions versus the appropriate comparator therapy (ACT) specified by the G-BA. These are shown in Table 2.

Table 2: Subindications considered in the benefit assessment, research questions and ACTs on empagliflozin

Subindication	Research question	ACT specified by the G-BA
Monotherapy when diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance	A Monotherapy with empagliflozin	Sulfonylurea (glibenclamide, glimepiride)
Combination with another blood-glucose lowering drug (except insulin), when this, together with diet and exercise, does not provide adequate glycaemic control	B1 Empagliflozin plus metformin B2 Empagliflozin plus another blood-glucose lowering drug except metformin and insulin	Metformin plus sulfonylurea (glibenclamide, glimepiride) <i>(note: if metformin is inappropriate according to the SPC, human insulin is to be used as treatment option)</i>
Combination with at least 2 other blood-glucose lowering drugs, when these, together with diet and exercise, do not provide adequate glycaemic control	C Empagliflozin plus at least 2 other blood-glucose lowering drugs except insulin	Metformin plus human insulin <i>(note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)</i>
Combination with insulin (with or without OAD)	D Empagliflozin plus insulin (with or without OAD)	Metformin plus human insulin <i>(note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)</i>
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetic; SPC: Summary of Product Characteristics		

The assessment was conducted based on patient-relevant outcomes and on RCTs with a minimum duration of 24 weeks.

Results

Research question A: monotherapy with empagliflozin

No relevant data were available for research question A. Hence the added benefit of empagliflozin in monotherapy is not proven.

Research question B1: empagliflozin plus metformin

For research question B1, the company presented a direct comparative study investigating empagliflozin in the 25 mg fixed dose (in combination with metformin). It also presented 3 studies for 2 indirect comparisons to investigate empagliflozin in the 10 mg fixed dose (in combination with metformin).

Direct comparison

The company presented Study 1245.28, which compared empagliflozin 25 mg plus metformin with glimepiride 1 to 4 mg. Titration of glimepiride was oriented towards a uniform blood glucose level. It could not be inferred from Appendix of Study 1245.28 that the physician had any flexibility to perform the titration based on variable threshold values according to an individual balancing of benefits and risks. In contrast, empagliflozin was administered at a fixed dose of 25 mg over the entire course of the study. As a consequence, patients in the glimepiride group had a considerably lower mean glycosylated haemoglobin A1c (HbA1c) value in the first part of the study, and therefore were subject to a higher risk of hypoglycaemia due to the differing treatment regimens. Accordingly, the number of events in the glimepiride arm was above average during and shortly after the titration phase of the study. Nonetheless, a clear difference with regard to the occurrence of hypoglycaemias in favour of empagliflozin remains detectable in the further course of the study. Overall, the substance-specific effect on hypoglycaemias remains unclear, however.

In addition, the initial administration of 25 mg/day in Study 1245.28 is equivalent to 2.5 times the starting dose recommended in the approval. Study 1245.28 cannot provide a sufficiently certain assessment of the blood-glucose lowering potency of empagliflozin 10 mg in comparison with glimepiride.

Overall, the results of Study 1245.28 cannot be interpreted with sufficient certainty because of the different treatment regimens and the starting dosage used. It should also be noted that no added benefit of empagliflozin could be derived even if Study 1245.28 was considered. An advantage regarding non-serious hypoglycaemias is offset by disadvantages regarding other non-serious adverse events (AEs) (including renal and urinary disorders and genital infection), as well as serious AEs (overall SAEs).

Indirect comparison I

The company presented Study 1275.1 and Study 1245.28 for an indirect comparison to investigate the research question on empagliflozin 10 mg plus metformin versus glimepiride 1 to 4 mg plus metformin (common comparator empagliflozin 25 mg plus metformin). The analysis was not evaluable for the benefit assessment because Study 1245.23/1245.31, which is also relevant for this comparison, was not considered by the company. Hence the comparison of empagliflozin 10 mg with the common comparator was based on an incomplete study pool. In addition, on the side of the comparator therapy, Study 1245.28 was used, which investigated different treatment regimens for the comparison of glimepiride with the common comparator empagliflozin 25 mg. It is therefore uncertain whether the effects observed in the study are only attributable to the respective drugs used.

Indirect comparison II

The company presented a second indirect comparison to investigate the research question of empagliflozin 10 mg plus metformin versus glimepiride 1 to 4 mg plus metformin, for which

it used the 2 studies 1275.1 (comparison of empagliflozin 10 mg plus metformin versus linagliptin 5 mg plus metformin) and 1218.20 (comparison of glimepiride 1 to 4 mg plus metformin versus linagliptin 5 mg plus metformin). Linagliptin 5 mg plus metformin was used as common comparator. This indirect comparison was not evaluable for the benefit assessment because, as discussed in the dossier assessment on linagliptin, Study 1218.20 was unsuitable for the assessment, and also because the studies were not sufficiently similar due to different treatment regimens.

Summary

In summary, no relevant data were available for research question B1. Hence the added benefit of empagliflozin plus metformin is not proven.

Research question B2: empagliflozin plus another blood-glucose lowering drug except metformin and insulin

No relevant data were available for research question B2. Hence the added benefit of empagliflozin plus another blood-glucose lowering drug except metformin and insulin is not proven.

Research question C: empagliflozin plus at least 2 other blood-glucose lowering drugs except insulin

No relevant data were available for research question C. Hence the added benefit of empagliflozin plus at least 2 other blood-glucose lowering drugs except insulin is not proven.

Research question D: empagliflozin plus insulin (with or without oral antidiabetics)

No relevant data were available for research question D. Hence the added benefit of empagliflozin plus insulin (with or without oral antidiabetics) is not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

On the basis of the results presented, the extent and probability of the added benefit of the drug empagliflozin compared with the ACT is assessed as presented in Table 3.

⁴ On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

Table 3: Empagliflozin – extent and probability of added benefit

Research question	Subindication	ACT	Extent and probability of added benefit
A	Monotherapy with empagliflozin	Sulfonylurea (glibenclamide, glimepiride)	Added benefit not proven
B1	Empagliflozin plus metformin	Metformin plus sulfonylurea (glibenclamide, glimepiride)	Added benefit not proven
B2	Empagliflozin plus another blood-glucose lowering drug except metformin and insulin	<i>(note: if metformin is inappropriate according to the SPC, human insulin is to be used as treatment option)</i>	Added benefit not proven
C	Empagliflozin plus at least 2 other blood-glucose lowering drugs except insulin	Metformin plus human insulin <i>(note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)</i>	Added benefit not proven
D	Empagliflozin plus insulin (with or without OAD)	Metformin plus human insulin <i>(note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)</i>	Added benefit not proven
ACT: appropriate comparator therapy; OAD: oral antidiabetic; SPC: Summary of Product Characteristics			

The G-BA decides on the added benefit.

2.2 Research questions

The aim of this report was to assess the added benefit of empagliflozin for the treatment of adults with type 2 diabetes mellitus in the following approved subindications:

- **monotherapy:** when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance
- **add-on combination therapy:** in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control

Following the G-BA's subdivision of the therapeutic indication, the assessment was conducted for 5 research questions versus the ACT specified by the G-BA. These are shown in Table 4.

Table 4: Subindications considered in the benefit assessment, research questions and ACTs on empagliflozin

Subindication	Research question	ACT specified by the G-BA
Monotherapy when diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance	A Monotherapy with empagliflozin	Sulfonylurea (glibenclamide, glimepiride)
Combination with another blood-glucose lowering drug (except insulin), when this, together with diet and exercise, does not provide adequate glycaemic control	B1 Empagliflozin plus metformin B2 Empagliflozin plus another blood-glucose lowering drug except metformin and insulin	Metformin plus sulfonylurea (glibenclamide, glimepiride) (note: if metformin is inappropriate according to the SPC, human insulin is to be used as treatment option)
Combination with at least 2 other blood-glucose lowering drugs, when these, together with diet and exercise, do not provide adequate glycaemic control	C Empagliflozin plus at least 2 other blood-glucose lowering drugs except insulin	Metformin plus human insulin (note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)
Combination with insulin (with or without OAD)	D Empagliflozin plus insulin (with or without OAD)	Metformin plus human insulin (note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetic; SPC: Summary of Product Characteristics		

The research questions mainly concur with the ones of the company, with the following exceptions:

- Since the evidence presented by the company in Module B was limited to the combination of empagliflozin with metformin, this combination was investigated as research question B1. The remaining approved combinations in the dual combination with empagliflozin are presented under research question B2.
- Deviating from the company, combinations with non-oral antidiabetics were also considered for research questions B2 and C. This had no consequence because the company stated that it had not identified any studies on non-oral antidiabetics.
- For research questions C and D, the company included both studies with human insulin and studies with insulin analogues. This had no consequence for the present assessment because it did not identify any relevant studies.
- In research questions A and B1/B2, the company chose no specific sulfonylurea as ACT. This had no relevance for the benefit assessment, however. On the one hand, the company identified no study for research questions A and B2 that met the inclusion criteria, anyway. On the other hand, it only included one study that investigated one of the 2 drugs specified by the G-BA (glimepiride) for research question B1.

The assessment was conducted based on patient-relevant outcomes and on RCTs with a minimum duration of 24 weeks.

2.3 Research question A: empagliflozin monotherapy

2.3.1 Information retrieval and study pool (research question A)

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on empagliflozin (studies completed up to 8 July 2014)
- bibliographical literature search on empagliflozin (last search on 8 July 2014)
- search in trial registries for studies on empagliflozin (last search on 8 July 2014)

The company identified no relevant study for a comparison of empagliflozin in monotherapy versus the ACT specified by the G-BA.

2.3.2 Results on added benefit (research question A)

The company presented no relevant data for research question A. Hence the added benefit of empagliflozin in monotherapy versus the ACT specified by the G-BA is not proven.

2.3.3 Extent and probability of added benefit (research question A)

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of empagliflozin in monotherapy in comparison with the ACT specified by the G-BA (sulfonylurea [glibenclamide, glimepiride]). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This assessment deviates from that of the company, which derived an indication of a non-quantifiable added benefit of empagliflozin in monotherapy.

2.4 Research question B1: empagliflozin plus metformin

2.4.1 Information retrieval and study pool (research question B1)

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on empagliflozin (studies completed up to 8 July 2014)
- bibliographical literature search on empagliflozin (last search on 8 July 2014)
- search in trial registries for studies on empagliflozin (last search on 8 July 2014)
- bibliographical literature search on the ACT (last search on 8 July 2014)
- search in trial registries for studies on the ACT (last search on 19 May 2014)

To check the completeness of the study pool:

- search in trial registries for studies on empagliflozin (last search on 1 September 2014)

No studies other than the ones cited by the company in the dossier were identified from this check. However, the study pool was shown to be incomplete for the indirect comparison I conducted by the company because the company cited one additional relevant study in its study list, but excluded this study from its study pool (see explanations below).

From the steps of information retrieval mentioned, the company identified one direct comparative study (1245.28), and 3 studies for 2 indirect comparisons (1245.28, 1275.1, 1218.20).

Neither the direct comparative study nor the indirect comparisons presented were suitable to assess the added benefit of empagliflozin plus metformin versus the ACT specified by the G-BA.

Hereinafter, the reasons for the non-consideration of the direct comparative study 1245.28 and of the 2 indirect comparisons presented are explained.

Reasons for the non-consideration of Study 1245.28

Study 1245.28 is presented in Table 5 and Table 6.

Table 5: Characteristics of the study included by the company – RCT, direct comparison: empagliflozin + metformin vs. glimepiride + metformin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
1245.28	RCT, double-blind, parallel	Adult patients with type 2 diabetes mellitus, BMI ≤ 45 kg/m ² , and inadequate glycaemic control under metformin monotherapy	Each in combination with metformin: ▪ empagliflozin 25 mg (N = 769) ▪ glimepiride 1–4 mg (N = 780)	▪ run-in phase: 2 weeks ▪ study treatment: 104 weeks ▪ extension phase: 104 weeks (ongoing) ▪ follow-up: 4 weeks	181 study centres in 23 countries: Argentina, Austria, Canada, Colombia, Czech Republic, Finland, Hong Kong, India, Italy, Malaysia, Mexico, the Netherlands, Norway, Philippines, Portugal, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, United Kingdom, United States 8/2010–9/2013 (104 weeks) 8/2010–8/2015 (planned end of extension 208 weeks)	Primary outcome: change in HbA1c after 52 and 104 weeks of treatment secondary outcomes: morbidity, AEs, hypoglycaemia
a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment. AE: adverse event; BMI: body mass index; HbA1c: glycosylated haemoglobin A1c; RCT: randomized controlled trial; vs.: versus						

Table 6: Characteristics of the interventions of the study included by the company – RCT, direct comparison: empagliflozin + metformin vs. glimepiride + metformin

Study	Intervention	Comparison
1245.28	Empagliflozin 25 mg/day in combination with metformin + placebo for glimepiride 1–4 mg orally once daily before or with meal <u>Titration, dose increase:</u> sham titration to maintain blinding, no dose increase	Glimepiride 1–4 mg/day in combination with metformin + placebo for empagliflozin 25 mg orally once daily before or with meal <u>Titration, dose increase:</u> starting dose: 1 mg/day (dose level 1) dose increase during the course of the study was possible in 4-week intervals: dose level 2: 2 mg/day dose level 3: 3 mg/day dose level 3: 4 mg/day <u>Basis of decision on dose increase:</u> Fasting plasma glucose levels: > 110 mg/dL (> 6 mmol/L)^a Dose increase could be withheld in case of increased risk of hypoglycaemia. <u>Dose reduction and discontinuation of medication:</u> The dose could be reduced to prevent recurrent hypoglycaemia. The study medication was to be discontinued in case of uncontrollable hyperglycaemia or hypoglycaemia.
Pretreatment: - no antidiabetics except metformin were allowed 12 weeks before randomization - at least 12 weeks before randomization metformin $\geq$ 1500 mg/day (or maximum tolerated dose, or maximum dose according to the approval) at a stable dosage Concomitant treatment: - The metformin dose was to be maintained unchanged during the entire study. - Hyperglycaemic rescue medication was allowed within a defined range of glucose levels.		
a: Under consideration of the measurements in the study centre and of the patients' self-measurements. RCT: randomized controlled trial; vs.: versus		

Study design of Study 1245.28

Study 1245.28 was a company-sponsored randomized active-controlled double-blind approval study. Adult patients with type 2 diabetes mellitus were enrolled in whom no sufficient glycaemic control was achieved despite treatment with metformin at a stable dose of $\geq$ 1500 mg/day (or maximum tolerated dose or maximum dosage according to the approval) during at least 12 weeks (HbA1c at the first visit before the start of the run-in phase $\geq$ 7.0% and $\leq$ 10.0%).

The study comprised a run-in phase of 2 weeks and a double-blind, randomized treatment phase of 104 weeks, as well as an (ongoing) 104-week extension phase. All patients were required to continue taking their metformin dose from the stable phase of at least 12 weeks before randomization unchanged during the entire study duration (including the run-in phase) (other antidiabetics were not allowed). After administration of the last dose of the randomized study medication, follow-up of the patients for 4 weeks was planned.

A total of 1549 patients were randomly assigned in a ratio of 1:1 to the 2 treatment arms to empagliflozin and glimepiride.

Assessment of the relevance of the study

Comparison of different treatment regimens

After randomization, patients in Study 1245.28 received either 25 mg/day empagliflozin (fixed dosage) or glimepiride (planned titration depending on the fasting plasma glucose level). After a starting dose of 1 mg/day, dose steps of 2, 3 and 4 mg/day were planned for titration in the glimepiride arm. The double-dummy design ensured blinding despite the different dosing. The dose level was to be increased in 4-week intervals. According to the study protocol, the decision for dose increase was based on the measurement in the clinic during the study visit if the fasting plasma glucose level was greater than the target value of 110 mg/dL. In another section, however, it was stated that the patients' self-measurements were also considered. No further details were provided. Dose increase could be withheld in case of increased risk of hypoglycaemia. In case of recurrent hypoglycaemia, the dose could also be reduced again (see Table 6). Approximately 40% of the patients received the highest dose of 4 mg glimepiride.

It was clear that titration with a blood-glucose lowering drug aimed at a target blood glucose level (fasting plasma glucose $\leq$ 110 mg/dL) was only conducted in the glimepiride arm, but not in the empagliflozin arm. Hence Study 1245.28 constituted a comparison of 2 treatment regimens (therapeutic strategy plus drug) and not of 2 drugs alone. It is therefore uncertain whether the effects observed in the study are solely attributable to the respective drugs used.

Adaptation of the glimepiride dosage was rigidly based on the specification of a near-normal target blood glucose level (fasting plasma glucose $\leq$ 110 mg/dL) and it could not be inferred from the Appendix of Study 1245.28 that the physician had sufficient flexibility for an individual balancing of benefits and risks, even if the aim was normoglycaemia. On the one hand, there were patients in the study for whom the near-normal fasting plasma glucose level specified in the study was not the optimum treatment goal (e.g. 21% of the patients in Study 1245.28 were aged 65 years or older). On the other hand, almost 60% of the study participants already had a baseline HbA1c level of $< 8\%$ (there was no information on the proportion of patients with baseline HbA1c $< 7.5\%$ or $< 7\%$).

Figure 1 shows the change in HbA1c value in the target population from Study 1245.28 after 104 weeks in comparison with the baseline value and illustrates the effect of the different treatment regimens in the study arms.

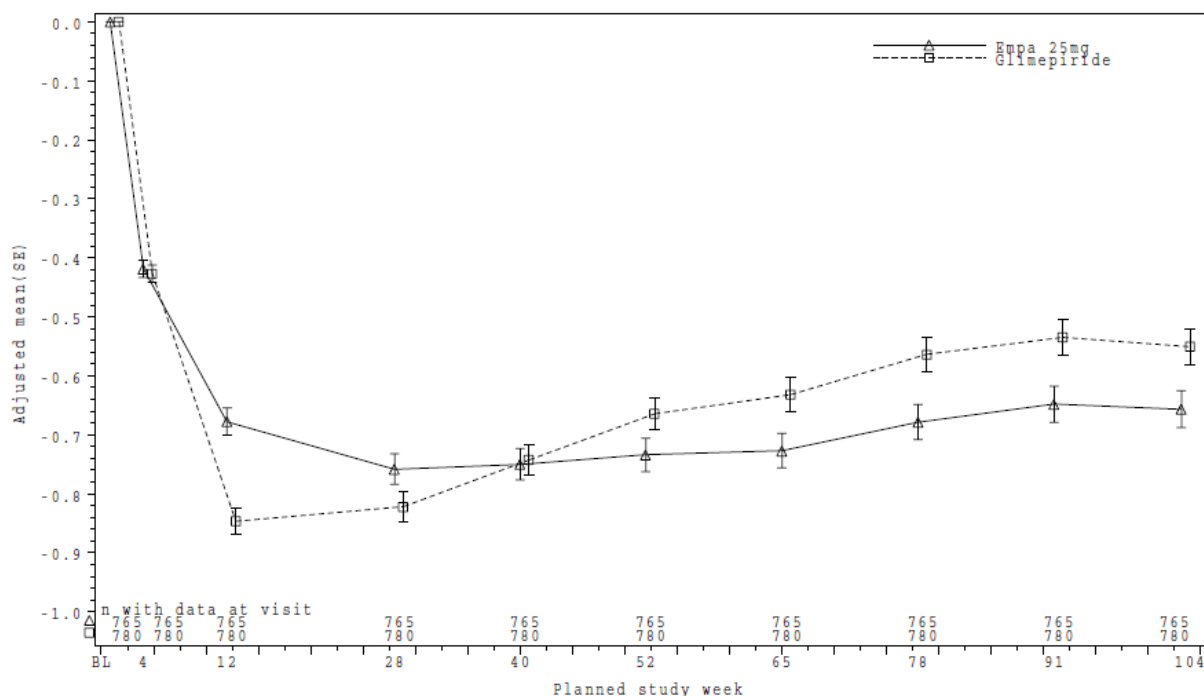


Figure 1: Change in HbA1c value in comparison with the baseline value in Study 1245.28 (ANCOVA, LOCF)

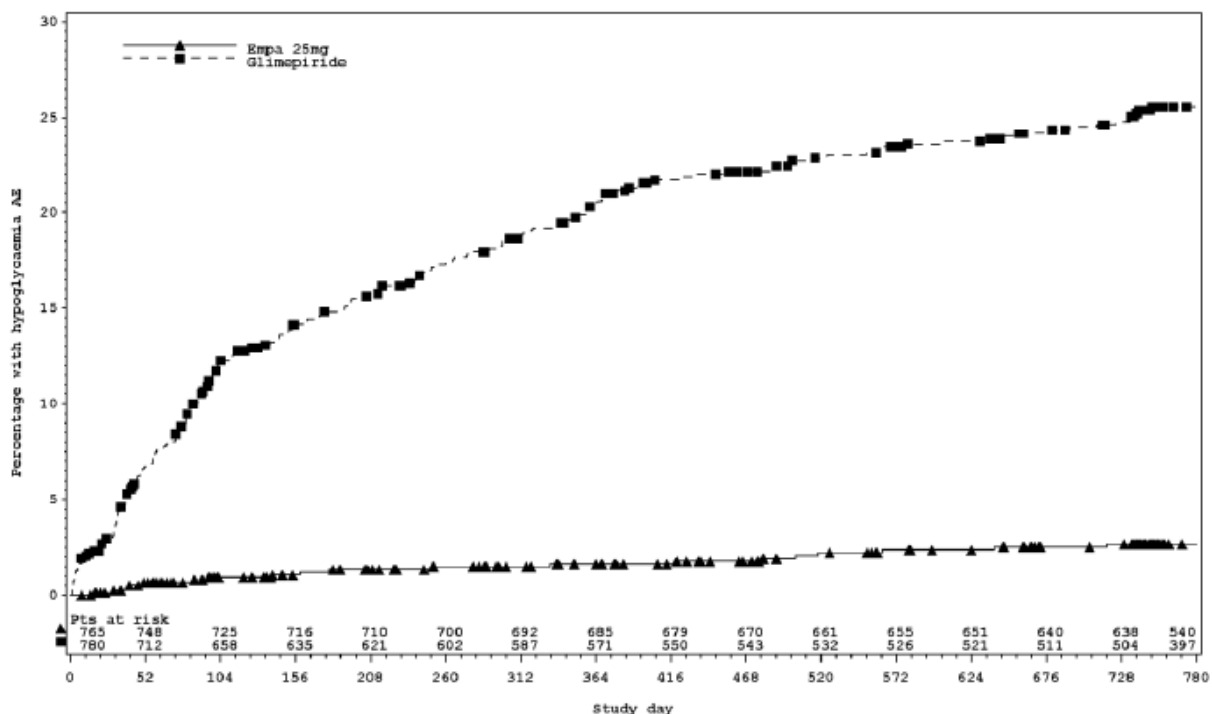
Due to the treatment regimen of titration based on the target blood glucose level used, the mean HbA1c value was lowered rapidly and considerably (approximately 0.85 percentage points maximum at week 12) under glimepiride. Initially, the decrease in HbA1c values was considerably less pronounced in the empagliflozin arm. The difference in measurements between the empagliflozin arm and the glimepiride arm was greatest after 12 weeks (approximately 0.2 percentage points). After the initially marked blood-glucose lowering, the mean HbA1c value increased under glimepiride in the further course of the study, whereas it remained mostly stable under empagliflozin. From about the middle of the study until the end of the study, the mean decrease in HbA1c was more pronounced under empagliflozin than under glimepiride.

Overall, Study 1245.28 constituted a comparison of 2 treatment regimens (therapeutic strategy plus drug) and not of 2 drugs alone. The observed rapid and considerable lowering is associated with a higher risk of hypoglycaemia, and an associated influence on the observed rate of hypoglycaemia under glimepiride cannot be excluded. It is unclear how strong this influence is.

Increased occurrence of hypoglycaemia during the titration phase

Hereinafter it is investigated whether the increased risk of hypoglycaemia mentioned above is reflected in the time course of the occurrence of hypoglycaemia. There were no corresponding analyses for the analysis of symptomatic hypoglycaemias (plasma glucose concentration < 54 mg/dL), which is to be regarded as valid and patient-relevant. Only data on confirmed hypoglycaemias were available. In Study 1245.28, a hypoglycaemic event was defined as “confirmed” if it was associated with a plasma glucose concentration of ≤ 70 mg/dL or if assistance of another person was required to administer carbohydrates or glucagon or other life-saving measures. This definition also included asymptomatic events, which are to be regarded as not patient-relevant. However, it could be inferred from the study documents that approximately 87% of the patients with confirmed hypoglycaemia also had at least one symptomatic event. Hence as an approximation it can be assumed that the outcome “confirmed hypoglycaemia” to a large degree represents patient-relevant events, and is therefore suitable for the assessment of the time course of non-serious hypoglycaemias.

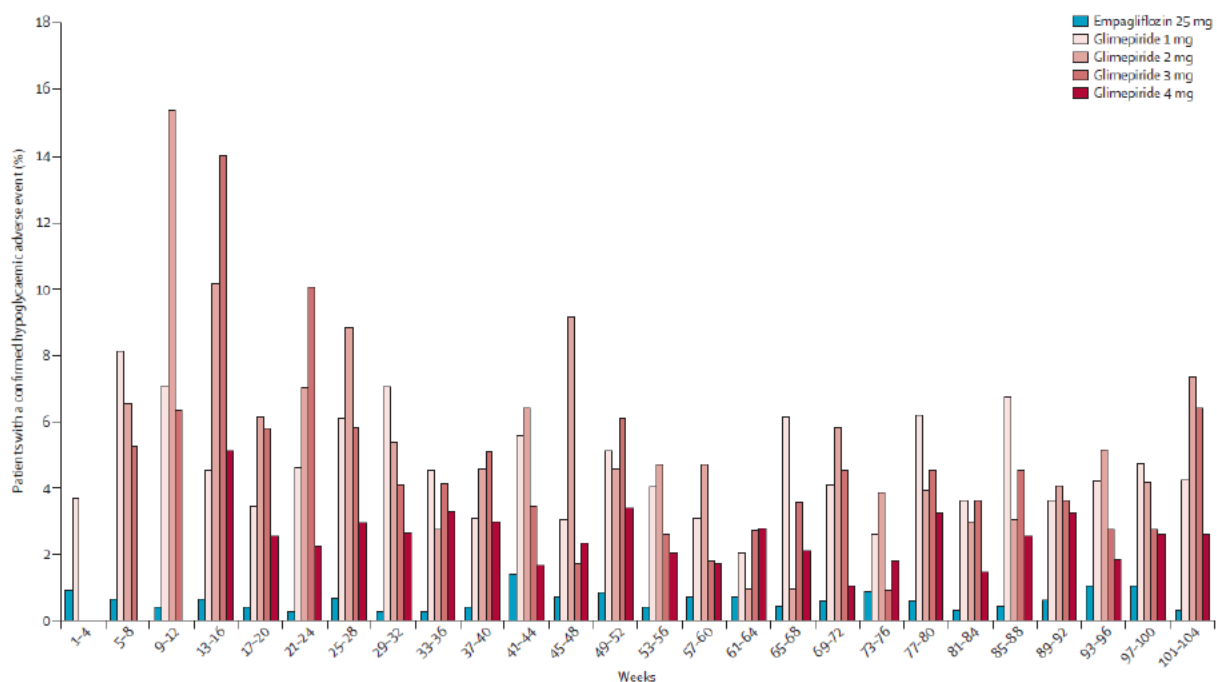
The cumulative proportion of patients with at least one confirmed hypoglycaemia is presented in Figure 2. It can be seen that, in the glimepiride arm, a particularly high number of first events occurred at the time of titration in the first 12 weeks. Also after week 40/after day 280 (after HbA1c values in the 2 arms had approximated each other), confirmed hypoglycaemias under glimepiride occurred more frequently for the first time than in the empagliflozin arm, however.



“Confirmed” hypoglycaemias: hypoglycaemic event with plasma glucose concentration ≤ 70 mg/dL or necessity of assistance of another person to administer carbohydrates or glucagon or other life-saving measures

Figure 2: Time course of the proportion of patients with “confirmed” hypoglycaemias, Study 1245.28

Figure 3 shows the time course of confirmed hypoglycaemic events under consideration of their repeated occurrence, differentiated by glimepiride dose.



“Confirmed” hypoglycaemias: hypoglycaemic event with plasma glucose concentration ≤ 70 mg/dL or necessity of assistance of another person to administer carbohydrates or glucagon or other life-saving measures

Figure 3: Patients with confirmed hypoglycaemias by dose for each 4-week interval, Study 1245.28

It can also be seen in Figure 3 that the number of events in the glimepiride arm was above average during and shortly after the titration phase of the study. Nonetheless, irrespective of the dose actually administered, a clear difference with regard to the occurrence of hypoglycaemias between the 2 treatment arms remains detectable in the further course of the study.

The 2 figures suggest that the greater frequency occurrence of hypoglycaemias under glimepiride cannot be explained by the difference in blood-glucose lowering alone. Overall, the substance-specific effect on hypoglycaemias remains unclear, however.

Starting dose of empagliflozin too high

In Study 1245.28, empagliflozin was administered in a fixed dose of 25 mg/day. According to the specifications in the Summary of Product Characteristics (SPC) [3,4], the recommended starting dose is exclusively 10 mg/day, however. If the dose is tolerated and tighter glycaemic control is needed, the dose can be increased to 25 mg in patients without severe renal impairment. Hence the initial administration of 25 mg/day in Study 1245.28 is equivalent to 2.5 times the starting dose recommended in the approval.

The company made the general statement that the studies 1275.1 and 1245.23 had shown no relevant differences between the 10 mg and the 25 mg fixed doses of empagliflozin in combination with metformin, but provided no justification based on data.

The comparison of the 2 empagliflozin groups of Study 1245.23 (with the 1245.31 extension study) cited by the company showed that the HbA1c value of the study participants with 10 mg empagliflozin from week 12 until the end of the study (week 76) was approximately 0.1% higher than the one of the participants with 25 mg empagliflozin (Figure 4). Equivalence of the blood-glucose lowering potency of the 2 empagliflozin dosages cannot be derived from this. Consequently, Study 1245.28 (direct comparison of empagliflozin 25 mg with glimepiride) cannot provide a sufficiently certain assessment of the blood-glucose lowering potency of empagliflozin 10 mg in comparison with glimepiride.

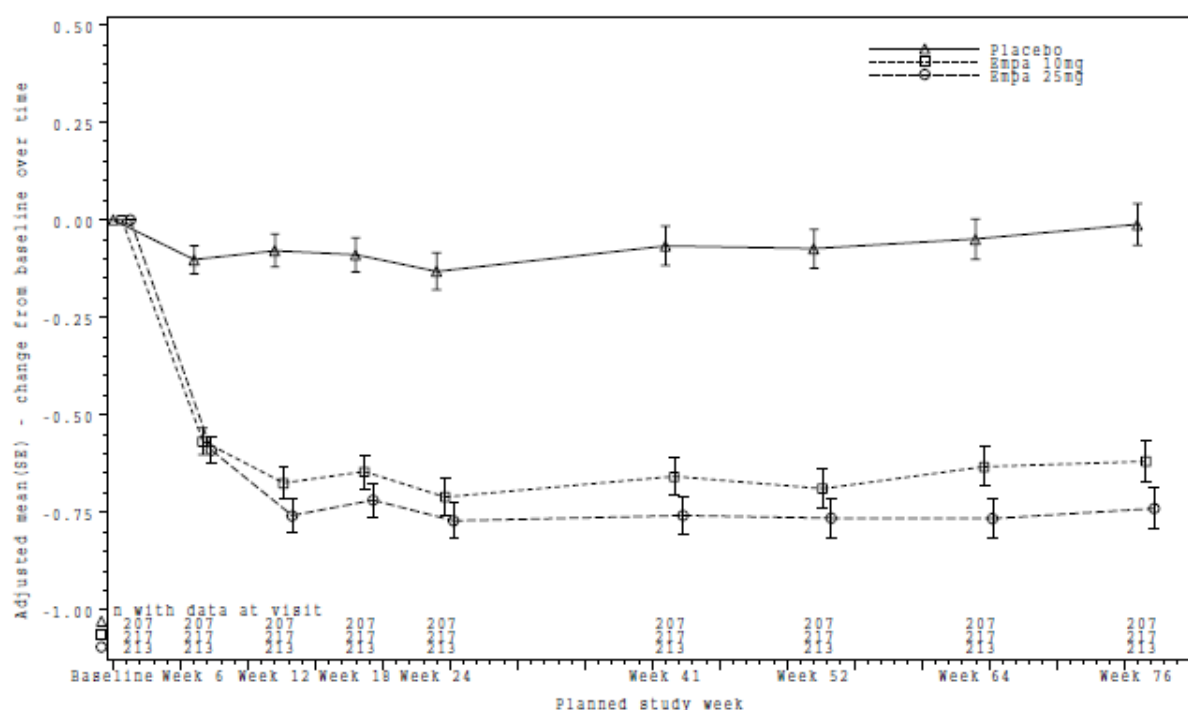


Figure 4: Change in HbA1c value in comparison with the baseline value in Study 1245.23/1245.3, patients with metformin alone as concomitant treatment (ANCOVA, LOCF)

Conclusions

Overall, the results of Study 1245.28 cannot be interpreted with sufficient certainty because of the different treatment regimens and the starting dosage used.

It should also be noted that no added benefit of empagliflozin could be derived even if Study 1245.28 was considered. The corresponding results are presented as additional information in Appendix A of the full dossier assessment. An advantage regarding non-serious hypoglycaemias is offset by disadvantages regarding other non-serious AEs (including renal and urinary disorders and genital infection), as well as SAEs (overall SAEs).

Reasons for the non-consideration of the indirect comparisons

The company presented 2 indirect comparisons to prove the added benefit of empagliflozin in a 10 mg dosage plus metformin versus the ACT. The company identified no direct comparative study for this constellation.

Indirect comparison I

For an indirect comparison, the company presented the multi-arm Study 1275.1 (comparison of empagliflozin 10 mg plus metformin versus empagliflozin 25 mg plus metformin) and Study 1245.28, which was presented for the direct comparison (empagliflozin 25 mg versus glimepiride 1 to 4 mg), to investigate the research question of empagliflozin 10 mg plus metformin versus glimepiride 1 to 4 mg plus metformin. Empagliflozin 25 mg plus metformin was used as common comparator. The analysis was not evaluable for the benefit assessment because Study 1245.23/1245.31, which is also relevant for this comparison, was not considered by the company. Hence the comparison of empagliflozin 10 mg with the common comparator was based on an incomplete study pool. A detailed explanation about this can be found in Section 2.9.3.2.3.2 of the full dossier assessment. In addition, on the side of the comparator therapy, Study 1245.28 was used, which investigated different treatment regimens for the comparison of glimepiride with the common comparator empagliflozin 25 mg. It is therefore uncertain whether the effects observed in the study are only attributable to the respective drugs used (see explanation provided above on the non-consideration of the direct comparison).

Indirect comparison II

The company presented a second indirect comparison to investigate the research question of empagliflozin 10 mg plus metformin versus glimepiride 1 to 4 mg plus metformin, for which it used the multi-arm Study 1275.1 (comparison of empagliflozin 10 mg plus metformin versus linagliptin 5 mg plus metformin) and Study 1218.20 (comparison of glimepiride 1 to 4 mg plus metformin versus linagliptin 5 mg plus metformin). Linagliptin 5 mg plus metformin was used as common comparator. This indirect comparison was not evaluable for the benefit assessment because, as discussed in the dossier assessment on linagliptin [5], Study 1218.20 was unsuitable for the assessment, and also because the studies were not sufficiently similar due to different treatment regimens (see Section 2.9.3.2.3.2 of the full dossier assessment).

2.4.2 Results on added benefit (research question B1)

The company presented no relevant data for research question B1. Hence the added benefit of empagliflozin plus metformin versus the ACT specified by the G-BA (metformin plus sulfonylurea [glibenclamide, glimepiride]) is not proven.

2.4.3 Extent and probability of added benefit (research question B1)

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of empagliflozin plus metformin in comparison with the ACT specified by the

G-BA (metformin plus sulfonyleurea [glibenclamide, glimepiride]). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

This deviates from the company's assessment, which derived proof of a considerable added benefit for empagliflozin plus metformin.

2.4.4 List of included studies (research question B1)

Not applicable as the company did not present any relevant studies in its dossier, from which an added benefit of empagliflozin plus metformin versus the ACT (metformin plus sulfonyleurea [glibenclamide, glimepiride]) could be derived.

2.5 Research question B2: empagliflozin plus another blood-glucose lowering drug except metformin and insulin

2.5.1 Information retrieval and study pool (research question B2)

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on empagliflozin (studies completed up to 8 July 2014)
- bibliographical literature search on empagliflozin (last search on 8 July 2014)
- search in trial registries for studies on empagliflozin (last search on 8 July 2014)
- bibliographical literature search on the ACT (last search on 8 July 2014)
- search in trial registries for studies on the ACT (last search on 19 May 2014)

The company identified no relevant study for a comparison of empagliflozin plus another blood-glucose lowering drug except metformin and insulin versus the ACT specified by the G-BA.

2.5.2 Results on added benefit (research question B2)

The company presented no relevant data for research question B2. Hence the added benefit of empagliflozin plus another blood-glucose lowering drug except metformin and insulin versus the ACT specified by the G-BA is not proven.

2.5.3 Extent and probability of added benefit (research question B2)

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of empagliflozin plus another blood-glucose lowering drug except metformin and insulin in comparison with the ACT specified by the G-BA (sulfonylurea [glibenclamide, glimepiride]). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

This deviates from the company's assessment, which derived a considerable added benefit for empagliflozin in further combinations of dual therapy even without a relevant study.

2.6 Research question C: empagliflozin plus at least 2 other blood-glucose lowering drugs except insulin

2.6.1 Information retrieval and study pool (research question C)

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on empagliflozin (studies completed up to 8 July 2014)
- bibliographical literature search on empagliflozin (last search on 8 July 2014)
- search in trial registries for studies on empagliflozin (last search on 8 July 2014)
- bibliographical literature search on the ACT (last search on 10 July 2014)
- search in trial registries for studies on the ACT (last search on 19 May 2014)

The company identified no study for a comparison of empagliflozin plus at least 2 other blood-glucose lowering drugs except insulin versus the ACT specified by the G-BA.

2.6.2 Results on added benefit (research question C)

The company presented no relevant data for research question C. Hence the added benefit of empagliflozin plus at least 2 other blood-glucose lowering drugs except insulin versus the ACT specified by the G-BA is not proven.

2.6.3 Extent and probability of added benefit (research question C)

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of empagliflozin plus at least 2 other blood-glucose lowering drugs except insulin in comparison with the ACT specified by the G-BA (human insulin plus metformin). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

This deviates from the company's assessment, which derived a non-quantifiable added benefit for empagliflozin in the triple therapy with 2 oral antidiabetics even without a relevant study.

2.7 Research question D: empagliflozin plus insulin (with or without oral antidiabetic)

2.7.1 Information retrieval and study pool (research question D)

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on empagliflozin (studies completed up to 8 July 2014)
- bibliographical literature search on empagliflozin (last search on 8 July 2014)
- search in trial registries for studies on empagliflozin (last search on 8 July 2014)
- bibliographical literature search on the ACT (last search on 10 July 2014)
- search in trial registries for studies on the ACT (last search on 19 May 2014)

With the steps of information retrieval mentioned, the company identified no studies suitable for assessing the added benefit of empagliflozin plus insulin (with or without oral antidiabetic) versus the ACT specified by the G-BA.

2.7.2 Results on added benefit (research question D)

The company presented no relevant data for research question D. Hence the added benefit of empagliflozin plus insulin (with or without oral antidiabetic) versus the ACT specified by the G-BA is not proven.

2.7.3 Extent and probability of added benefit (research question D)

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of empagliflozin plus insulin (with or without oral antidiabetic) in comparison with the ACT specified by the G-BA (human insulin plus metformin). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

This deviates from the company's assessment, which derived a non-quantifiable added benefit for empagliflozin as add-on therapy to insulin ($\pm$ one or 2 oral antidiabetics) even without a relevant study.

2.8 Extent and probability of added benefit – summary

An overview of the extent and probability of added benefit for the different subindications of empagliflozin in comparison with the relevant ACTs is given Table 7.

Table 7: Empagliflozin – extent and probability of added benefit

Research question	Subindication	ACT	Extent and probability of added benefit
A	Monotherapy with empagliflozin	Sulfonylurea (glibenclamide, glimepiride)	Added benefit not proven
B1	Empagliflozin plus metformin	Metformin plus sulfonylurea (glibenclamide, glimepiride)	Added benefit not proven
B2	Empagliflozin plus another blood-glucose lowering drug except metformin and insulin	<i>(note: if metformin is inappropriate according to the SPC, human insulin is to be used as treatment option)</i>	Added benefit not proven
C	Empagliflozin plus at least 2 other blood-glucose lowering drugs except insulin	Metformin plus human insulin <i>(note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)</i>	Added benefit not proven
D	Empagliflozin plus insulin (with or without OAD)	Metformin plus human insulin <i>(note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)</i>	Added benefit not proven
ACT: appropriate comparator therapy; OAD: oral antidiabetic; SPC: Summary of Product Characteristics			

This assessment deviates from that of the company, which claimed a non-quantifiable added benefit for each of the subindications of research questions A, C, and D, without providing relevant studies. In addition, the company claimed considerable added benefit for empagliflozin in dual therapy (research questions B1 and B2). With regard to the certainty of conclusions, it only made a statement on the subindication of dual therapy with metformin (research question B1), for which it considered there to be a proof of considerable added benefit.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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