Empagliflozin (type 2 diabetes mellitus in children and adolescents)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Medical and scientific advice

No advisor on medical and scientific questions was available for the present dossier assessment.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent and the German Diabetes Federation (Deutsche Diabetes Föderation e. V.) for participating in the written exchange and for their support. The respondent and the German Diabetes Federation were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CT	conventional insulin therapy
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycosylated haemoglobin A1c
ICT	intensified conventional insulin therapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
T2DM	type 2 diabetes mellitus

I 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 is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 20 December 2023.

Research question

The aim of this report is to assess the added benefit of empagliflozin in children and adolescents aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise either as monotherapy in patients with metformin intolerance or in addition to other blood glucose-lowering drugs in comparison with the appropriate comparator therapy (ACT).

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of empagliflozina

Therapeutic indication	**ACT[b]**
Children and adolescents aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous drug therapy consisting of at least one blood glucose-lowering drug in addition to diet and exercise	Individualized treatment[c] taking into account the HbA1c value, prior therapies, and complications with a choice of ▪ metformin + human insulin ▪ metformin + liraglutide ▪ an escalation of insulin therapy (conventional insulin therapy [CT] possibly + metformin or intensified conventional insulin therapy [ICT])

a. As monotherapy when metformin is considered unsuitable due to intolerance, or in addition to other drugs for the treatment of diabetes.
b. Presented is the ACT specified by the G-BA.
c. The continuation of an inadequate therapy (or an inadequate therapy regimen) for the treatment of type 2 diabetes mellitus, if there are still possibilities for treatment escalation, does not correspond to the ACT. It was assumed that potential comorbidities or risk factors of type 2 diabetes mellitus (e.g. hypertension, dyslipidaemia, microvascular complications – nephropathy, neuropathy, retinopathy) were treated in an individualized manner according to the medical state of the art, particularly using antihypertensives and/or lipid-lowering drugs. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.

ACT: appropriate comparator therapy; CT: conventional insulin therapy; G-BA: Federal Joint Committee; HbA1c: glycosylated haemoglobin A1c; ICT: intensified conventional insulin therapy

The company followed the G-BA's specification on the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for deriving any added benefit.

Results

The check of the completeness of the study pool produced no relevant studies on the comparison of empagliflozin versus the ACT in children and adolescents aged 10 to 17 years with T2DM.

The company included the DINAMO study to derive an added benefit. However, this study was not relevant for the present benefit assessment.

Evidence presented by the company – DINAMO study

The DINAMO study is a double-blind, multicentre RCT comparing empagliflozin with linagliptin and placebo in patients aged 10 to 17 years inclusive with T2DM, each in addition to diet, exercise, and a stable dose of metformin, insulin, or metformin + insulin. Patients with a glycated haemoglobin (HbA1c) value ≥ 6.5% and ≤ 10.5% who had been diagnosed with T2DM for ≥ 8 weeks at the time of screening were included. Antidiabetic treatment with metformin, insulin, or metformin + insulin had to have been in place at a stable dose for ≥ 8 weeks prior to the start of the study in accordance with the inclusion criteria. A total of 158 patients were enrolled in the DINAMO study. After screening, all patients entered a 2-week run-in phase, where they received placebo in addition to diet, exercise, and the existing stable dose of metformin, insulin, or metformin + insulin. Subsequently, 52 patients were randomized to the empagliflozin arm, 53 patients to the linagliptin arm and 53 patients to the placebo arm.

All patients in the empagliflozin arm initially received 10 mg empagliflozin once daily. Patients whose HbA1c value was not below 7.0% at week 14 were rerandomized in a 1:1 ratio and either continued to receive 10 mg empagliflozin or went on to receive 25 mg empagliflozin once daily. This affected 24 of the 53 patients in the empagliflozin arm. Of these, 11 patients continued to receive 10 mg/day and 13 received 25 mg/day. Patients who continued to receive the initial dose of 10 mg after randomization despite not responding to it may therefore have been undertreated.

All patients continued to receive their background therapy of metformin, insulin, or metformin + insulin in addition to the study medication. The dosages were to remain unchanged as far as medically appropriate. The study documents show that the investigators were instructed to adjust the total insulin dose at baseline to the actual needs of the patients, with an apparent aim to reduce the insulin dose. However, it was possible to adjust the insulin dose to avoid hyper- and hypoglycaemia as the study progressed. Switching to a different type of insulin, a different insulin manufacturer, or changing the insulin pen was to be avoided.

Furthermore, the use of insulin (or an increase in the existing insulin therapy) and/or metformin as rescue medication was allowed.

The primary outcome of the study was change in HbA1c value from the beginning of the study to week 26. Further outcomes were recorded in the morbidity and side effects categories.

Federal Joint Committee's appropriate comparator therapy not implemented in the DINAMO study

The treatment carried out in the comparator arms in the DINAMO study does not correspond to the ACT specified by the G-BA for the majority of the patients included. The reasons for this are as follows:

In the placebo arm, 53% of the patients were treated for diabetes using metformin monotherapy. This is not an ACT specified by the G-BA in the present therapeutic indication, however.

Since the patients had a mean HbA1c value of approximately 8.0% at baseline, it can also be assumed that for a large proportion of the patients in the comparator arm, treatment escalation to reduce the HbA1c value would have been indicated and, in principle, possible (e.g. by adding insulin). However, background antidiabetic therapy should remain as unchanged as possible during the study. In addition, there is no information in the study documents as to whether the antidiabetic medication was adjusted at baseline. Although adjustments were possible during the course of the study if necessary, the study documents show that by week 26, only 3 patients each in the empagliflozin and placebo arms (5.7% and 5.8% respectively) had started a new antidiabetic therapy. In addition, up to week 26, 6 patients in the placebo group (11.3%) received at least one rescue medication (use of insulin [or a dose increase in the existing insulin therapy] and/or metformin as rescue medication for certain criteria, e.g. presence of symptomatic acute metabolic decompensation). However, the possibility of rescue medication with insulin and/or metformin does not correspond to guideline-compliant therapy optimization and does not correspond to the required individualized treatment with exhaustion of all existing possibilities for treatment escalation at baseline.

Evidence transfer by the company not usable

The company states that it wants to transfer results from the adult population with T2DM to the paediatric population. With the evidence transfer, it wants to show that the benefits shown in adults treated with empagliflozin in terms of cardiovascular and renal effects can be transferred to children and adolescents. It states that this is important due to the early onset of the disease and the associated long course of the disease.

With regard to the clinical response in adults, the company cites the EMPA-REG OUTCOME and EMPA-KIDNEY studies as source studies for evidence transfer. However, results from these studies cannot be extrapolated to the population of children and adolescents with T2DM because there is no sufficient similarity between the populations. The EMPA-REG OUTCOME study enrolled adult patients with T2DM who were at high cardiovascular risk. Children and adolescents 10 to 17 years of age with T2DM, however, very rarely exhibit high cardiovascular risk. In contrast, no patients with T2DM were included in the EMPA-KIDNEY study, as the study served to demonstrate the efficacy of empagliflozin in chronic renal failure.

Results on added benefit

No suitable data are available to assess the added benefit of empagliflozin in comparison with the ACT in children and adolescents aged 10 to 17 years with uncontrolled T2DM. There is no hint of an added benefit of empagliflozin in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of the probability and extent of added benefit of empagliflozin.

[3] 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, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Empagliflozin – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
Children and adolescents aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous drug therapy consisting of at least one blood glucose-lowering drug in addition to diet and exercise	Individualized treatment[c] taking into account the HbA1c value, prior therapies, and complications with a choice of ▪ metformin + human insulin ▪ metformin + liraglutide an escalation of insulin therapy (conventional insulin therapy [CT] possibly + metformin or intensified conventional insulin therapy [ICT])	Added benefit not proven

a. As monotherapy when metformin is considered unsuitable due to intolerance, or in addition to other drugs for the treatment of diabetes.
b. Presented is the ACT specified by the G-BA.
c. The continuation of an inadequate therapy (or an inadequate therapy regimen) for the treatment of type 2 diabetes mellitus, if there are still possibilities for treatment escalation, does not correspond to the ACT. It was assumed that potential comorbidities or risk factors of type 2 diabetes mellitus (e.g. hypertension, dyslipidaemia, microvascular complications – nephropathy, neuropathy, retinopathy) were treated in an individualized manner according to the medical state of the art, particularly using antihypertensives and/or lipid-lowering drugs. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HbA1c: glycosylated haemoglobin A1c

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of empagliflozin in children and adolescents aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise either as monotherapy in patients with metformin intolerance or in addition to other blood glucose-lowering drugs in comparison with the ACT.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of empagliflozina

Therapeutic indication	**ACT[b]**
Children and adolescents aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous drug therapy consisting of at least one blood glucose-lowering drug in addition to diet and exercise	Individualized treatment[c] taking into account the HbA1c value, prior therapies, and complications with a choice of ▪ metformin + human insulin ▪ metformin + liraglutide ▪ an escalation of insulin therapy (conventional insulin therapy [CT] possibly + metformin or intensified conventional insulin therapy [ICT])

a. As monotherapy when metformin is considered unsuitable due to intolerance, or in addition to other drugs for the treatment of diabetes.
b. Presented is the ACT specified by the G-BA.
c. The continuation of an inadequate therapy (or an inadequate therapy regimen) for the treatment of type 2 diabetes mellitus, if there are still possibilities for treatment escalation, does not correspond to the ACT. It was assumed that potential comorbidities or risk factors of type 2 diabetes mellitus (e.g. hypertension, dyslipidaemia, microvascular complications – nephropathy, neuropathy, retinopathy) were treated in an individualized manner according to the medical state of the art, particularly using antihypertensives and/or lipid-lowering drugs. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.

ACT: appropriate comparator therapy; CT: conventional insulin therapy; G-BA: Federal Joint Committee; HbA1c: glycosylated haemoglobin A1c; ICT: intensified conventional insulin therapy

The company followed the G-BA's specification on the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for deriving any added benefit. This concurs with the company’s inclusion criteria.

I 3 Information retrieval and study pool

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: 5 October 2023)
- bibliographical literature search on empagliflozin (last search on 4 October 2023)
- search in trial registries / trial results databases for studies on empagliflozin (last search on 5 October 2023)
- search on the G-BA website for empagliflozin (last search on 19 October 2023)

To check the completeness of the study pool:

- search in trial registries for studies on empagliflozin (last search on 17 January 2024); for search strategies, see I Appendix A of the full dossier assessment

The check of the completeness of the study pool produced no relevant studies on the comparison of empagliflozin versus the ACT in children and adolescents aged 10 to 17 years with T2DM.

To derive an added benefit, the company included the DINAMO study [3-6] (for study and intervention characteristics see I Appendix B of the full dossier assessment). In addition, the company also used an evidence transfer from the EMPA-REG-OUTCOME [7] and EMPA-KIDNEY [8] studies. The approach of the company is not appropriate. Neither the DINAMO study nor the additional evidence transfer presented by the company are suitable for the present benefit assessment. This is explained below.

Evidence provided by the company

DINAMO study

The DINAMO study submitted by the company is a double-blind, multicentre RCT comparing empagliflozin with linagliptin and placebo in patients aged 10 to 17 years inclusive with T2DM, each in addition to diet, exercise, and a stable dose of metformin, insulin, or metformin + insulin. Patients with a glycated haemoglobin (HbA1c) value ≥ 6.5% and ≤ 10.5% who had been diagnosed with T2DM for ≥ 8 weeks at the time of screening were included. According to the inclusion criteria, antidiabetic treatment with metformin, insulin, or metformin + insulin had to have been at a stable dose for ≥ 8 weeks prior to the start of the study, with the daily metformin dose being ≥ 1000 mg.

The study also included the DINAMO Mono sub-study, which, however, only included treatment-naive patients. It was therefore not presented by the company in Module 4A of the dossier.

A total of 158 patients were enrolled in the DINAMO study. After screening, all patients entered a 2-week run-in phase, where they received placebo in addition to diet, exercise, and the existing stable dose of metformin, insulin, or metformin + insulin. Subsequently, 52 patients were randomized to the empagliflozin arm, 53 patients to the linagliptin arm and 53 patients to the placebo arm. Randomization was stratified by age and sex. As linagliptin is not part of the G-BA's ACT, the company did not present the results of the linagliptin arm.

All patients in the empagliflozin arm initially received 10 mg empagliflozin once daily. Patients whose HbA1c value was not below 7.0% at week 14 were rerandomized in a 1:1 ratio and either continued to receive 10 mg empagliflozin or went on to receive 25 mg empagliflozin once daily. This affected 24 of the 53 patients in the empagliflozin arm. Of these, 11 patients continued to receive 10 mg/day and 13 received 25 mg/day. Module 4A shows the results for the pooled empagliflozin arm, irrespective of whether and to which dose the patients were subsequently rerandomized. There was no division into subgroups according to empagliflozin dose in Module 4A.

The administration of empagliflozin in the study largely corresponded to the specifications in the Summary of Product Characteristics (SPC) [9]. It states that an increase to 25 mg/day can be implemented if the children and adolescents affected have tolerated the starting dose of 10 mg/day and require additional blood glucose control. The SPC does not specify a fixed time and clinical guideline for increasing the dose as in the DINAMO study. However, the rerandomization at week 14 meant that some of the patients for whom a dose increase might have been indicated continued to receive only the starting dose. According to the current guideline of the German Diabetes Society (DDG), an HbA1c value of less than 7% should be aimed for in adolescents; a lower target value may also be appropriate in individual cases [10]. The National Disease Management Guideline for Diabetes (NVL) also recommends that a low HbA1c target value (more likely 6.5%) should be aimed for if life expectancy is high and the duration of diabetes is short [11]. Patients who continued to receive the initial dose of 10 mg after randomization despite not responding to it may therefore have been undertreated.

All patients continued to receive their background therapy of metformin, insulin, or metformin + insulin in addition to the study medication. The dosages were to remain unchanged as far as medically appropriate. For insulin therapy, an average weekly fluctuation of no more than 0.1 insulin units/kg was aimed for. The study documents show that the investigators were instructed to adjust the total insulin dose at baseline to the actual needs of the patients, with an apparent aim to reduce the insulin dose depending on the glucose values according to the company’s study documents. However, it was possible to adjust the

insulin dose to avoid hyper- and hypoglycaemia as the study progressed. Switching to a different type of insulin, a different insulin manufacturer, or changing the insulin pen was to be avoided. Furthermore, the use of insulin (or an increase in the existing insulin therapy) and/or metformin as rescue medication was allowed. Prerequisite was the presence of symptomatic acute metabolic decompensation and/or repeatedly elevated ketone levels (> 1.5 mmol/L), persistent hyperglycaemia, or (from week 12) an HbA1c value of ≥ 9.0% in 2 consecutive visits and an increase of ≥ 1% compared to the start of the study. The use of other antidiabetic drugs besides metformin and insulin was not allowed in the study.

The primary outcome of the study was change in HbA1c value from the beginning of the study to week 26. Further outcomes were recorded in the morbidity and side effects categories.

After 25 weeks of treatment, all patients in the placebo arm were rerandomized and then received either 10 mg empagliflozin, 25 mg empagliflozin, or 5 mg linagliptin once daily. They were then blinded and compared with the other drug. This study phase lasted from week 26 to week 52, after which the patients were followed up for another 3 weeks without study medication. The company did not present this study phase; all data in Module 4A of the dossier refer to the period up to week 26.

Federal Joint Committee's appropriate comparator therapy not implemented in the DINAMO study

The treatment carried out in the comparator arms in the DINAMO study does not correspond to the ACT specified by the G-BA for the majority of the patients included. The reasons for this are as follows:

In the placebo arm, 53% of the patients were treated for diabetes using metformin monotherapy. This is not an ACT specified by the G-BA in the present therapeutic indication, however.

The G-BA notes that continuation of insufficient treatment of T2DM does not constitute an ACT as long as options for treatment escalation are still available. Since the patients had a mean HbA1c value of approximately 8.0% at baseline, it can be assumed that, as per guideline recommendations [10,11], for a large proportion of the patients in the comparator arm, treatment escalation to reduce the HbA1c value would have been indicated and, in principle, possible (e.g. by adding insulin). However, as described in the previous section on study design, background antidiabetic therapy should remain as unchanged as possible during the study. In addition, there is no information in the study documents as to whether the antidiabetic medication was adjusted at baseline. Although adjustments were possible during the course of the study if necessary, the study documents show that by week 26, only 3 patients each in the empagliflozin and placebo arms (5.7% and 5.8% respectively) had started a new antidiabetic therapy. Furthermore, by week 26, 6 patients in the placebo group (11.3%)

received at least one rescue medication. However, the possibility of rescue medication with insulin and/or metformin according to the criteria described above does not correspond to guideline-compliant therapy optimization and does not correspond to the individualized treatment required by the GB-A with exhaustion of all existing options for treatment escalation at baseline.

The lack of escalation of antidiabetic therapy is also reflected in the continuous increase in HbA1c values compared to the start of the study in the placebo arm (see Figure 1).

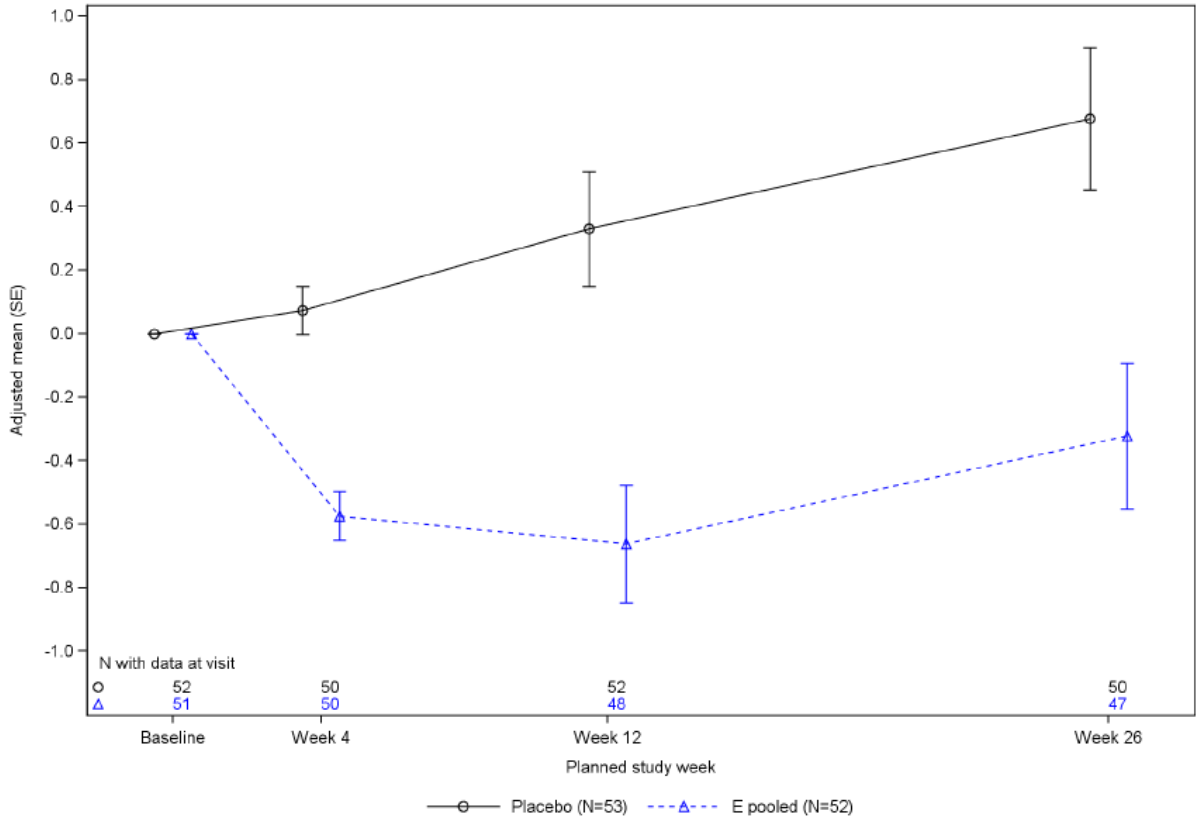

Figure 1: Mean change in HbA1c (%) from baseline to week 26 (DINAMO study)

Summary

In summary, the DINAMO study presented is not suitable for benefit assessment. Empagliflozin was not compared with the G-BA's ACT, as no individualized treatment was carried out in the study with exhaustion of all existing options for treatment escalation at baseline. In the study, only the existing antidiabetic therapy was continued for the most part without adjustment, although it can be assumed that there were still options for treatment escalation in individual patients.

Irrespective of this, around half of the patients received metformin monotherapy, which is not included in the ACT. For the reasons described above, analyses that are conceivable in

principle for the subpopulation of patients who did not receive metformin monotherapy are also not suitable for the benefit assessment.

EMPA-REG OUTCOME and EMPA-KIDNEY studies not suitable for evidence transfer

In Module 4A of the dossier, the company states that it wants to transfer results from the adult population with T2DM to the paediatric population. It considers this necessary due to the low prevalence of the disease in the paediatric population. With the evidence transfer, the company wants to show that the benefits shown in adults treated with empagliflozin in terms of cardiovascular and renal effects can be transferred to children and adolescents. It states that this is important due to the early onset of the disease and the associated long course of the disease.

The company argues that evidence transfer is possible because the essential criteria as stated in the Reflection Paper of the European Medicines Agency (EMA) on evidence transfer to paediatric populations [12] are fulfilled. In addition, the company cites an identical or comparable ACT and an added benefit in adult patients as criteria. In the company's view, these criteria are fulfilled.

With regard to the clinical response in adults, the company cites the EMPA-REG OUTCOME and EMPA-KIDNEY studies as source studies for evidence transfer. Accordingly, in the EMPA-REG OUTCOME study, empagliflozin reportedly led to a reduction in cardiovascular and renal events, cardiovascular mortality, and nephropathies, among other things, compared to the comparator therapy. For the EMPA-KIDNEY study, the company states that a significant reduction in the risk of progression to chronic renal failure or cardiovascular death was shown. Since the paediatric patients in the DINAMO study showed an improvement in HbA1c value, fasting glucose and weight analogous to the adult populations mentioned, the company assumes that the effects on cardiovascular and renal outcomes observed in adults are transferable to children and adolescents.

The approach of the company is not appropriate. Results from the EMPA-REG OUTCOME and EMPA-KIDNEY studies cannot be extrapolated to the population of children and adolescents with T2DM because there is no sufficient similarity between the populations. The EMPA-REG OUTCOME study enrolled adult patients with T2DM who were at high cardiovascular risk [13]. Children and adolescents 10 to 17 years of age with T2DM, however, very rarely exhibit high cardiovascular risk. In contrast, no patients with T2DM were included in the EMPA-KIDNEY study, as the study served to demonstrate the efficacy of empagliflozin in chronic renal failure [14]. Against this background, the pharmacokinetic data from phase 1 study 1245.87 [15], which the company uses as proof for the comparability of the mechanism of action, are not relevant for the benefit assessment.

Furthermore, in its dossier the company does not provide any quantitative comparison of the results of the EMPA-REG OUTCOME or EMPA-KIDNEY studies and the DINAMO study.

Summary

Overall, the company's approach was not appropriate. The presented data are unsuitable for assessing the added benefit of empagliflozin in comparison with the ACT specified by the G-BA.

I 4 Results on added benefit

No suitable data are available to assess the added benefit of empagliflozin in comparison with the ACT in children and adolescents aged 10 to 17 years with uncontrolled T2DM. There is no hint of an added benefit of empagliflozin in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of empagliflozin in comparison with the ACT is summarized in Table 5.

Table 5: Empagliflozin – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
Children and adolescents aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous drug therapy consisting of at least one blood glucose-lowering drug in addition to diet and exercise	Individualized treatment[c] taking into account the HbA1c value, prior therapies, and complications with a choice of ▪ metformin + human insulin ▪ metformin + liraglutide an escalation of insulin therapy (conventional insulin therapy [CT] possibly + metformin or intensified conventional insulin therapy [ICT])	Added benefit not proven

a. As monotherapy when metformin is considered unsuitable due to intolerance, or in addition to other drugs for the treatment of diabetes.
b. Presented is the ACT specified by the G-BA.
c. The continuation of an inadequate therapy (or an inadequate therapy regimen) for the treatment of type 2 diabetes mellitus, if there are still possibilities for treatment escalation, does not correspond to the ACT. It was assumed that potential comorbidities or risk factors of type 2 diabetes mellitus (e.g. hypertension, dyslipidaemia, microvascular complications – nephropathy, neuropathy, retinopathy) were treated in an individualized manner according to the medical state of the art, particularly using antihypertensives and/or lipid-lowering drugs. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HbA1c: glycosylated haemoglobin A1c

The assessment described above deviates from that of the company, which derived an indication of minor added benefit of empagliflozin.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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