IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-12

Empagliflozin – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.7 and Appendix A of the dossier assessment *Empagliflozin – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 May 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Empagliflozin – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
29 February 2016

Internal Commission No.:
A16-12

Address of publisher:
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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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Keywords: empagliflozin, diabetes mellitus – type 2, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CSR	clinical study report
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)
ITT	intention to treat
MACE	major adverse cardiovascular events
RCT	randomized controlled trial
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 pharmaceutical company (hereinafter referred to as "the company") submitted a first dossier of the drug to be evaluated on 15 August 2014 for the early benefit assessment. This dossier was assessed in dossier assessment A14-26 and in the corresponding addendum A14-50. The company now requested a new benefit assessment because of new scientific findings. The assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 29 February 2016.

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 4 research questions versus the appropriate comparator therapy (ACT) specified by the G-BA. These are shown in Table 2.

Table 2: Research questions of the benefit assessment of empagliflozin

Research question	Subindication[a]	ACT specified by the G-BA
A	Monotherapy when diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance	Sulfonylurea (glibenclamide, glimepiride)
B	Combination with another blood-glucose lowering drug (except insulin), when this, together with diet and exercise, does not provide adequate glycaemic control	Metformin plus sulfonylurea (glibenclamide, glimepiride) *(note: if metformin is inappropriate according to the SPC, human insulin is to be used as treatment option)*
C	Combination with at least 2 other blood-glucose lowering drugs, when these, together with diet and exercise, do not provide adequate glycaemic control	Metformin plus human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)*
D	Combination with insulin, with or without OAD, when this, together with diet and exercise, does not provide adequate glycaemic control	Metformin plus human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)*

a: Subdivisions of the therapeutic indication according to the G-BA.
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 randomized controlled trials (RCTs) with a minimum duration of 24 weeks.

Results

Research question A: monotherapy with empagliflozin

As in the first assessment, no relevant data were available for research question A. Hence the added benefit of empagliflozin in monotherapy is not proven.

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

For research question B, the company presented a study of direct comparison (1245.28) investigating empagliflozin in the 25 mg/day fixed dose (in combination with metformin). It additionally presented 3 further studies for 2 indirect comparisons to investigate empagliflozin in the 10 mg/day fixed dose (in combination with metformin). These 4 studies in total had already been presented in the first dossier and in the corresponding commenting procedure on empagliflozin.

The company presented no new studies with the new dossier, but new long-term data on one of the 4 studies (study 1245.28) as well as new analyses on the indirect comparisons already known from the first benefit assessment.

Irrespective of the question whether the data presented by the company were at all relevant for the benefit assessment, the company's assessment was incomplete with regard to content because it did not analyse all relevant outcomes. Moreover, the documents presented by the company were self-contradictory.

Direct comparison

The company presented study 1245.28 to prove the added benefit of empagliflozin. In comparison with the first assessment, the company added data on the time point of observation 4 years after the start of the study (in the first assessment, data on the time point 2 years after the start of the study were available). Study 1245.28 cannot provide a sufficiently certain assessment on the approval-compliant use of empagliflozin (starting dose 10 mg/day) in comparison with glimepiride (see first assessment A14-26).

In its analysis of the study 1245.28, the company did not present results on several patient-relevant outcomes, although it was already known from the first dossier assessment of empagliflozin, from the corresponding addendum and from the G-BA's decision which patient-relevant outcomes were relevant for the benefit assessment. In particular, the company partly did not analyse specific adverse events (AEs) in which a disadvantage of empagliflozin in comparison with glimepiride was shown (e.g. renal and urinary disorders).

Indirect comparisons

Since the company identified no study of direct comparison for the approval-compliant empagliflozin starting dose of 10 mg/day, it presented 2 indirect comparisons based on RCTs (referred to as "indirect comparisons I to IV"). The indirect comparison I (including the corresponding sensitivity analyses, referred to by the company as "indirect comparisons III and IV") was conducted with the common comparator empagliflozin 25 mg/day plus metformin, the indirect comparison II with the common comparator linagliptin + metformin.

For its indirect comparison I, the company included the studies 1275.1 and 1245.23/1245.31 on the side of the intervention therapy, and the study 1245.28, which was already presented for the direct comparison, on the side of the comparator therapy. Hence this corresponds to the indirect comparison subsequently submitted in the commenting procedure on the first assessment; this indirect comparison could also only be interpreted to a limited extent because of the design of study 1245.28. As was the case for the direct comparison, analyses on relevant outcomes were missing, and there were contradictions in comparison with the information provided in the clinical study reports (CSRs) of the studies used. Due to the described deficiencies, the indirect comparison I presented by the company was also incomplete with regard to content. This also applied to the corresponding sensitivity analyses (referred to by the company as "indirect comparisons III and IV").

For its indirect comparison II, the company included study 1275.1 on the side of the intervention therapy, and study 1218.20 on the side of the comparator therapy. As described in the addendum to the first dossier assessment on empagliflozin, this indirect comparison

was not evaluable for the benefit assessment because the studies were not sufficiently similar. In addition, no conclusive interpretation was possible for study 1218.20 (linagliptin + metformin versus glimepiride + metformin) because not drugs, but therapeutic strategies were compared in this study.

Summary

In summary, the company presented no data suitable for the benefit assessment. Hence the added benefit of empagliflozin plus another blood-glucose lowering drug except insulin is not proven.

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

As in the first assessment, 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)

As in the first assessment, 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 benefit[4]

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). 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). For further details see [1,2].

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
B	Empagliflozin plus another blood-glucose lowering drug except insulin	Metformin plus sulfonylurea (glibenclamide, glimepiride) *(note: if metformin is inappropriate according to the SPC, human insulin is to be used as treatment option)*	Added benefit not proven
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)*	Added benefit not proven
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)*	Added benefit not proven
ACT: appropriate comparator therapy; OAD: oral antidiabetic; SPC: Summary of Product Characteristics			

The G-BA decides on the added benefit.

Research question additionally investigated by the company – study EMPA-REG-Outcome

In its dossier, the company described the study EMPA-REG-Outcome for the following research question defined by the company: comparison of treatment with empagliflozin in addition to standard treatment versus standard treatment (plus placebo) in patients at high cardiovascular risk. This research question concurred with the design of the EMPA-REG-Outcome study. However, the company presented no analyses on the EMPA-REG-Outcome study that allow a comparison with the ACT. The company argued that a different comparator therapy (standard treatment) should be defined for patients at high cardiovascular risk, but its arguments were self-contradictory.

Irrespective of this, the EMPA-REG-Outcome study can be used for the research question whether additional administration of empagliflozin has an advantage in a situation in which the treating physicians do not exhaust the available treatment options except empagliflozin. However, this research question was not relevant for the present benefit assessment. In contrast, the EMPA-REG-Outcome study was unsuitable for the research question investigated by the company (comparison of empagliflozin plus standard treatment versus standard treatment [plus placebo] for the benefit assessment in Germany):

- On the one hand, the treatment used in the EMPA-REG-Outcome study was no adequate standard treatment. On the contrary, it was noted that neither the study definition of the necessity for escalation of the antihyperglycaemic therapy (according to the inclusion criteria, all patients had received inadequate treatment) nor the upper threshold values mentioned in the guidelines (more than 70% of the patients in the control group did not reach these threshold values) were consistently adhered to. In addition, by far the largest part of treatment escalation was not conducted during "regular" treatment, but as part of emergency treatment. The large proportion of hypertensive patients whose systolic blood pressure was above the threshold value of 140 mmHg over the course of the study suggests that the options of drug adjustment to lower systolic blood pressure were not exhausted. However, there were no specific analyses on the proportion of patients with increased systolic value whose treatment was escalated by dose increase or administration of a further drug.
- On the other hand, marked regional differences were shown in the results on patient-relevant outcomes. The difference observed in the total population in favour of empagliflozin was largely determined by a marked difference in the regions Latin America and Asia, whereas no such difference was shown in the region Europe. The company's dossier contained no analyses on the quality of treatment in the different regions.

2.2 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 4 research questions versus the ACT specified by the G-BA. These are shown in Table 4.

Table 4: Research questions of the benefit assessment of empagliflozin

Research question	Subindication[a]	ACT specified by the G-BA
A	Monotherapy when diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance	Sulfonylurea (glibenclamide, glimepiride)
B	Combination with another blood-glucose lowering drug (except insulin), when this, together with diet and exercise, does not provide adequate glycaemic control	Metformin plus sulfonylurea (glibenclamide, glimepiride) *(note: if metformin is inappropriate according to the SPC, human insulin is to be used as treatment option)*
C	Combination with at least 2 other blood-glucose lowering drugs, when these, together with diet and exercise, do not provide adequate glycaemic control	Metformin plus human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)*
D	Combination with insulin, with or without OAD, when this, together with diet and exercise, does not provide adequate glycaemic control	Metformin plus human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)*

a: Subdivisions of the therapeutic indication according to the G-BA.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetic; SPC: Summary of Product Characteristics

Regarding the ACT, the company followed the G-BA's specifications for all 4 research questions.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Research question additionally investigated by the company

The company investigated an additional research question in its dossier: empagliflozin in addition to antidiabetic standard treatment in adult patients with type 2 diabetes mellitus and high cardiovascular risk in comparison with placebo treatment in addition to antidiabetic standard treatment. The company presented the study EMPA-REG-Outcome for this research question.

Adult patients with type 2 diabetes mellitus and high cardiovascular risk are a subpopulation of the approval population of empagliflozin and are comprised by the 4 research questions mentioned above. The added benefit in comparison with the ACT has to be proven also for this subpopulation. The company did not present such an analysis. Due to the size and the outcomes investigated (particularly cardiovascular events and all-cause mortality), the EMPA-REG-Outcome study is described in Appendix A irrespective of this.

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 (status: 8 December 2015)
- bibliographical literature search on empagliflozin (last search on 10 December 2015)
- search in trial registries for studies on empagliflozin (last search on 18 December 2015)

To check the completeness of the study pool:

- search in trial registries for studies on empagliflozin (last search on 18 March 2016)

No relevant studies were identified from this check. The company also identified no relevant study for a comparison of empagliflozin in monotherapy versus the ACT specified by the G-BA. Hence in comparison with the first assessment [3], no new scientific findings were available on research question A.

2.3.2 Results on added benefit (research question A)

The company presented no relevant data for research question A. Hence there was no hint of an added benefit of empagliflozin in monotherapy for adults with type 2 diabetes mellitus in comparison with the ACT. An added benefit is therefore not proven.

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

Since the company presented no relevant data for the assessment of the added benefit of empagliflozin in monotherapy for adults with type 2 diabetes mellitus, an added benefit of empagliflozin is not proven. The company claimed no added benefit for this research question.

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

2.4.1 Information retrieval and study pool (research question B)

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 (status: 8 December 2015)
- bibliographical literature search on empagliflozin (last search on 10 December 2015)
- search in trial registries for studies on empagliflozin (last search on 18 December 2015)
- bibliographical literature search on the ACT (last search on 10 December 2015)
- search in trial registries for studies on the ACT (last search on 18 December 2015)

To check the completeness of the study pool:

- search in trial registries for studies on empagliflozin (last search on 18 March 2016)
- search in trial registries for studies on linagliptin (last search on 13 May 2016)

No studies other than the ones cited by the company in the dossier were identified from this check.

From the steps of information retrieval mentioned, the company identified one study of direct comparison (1245.28 [4]), and 4 studies for indirect comparisons (1245.28 [4], 1245.23/1245.31 [5], 1275.1 [6] and 1218.20 [7]). These 4 studies had already been presented in the first dossier and in the corresponding commenting procedure on empagliflozin [3,8]. The company presented no new studies with the new dossier, but new long-term data on one of the 4 studies (study 1245.28) as well as new analyses on the indirect comparisons already known from the first benefit assessment.

Irrespective of the question whether the data presented by the company were at all relevant for the benefit assessment, the company's assessment was incomplete with regard to content because it did not analyse all relevant outcomes. Moreover, the documents presented by the company were self-contradictory. This is further explained below.

Study of direct comparison 1245.28

The company presented study 1245.28 to prove the added benefit of empagliflozin. This was a randomized, active-controlled approval study sponsored by the company on the comparison of empagliflozin 25 mg/day versus glimepiride 1-4 mg/day, each in combination with metformin. The design and the study characteristics of study 1245.28 are described in detail in dossier assessment A14-26 [3].

As already explained extensively in the first assessment, study 1245.28 was not sufficiently interpretable for the benefit assessment [3]. This was caused, on the one hand, by the treatment regimen used in the control group (uniform blood-glucose lowering to the near-normal level without individual target levels) in combination with the population included in the study (glycosylated haemoglobin A1c [HbA1c] values partly already low at baseline). On the other hand, the starting dose of 25 mg/day empagliflozin used in the study was too high. According to the specifications in the Summary of Product Characteristics (SPC) [9,10], the recommended starting dose is exclusively 10 mg/day. Irrespective of this, no advantage of empagliflozin resulted from study 1245.28 overall because, compared with glimepiride, there were both positive and negative effects regarding AEs [3].

In Module 4 B, the company presented results of study 1245.28 on the data cut-offs 104 weeks and 208 weeks. The results on the data cut-off after a treatment duration of 104 weeks were already presented in the report on the first assessment of empagliflozin [3].

Results on several patient-relevant outcomes were not shown in Module 4 B now presented by the company, however. This was neither appropriate nor comprehensible because the company knew both from the first dossier assessment of empagliflozin and the corresponding addendum and from the G-BA's decision which patient-relevant outcomes were relevant for the benefit assessment [3,8,11]. In particular, the company partly did not analyse specific AEs in which a disadvantage of empagliflozin in comparison with glimepiride was shown (e.g. renal and urinary disorders). In addition, as in the first dossier, the company presented no adequate operationalization on the outcome "severe hypoglycaemias".

In summary, the direct comparison presented by the company was incomplete with regard to content.

Indirect comparisons

Since the company identified no study of direct comparison for the approval-compliant empagliflozin starting dose of 10 mg/day, it presented 2 indirect comparisons based on RCTs (referred to as "indirect comparisons I to IV"). The indirect comparison I (including the corresponding sensitivity analyses, referred to by the company as "indirect comparisons III and IV") was conducted with the common comparator empagliflozin 25 mg/day plus metformin, the indirect comparison II with the common comparator linagliptin + metformin. Both indirect comparisons had already been presented in the first dossier and in the corresponding comment of the company on the dossier assessment [3,8].

Indirect comparison I

The following Figure 1 shows the data referred to by the company as "indirect comparison I".

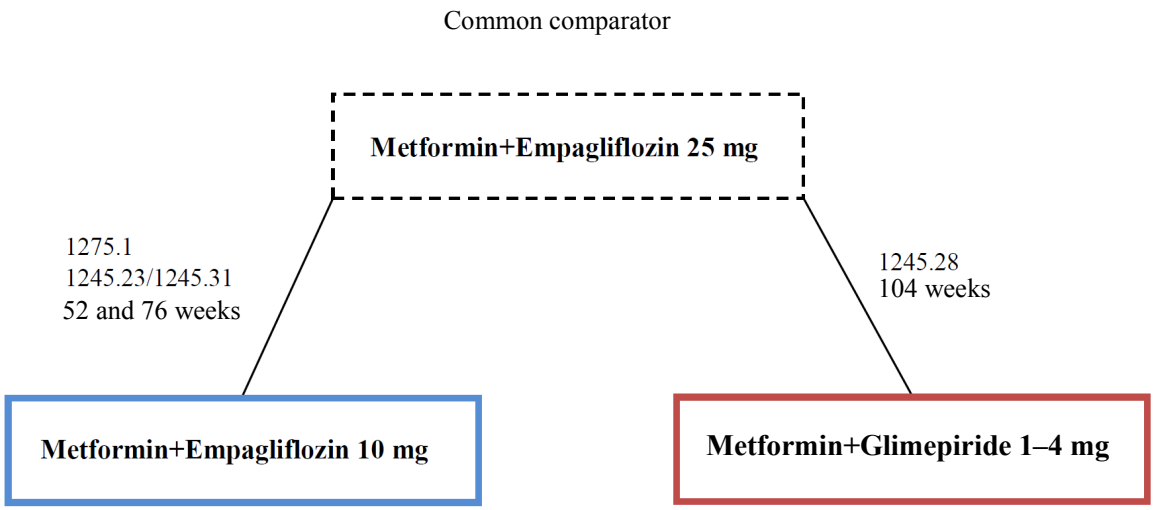

Figure 1: Data of the company for the indirect comparison I

The company included the studies 1275.1 and 1245.23/1245.31 on the side of the intervention therapy, and the study 1245.28, which was already presented for the direct comparison, on the side of the comparator therapy. Hence this comparison corresponds to the indirect comparison subsequently submitted in the commenting procedure on the first assessment; this indirect comparison could also only be interpreted to a limited extent because of the design of study 1245.28 (see above). At that time, the company presented only an analysis on the basis of 52 treatment weeks for all 3 studies, however. This was inadequate because the accompanying information loss was too large [8].

In Module 4 B of its dossier now submitted, the company presented analyses for 1 year (52 weeks; study 1275.1), 1.5 years (76 weeks, study 1245.23/31) and 2 years (104 weeks; study 1245.28). As was the case for the direct comparison, analyses on relevant outcomes were missing, however. In addition, for several outcomes, the data considered by the company for its analyses deviated from the information provided in the CSRs of the studies used. The company did not address the reasons for these deviations, however. Due to these contradictions, the effect estimates from the indirect comparison I presented by the company in Module 4 B were not evaluable.

Due to the described deficiencies, the indirect comparison I presented by the company was also incomplete with regard to content.

This also applied to the analyses referred to by the company as “indirect comparisons III and IV”. These analyses were sensitivity analyses on the indirect comparison I in which only one of both studies (1275.1 or 1245.23/31) was used for empagliflozin 10 mg/day.

Indirect comparison II

The following Figure 2 shows the data referred to by the company as "indirect comparison II".

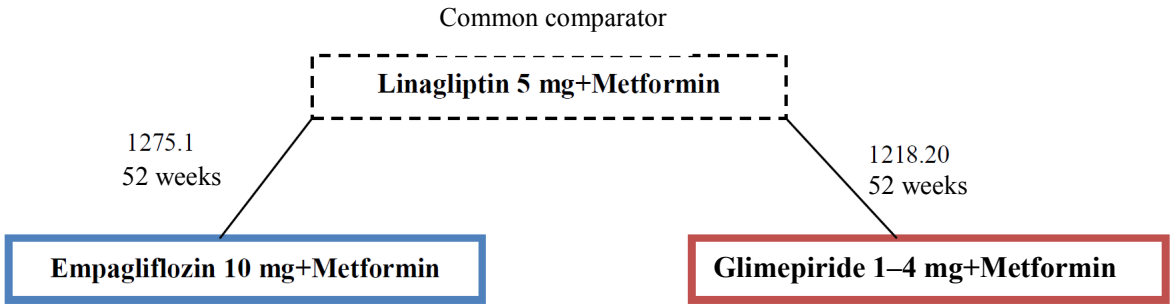

Figure 2: Data of the company for the indirect comparison II

Study 1275.1 was used on the side of the intervention therapy, and study 1218.20 on the side of the comparator therapy. As described in the addendum to the first dossier assessment on empagliflozin, this indirect comparison was not evaluable for the benefit assessment because the studies were not sufficiently similar [8]. In addition, study 1218.20 was unsuitable for the benefit assessment also for the issues already discussed in the dossier assessment on linagliptin [12].

2.4.2 Results on added benefit (research question B)

The company presented no data suitable for the benefit assessment for research question B. Hence there was no hint of an added benefit of empagliflozin plus another blood-glucose lowering drug except insulin for adults with type 2 diabetes mellitus in comparison with the ACT. An added benefit is therefore not proven.

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

Since no relevant data were presented for the benefit assessment, there is no proof of an added benefit of empagliflozin plus another blood-glucose lowering drug except insulin.

This deviates from the company's assessment, which derived proof of a considerable added benefit for empagliflozin plus another blood-glucose lowering drug except insulin.

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

2.5.1 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 (status: 8 December 2015)
- bibliographical literature search on empagliflozin (last search on 10 December 2015)
- search in trial registries for studies on empagliflozin (last search on 18 December 2015)

To check the completeness of the study pool:

- search in trial registries for studies on empagliflozin (last search on 18 March 2016)

No relevant studies were identified from this check. The company also 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. Hence in comparison with the first assessment [3], no new scientific findings were available on research question C.

2.5.2 Results on added benefit (research question C)

The company presented no relevant data for research question C. Hence there was no hint of an added benefit of empagliflozin plus at least 2 other blood-glucose lowering drugs except insulin for adults with type 2 diabetes mellitus in comparison with the ACT. An added benefit is therefore not proven.

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

Since no relevant data were 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. The company claimed no added benefit for this research question.

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

2.6.1 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 (status: 8 December 2015)
- bibliographical literature search on empagliflozin (last search on 10 December 2015)
- search in trial registries for studies on empagliflozin (last search on 18 December 2015)

To check the completeness of the study pool:

- search in trial registries for studies on empagliflozin (last search on 18 March 2016)

No relevant studies were identified from this check. The company also 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. Hence in comparison with the first assessment [3], no new scientific findings were available on research question D.

2.6.2 Results on added benefit (research question D)

The company presented no relevant data for research question D. Hence there was no hint of an added benefit of empagliflozin plus insulin (with or without oral antidiabetic) for adults with type 2 diabetes mellitus in comparison with the ACT. An added benefit is therefore not proven.

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

Since no relevant data were presented for the benefit assessment, there is no proof of an added benefit of empagliflozin plus insulin (with or without oral antidiabetic). The company claimed no added benefit for this research question.

2.7 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 5.

Table 5: 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
B	Empagliflozin plus another blood-glucose lowering drug except insulin	Metformin plus sulfonylurea (glibenclamide, glimepiride) *(note: if metformin is inappropriate according to the SPC, human insulin is to be used as treatment option)*	Added benefit not proven
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)*	Added benefit not proven
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)*	Added benefit not proven
ACT: appropriate comparator therapy; OAD: oral antidiabetic; SPC: Summary of Product Characteristics			

For research question B (empagliflozin plus metformin), this assessment deviates from that of the company, which claimed considerable added benefit for this research question. The company also claimed no added benefit for the subindications of research questions A, C and D.

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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Appendix A – Comment on the additional research question of the company and on the EMPA-REG-Outcome study

A.1 – Research question of the company

The company described the EMPA-REG-Outcome study in Module 4 D of its dossier, defining the following research question: comparison of treatment with empagliflozin in addition to standard treatment versus standard treatment (plus placebo) in patients at high cardiovascular risk. As expected, the company identified no further studies for this research question because it corresponded to the inclusion criteria and to the (planned) design of the EMPA-REG-Outcome study.

As described in Section 2.2, the company presented no analyses on the EMPA-REG-Outcome study that allow a comparison with the ACT. The company argued that a different comparator therapy should be defined for patients at high cardiovascular risk, but its arguments were self-contradictory:

- Firstly, the classification of the patient populations was contradictory between the individual Modules A to D (see Section 2.8 of the full dossier assessment).
- Secondly, the company argued that sulfonylureas are not appropriate for patients at high cardiovascular risk. However, a large proportion of the patients (about 43%) in the EMPA-REG-Outcome study were treated with sulfonylureas; the majority of them received a combination therapy with metformin (if applicable, plus insulin).
- Thirdly, the company correctly stated that the subgroup of patients at high cardiovascular risk has been comprised by the approval of empagliflozin from the beginning. However, it defined a separate comparator therapy for this group only in the present dossier, whereas in the first benefit assessment it had considered the G-BA's comparator therapy as appropriate for this subgroup.

The company's research question investigated in Module 4 D was therefore neither sufficient nor consistently justified in itself.

Irrespective of this, the EMPA-REG-Outcome study can be used for the research question whether additional administration of empagliflozin has an advantage in a situation in which the treating physicians do not exhaust the available treatment options except empagliflozin. However, this research question was not relevant for the present benefit assessment. In contrast, the EMPA-REG-Outcome study was unsuitable for the research question investigated by the company (comparison of empagliflozin plus standard treatment versus standard treatment [plus placebo] for the benefit assessment in Germany). This is justified in detail below.

A.2 – Description of the EMPA-REG-Outcome study

The design of the EMPA-REG-Outcome study is described in Table 10 and Table 11.

Table 10: Characteristics of the study – EMPA-REG-Outcome

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
EMPA-REG-Outcome	RCT, double-blind, parallel	Treatment-naive[b] or pretreated[c] adult patients with type 2 diabetes mellitus at high cardiovascular risk[d] with inadequate glycaemic control	In each case in addition to other antidiabetic treatment: ▪ empagliflozin 10 mg (N = 2347) ▪ empagliflozin 25 mg (N = 2344) ▪ placebo (N = 2337)	▪ Screening: 3 weeks ▪ Run-in: 2 weeks ▪ Planned end of study: after 691 3-point MACE events ▪ Treatment: Until withdrawal of consent or end of study ▪ Follow-up: 30 days	607 centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, Columbia, Croatia, Czech Republic, Denmark, Estonia, France, Georgia, Greece, Hong Kong, Hungary, India, Israel, Indonesia, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, New Zealand, Norway, Peru, Philippines, Poland, Portugal, Romania, Russia, Singapore, South Africa, Spain, Sri Lanka, Taiwan, Thailand, Ukraine, United Kingdom, USA 8/2010–4/2015	Primary: time to occurrence of a 3-point MACE Secondary: mortality, morbidity, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes from the information provided by the company in Module 4 D of the dossier.
b: The patients had received no antidiabetic therapy at least 12 weeks before randomization.
c: Any antidiabetic therapy (in Japan without pioglitazone) at a constant dosage over the last 12 weeks before randomization.
d: At least one of the following conditions had to be fulfilled: confirmed myocardial infarction, multivessel disease in at least 2 large coronary arteries, disease of a coronary artery, unstable angina pectoris, stroke, or peripheral arterial disease.

AE: adverse event; MACE: major adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke); N: number of randomized patients; RCT: randomized controlled trial

Table 11: Characteristics of the intervention of the study – EMPA-REG-Outcome

Study	Intervention 1	Intervention 2	Comparison
EMPA-REG-Outcome	Empagliflozin 25 mg once daily orally + antidiabetic therapy[a]	Empagliflozin 10 mg once daily orally + antidiabetic therapy[a]	Placebo once daily orally + antidiabetic therapy[a]
	Pretreatment: 12 weeks of stable antidiabetic therapy, additional placebo in the last 2 weeks before randomization **Concomitant treatment:** ▪ rescue medication for the treatment of hyperglycaemia[b] ▪ drugs that were necessary for the treatment of the cardiovascular risk factors could be used at the treating physician's discretion (e.g. antihypertensive medications, anticoagulants or lipid-lowering drugs) ▪ non-systemic steroids **Non-permitted concomitant treatment:** ▪ anti-obesity drugs ▪ systemic steroids > 2 weeks treatment ▪ avoidance of a change in dosage of thyroid hormones		

a: Unchanged for the first 12 weeks of the study. Then the therapy was to be adjusted at the physician's discretion to achieve "best standard of care" according to local guidelines.
b: FPG < 240 mg/L or 13.3 mmol/L (France and Portugal [week 12–28]: 200 mg/L or 11.1 mmol/L; Portugal [week 28–end of study]: 180 mg/L or 10.0 mmol/L); treatment was chosen at the discretion of the treating physician.
FPG: fasting plasma glucose

Study design of the EMPA-REG-Outcome study

The EMPA-REG-Outcome study was a randomized 3-arm, placebo-controlled, double-blind study sponsored by the company. The multicentre study was conducted in North America, Latin America, Europe, Africa and Asia. Adults with type 2 diabetes mellitus were included who additionally had at least one of the following cardiovascular risk factors: coronary heart disease, angina pectoris, history of myocardial infarction, coronary artery bypass, cardiac failure, history of stroke, or peripheral arterial occlusive disease. Despite stable antidiabetic therapy for the last 12 weeks before randomization, patients had not achieved adequate glycaemic control (HbA1c value at the start of the study ≥ 7 to ≤ 10%).

A total of 7028 patients were randomly assigned in a ratio of 1:1:1 to the 3 treatment arms empagliflozin 10 mg, empagliflozin 25 mg and placebo, each of which was administered in addition to the ongoing antidiabetic therapy. According to the study protocol, the composition and dosage of the antidiabetic therapy had to be stable for a period of 12 weeks after randomization, if possible, although the patients' previous antidiabetic therapy was insufficient according to the study definition. According to the study protocol, exceptions were only envisaged for severe uncontrolled hyperglycaemia. This was operationalized as fasting blood glucose of > 240 mg/dL, which had to be confirmed by a repeated blood glucose measurement. Administration of antidiabetic rescue medication was envisaged in such cases (not only in the first 12 weeks, but during the total course of the study). The choice and dosage of this medication were determined by the investigator. After 12 weeks of treatment,

the adjustment of antidiabetic therapy was allowed in all 3 arms. Subsequently, sufficient glycaemic control according to regional guideline recommendations was to be ensured.

Moreover, adequate treatment of the cardiovascular risk factors was envisaged in all 3 treatment arms. The concomitant medications necessary for this were used at the investigator's discretion (e.g. antihypertensive medications, anticoagulants or lipid-lowering drugs) to ensure treatment according to regional guideline recommendations.

Primary outcome of the study was the time to first occurrence of any of the following events of the composite outcome "3-point major adverse cardiovascular events (MACE)": cardiovascular death, nonfatal myocardial infarction or nonfatal stroke. The study was event-driven and had an anticipated duration of up to 8 years (420 weeks). The specified event rate was achieved already after less than 5 years (242 weeks).

Figure 3 shows a summary of the study design of the EMPA-REG-Outcome study.

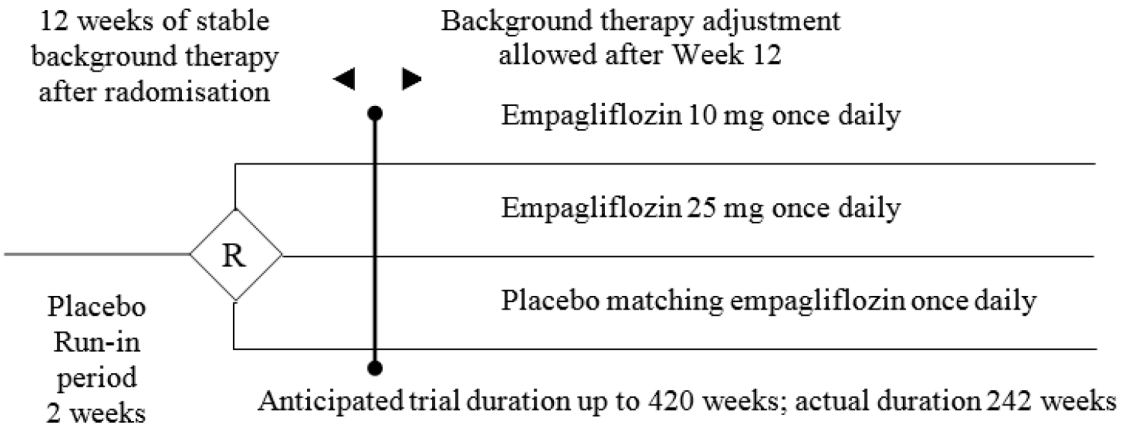


Figure 3: Study design of the EMPA-REG-Outcome study

Characteristics of the study population

Table 12, Table 13 and Table 14 show the characteristics of the patients included in the EMPA-REG-Outcome study. Table 15 and Table 16 contain information on the antidiabetic and antihypertensive treatments of the patients included that were already ongoing at the start of the study.

Table 12: Characteristics of the populations in the EMPA-REG-Outcome study (age, sex, BMI, ethnicity, treatment and study discontinuation)

Study Group	N	Age [years] mean (SD)	Sex [F/M] %	BMI mean (SD)	Ethnicity n (%) White	Asian	Other[a]	Treat-ment discontin uation n (%)	Study discon-tinuation n (%)
EMPA-REG-Outcome									
Empa 25 mg	2342	63 (9)	28/72	30.6 (5.3)	1696 (72.4)	501 (21.4)	144 (6.1)	542 (23.1)	63 (2.7)
Empa 10 mg	2345	63 (9)	30/70	30.6 (5.2)	1707 (72.8)	505 (21.5)	133 (5.7)	555 (23.7)	81 (3.5)
Placebo	2333	63 (9)	28/72	30.7 (5.2)	1678 (71.9)	511 (21.9)	144 (6.2)	683 (29.3)	67 (2.9)

a: Institute's calculation.

BMI: body mass index; empa: empagliflozin; F: female; HbA1c: glycosylated haemoglobin A1c; M: male; n: number of patients with event; N: number of patients who received at least one dose of the study medication; SD: standard deviation

Table 13: Characteristics of the populations in the EMPA-REG-Outcome study (diabetes duration)

Study Group	N	Diabetes duration [years] n (%) ≤ 1	> 1 and ≤ 5	> 5 and ≤ 10	> 10
EMPA-REG-Outcome					
Empa 25 mg	2342	60 (2.6)	374 (16.0)	590 (25.2)	1318 (56.3)
Empa 10 mg	2345	68 (2.9)	338 (14.4)	585 (24.9)	1354 (57.7)
Placebo	2333	52 (2.2)	371 (15.9)	571 (24.5)	1339 (57.4)

empa: empagliflozin; n: number of patients with event; N: number of patients who received at least one dose of the study medication

Table 14: Characteristics of the populations in the EMPA-REG-Outcome study (fasting blood glucose, HbA1c and renal function)

Study Group	N	FPG	HbA1c			Renal function[a] eGFR (mL/min/1.73 m^2)		
		mean (SE)	n (%)			n (%)		
			< 8	≥ 8 and < 9	≥ 9	< 60[b, c]	≥ 60 and < 90	≥ 90
EMPA-REG-Outcome								
Empa 25 mg	2342	151.8 (0.9)	1151 (49.1)	804 (34.3)	386 (16.5)	607 (25.9)	1202 (51.3)	531 (22.7)
Empa 10 mg	2345	153.2 (0.9)	1188 (50.7)	730 (31.1)	426 (18.2)	605 (25.8)	1221 (52.1)	519 (22.1)
Placebo	2333	153.5 (0.9)	1156 (49.5)	795 (34.1)	382 (16.4)	607 (26.0)	1238 (53.1)	488 (20.9)

a: Data on one patient in each of the study arms empa 25 mg and empa 10 mg are missing.
b: Data on 2 patients in the study arm empa 25 mg are missing.
c: Institute's calculation.

eGFR: estimated glomerular filtration rate; empa: empagliflozin; FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin A1c; n: number of patients with event; N: number of patients who received at least one dose of the study medication and whose HbA1c baseline value was measured; SE: standard error

Table 15: Antidiabetic therapy at the start of the study in the EMPA-REG-Outcome study

Study Group	Empa 25 mg		Empa 10 mg		Placebo	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
EMPA-REG-Outcome						
Patients with any antidiabetic therapy	2342	2295 (98.0)	2345	2299 (98.0)	2333	2297 (98.5)
Metformin	2342	1730 (73.9)	2345	1729 (73.7)	2333	1734 (74.3)
Insulin	2342	1120 (47.8)	2345	1132 (48.3)	2333	1135 (48.6)
Sulfonylurea	2342	1029 (43.9)	2345	985 (42.0)	2333	992 (42.5)
DPP-4 inhibitor	2342	247 (10.5)	2345	282 (12.0)	2333	267 (11.4)
Patients with one therapy	2342	676 (28.9)	2345	704 (30.0)	2333	691 (29.6)
Only insulin	2342	309 (13.2)	2345	317 (13.5)	2333	326 (14.0)
Only metformin	2342	242 (10.3)	2345	264 (11.3)	2333	234 (10.0)
Patients with 2 therapies	2342	1149 (49.1)	2345	1110 (47.3)	2333	1148 (49.2)
Metformin + insulin	2342	464 (19.8)	2345	448 (19.1)	2333	506 (21.7)
Metformin + sulfonylurea	2342	480 (20.5)	2345	443 (18.9)	2333	461 (19.8)
Patients with 3 therapies	2342	411 (17.5)	2345	419 (17.9)	2333	387 (16.6)
Metformin + sulfonylurea + insulin	2342	146 (6.2)	2345	149 (6.4)	2333	123 (5.3)
Patients with 4 or more therapies	2342	59 (2.5)	2345	66 (2.8)	2333	71 (3.0)

DPP-4: dipeptidyl peptidase-4; empa: empagliflozin; n: number of patients with (at least one) event; N: number of analysed patients

Table 16: Concomitant treatment at the start of the study in the EMPA-REG-Outcome study (antihypertensive medications)

Study Group	Empa 25 mg		Empa 10 mg		Placebo	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
EMPA-REG-Outcome						
ACE inhibitors/AT1 antagonists	2342	1902 (81.2)	2345	1896 (80.9)	2333	1868 (80.1)
Beta-blockers	2342	1526 (65.2)	2345	1530 (65.2)	2333	1498 (64.2)
Diuretics	2342	1011 (43.2)	2345	1036 (44.2)	2333	988 (42.3)
Calcium channel blockers	2342	748 (31.9)	2345	781 (33.3)	2333	788 (33.8)
Mineralocorticoid receptor antagonists	2342	148 (6.3)	2345	157 (6.7)	2333	136 (5.8)
Renin inhibitors	2342	11 (0.5)	2345	16 (0.7)	2333	19 (0.8)
Other	2342	190 (8.1)	2345	193 (8.2)	2333	191 (8.2)
Total	2342	2219 (94.7)	2345	2227 (95.0)	2333	2221 (95.2)

ACE: angiotensin converting enzyme; AT1: angiotensin receptor subtype 1; empa: empagliflozin; n: number of patients with (at least one) event; N: number of analysed patients

The patient characteristics were balanced between the 3 treatment groups. Most patients (about 70%) were male. About 50% of the patients included had an HbA1c value of ≥ 8 at the start of the study. About 57% had had diabetes mellitus for more than 10 years.

Almost all patients were receiving antidiabetic therapy already at the start of treatment; about 30% of the patients were treated with monotherapy (mostly insulin or metformin); about 50% of the patients were treated with a dual combination (mostly metformin + sulfonylurea or metformin + insulin).

Almost 95% of the patients included were receiving therapy with a blood-pressure-lowering medication (often as a combination of 2 or more drugs) at the start of treatment.

Requirements of the study protocol to adjust antidiabetic therapy not implemented

It can be inferred from the observed courses of blood glucose (fasting blood glucose and HbA1c value at the start of the study, after week 12 and over the further course of the study) that the requirements of the study protocol to adjust the antidiabetic therapy were not implemented. This was supported by the information on the escalation of the antidiabetic therapy in the course of the study. Both are described in detail below.

Blood glucose at the start of the study and in the course of the study

Figure 4 shows the change of the fasting plasma glucose values over the course of the treatment in comparison with the baseline value in the EMPA-REG-Outcome study.

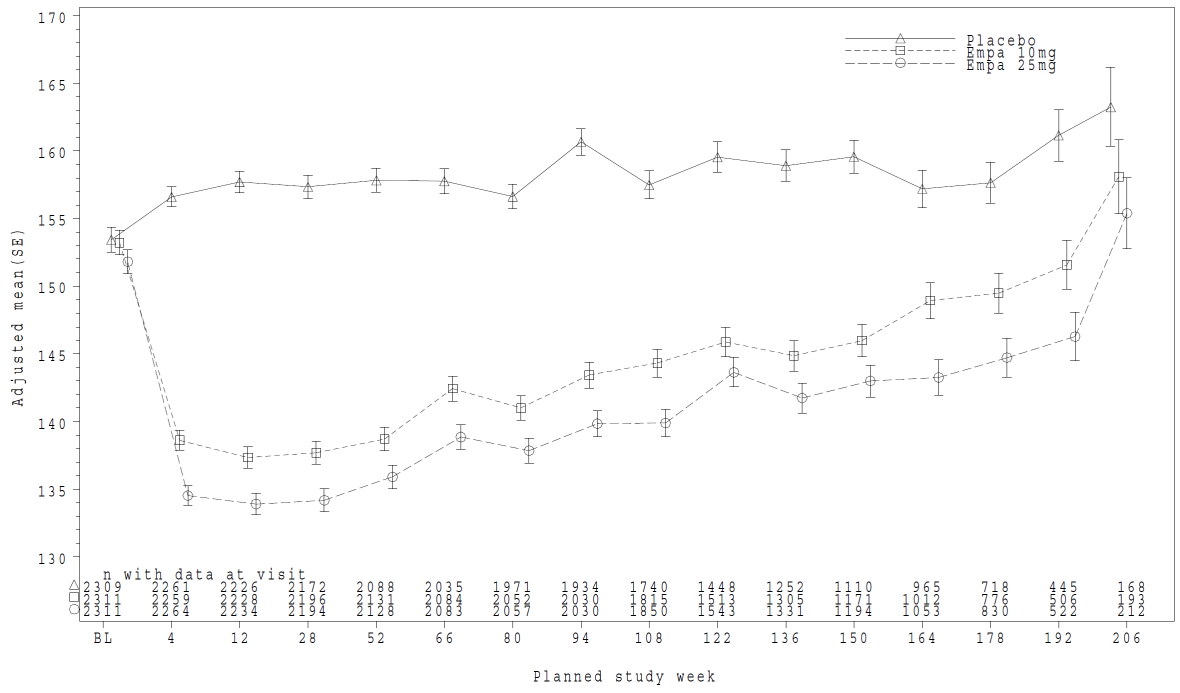


Figure 4: Change in fasting blood glucose value in comparison with the baseline value in the EMPA-REG-Outcome study (intention to treat [ITT])

Figure 5 shows the change of the HbA1c values over the course of the treatment in comparison with the baseline value in the EMPA-REG-Outcome study.

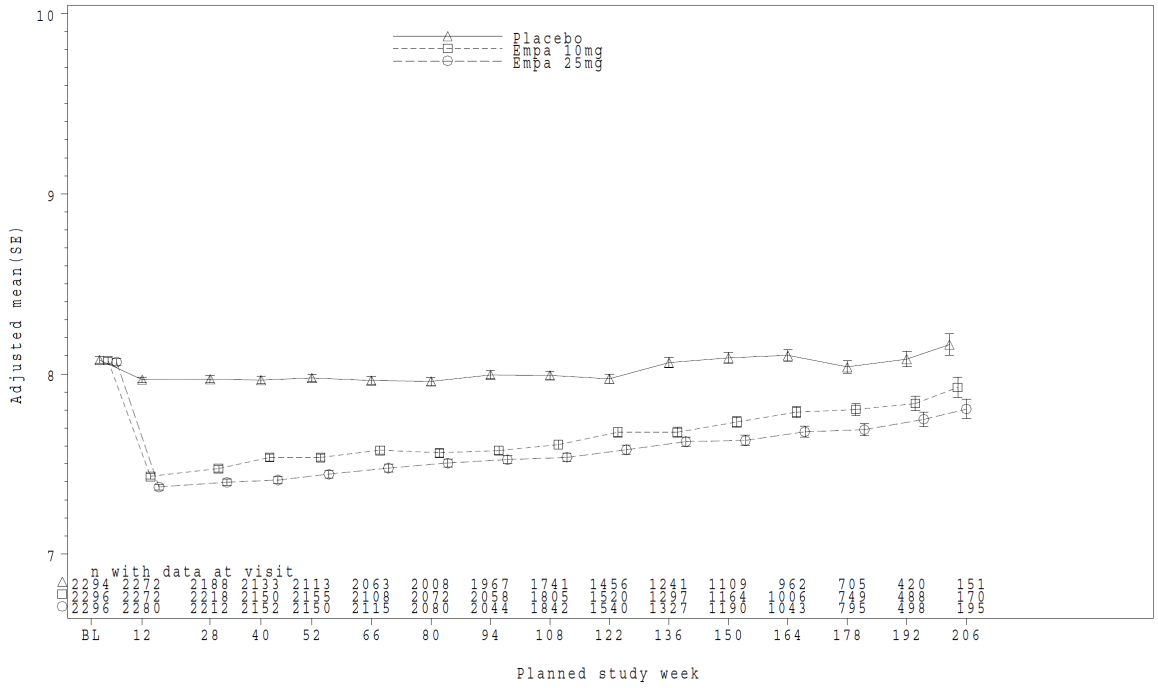


Figure 5: Change in HbA1c value in comparison with the baseline value in the EMPA-REG-Outcome study (ITT)

After randomization, only the patients in the 2 treatment arms with empagliflozin received an additional antidiabetic intervention (empagliflozin) during the first 12 treatment weeks. The patients in the control arm, in contrast, initially continued their ongoing antidiabetic therapy unchanged because the study protocol allowed no adjustment of the antidiabetic therapy during the first 12 treatment weeks. Correspondingly, a lowering of the average fasting blood glucose levels in this time period was observed only in the empagliflozin arms, but not in the control arm. Since on average there was no lowering of the blood glucose levels in the comparator group despite study intervention (placebo), this first study phase potentially led to a (partial) unblinding of the study.

It was notable that no lowering of the fasting blood glucose levels was observed in the patients in the control arm also after week 12, although blood-glucose lowering therapy was previously insufficient according to the inclusion criteria, and antidiabetic therapy according to guidelines was to be ensured from week 12 according to requirements in the study protocol. Correspondingly, also no change in HbA1c value was shown after adjustment of the antidiabetic therapy was allowed from week 12.

In the empagliflozin arms, in contrast, rapid lowering of the fasting blood glucose levels to about 135 to 140 mg/dL was initially achieved, which was accompanied by a marked

lowering of the HbA1c value. In the further course of treatment, blood glucose levels continuously increased again also in these arms until they reached approximately the baseline value of about 155 mg/dL. A consideration of the glycaemic threshold values at different time points of observation illustrates the missing implementation of the requirements for escalation of the antihyperglycaemic therapy. Assuming normal distribution, Figure 6 and Figure 7 show the proportions of patients who exceeded a given fasting blood glucose threshold value of 130 mg/dL, 150 mg/dL or 180 mg/dL after 12 or 52 treatment weeks. The choice of the threshold values of the fasting blood glucose of 130 mg/dL, 150 mg/dL and 180 mg/dL was based on the following rationale:

- A fasting blood glucose level of 130 mg/dL is the upper threshold of the range recommended in guidelines (National Care Guideline of the German Medical Association [13], Guideline of the American Diabetes Association [14]). Antidiabetic medication is to be escalated on exceeding the fasting blood glucose level of 130 mg/dL at the latest.
- The consideration of the fasting blood glucose threshold value of 150 mg/dL was derived from the average value of the patients at the start of the study (see Table 14).
- A fasting blood glucose of 180 mg/dL is a value in the area of the renal threshold; if this threshold is exceeded, osmotic diuresis can be expected [15]. This should be avoided because of the corresponding late symptoms.

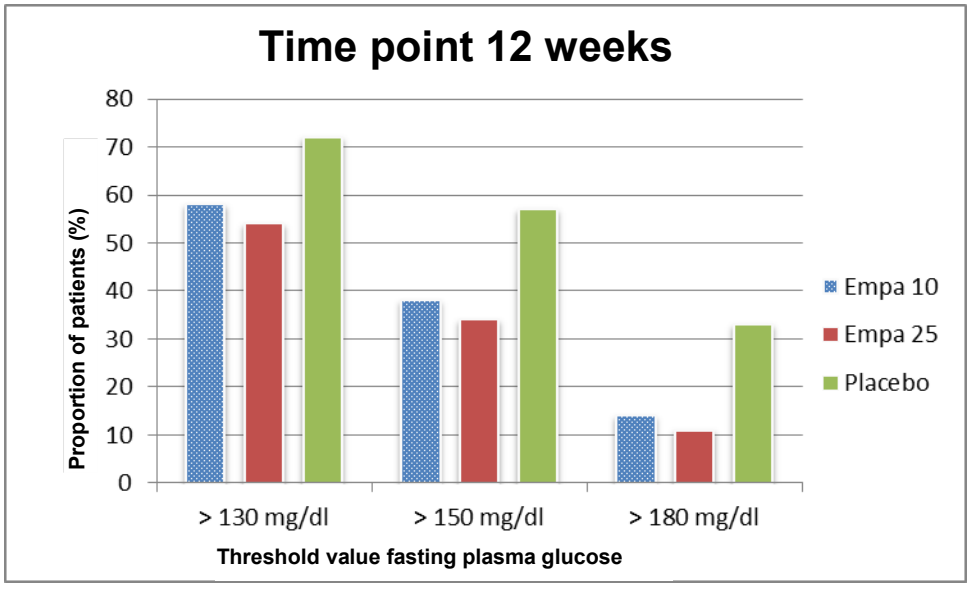


Figure 6: Proportions of patients in the EMPA-REG-Outcome study who exceeded a given fasting blood glucose threshold value after 12 treatment weeks (calculation on the basis of the observed mean and standard deviation under assumption of a normal distribution)

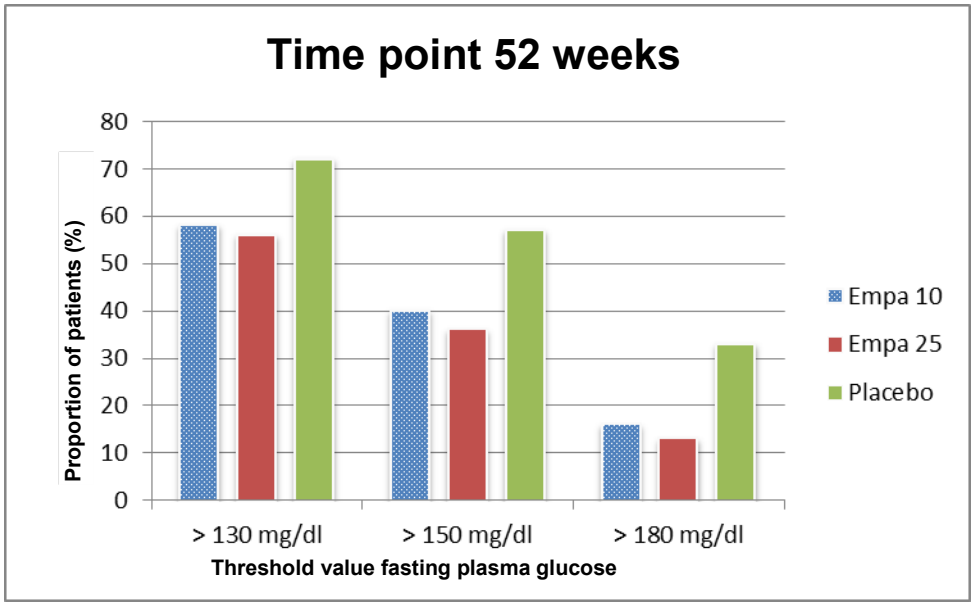


Figure 7: Proportions of patients in the EMPA-REG-Outcome study who exceeded a given fasting blood glucose threshold value after 52 treatment weeks (calculation on the basis of the observed mean and standard deviation under assumption of a normal distribution)

The proportion of patients with a fasting blood glucose level of > 130 mg/dL after 12 weeks was about 55% in the empagliflozin arms and about 70% in the control arm. Hence according to guidelines (which were guiding the action, according to the study protocol) treatment escalation was already required for these patients. Moreover, more than 50% of the patients in the control arm exceeded a fasting blood glucose threshold value of 150 mg/dL, and about 30% of the patients a value of 180 mg/dL. Particularly for the latter, there was an increased need for escalation of the antidiabetic medication beyond the guideline recommendations. In contrast, the proportion of patients exceeding the fasting blood glucose threshold values of 150 mg/dL or 180 mg/dL was consistently lower in the intervention arms than in the control arm.

After a treatment duration of 52 weeks, the proportion of patients who exceeded the respective threshold values was almost unchanged, although, in the meantime, antidiabetic therapy would have had to be adjusted in all 3 arms. Specifically, one year after the start of the study and despite supposed “standard of care according to guidelines”

- more than 70% of the patients in the control group had a fasting blood glucose level above the upper threshold value recommended in guidelines, and
- more than 30% of the patients in the control group had a fasting blood glucose level above the renal threshold of 180 mg/dL.

Escalation of the antidiabetic therapy in the course of the study

At the start of the study, about 48% of the patients were receiving insulin (alone or in combination with other antidiabetics, see Table 15). Despite the required escalation described above, only about 22% of the patients in the control arm received a long-term increase of their daily dose of insulin. Whether and in how far a change of the therapeutic strategy was conducted (e.g. switch from basal supported oral therapy to intensified insulin therapy) was unclear because the corresponding information on this was missing. Table 17 shows an overview of this.

Table 17: Changes in the insulin therapy in comparison with the start of the study in the EMPA-REG-Outcome study

Study	Empa 25 mg		Empa 10 mg		Placebo	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
EMPA-REG-Outcome						
Antidiabetic therapy: insulin						
Change of the daily dose for at least 7 consecutive days	2341	666 (28.4)	2344	689 (29.4)	2333	739 (31.7)
Increase of the daily dose for at least 7 consecutive days	2341	278 (11.9)	2344	310 (13.2)	2333	522 (22.4)
Decrease of the daily dose for at least 7 consecutive days	2341	450 (19.2)	2344	466 (19.9)	2333	325 (13.9)
empa: empagliflozin; n: number of patients with (at least one) event; N: number of analysed patients						

Additional antidiabetic medications beyond the therapy already existing were additionally introduced in the course of the study. Table 18 shows an overview of this.

Table 18: Additional antidiabetic medication after the start of the study in the EMPA-REG-Outcome study

Study	Empa 25 mg		Empa 10 mg		Placebo	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
EMPA-REG-Outcome						
Any antidiabetic medication	2342	429 (18.3)	2345	484 (20.6)	2333	736 (31.5)
Metformin	2342	82 (3.5)	2345	90 (3.8)	2333	112 (4.8)
Sulfonylurea	2342	70 (3.0)	2345	106 (4.5)	2333	164 (7.0)
Glitazones	2342	33 (1.4)	2345	23 (1.0)	2333	68 (2.9)
Alpha glucosidase inhibitor	2342	24 (1.0)	2345	30 (1.3)	2333	34 (1.5)
Glinides	2342	17 (0.7)	2345	16 (0.7)	2333	30 (1.3)
DPP-4 inhibitor	2342	121 (5.2)	2345	142 (6.1)	2333	193 (8.3)
GLP-1 antagonist	2342	36 (1.5)	2345	29 (1.2)	2333	57 (2.4)
Insulin	2342	118 (5.0)	2345	154 (6.6)	2333	268 (11.5)
Other antidiabetics	2342	29 (1.2)	2345	19 (0.8)	2333	26 (1.1)
No treatment	2342	1913 (81.7)	2345	1861 (79.4)	2333	1597 (68.5)

DPP-4: dipeptidyl peptidase-4; empa: empagliflozin; GLP-1: glucagon-like peptide 1; n: number of patients with (at least one) event; N: number of analysed patients

Hence only about 31.5% of the patients in the control arm received additional antidiabetic therapy, although the previous antihyperglycaemic therapy of all patients (i.e. 100%) was insufficient according to the inclusion criteria, and the upper limit of the range for the fasting blood glucose level recommended in guidelines was exceeded in more than 70% of the patients.

Further analyses showed that even these minor escalation rates were mainly caused by emergency interventions. As described above, an antidiabetic rescue medication was envisaged in the study protocol for severe uncontrolled hyperglycaemia (operationalized as fasting blood glucose levels of > 240 mg/dL). This rescue medication could be provided at the physician's discretion either in the form of dose increases in the existing antidiabetic therapy or as the administration of additional medication. Table 19 shows an overview of the use of antidiabetic rescue medication over the course of the study.

Table 19: Use of antidiabetic rescue medication in the EMPA-REG-Outcome study

Study	Empa 25 mg		Empa 10 mg		Placebo	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
EMPA-REG-Outcome						
Any rescue medication	2341	745 (31.8)	2344	777 (33.1)	2333	1265 (54.2)
Increase of dosage compared with the baseline dosage over at least 7 consecutive days or until discontinuation of treatment	2341	537 (22.9)	2344	555 (23.7)	2333	931 (39.9)
Additional medication over at least 7 consecutive days or until discontinuation of treatment	2341	328 (14.0)	2344	364 (15.5)	2333	631 (27.0)
Metformin	2341	60 (2.6)	2344	69 (2.9)	2333	96 (4.1)
Sulfonylurea	2341	61 (2.6)	2344	79 (3.4)	2333	147 (6.3)
Glitazones	2341	29 (1.2)	2344	17 (0.7)	2333	60 (2.6)
Alpha glucosidase inhibitor	2341	20 (0.9)	2344	28 (1.2)	2333	29 (1.2)
Glinides	2341	14 (0.6)	2344	11 (0.5)	2333	26 (1.1)
DPP-4 inhibitor	2341	88 (3.8)	2344	106 (4.5)	2333	151 (6.5)
GLP-1 antagonist	2341	31 (1.3)	2344	22 (0.9)	2333	51 (2.2)
Insulin	2341	87 (3.7)	2344	110 (4.7)	2333	221 (9.5)
Other antidiabetics	2341	4 (0.2)	2344	1 (< 0.1)	2333	11 (0.5)

DPP-4: dipeptidyl peptidase-4; empa: empagliflozin; GLP-1: glucagon-like peptide 1; n: number of patients with (at least one) event; N: number of analysed patients

Overall more than half of the patients in the control arm (about 54%) received antidiabetic rescue medication. Escalation by administration of an additional drug for 7 days or longer was required in half of these patients (i.e. about 27% of the total control group). This means that the vast majority of the patients in the control arm who received an additional antidiabetic in the course of the study (about 31%) received this drug not as part of a regulated escalation, but as part of an emergency treatment. Analyses over the time course (see Table 20 and Figure 8) additionally showed that some of the patients needed antidiabetic rescue medication already at the start of the study or shortly afterwards (about 11% of the patients received rescue medication already in the first 12 weeks), but that this increased notably over the total course of the study.

Table 20: Need of antidiabetic rescue medication in the EMPA-REG-Outcome study over time

Study Time point	Empa 25 mg		Empa 10 mg		Placebo	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
EMPA-REG-Outcome						
Start of study	2341	0 (0)	2344	0 (0)	2333	0 (0)
12 weeks	2236[a]	246 (11.0)	2233[a]	238 (10.7)	2234[a]	268 (12.0)
28 weeks	2196[a]	465 (21.2)	2201[a]	461 (20.9)	2178[a]	630 (28.9)
52 weeks	2130[a]	726 (34.1)	2135[a]	715 (33.5)	2093[a]	957 (45.7)
End of study	2341	745 (31.8)	2344	777 (33.1)	2333	1265 (54.2)

a: Number of analysed patients based on the outcome "fasting plasma glucose".
empa: empagliflozin; n: number of patients with (at least one) event; N: number of analysed patients

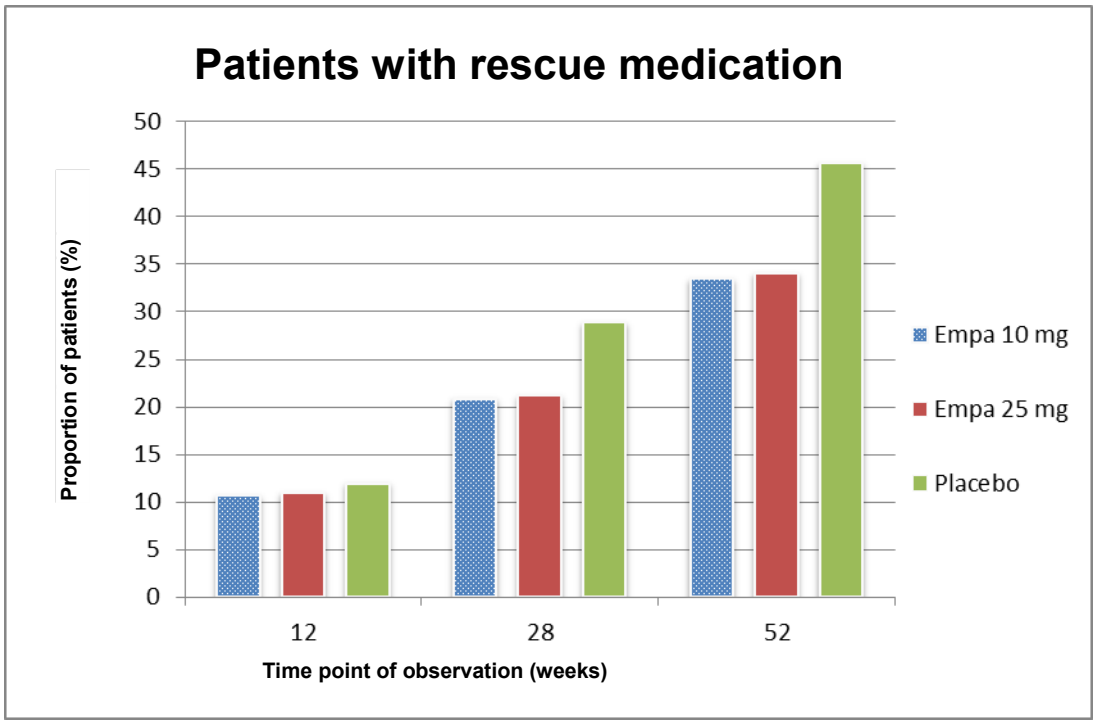


Figure 8: Proportion of patients in the EMPA-REG-Outcome study with rescue medication over time

Summary

In summary, it cannot be derived that the antihyperglycaemic treatment used in the EMPA-REG-Outcome study was adequate. On the contrary, it was noted that neither the study definition of necessity for escalation (according to the inclusion criteria, all patients had received inadequate treatment) nor the upper threshold values mentioned in the guidelines (more than 70% of the patients in the control group did not reach these threshold values) were

consistently adhered to. Moreover, the vast majority of the treatment escalation was not conducted as part of "regular" treatment, but as part of emergency treatment.

Implementation of the requirements from the study protocol on antihypertensive treatment questionable

Systolic blood pressure is an important parameter for the treatment of cardiovascular risk factors. Hereinafter, the drug treatment of systolic blood pressure in the EMPA-REG-Outcome study is described, and the systolic blood pressure in the course of the study is considered. About 95% of the patients already received antihypertensive therapy at the start of the study (see Table 16). Beyond that, additional antihypertensive medications were administered in the course of the study. Table 21 shows an overview of this.

Table 21: Concomitant treatment after the start of the study in the EMPA-REG-Outcome study (antihypertensive medications)

Study	Empa 25 mg		Empa 10 mg		Placebo	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
EMPA-REG-Outcome						
ACE inhibitors/AT1 antagonists	2342	622 (26.6)	2345	602 (25.7)	2333	702 (30.1)
Beta-blockers	2342	470 (20.1)	2345	429 (18.3)	2333	608 (26.1)
Diuretics	2342	438 (18.7)	2345	420 (17.9)	2333	481 (20.6)
Calcium channel blockers	2342	361 (15.4)	2345	311 (13.3)	2333	481 (20.6)
Mineralocorticoid receptor antagonists	2342	90 (3.8)	2345	87 (3.7)	2333	136 (5.8)
Renin inhibitors	2342	4 (0.2)	2345	5 (0.2)	2333	6 (0.3)
Other	2342	145 (6.2)	2345	129 (5.5)	2333	165 (7.1)
Total	2342	1058 (45.2)	2345	1030 (43.9)	2333	1190 (51.0)

ACE: angiotensin converting enzyme; AT1: angiotensin receptor subtype 1;empa: empagliflozin; n: number of patients with (at least one) event; N: number of analysed patients

In total, additional antihypertensive medications after the start of the study were administered in about 44% and 45% of the patients in both empagliflozin arms, and in about 51% of the patients in the control arm.

Figure 9 shows the change of the systolic blood pressure over the course of the treatment in comparison with the baseline value in the EMPA-REG-Outcome study.

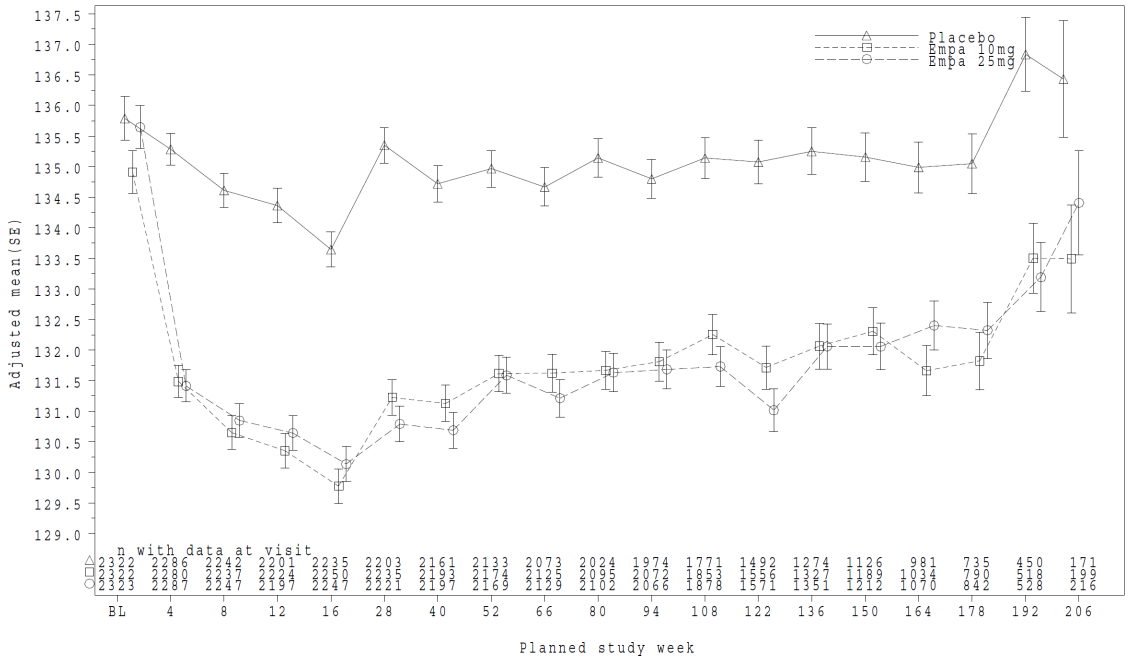


Figure 9: Change in systolic blood pressure in comparison with the baseline value in the EMPA-REG-Outcome study (ITT)

Systolic blood pressure was lowered in all 3 treatment arms after the start of treatment until week 16, with a notably greater decrease in both empagliflozin arms than in the control arm. The greater decrease in blood pressure in both empagliflozin arms after the start of treatment was possibly due to the diuretic effect of empagliflozin caused by the mechanisms of action of the drug [9,10].

The systolic blood pressure values continuously increased in all 3 treatment arms over the further course of treatment; a higher systolic value by about 4 mmHg in the control arm continuously remained. It was notable that immediately after adjustment of the blood-glucose lowering therapy (from week 12) was allowed, the mean blood pressure increased acutely, in the control group to about baseline levels.

The following Figure 10 and Figure 11 show the proportion of patients who exceeded a systolic threshold value of 140 mmHg (threshold value for normotension) (after 12 and after 52 weeks).

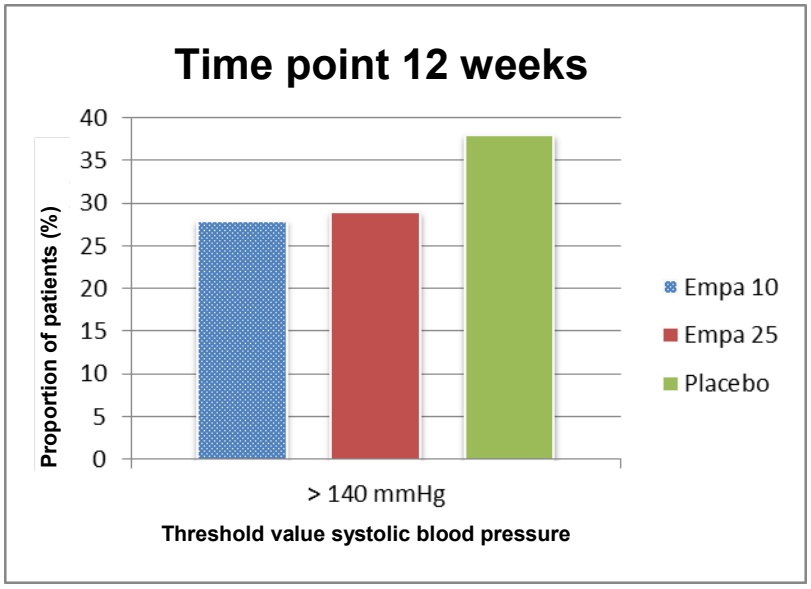


Figure 10: Proportions of patients in the EMPA-REG-Outcome study who exceeded a given systolic threshold value of 140 mmHg after 12 treatment weeks (calculation on the basis of the observed mean and standard deviation under assumption of a normal distribution)

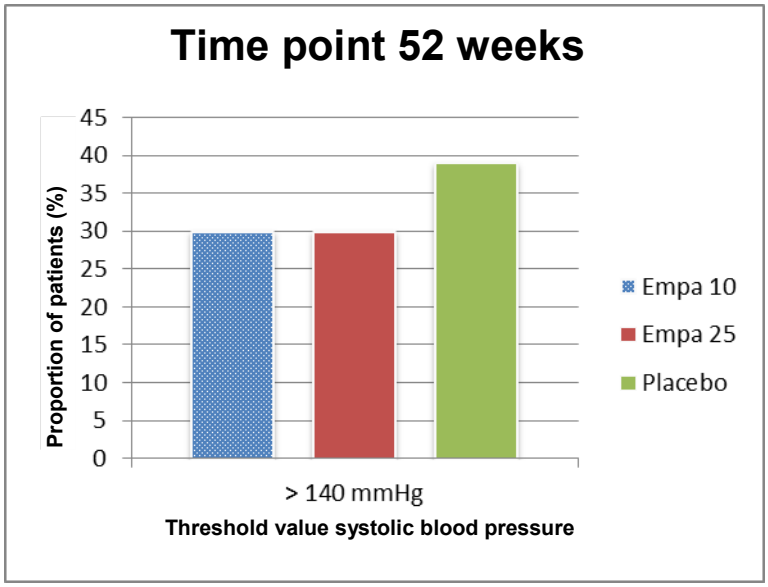


Figure 11: Proportions of patients in the EMPA-REG-Outcome study who exceeded a given systolic threshold value of 140 mmHg after 52 treatment weeks (calculation on the basis of the observed mean and standard deviation under assumption of a normal distribution)

After 12 weeks, the proportion of patients with a systolic blood pressure of > 140 mmHg was about 37% in the control arm. Treatment escalation was therefore needed for these patients because no sufficient blood pressure control was achieved under the existing therapy. After a treatment duration of 52 weeks however, the proportion of patients who exceeded the threshold value was almost unchanged, although the antihypertensive concomitant treatment

would have had to be adjusted in all 3 treatment arms to ensure the requirements in the study protocol for sufficient control of cardiovascular risk factors according to regional guideline recommendations.

The large proportion of patients who were exceeding the systolic threshold value of 140 mmHg in the course of the study suggests that the options of drug adjustment to lower systolic blood pressure were not exhausted to achieve the treatment goals required by the study protocol. However, there were no specific analyses on the question whether in patients with an increased systolic value an escalation was performed by dose increase or by administration of a further drug, including an analysis of when this was conducted in the course of the study.

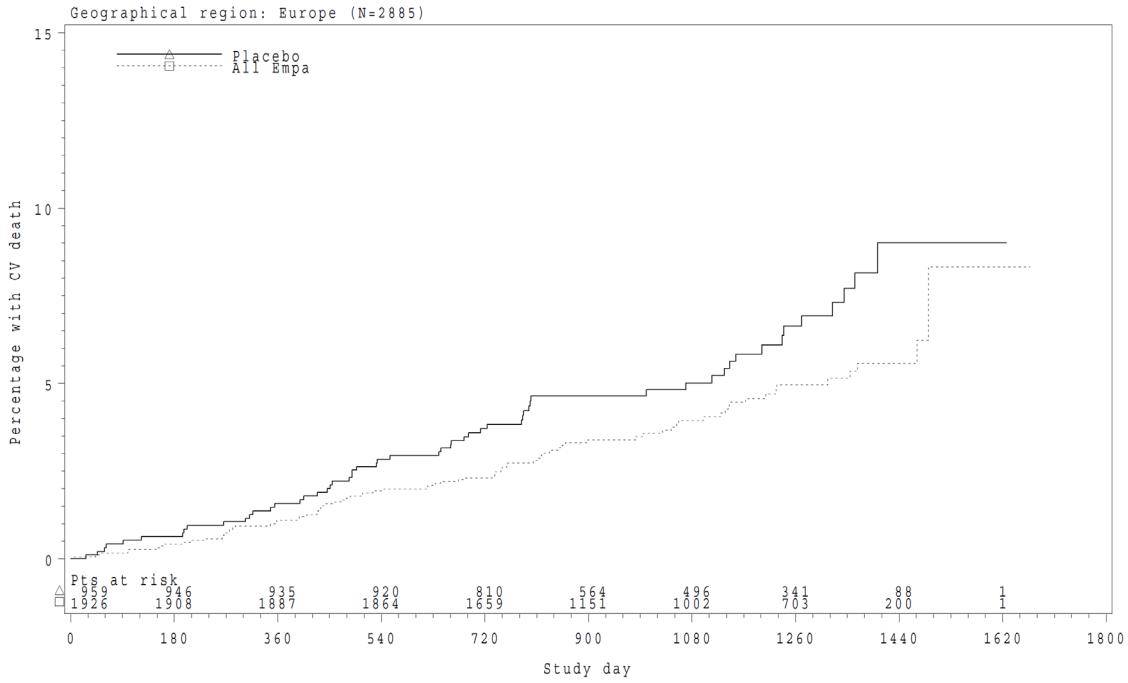
Region as effect modifier

The multicentre EMPA-REG-Outcome study was conducted in North America, Latin America, Europe, Africa and Asia; within the continents, it was conducted in many different countries except for Africa (only South Africa). A very heterogeneous quality of health care can therefore be assumed. On the one hand, the transferability of the overall results to the German situation can therefore be questioned in a study such as the EMPA-REG-Outcome study, in which no comparator therapy was defined, but where treatment was conducted at the physician's discretion under consideration of regional circumstances. On the other, it can be assumed that the different health care standards are also reflected in differences in the antihyperglycaemic and antihypertensive treatment. The company's dossier contained no analyses on this. In particular, there were no corresponding subgroup analyses for the course of the fasting blood glucose and the HbA1c value and of the antihyperglycaemic treatment escalation on one side, and the course of the systolic blood pressure and the antihypertensive treatment escalation on the other side. The regression models for the analysis of the change in fasting blood glucose and the systolic blood pressure over the course of the study provide an indication of the dependence of the parameters mentioned on the region. Region was considered as covariable. In each case, the influence of the region was statistically significant ($p < 0.001$).

The company's dossier contained subgroup analyses by region for some of the patient-relevant outcomes, however. It can be concluded on their basis that there was a relevant influence of the different health care standards on the study results. In particular, it can be inferred from them that the advantage of empagliflozin observed in the study was largely caused by a difference in the regions Latin America and Asia; such a difference was not visible in the region Europe, however.

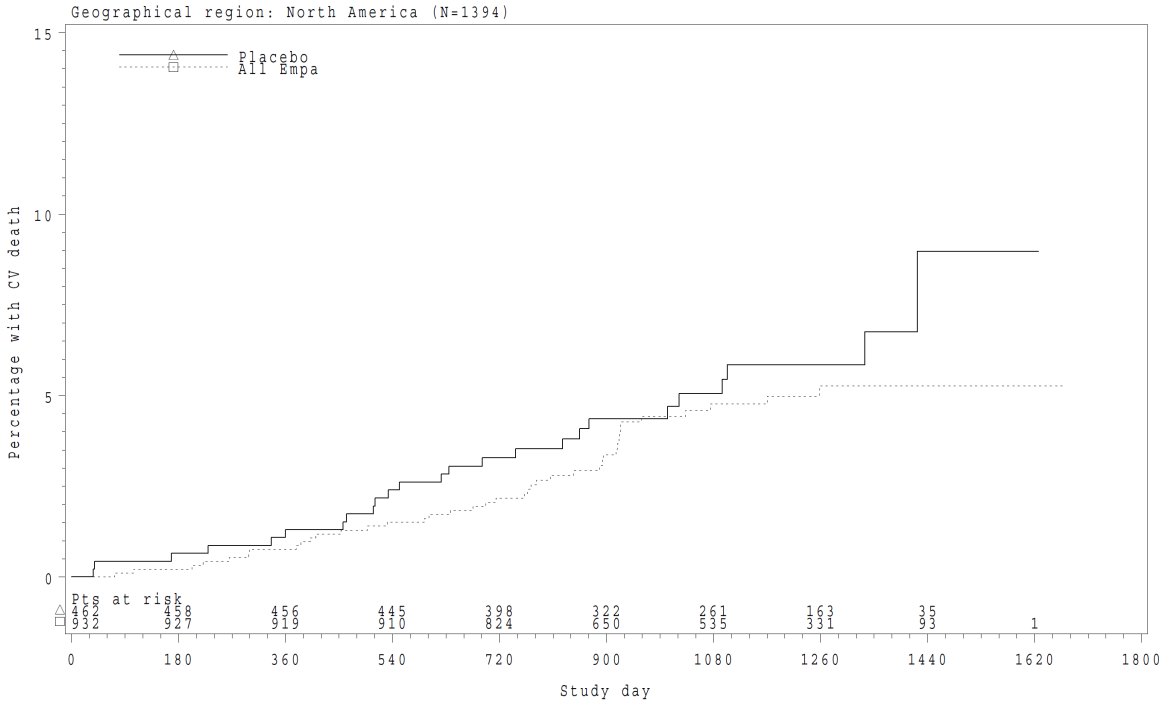
The results on the individual components of the primary outcome of the EMPA-REG-Outcome study are presented in the following Figure 12 to Figure 26.

Outcome "cardiovascular death"



Comparison vs Placebo*	
Hazard ratio	0.72
95% confidence interval	(0.51,1.01)
p-value	0.0552

Figure 12: Kaplan-Meier curve for the outcome "cardiovascular death" (subpopulation Europe)



Comparison vs Placebo*	
Hazard ratio	0.81
95% confidence interval	(0.49,1.33)
p-value	0.3955

Figure 13: Kaplan-Meier curve for the outcome “cardiovascular death” (subpopulation North America)

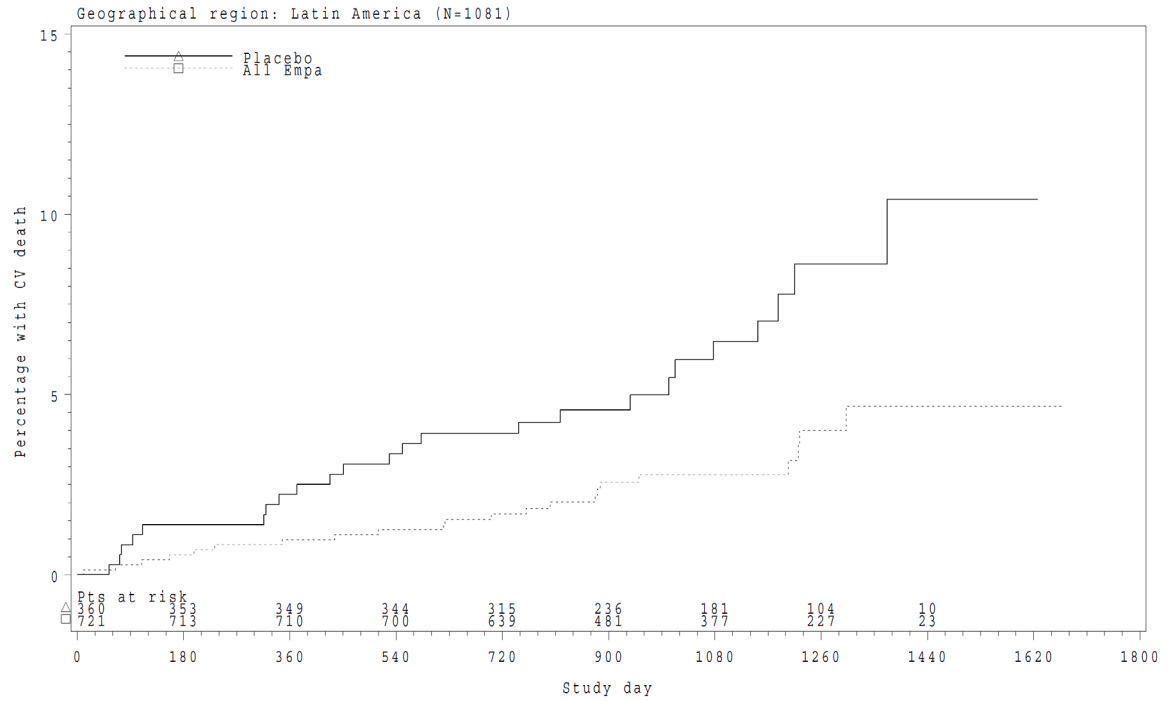
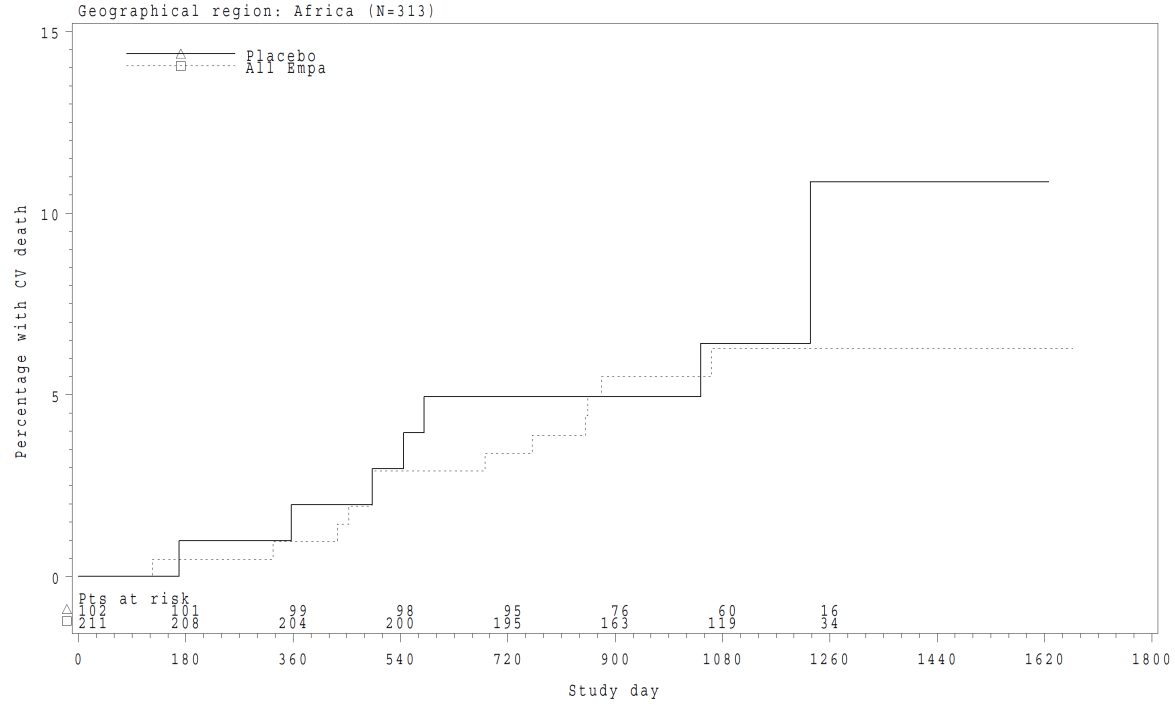
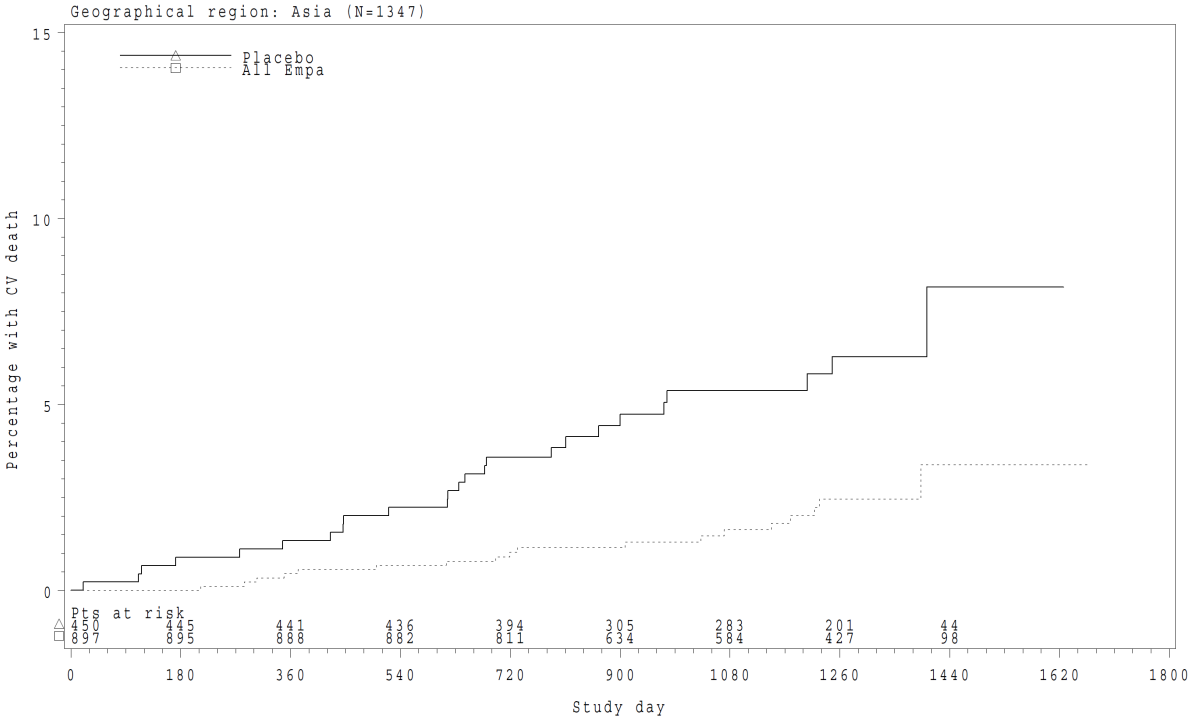


Figure 14: Kaplan-Meier curve for the outcome “cardiovascular death” (subpopulation Latin America)



Comparison vs Placebo*	
Hazard ratio	0.80
95% confidence interval	(0.31,2.03)
p-value	0.6333

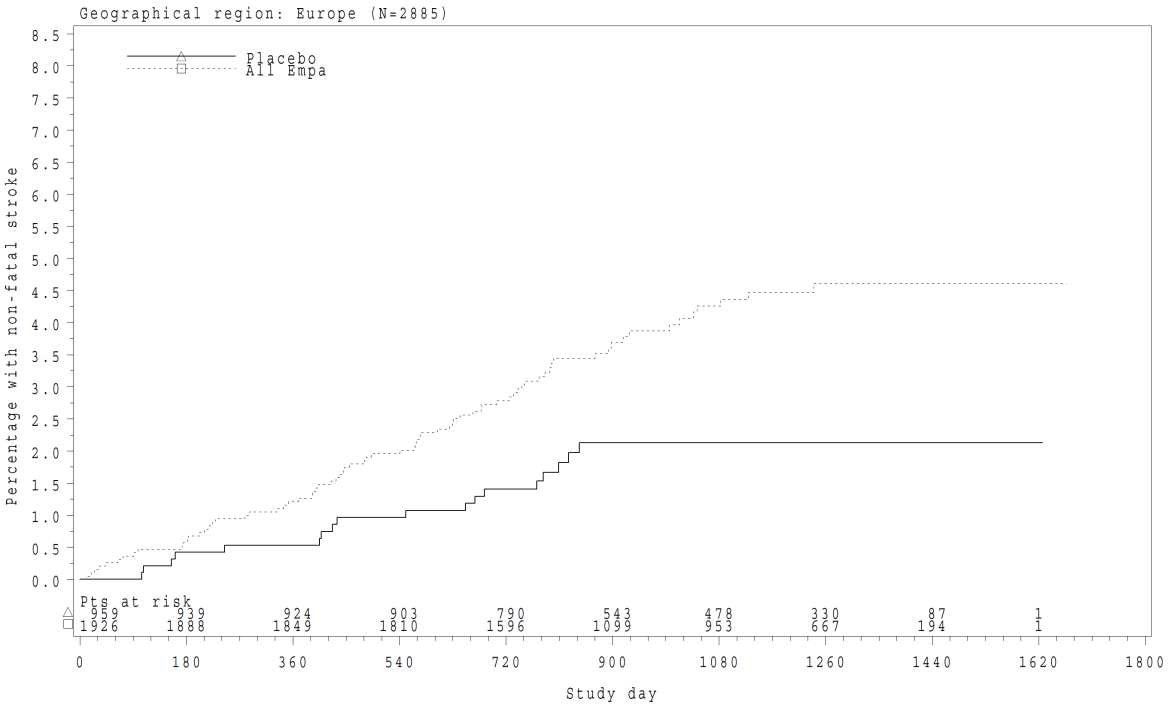
Figure 15: Kaplan-Meier curve for the outcome “cardiovascular death” (subpopulation Africa)



Comparison vs Placebo*	
Hazard ratio	0.35
95% confidence interval	(0.19,0.65)
p-value	0.0008

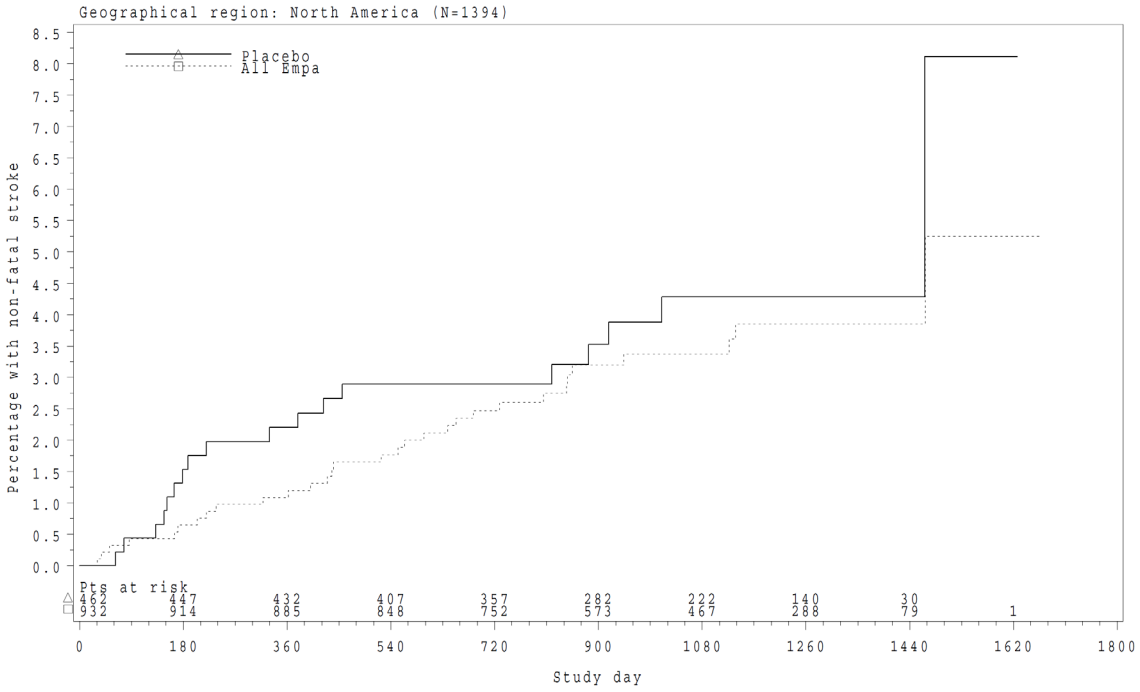
Figure 16: Kaplan-Meier curve for the outcome “cardiovascular death” (subpopulation Asia)

Outcome “nonfatal stroke”



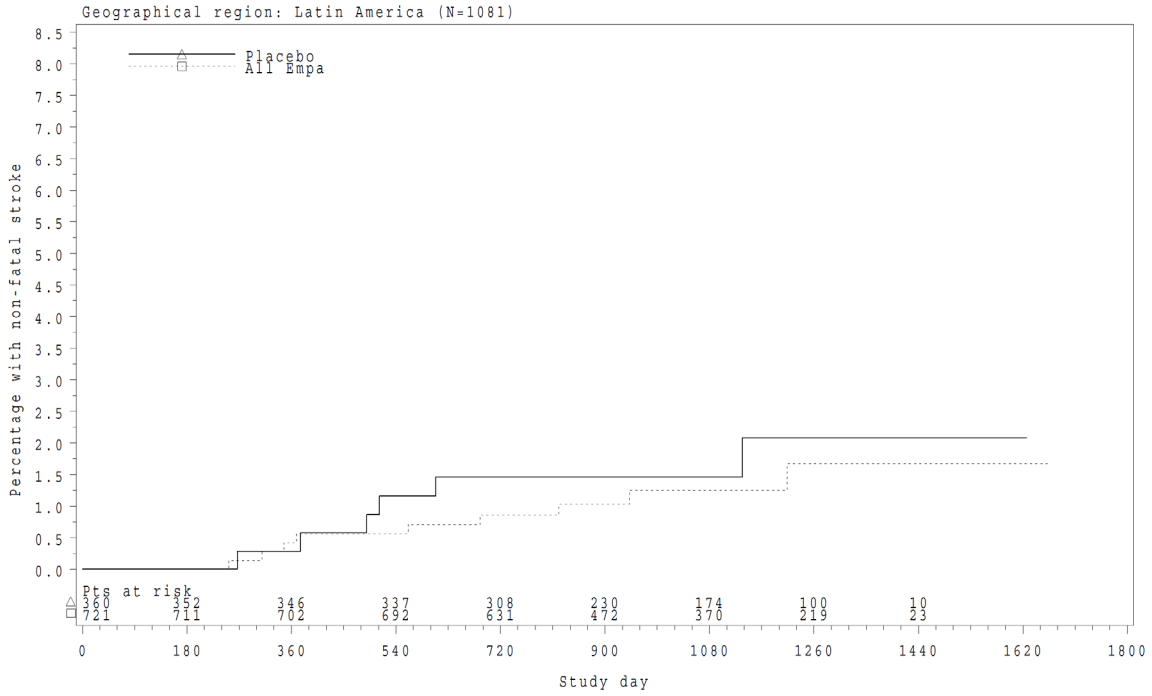
Comparison vs Placebo*	
Hazard ratio	2.06
95% confidence interval	(1.23,3.46)
p-value	0.0058

Figure 17: Kaplan-Meier curve for the outcome “nonfatal stroke” (subpopulation Europe)



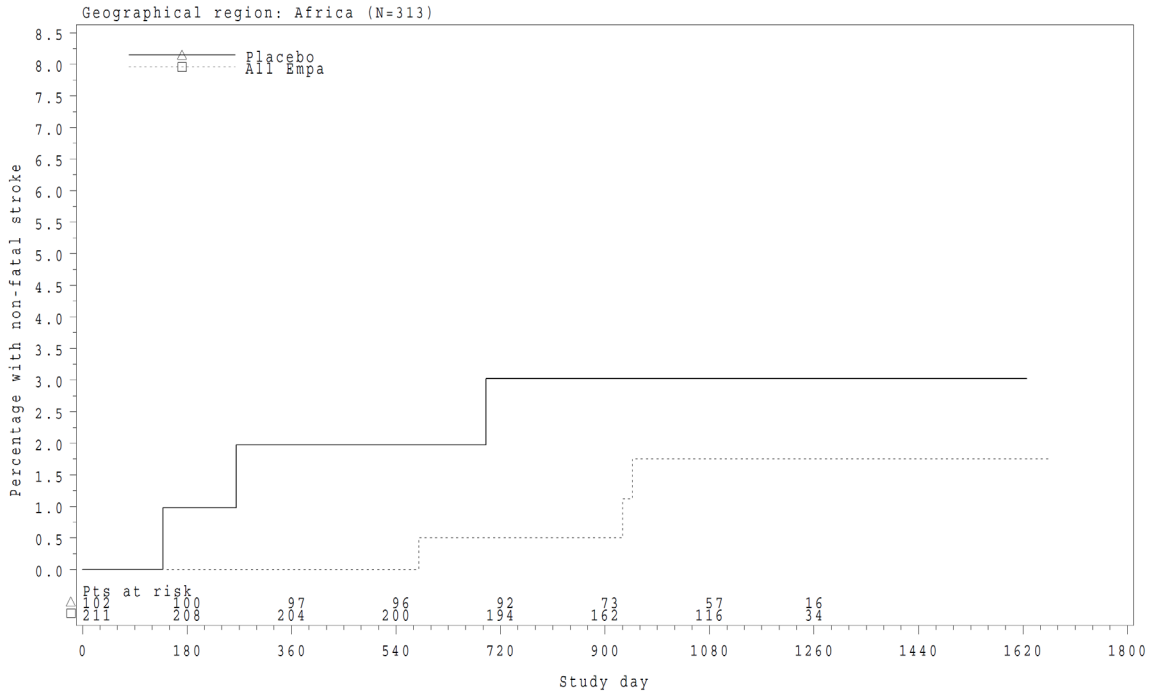
Comparison vs Placebo*	
Hazard ratio	0.84
95% confidence interval	(0.47,1.50)
p-value	0.5605

Figure 18: Kaplan-Meier curve for the outcome “nonfatal stroke” (subpopulation North America)



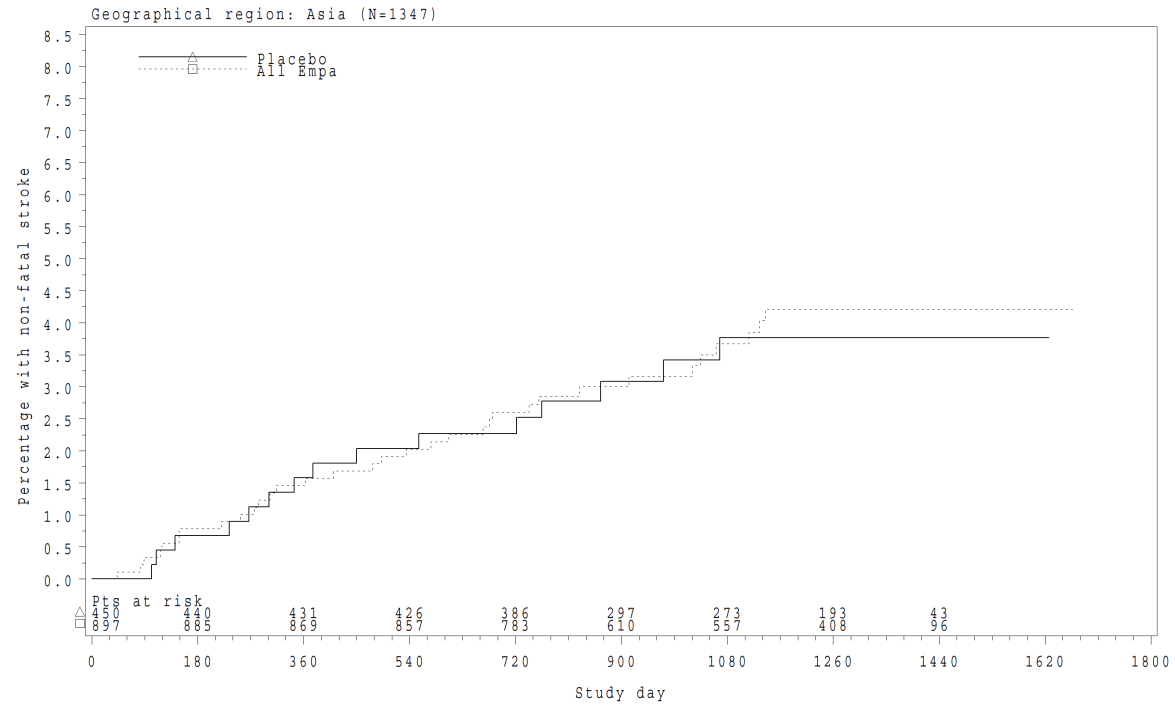
Comparison vs Placebo*	
Hazard ratio	0.72
95% confidence interval	(0.26,2.04)
p-value	0.5414

Figure 19: Kaplan-Meier curve for the outcome “nonfatal stroke” (subpopulation Latin America)



Subgroup was not included in the PH model, no further output is produced

Figure 20: Kaplan-Meier curve for the outcome “nonfatal stroke” (subpopulation Africa)

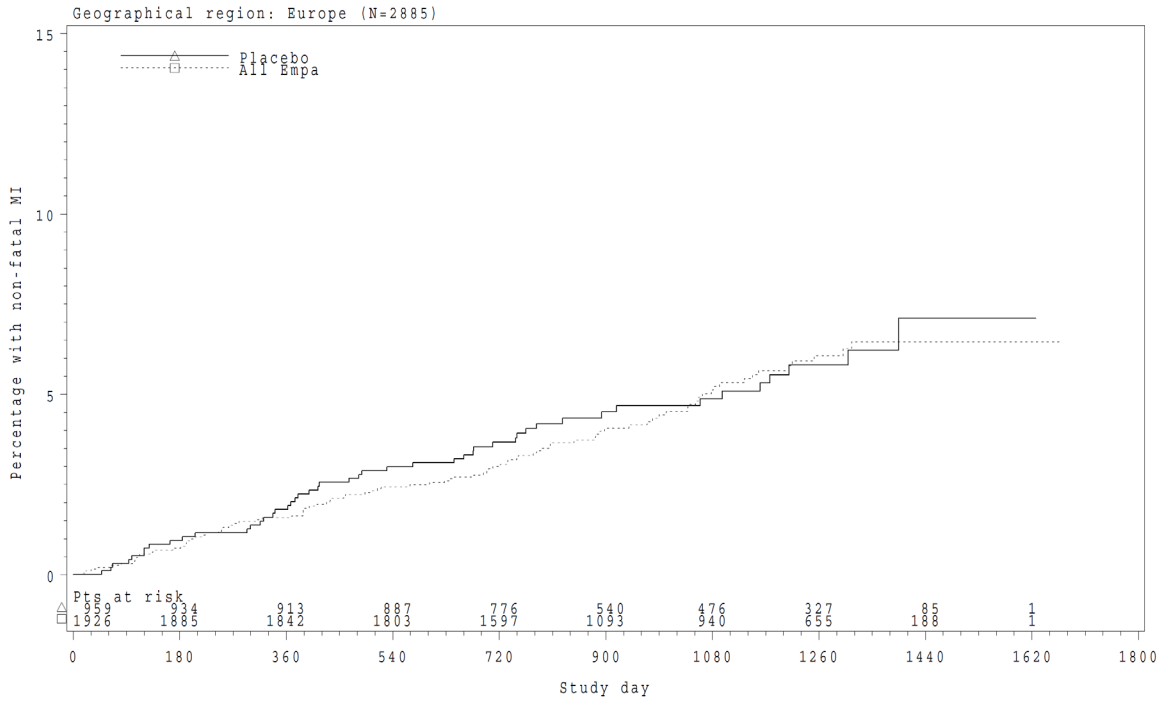


Comparison vs Placebo*

Hazard ratio	1.09
95% confidence interval	(0.59,2.00)
p-value	0.7869

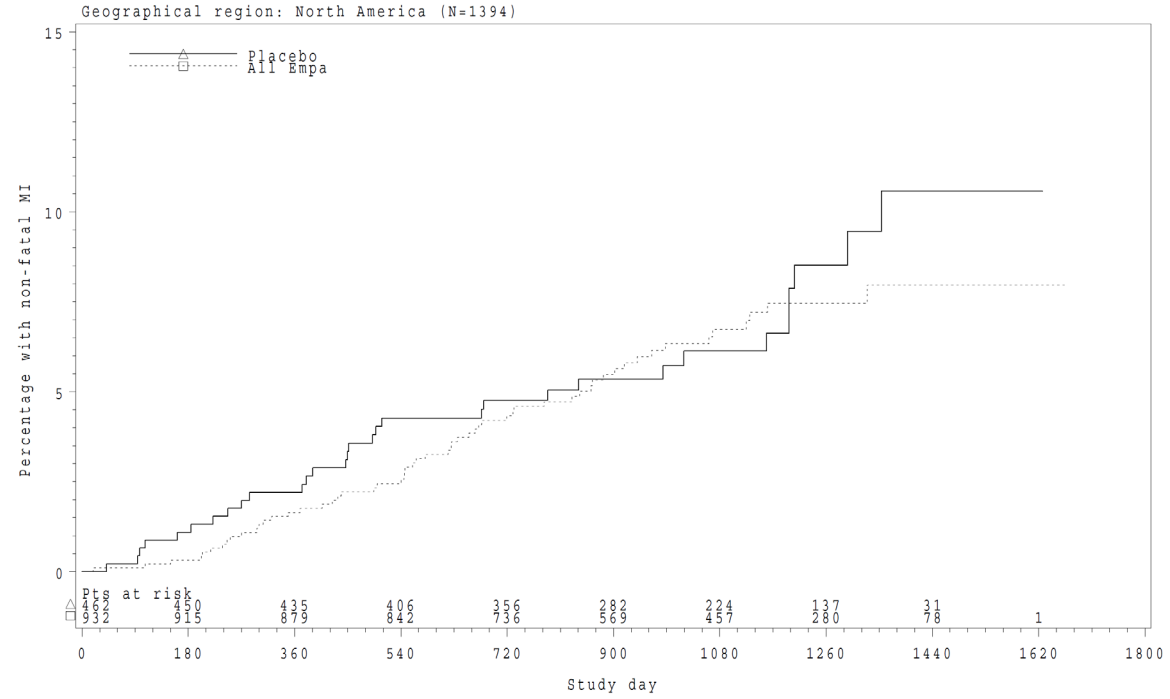
Figure 21: Kaplan-Meier curve for the outcome “nonfatal stroke” (subpopulation Asia)

Outcome "nonfatal myocardial infarction"



Comparison vs Placebo*	
Hazard ratio	0.96
95% confidence interval	(0.68,1.36)
p-value	0.8200

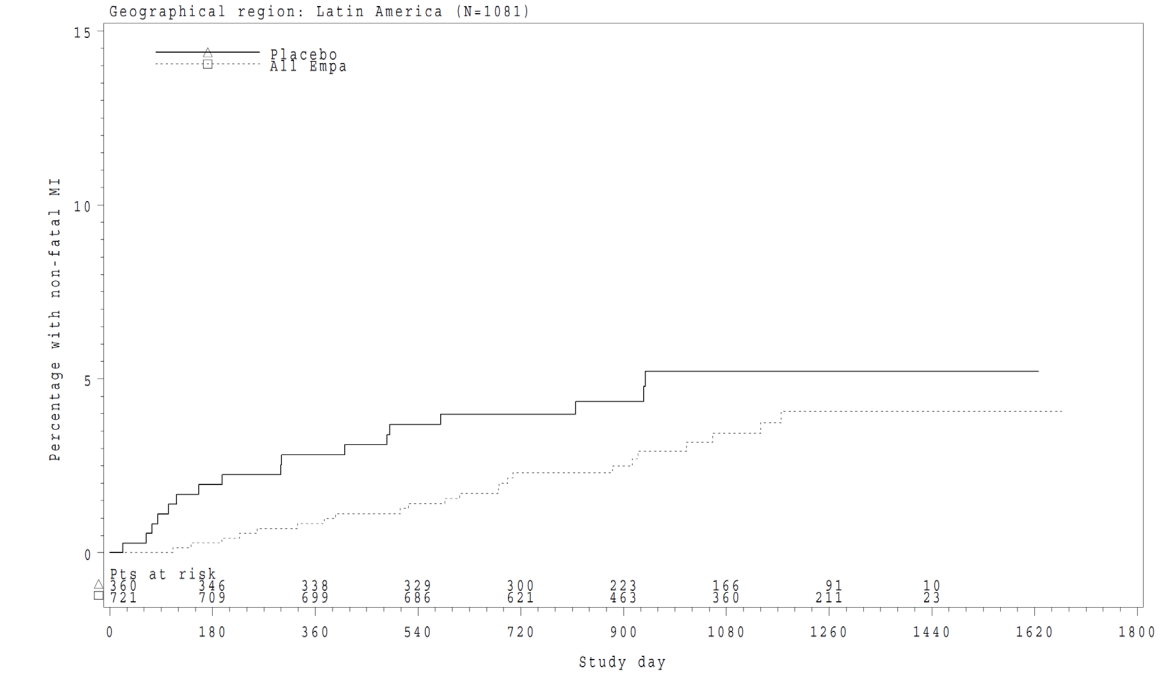
Figure 22: Kaplan-Meier curve for the outcome "nonfatal myocardial infarction" (subpopulation Europe)



Comparison vs Placebo*

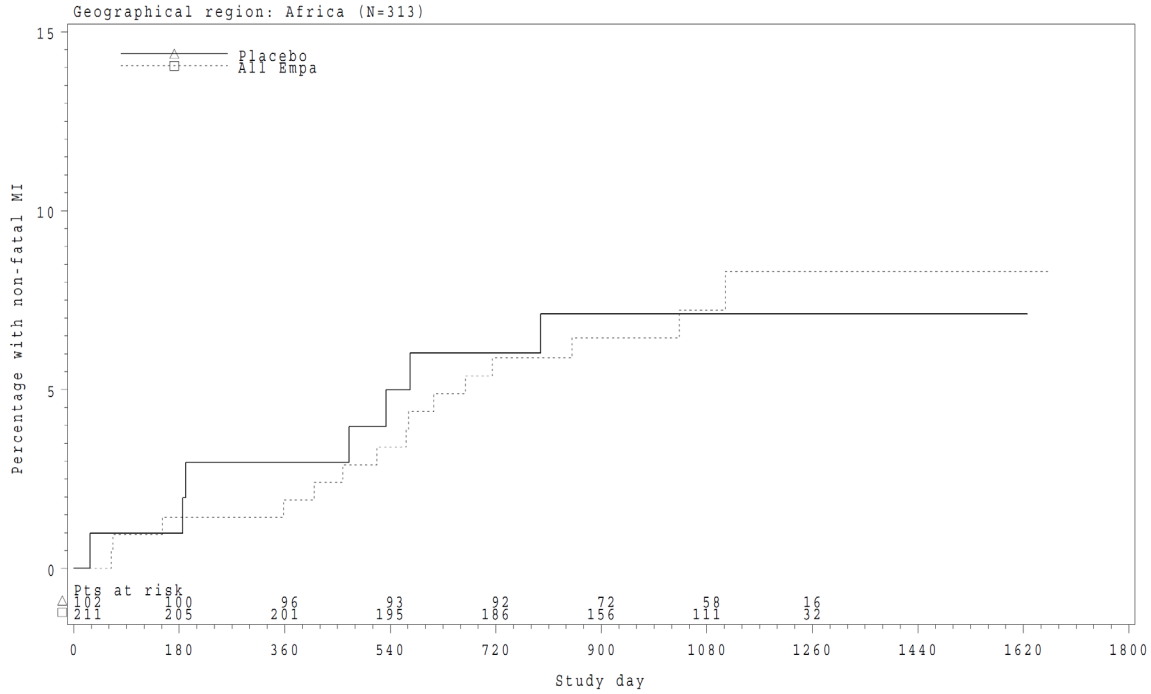
Hazard ratio	0.93
95% confidence interval	(0.60,1.43)
p-value	0.7278

Figure 23: Kaplan-Meier curve for the outcome “nonfatal myocardial infarction” (subpopulation North America)



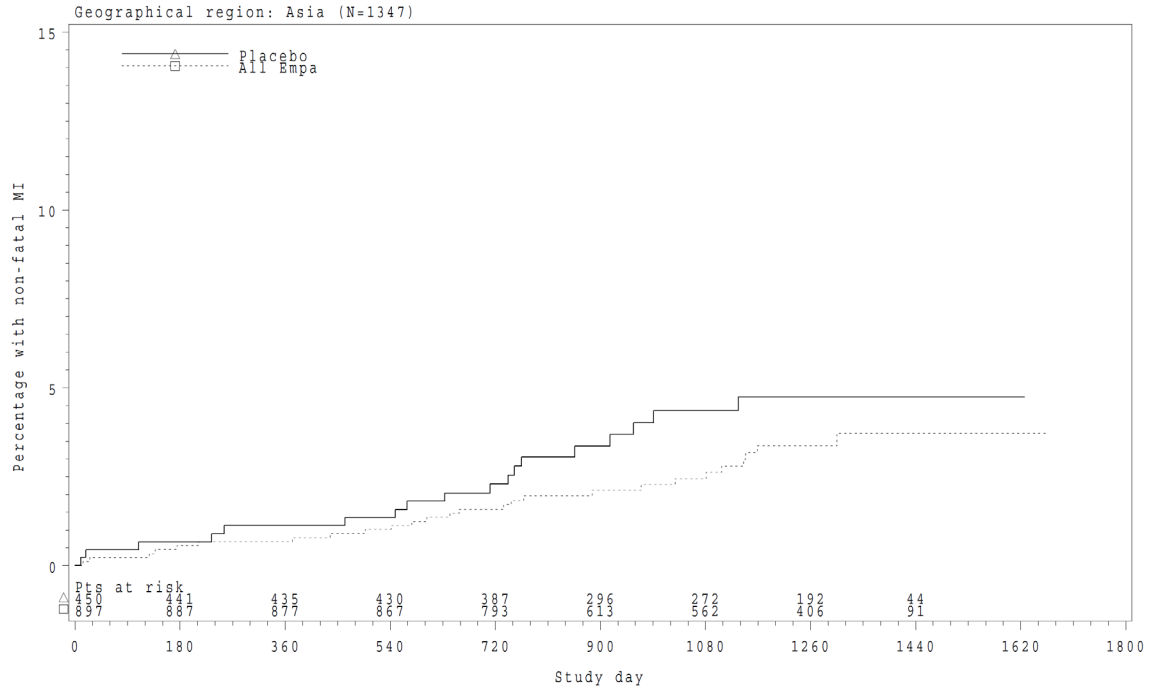
Comparison vs Placebo*	
Hazard ratio	0.64
95% confidence interval	(0.34,1.19)
p-value	0.1586

Figure 24: Kaplan-Meier curve for the outcome “nonfatal myocardial infarction” (subpopulation Latin America)



Comparison vs Placebo*	
Hazard ratio	1.01
95% confidence interval	(0.41,2.48)
p-value	0.9846

Figure 25: Kaplan-Meier curve for the outcome “nonfatal myocardial infarction” (subpopulation Africa)



Comparison vs Placebo*

Hazard ratio	0.70
95% confidence interval	(0.38,1.28)
p-value	0.2484

Figure 26: Kaplan-Meier curve for the outcome "nonfatal myocardial infarction" (subpopulation Asia)

A.3 – Summary

In its dossier, the company described the study EMPA-REG-Outcome for the following research question defined by the company: comparison of treatment with empagliflozin in addition to standard treatment versus standard treatment (plus placebo) in patients at high cardiovascular risk. This research question concurred with the design of the EMPA-REG-Outcome study. However, the company presented no analyses on the EMPA-REG-Outcome study that allow a comparison with the ACT. The company argued that a different comparator therapy (standard treatment) should be defined for patients at high cardiovascular risk, but its arguments were self-contradictory.

Irrespective of this, the EMPA-REG-Outcome study can be used for the research question whether additional administration of empagliflozin has an advantage in a situation in which the treating physicians do not exhaust the available treatment options except empagliflozin. However, this research question was not relevant for the present benefit assessment. In contrast, the EMPA-REG-Outcome study was unsuitable for the research question investigated by the company (comparison of empagliflozin plus standard treatment versus standard treatment [plus placebo] for the benefit assessment in Germany):

- On the one hand, the treatment used in the EMPA-REG-Outcome study was no adequate standard treatment. On the contrary, it was noted that neither the study definition of the necessity for escalation of the antihyperglycaemic therapy (according to the inclusion criteria, all patients had received inadequate treatment) nor the upper threshold values mentioned in the guidelines (more than 70% of the patients in the control group did not reach these threshold values) were consistently adhered to. Moreover, the vast majority of the treatment escalation was not conducted as part of "regular" treatment, but as part of emergency treatment. The large proportion of hypertensive patients whose systolic blood pressure was above the threshold value of 140 mmHg over the course of the study suggests that the options of drug adjustment to lower systolic blood pressure were not exhausted. However, there were no specific analyses on the proportion of patients with increased systolic value whose treatment was escalated by dose increase or administration of a further drug.
- On the other hand, marked regional differences were shown in the results on patient-relevant outcomes. The difference observed in the total population in favour of empagliflozin was largely determined by a marked difference in the regions Latin America and Asia, whereas no such difference was shown in the region Europe. The company's dossier contained no analyses on the quality of treatment in the different regions.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a16-12-empagliflozin-nutzenbewertung-gemaess-35a-sgb-v.7311.html.