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Dapagliflozin (type 2 diabetes mellitus in children and adolescents) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Dapagliflozin (Diabetes mellitus Typ 2 bei Kindern und Jugendlichen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 10 March 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Wolfgang Rascher, Department of Pediatrics and Adolescent Medicine, FAU Erlangen-Nürnberg, Germany

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.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Tobias Depke
- Lars Beckmann
- Wiebke Hoffmann-Eßer
- Marco Knelangen
- Philip Kranz
- Prateek Mishra
- Daniela Preukschat
- Min Ripoll

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
FPG	fasting blood glucose
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycated haemoglobin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD	pharmacodynamic
PK	pharmacokinetic
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
T2DM	type 2 diabetes mellitus

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 dapagliflozin. 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 13 December 2021.

Research question

The aim of this report is to assess the added benefit of dapagliflozin 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 questions shown in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of dapagliflozin

Research question	Therapeutic indication	ACT[a]
1	Insulin-naive children 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[b] in addition to diet and exercise	Human insulin + metformin[c]
2	Insulin-experienced children aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous insulin regimen in addition to diet and exercise	Escalation of insulin therapy (conventional insulin therapy [CT], if necessary + metformin or intensified conventional insulin therapy [ICT])[c, d, e]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, metformin is the treatment of first choice for the drug therapy of type 2 diabetes mellitus in children and adolescents.
c. Treatment with insulin is indicated, if necessary in combination with metformin, in case of signs of ketoacidosis or ketonuria, inadequate blood glucose control under metformin therapy, or in very advanced stages of disease. If treatment escalation options are still available, continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus is not an 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.
d. Insulin therapy should be escalated in the form of CT (mixed insulin) or ICT, taking into account the patient's individual living situation. In ICT, the administration of an additional blood glucose-lowering drug is not typically deemed indicated. In addition to CT, metformin may be administered if necessary.
e. According to the G-BA, single-comparator studies are typically inadequate for implementing the ACT in a direct comparative study. The investigator is expected to have a choice between several treatment options (CT or ICT) (multi-comparator 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; ICT: intensified conventional insulin therapy

The G-BA adjusted the ACT in the course of the procedure, after the dossier had been submitted. The ACT change remains without consequence for the present benefit assessment because the company's dossier departs both from the original and the updated patient populations and ACTs specified by the G-BA.

The company's rationale for deviating from the G-BA's specified patient populations and ACT is not plausible. The present assessment is therefore carried out for the G-BA's specified patient populations in comparison with the respective ACTs as of 11 January 2022.

The assessment was 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 the derivation of the added benefit.

Inappropriate departure from the G-BA's specified patient populations and ACT

The company followed neither the G-BA's specifications regarding the categorization of the therapeutic indication into 2 patient populations nor the defined ACT. Instead, its dossier discusses only 1 research question under which it analyses all patients of the present therapeutic indication jointly (children and adolescents 10 years and older with T2DM). The company defined the ACT using the term "individualized therapy", which represents a choice of the drugs metformin, insulin, and liraglutide. The company justifies said choice with high unmet therapeutic needs in this therapeutic indication and a limited selection of approved treatment options.

The company's approach was not appropriate. Neither high unmet therapeutic needs nor a limited selection of approved treatment options represents sufficient grounds for departing from the patient populations and ACT specified by the G-BA.

Results

The check for completeness of the study pool revealed no relevant studies on the comparison of dapagliflozin versus the ACT for research question 1 or 2.

The company analysed all patients in the present therapeutic indication jointly under 1 research question using (1) the results for the relevant age group from the D1690C00017 RCT and (2) an evidence transfer from the DECLARE TIMI 58 study. The company's approach was not appropriate. Neither the D1690C00017 RCT nor the evidence transfer submitted by the company are suitable for assessing the benefit of dapagliflozin versus the ACT. The rationale is provided below.

Evidence provided by the company

Study D1690C00017

The D1690C00017 study submitted by the company is a double-blind, multicentre RCT comparing dapagliflozin with placebo in patients aged 10 to 24 years with T2DM, each in addition to diet, exercise, and a stable dose of metformin, insulin, or metformin + insulin. According to the inclusion criteria, diabetes treatment with metformin, insulin, or metformin + insulin had to have been at a stable dose for at least 8 weeks before screening, with the daily metformin dose being ≥ 1000 mg.

A total of 72 patients were enrolled in the study. Participants were screened, underwent a 4-week lead-in phase with placebo in addition to diet, exercise and the existing stable dose of metformin, insulin, or metformin + insulin, and were then randomized to the intervention arm (N = 39) or the comparator arm (N = 33). For deriving added benefit, the company used the D1690C00017 study's subpopulation of patients aged 10 to 17 years who fall under the new therapeutic indication to be assessed. This applied to 29 patients in the intervention arm and 24 patients in the comparator arm.

During the 24-week randomized treatment phase, patients in the intervention arm were treated in accordance with the summary of product characteristics (SPC) for dapagliflozin. Patients in the comparator arm received placebo. Except for insulin dose reductions in case of multiple or severe hypoglycaemic episodes, no adjustments of the existing, stable diabetes therapy were allowed. In case of sustained hyperglycaemia, both treatment arms allowed unblinded rescue therapy with insulin in addition to the existing diabetes therapy.

The primary outcome of the D1690C00017 study was a change in glycated haemoglobin (HbA1c) value by the end of the randomized treatment phase. Further outcomes were surveyed in the categories of morbidity and side effects.

D1690C00017 study did not implement the G-BA's specifications regarding the patient population and ACT

Regarding the D1690C00017 study, the company did not submit any analyses for the patient populations specified by the G-BA. Instead, the company's dossier examined only 1 research question under which it jointly analysed all patients in the present therapeutic indication. Hence, the company's dossier does not allow assessing the added benefit of dapagliflozin versus the ACT for the 2 research questions specified by the G-A.

Irrespective of the missing categorization into different patient populations, the majority of patients enrolled in the D1690C00017 study were not treated in accordance with the ACTs specified by the G-BA for the 2 patient populations. For instance, 58% of patients in the comparator arm were treated for diabetes using metformin monotherapy. However, metformin monotherapy is not an ACT specified by the G-BA for the present research question. Furthermore, at a mean baseline HbA1c value of about 8.1%, the majority of patients in the comparator arm would have been indicated for treatment escalation to reduce the HbA1c values, and in principle, such treatment would have been possible (e.g. by adding insulin). However, optimization of diabetes therapy was allowed neither during screening nor during the randomized treatment phase.

In summary, the submitted D1690C00017 study was unsuitable for the benefit assessment because (1) no separate analysis was submitted for the patient populations specified by the G-BA and (2) the associated ACT was not implemented. Irrespective of this, the study would not even be suitable for assessing the benefit of dapagliflozin versus the ACT as specified by the company because rather than providing for individualized therapy, the study continued the existing diabetes therapy without adjustments.

DECLARE-TIMI 58 study unsuitable for evidence transfer

The company argues that data collected from dapagliflozin treatment of adults can be extrapolated to children and adolescents, making them relevant for the benefit assessment. The company's reasoning is based on results from the DECLARE-TIMI 58 RCT in conjunction with data on the dapagliflozin pharmacokinetic-pharmacodynamic (PK/PD) profile obtained from the D1690C00016 phase-I study as well as the D1690C00017 study described above.

The company's rationale is not plausible. Results from the DECLARE-TIMI 58 study cannot be extrapolated to the population of children and adolescents with T2DM because the populations are insufficiently similar. The DECLARE-TIMI 58 study enrolled adult patients with T2DM who were at least 40 years of age and at high cardiovascular risk. Children and adolescents 10 to 17 years of age with T2DM, in contrast, very rarely exhibit high cardiovascular risk. Against this background, PK/PD data from the D1690C00016 and D1690C00017 studies, which the company listed as proof for comparability, are irrelevant for the benefit assessment.

In addition, fundamental objections were raised against the relevance of DECLARE-TIMI 58 study results in the benefit assessment of dapagliflozin. In a benefit assessment, it is permissible to extrapolate results from one research question to another only if the available results are relevant for the original research question. The DECLARE-TIMI 58 study is unsuitable for the benefit assessment because said study did not implement the current ACT in the therapeutic indication of T2DM in adult patients; therefore, evidence cannot be transferred to the population relevant in this case, i.e. children and adolescents 10 to 17 years of age with T2DM.

Summary

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

Results on added benefit

No suitable data are available for assessing the added benefit of dapagliflozin in comparison with the ACT, neither for research question 1 (insulin-naive children aged 10 to 17 years with T2DM who have not achieved sufficient blood glucose control with their previous drug treatment consisting of at least 1 blood glucose-lowering drug in addition to diet and exercise) nor for research question 2 (insulin-experienced children aged 10 to 17 years with T2DM who have not achieved sufficient blood glucose control with their previous insulin regimen in addition to diet and exercise). In each case, this results in no hint of an added benefit of dapagliflozin 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 dapagliflozin.

[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: Dapagliflozin – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	Insulin-naive children 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[b] in addition to diet and exercise	Human insulin + metformin[b]	Added benefit not proven
2	Insulin-experienced children aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous insulin regimen in addition to diet and exercise	Escalation of insulin therapy (conventional insulin therapy [CT], possibly + metformin or intensified conventional insulin therapy [ICT])[c,d,e]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, metformin is the treatment of first choice for the drug treatment of type 2 diabetes mellitus in children and adolescents.
c. Treatment with insulin is indicated, if necessary in combination with metformin, in case of signs of ketoacidosis or ketonuria, inadequate blood glucose control under metformin therapy, or in very advanced stages of disease. If treatment escalation options are still available, continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus is not an 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.
d. Insulin therapy should be escalated in the form of CT (mixed insulin) or ICT, taking into account the patient's individual life situation. In ICT, the administration of an additional blood glucose-lowering drug is not typically deemed indicated. In addition to CT, metformin may be administered if necessary.
e. According to the G-BA, single-comparator studies are typically inadequate for implementing the ACT in a direct comparative study. The investigator is expected to have a choice between several treatment options (CT or ICT) (multi-comparator study). The available selection and potential limitation of treatment options must be justified.

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

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of dapagliflozin in children and adolescents aged 10 to 17 years with inadequately controlled 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 questions shown in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of dapagliflozin

Research question	Therapeutic indication	ACT[a]
1	Insulin-naive children 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[b] in addition to diet and exercise	Human insulin + metformin[c]
2	Insulin-experienced children aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous insulin regimen in addition to diet and exercise	Escalation of insulin therapy (conventional insulin therapy [CT], if necessary + metformin or intensified conventional insulin therapy [ICT])[c, d, e]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, metformin is the treatment of first choice for the drug therapy of type 2 diabetes mellitus in children and adolescents.
c. Treatment with insulin is indicated, if necessary in combination with metformin, in case of signs of ketoacidosis or ketonuria, inadequate blood glucose control under metformin therapy, or in very advanced stages of disease. If treatment escalation options are still available, continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus is not an 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.
d. Insulin therapy should be escalated in the form of CT (mixed insulin) or ICT, taking into account the patient's individual living situation. In ICT, the administration of an additional blood glucose-lowering drug is not typically deemed indicated. In addition to CT, metformin may be administered if necessary.
e. According to the G-BA, single-comparator studies are typically inadequate for implementing the ACT in a direct comparative study. The investigator is expected to have a choice between several treatment options (CT or ICT) (multi-comparator 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; ICT: intensified conventional insulin therapy

The G-BA adjusted the ACT on 11 January 2022, during the procedure and after dossier submission [3]. This adjustment eliminated the originally specified 3rd group of patients who are contraindicated or intolerant to metformin. In its notes on the updated ACT, the G-BA argues that compared with the total population, a presumably smaller percentage of children and adolescents are contraindicated or intolerant to metformin, even at low dosages. Therefore, no separate patient population with metformin contraindication or intolerance was established. The change in ACT remains without consequence for the present benefit assessment because

the company's dossier departs from both the original and the updated G-BA specification of the patient populations and ACT.

The company's rationale for deviating from the G-BA's specified patient populations and ACT is not plausible. The present assessment was therefore carried out for the patient populations specified by the G-BA in comparison with the respective ACT from 11 January 2022 [3].

The assessment was 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 the derivation of the added benefit.

Inappropriate departure from the G-BA's specifications of patient populations and ACT

The company did not follow the G-BA's specifications regarding the categorization of the therapeutic indication into 2 patient populations or of the ACT. Instead, its dossier discusses only 1 research question under which it analyses all patients of the present therapeutic indication jointly (children and adolescents 10 years and older with T2DM). The company defined the ACT using the term "individualized therapy", which represents a choice of the drugs metformin, insulin, and liraglutide. The company justifies this choice with high unmet therapeutic needs in this therapeutic indication and a limited selection of approved treatment options.

The company's approach was not appropriate. Neither high unmet therapeutic needs nor a limited selection of approved treatment options represents sufficient grounds for departing from the patient populations and ACT specified by the G-BA. Furthermore, national and international guidelines [4-8] unambiguously show that, in the present therapeutic indication, defined patient populations with clear treatment recommendations do exist. The presentation in the guidelines reflects the G-BA's categorization into the 2 patient populations and the respective specified comparator therapy (see Table 4).

Overall, the company hence does not provide sufficient justification for deviating from the patient populations and ACT specified by the G-BA [3].

2.3 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 dapagliflozin (status: 20 October 2021)
- bibliographical literature search on dapagliflozin (last search on 18 October 2021)
- search in trial registries / trial results databases for studies on dapagliflozin (last search on 20 October 2021)
- search on the G-BA website for dapagliflozin (last search on 20 October 2021)

To check the completeness of the study pool:

- search in trial registries for studies on dapagliflozin (last search on 12 January 2022); for search strategies, see Appendix A of the full dossier assessment

For both research questions 1 and 2, the check of the completeness of the study pool produced no relevant studies on the comparison of dapagliflozin versus the ACT in children and adolescents with T2DM who are 10 to 17 years of age.

The company analysed all patients in the present therapeutic indication jointly under 1 research question and, for this purpose, used both the results for the relevant age group [9,10] from the D1690C00017 RCT [11-15] (see Appendix B of the full dossier assessment regarding study and intervention characteristics) and an evidence transfer from the DECLARE TIMI 58 study [16,17].

The company's approach was not appropriate. Neither the D1690C00017 RCT nor the evidence transfer submitted by the company are suitable for assessing the benefit of dapagliflozin versus the ACT. The rationale is provided below.

Evidence provided by the company

D1690C00017 study

The D1690C00017 study submitted by the company is a double-blind, multicentre RCT comparing dapagliflozin with placebo in patients aged 10 to 24 years with T2DM, each in addition to diet, exercise, and a stable dose of metformin, insulin, or metformin + insulin. The study included patients with an HbA1c ≥ 6.5% and ≤ 11% and fasting blood glucose (FPG) ≤ 255 mg/dL (≤ 14.2 mmol/L). According to the inclusion criteria, diabetes treatment with metformin, insulin, or metformin + insulin had to have been at a stable dose for ≥ 8 weeks prior to screening, with the daily metformin dose being ≥ 1000 mg.

A total of 72 patients were enrolled in the study. After screening, all patients entered a 4-week lead-in phase, where they received placebo in addition to diet, exercise, and the existing stable dose of metformin, insulin, or metformin + insulin. Afterwards, 39 patients were randomized to the intervention arm and 33 to the comparator arm. Randomization was stratified by sex, age (≥ 18 years versus > 15 to < 18 years versus ≤ 15 years), and type of diabetes treatment (metformin versus insulin versus insulin + metformin). For assessing added benefit regarding its research question, the company used the D1690C00017 study's subpopulation of patients aged 10 to 17 years who fall under the new therapeutic indication to be assessed. This applied to 29 patients in the intervention arm and 24 patients in the comparator arm.

During the randomized treatment phase, patients in the intervention arm were treated in accordance with the dapagliflozin SPC [18]. Patients in the comparator arm received placebo. Except for insulin dose reductions in case of multiple or severe hypoglycaemic episodes, no adjustments of the existing stable diabetes therapy were allowed. In case of sustained

hyperglycaemia, both treatment arms allowed unblinded rescue therapy with insulin in addition to the existing diabetes therapy. To qualify for this rescue therapy, patients had to have an FPG of > 13.3 mmol/L (> 240 mg/dL) either in 1 test performed by the central laboratory or on 3 consecutive days of self-monitoring, with each requiring confirmation via another test taken by the central laboratory.

The primary outcome of the D1690C00017 study was a change in HbA1c value by the end of the randomized treatment phase. Further outcomes were surveyed in the categories of morbidity and side effects.

The randomized treatment phase lasted 24 weeks and was followed by a 28-week open extension phase in which all patients received dapagliflozin. After the extension phase, patients were followed up for a further 4 weeks.

D1690C00017 study did not implement the G-BA's specifications regarding the patient population and ACT

For the D1690C00017 study, the company did not submit any analyses regarding the patient populations specified by the G-BA. Instead, the company's dossier examined only 1 research question under which it jointly analysed all patients in the present therapeutic indication. An assessment of added benefit of dapagliflozin in comparison with the ACT for the 2 research questions of the G-BA is therefore not possible on the basis of the company's dossier.

Irrespective of the lack of categorization into different patient populations, the majority of patients enrolled in the D1690C00017 study were not treated in accordance with the ACTs specified by the G-BA for the 2 patient populations. For instance, 58% of patients in the comparator arm were treated for diabetes using metformin monotherapy. Metformin monotherapy is not an ACT specified by the G-BA for the present research question. The G-BA notes that continuation of insufficient treatment of T2DM does not constitute an ACT as long as options to escalate treatment are still available. Since patients had a mean baseline HbA1c value of about 8.1%, the majority of comparator arm patients were presumably indicated for treatment escalation to lower the HbA1c value in accordance with guideline recommendations [4-8], and, in principle, such escalation would have been possible (e. g. by adding insulin). However, any optimizations of diabetes therapy were disallowed both during screening and during the randomized treatment phase. The above-described option of rescue therapy via insulin after repeated FPG readings > 13.3 mmol/L (> 240 mg/dL) represents neither guideline-compliant treatment optimization nor the treatment escalation called for by the G-BA; in addition, it was carried out in only 4 patients in total. The lack of escalation of diabetes treatment was also reflected by virtually unchanged HbA1c values over the course of the study (see Figure 1).

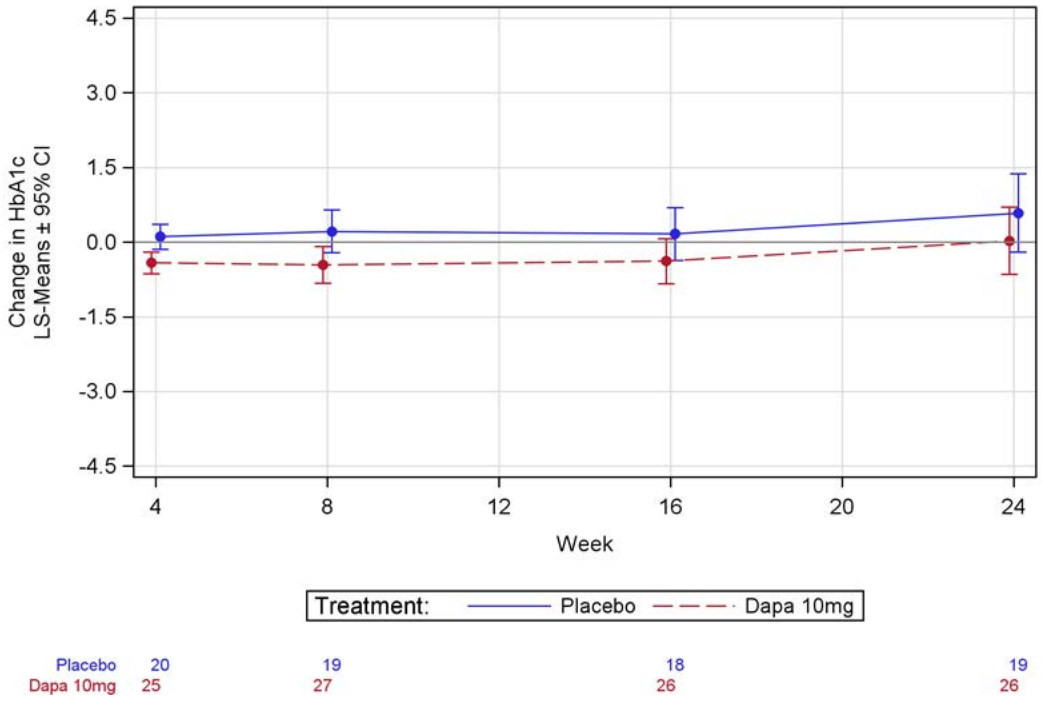

Figure 1: "Change in HbA1c (%) from baseline to Week 24" (D1690C00017 study)

In summary, the submitted D1690C00017 study was unsuitable for the benefit assessment because (1) no separate analysis was presented for the patient populations specified by the G-BA and (2) the respective ACTs were not implemented. Irrespective of this, the study would not even be suitable for assessing the benefit of dapagliflozin versus the ACT as specified by the company because, rather than providing for individualized therapy, the study continued the existing diabetes therapy without adjustments.

DECLARE-TIMI 58 study unsuitable for evidence transfer

The company argues that – like in the EMA's approval procedure [19] – data from the dapagliflozin treatment of adults can be extrapolated to children and adolescents and are therefore relevant for the benefit assessment. The company's reasoning is based on results from the DECLARE-TIMI 58 RCT [17,20,21] in conjunction with data on the dapagliflozin PK/PD profile from the D1690C00016 phase-I study [22] as well as the D1690C00017 study described above.

The company's rationale is not plausible. Results from the DECLARE-TIMI 58 study cannot be extrapolated to the population of children and adolescents with T2DM because the populations are insufficiently similar. The DECLARE-TIMI 58 study enrolled adult patients with T2DM who were at least 40 years of age and at high cardiovascular risk. Children and adolescents 10 to 17 years of age with T2DM, in contrast, very rarely exhibit high cardiovascular risk. Against this background, the PK/PD data from the D1690C00016 [22] and

D1690C00017 studies, which the company listed as proof of comparability, are irrelevant for the benefit assessment.

In addition, fundamental objections were raised against the relevance of DECLARE-TIMI 58 study results in the benefit assessment of dapagliflozin. Results cannot be extrapolated from one research question to another unless results relevant to the original research question are available. The DECLARE-TIMI 58 study is unsuitable for the benefit assessment because it did not implement the current ACT in the therapeutic indication of T2DM in adult patients; therefore, evidence cannot be transferred to the population relevant in this case, i.e. children and adolescents 10 to 17 years of age with T2DM.

Summary

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

2.4 Results on added benefit

No suitable data are available for assessing the added benefit of dapagliflozin in comparison with the ACT, neither for research question 1 (insulin-naive children aged 10 to 17 years with T2DM who have not achieved sufficient blood glucose control with their previous drug treatment consisting of at least 1 blood glucose-lowering drug in addition to diet and exercise) nor for research question 2 (insulin-experienced children aged 10 to 17 years with T2DM who have not achieved sufficient blood glucose control with their previous insulin regimen in addition to diet and exercise). In each case, this results in no hint of an added benefit of dapagliflozin in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit – summary

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

Table 5: Dapagliflozin – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Insulin-naive children 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[b] in addition to diet and exercise	Human insulin + metformin[b]	Added benefit not proven
2	Insulin-experienced children aged 10 to 17 years with type 2 diabetes mellitus who have not achieved sufficient blood glucose control with their previous insulin regimen in addition to diet and exercise	Escalation of insulin therapy (conventional insulin therapy [CT], if necessary + metformin or intensified conventional insulin therapy [ICT])[c, d, e]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, metformin is the treatment of first choice for the drug therapy of type 2 diabetes mellitus in children and adolescents.
c. Treatment with insulin is indicated, if necessary in combination with metformin, in case of signs of ketoacidosis or ketonuria, inadequate blood glucose control under metformin therapy, or in very advanced stages of disease. If treatment escalation options are still available, continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus is not an ACT. In both study arms, potential comorbidities or risk factors for T2DM (e.g. hypertension, dyslipidaemia, microvascular complications – nephropathy, neuropathy, retinopathy) were presumably treated in an individualized manner according to the latest medical knowledge, using in particular antihypertensives and/or lipid-lowering drugs.
d. Insulin therapy should be escalated in the form of CT (mixed insulin) or ICT, taking into account the patient's individual living situation. In ICT, the administration of an additional blood glucose-lowering drug is not typically deemed indicated. In addition to CT, metformin may be administered if necessary.
e. According to the G-BA, single-comparator studies are typically inadequate for implementing the ACT in a direct comparative study. The investigator is expected to have a choice between several treatment options (CT or ICT) (multi-comparator study). The choice and, if necessary, restriction of treatment options must be justified.

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

The assessment described above deviates from the assessment by the company, which derives a hint of non-quantifiable added benefit for all patients in the present therapeutic indication (children and adolescents with T2DM aged 10 years or older).

The G-BA decides on the added benefit.

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.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Dapagliflozin (Neues Anwendungsgebiet: Diabetes mellitus Typ 2, ≥ 10 Jahre); zweckmäßige Vergleichstherapie (aktualisierte Festlegung vom 11.01.2022). [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/775/#zweckmaessige-vergleichstherapie].

4. American Diabetes Association. 13. Children and Adolescents: Standards of Medical Care in Diabetes-2021. Diabetes Care 2021; 44(Suppl 1): S180-S199. https://dx.doi.org/10.2337/dc21-S013.

5. Pena AS, Curran JA, Fuery M et al. Screening, assessment and management of type 2 diabetes mellitus in children and adolescents: Australasian Paediatric Endocrine Group guidelines. Med J Aust 2020; 213(1): 30-43. https://dx.doi.org/10.5694/mja2.50666.

6. National Collaborating Centre for Women's and Children's Health. Diabetes (Type 1 and Type 2) in Children and Young People: Diagnosis and Management [online]. 2015 [Accessed: 21.02.2022]. URL: https://www.nice.org.uk/guidance/ng18/evidence/full-guideline-pdf-435396352.

7. Mayer-Davis EJ, Kahkoska AR, Jefferies C et al. ISPAD Clinical Practice Consensus Guidelines 2018: Definition, epidemiology, and classification of diabetes in children and adolescents. Pediatr Diabetes 2018; 19 Suppl 27: 7-19. https://dx.doi.org/10.1111/pedi.12773.

8. Deutsche Diabetes Gesellschaft. S3-Leitlinie Diagnostik, Therapie und Verlaufskontrolle des Diabetes mellitus im Kindes- und Jugendalter. 2015.

9. AstraZeneca. Statistische Nachberechnungen für die Studie D1690C00017. 2021.

10. AstraZeneca. Statistischer Analyseplan zu den statistischen Nachberechnungen der Studie D1690C00017. 2021.

11. AstraZeneca. ClinicalTrials.gov: Study to Evaluate Safety and Efficacy of Dapagliflozin in Patients With Type 2 Diabetes Mellitus Aged 10-24 Years (NCT02725593). 2016.

12. AstraZeneca. A 24-Week, Multicentre, Randomised, Double-Blind, Parallel Group, Phase 3 Trial with a 28-Week Long-Term Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 10 mg in T2DM Patients Aged 10-24 Years; Clinical Study Report. 2020.

13. AstraZeneca. A 24-Week, Multicentre, Randomised, Double-Blind, Parallel Group, Phase 3 Trial with a 28-Week Long-Term Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 10 mg in T2DM Patients Aged 10-24 Years; Clinical Study Protocol. 2020.

14. AstraZeneca. A 24-Week, Multicentre, Randomised, Double-Blind, Parallel Group, Phase 3 Trial with a 28-Week Long-Term Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 10 mg in T2DM Patients Aged 10-24 Years; Statistical Analysis Plan. 2020.

15. AstraZeneca. EU Clinical Trials: Study to Evaluate Safety and Efficacy of Dapagliflozin in Patients With Type 2 Diabetes Mellitus Aged 10-24 Years (2015-005041-31). 2016.

16. AstraZeneca. Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events [online]. 2020. URL: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT01730534.

17. AstraZeneca, Bristol-Myers Squibb, The TIMI Study Group et al. Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events [online]. 2019. URL: https://ClinicalTrials.gov/show/NCT01730534.

18. AstraZeneca. Forxiga 10 mg Filmtabletten (Stand: November 2021).

19. European Medicines Agency. European Public Assessment Report (EPAR) of Dapagliflozin. 2021.

20. AstraZeneca. DECLARE Dapagliflozin Effect on CardiovascuLAR Events A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence o [online]. 2013. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-000239-28.

21. Wiviott SD, Raz I, Bonaca MP et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019; 380(4): 347-357. https://dx.doi.org/10.1056/NEJMoa1812389.

22. AstraZeneca, Bristol-Myers Squibb. PK Study of Dapagliflozin in Pediatric Subjects With T2DM [online]. 2017. URL: https://ClinicalTrials.gov/show/NCT01525238.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-167.html.