IQWiG Reports – Commission No. A19-37

Dapagliflozin (type 1 diabetes mellitus) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Dapagliflozin (Diabetes mellitus Typ 1) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 July 2019). 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.

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List of abbreviations

Abbreviation	Meaning
ADA	American Diabetes Association
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
CGM	continuous glucose monitoring
CI	confidence interval
DKA	diabetic ketoacidosis
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GFR	glomerular filtration rate
HbA1c	haemoglobin A1c
HFS	Hypoglycemia Fear Survey
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IU	international units
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

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 was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 18 April 2019.

Research question

The aim of the present report is to assess the added benefit of dapagliflozin as an adjunct to insulin in patients with type 1 diabetes mellitus and with a body mass index (BMI) ≥ 27 kg/m², when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

The G-BA specified human insulin or insulin analogues as appropriate comparator therapy (ACT) for the therapeutic indication. For the assessment, this resulted in the following research question (see Table 2).

Table 2: Research question of the benefit assessment of dapagliflozin

Therapeutic indication	ACT
Type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m², when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy	Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin aspart, insulin glulisine, insulin lispro)[a]
a: The unchanged continuation of an inadequate therapy of type 1 diabetes mellitus, if there is still the option of optimizing insulin therapy, does not correspond to an ACT. The approvals and SPCs of the drugs of the ACT have to be considered. ACT: appropriate comparator therapy; BMI: body mass index; SPC: Summary of Product Characteristics	

The company followed the G-BA's specification for the benefit assessment.

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. This concurs with the company's inclusion criteria.

Results

Study pool and study characteristics

The study pool for the benefit assessment of dapagliflozin and insulin in comparison with the ACT (human insulin or insulin analogues) consists of the RCTs DEPICT 1 and DEPICT 2.

The studies DEPICT 1 and DEPICT 2 have an identical study design (so-called twin studies) and are described jointly below. Both studies were double-blind, parallel, randomized and placebo-controlled. The aim of the studies was to investigate the efficacy and safety of dapagliflozin compared with placebo as an add-on therapy to insulin.

The studies included patients aged 18 years and older with type 1 diabetes mellitus who had been treated with insulin for at least 12 months (multiple daily injections or insulin pump therapy). At the beginning of treatment, the patients had to have a haemoglobin A1c (HbA1c) between ≥ 7.5% and ≤ 10.5% and BMI ≥ 18 kg/m².

In accordance with the approved therapeutic indication, the subpopulation within the studies DEPICT 1 and DEPICT 2 relevant for the benefit assessment comprises only patients with BMI ≥ 27 kg/m². These were about 58% (DEPICT 1) and 48% (DEPICT 2) of the study population.

Eight weeks before randomization, the patients received an optimization of insulin treatment to improve their diabetes management (so-called lead-in phase). The optimization of insulin treatment was carried out at the physician's discretion on the basis of the blood glucose values measured by the patient and in accordance with the patient's individual needs and local guidelines. At the beginning of treatment with the study medication (dapagliflozin or placebo), the study protocol recommended a reduction of the insulin dose by up to 20% to reduce the initial risk of hypoglycaemia. This concurs with the recommendation in the Summary of Product Characteristics (SPC) of dapagliflozin. For the comparator arm, however, this initially resulted in inadequate treatment as the dose was lowered despite optimized insulin therapy. This was taken into account in the assessment of the outcome-specific risk of bias. In the further course of the study, the insulin treatment could be adapted and optimized to the individual patient according to the criteria mentioned above.

Treatment duration in both studies was 52 weeks and was divided into a 24-week short-term therapy followed by a 28-week long-term therapy.

Primary outcome in both studies was the change in HbA1c from baseline at week 24. Patient-relevant secondary outcomes were all-cause mortality and outcomes on morbidity as well as on adverse events (AEs) including episodes of hypoglycaemia and diabetic ketoacidosis (DKA).

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes was rated as low for both DEPICT studies.

For the DEPICT 2 study, the risk of bias for the results on the outcome "all-cause mortality" was rated as low. For the operationalizations of the outcomes "HbA1c" and "hypoglycaemic episodes", the risk of bias was rated as potentially high in both studies due to the reduction in insulin dose of up to 20% at the start of treatment.

The risk of bias of the results of the outcomes on morbidity measured with the Hypoglycemia Fear Survey II (HFS-II) Worry subscale and on health status measured with the European

Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS) was rated as high due to missing values.

The DEPICT 1 study had the problem that there was a randomization error for the first 55 patients included. The company, however, excluded these wrongly randomized patients only for the evaluation of efficacy outcomes without further justification. A high risk of bias was therefore assumed in the DEPICT 1 study for all outcomes of the categories of mortality and side effects.

For the DEPICT 2 study, the risk of bias of the results on all outcomes of the category of side effects (except hypoglycaemic episodes, see above) was rated as low.

The results from the meta-analysis of the studies DEPICT 1 and DEPICT 2 at week 52 were used for the benefit assessment. At most proof, e.g. of an added benefit, can be derived from the meta-analysis.

Results

Mortality

- All-cause mortality

In both studies, no deaths occurred after 52 weeks. Hence, there was no statistically significant difference between dapagliflozin and insulin versus placebo and insulin for the outcome "all-cause mortality". This resulted in no hint of an added benefit of dapagliflozin and insulin versus insulin; an added benefit is therefore not proven.

Morbidity

- HbA1c value as sufficiently valid surrogate for microvascular late complications

Two different operationalizations were used for the HbA1c value and considered jointly in the derivation of the added benefit.

The meta-analysis produced a statistically significant difference in favour of dapagliflozin and insulin versus placebo and insulin for the **change in HbA1c**. However, the 95% confidence interval (CI) of the effect is not completely outside the generally used relevance limit of 0.3 percentage points, which is also used by the regulatory authorities to assess a clinically relevant group difference. It can therefore not be inferred that the effect was relevant.

The meta-analysis produced a statistically significant difference in favour of dapagliflozin and insulin versus placebo and insulin for the **responder analysis HbA1c reduction ≥ 0.5%**.

In summary, a relevant difference was shown in the reduction of HbA1c value in favour of dapagliflozin and insulin versus placebo and insulin on the basis of the responder analysis (reduction by 0.5 percentage points). Under consideration of the mean change in HbA1c, an irrelevant group difference cannot be excluded, but the direction of the effect is consistent with the results of the responder analysis. Overall, there is an indication of an added benefit of

dapagliflozin and insulin in comparison with insulin for the outcome “HbA1c” (as sufficiently valid surrogate outcome for microvascular late complications).

- Health status (EQ-5D VAS)

The meta-analysis produced a statistically significant difference in favour of dapagliflozin and insulin versus placebo and insulin for the outcome “health status” measured with the EQ-5D VAS. However, the 95% CI of the standardized mean difference (Hedges’ g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect was relevant. This resulted in no hint of an added benefit of dapagliflozin and insulin in comparison with insulin; an added benefit is therefore not proven.

- HFS-II (Worry subscale)

The outcome “HFS-II (Worry subscale)” was only recorded in the DEPICT 2 study. The study showed no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of dapagliflozin and insulin in comparison with insulin for the outcome “HFS-II (Worry subscale)”; an added benefit is therefore not proven.

Health-related quality of life

No outcomes of the outcome category “health-related quality of life” were investigated in the studies DEPICT 1 and DEPICT 2. This resulted in no hint of an added benefit of dapagliflozin and insulin in comparison with insulin in this outcome category; an added benefit is therefore not proven.

Side effects

- Serious adverse events (SAEs)

The meta-analysis showed no statistically significant difference between dapagliflozin and insulin versus placebo and insulin for the outcome “SAEs”. This resulted in no hint of greater or lesser harm from dapagliflozin and insulin versus insulin; greater or lesser harm is therefore not proven.

- Discontinuation due to adverse events

The information on the number of events for this outcome is partly contradictory within the company’s dossier (Module 4 A or Module 5). From the available documents, it is not possible to determine which event rates are correct. However, both event rates showed no statistically significant difference between dapagliflozin and insulin versus placebo and insulin in the meta-analysis. This resulted in no hint of greater or lesser harm from dapagliflozin and insulin versus insulin; greater or lesser harm is therefore not proven.

- Symptomatic, confirmed hypoglycaemia

For the outcome “symptomatic confirmed hypoglycaemia”, results were only available for the plasma glucose threshold of 70 mg/dL. There were no analyses on the threshold value of

54 mg/dL. The meta-analysis for symptomatic, confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dL) showed a statistically significant difference to the disadvantage of dapagliflozin and insulin. This effect was no more than marginal, however. This resulted in no hint of greater or lesser harm from dapagliflozin and insulin versus insulin; greater or lesser harm is therefore not proven.

- Severe hypoglycaemia

The operationalization presented by the company was unsuitable to represent severe hypoglycaemic episodes.

- Serious hypoglycaemia (Preferred Term [PT], SAE)

The meta-analysis showed no statistically significant difference between dapagliflozin and insulin versus placebo and insulin for the outcome "serious hypoglycaemia" (PT, SAE). This resulted in no hint of greater or lesser harm from dapagliflozin and insulin versus insulin; greater or lesser harm is therefore not proven.

- Diabetic ketoacidosis

For the outcome "diabetic ketoacidosis", the company only presented results for the category "definite DKAs". The meta-analysis here showed no statistically significant difference between dapagliflozin and insulin versus placebo and insulin. Since relevant information on DKAs is missing, no final conclusion can be drawn based on the data on definite DKAs alone.

- Genital infections and gastrointestinal disorders (System Organ Class [SOC], AE)

The meta-analysis showed a statistically significant difference to the disadvantage of dapagliflozin and insulin versus placebo and insulin for each of the outcomes "genital infections" and "gastrointestinal disorders" (SOC, AE). In each case, this resulted in proof of greater harm from dapagliflozin and insulin in comparison with insulin.

- Urinary tract infections

The meta-analysis showed no statistically significant difference between dapagliflozin and insulin versus placebo and insulin for the outcome "urinary tract infections". This resulted in no hint of greater or lesser harm from dapagliflozin and insulin versus insulin; greater or lesser harm is therefore not proven.

- Specific SAEs

The results for SAEs at PT and SOC level were not available for the relevant subpopulation, so that an assessment of potentially relevant specific SAEs based on the study results was not possible.

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

Based on the results presented, probability and extent of the added benefit of the drug dapagliflozin and insulin in comparison with the ACT are assessed as follows:

In an incomplete data situation, the overall consideration showed 1 positive and 2 negative effects of dapagliflozin + insulin in comparison with placebo + insulin.

Overall, there is an indication of an added benefit for the outcome "change in HbA1c". For the HbA1c value as a sufficiently valid surrogate for microvascular late complications, however, there is no information available on the basis of which the extent of the added benefit could be determined (e.g. surrogate validation using the concept of a so-called surrogate threshold effect [1]. The extent of added benefit for this outcome can therefore not be quantified. This is offset by proof of greater harm of considerable extent for non-serious/non-severe side effects. For side effects, the data were not presented completely.

Overall, the added benefit of dapagliflozin and insulin versus insulin (human insulin and insulin analogues) is not proven in patients with type 1 diabetes mellitus and with BMI ≥ 27 kg/m², when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

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

Table 3: Dapagliflozin – probability and extent of added benefit

Therapeutic indication	**ACT**	**Probability and extent of added benefit**
Type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m², when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy	Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin aspart, insulin glulisine, insulin lispro)[a]	Added benefit not proven
a: The unchanged continuation of an inadequate therapy of type 1 diabetes mellitus, if there is still the option of optimizing insulin therapy, does not correspond to an ACT. The approvals and SPCs of the drugs of the ACT have to be considered. ACT: appropriate comparator therapy; BMI: body mass index; SPC: Summary of Product Characteristics		

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

[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].

2.2 Research question

The aim of the present report is to assess the added benefit of dapagliflozin as an adjunct to insulin in patients with type 1 diabetes mellitus and with BMI ≥ 27 kg/m², when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

The G-BA specified human insulin or insulin analogues as ACT for the therapeutic indication. For the assessment, this resulted in the following research question (see Table 4).

Table 4: Research question of the benefit assessment of dapagliflozin

Therapeutic indication	**ACT**
Type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m², when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy	Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin aspart, insulin glulisine, insulin lispro)[a]
a: The unchanged continuation of an inadequate therapy of type 1 diabetes mellitus, if there is still the option of optimizing insulin therapy, does not correspond to an ACT. The approvals and SPCs of the drugs of the ACT have to be considered. ACT: appropriate comparator therapy; BMI: body mass index; SPC: Summary of Product Characteristics	

The company followed the G-BA's specification for the benefit assessment.

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. This concurs with the company's inclusion criteria.

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 + insulin (status: 13 February 2019)
- bibliographical literature search on dapagliflozin (last search on 14 February 2019)
- search in trial registries for studies on dapagliflozin (last search on 13 February 2019)

To check the completeness of the study pool:

- search in trial registries for studies on dapagliflozin (last search on 29 April 2019)

The check identified no additional relevant study.

2.3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
MB102229 (DEPICT 1[b])	Yes	Yes	No
MB102230 (DEPICT 2[b])	Yes	Yes	No

a: Study for which the company was sponsor.
b: In the following tables, the study is referred to with this abbreviated form.
RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of dapagliflozin + insulin corresponded to that of the company. It included the 2 twin studies DEPICT 1 and DEPICT 2, which directly compared dapagliflozin + insulin with placebo + insulin treatment.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
DEPICT 1	RCT, double-blind, parallel	Adult patients (≥ 18 and ≤ 75 years) with type 1 diabetes mellitus: ▪ insulin use for at least 12 months ▪ HbA1c at screening ≥ 7.7% and ≤ 11% ▪ HbA1c ≥ 7.5% and ≤ 10.5% (1 week before start of treatment) ▪ BMI ≥ 18.5 kg/m² There were some exclusion criteria regarding medical history[b]	▪ dapagliflozin 5 mg + insulin (N = 259 + 18)[c] ▪ dapagliflozin 10 mg + insulin (N = 259 + 37)[c, d] ▪ placebo + insulin (N = 260) Relevant subpopulation thereof[e]: ▪ dapagliflozin 5 mg + insulin (n = 145 + 14)[c] ▪ placebo + insulin (n = 154)	▪ Screening: within 28 days before lead-in phase ▪ Lead-in phase: 8-week phase for the optimization of insulin treatment[f] ▪ Treatment phase: 52 weeks (24 weeks short-term therapy + 28 weeks long-term therapy) ▪ Follow-up: 4 weeks	96 centres in 17 countries: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Mexico, Romania, Spain, Sweden, United Kingdom, USA 11/2014–8/2017	Primary: change in HbA1c after 24 weeks Secondary: mortality, morbidity, health status, AEs
DEPICT 2	RCT, double-blind, parallel	Adult patients (≥ 18 and ≤ 75 years) with type 1 diabetes mellitus: ▪ insulin use for at least 12 months ▪ HbA1c at screening ≥ 7.7% and ≤ 11% ▪ HbA1c at start of treatment ≥ 7.5% and ≤ 10.5% ▪ BMI ≥ 18.5 kg/m² There were some exclusion criteria regarding medical history[b]	▪ dapagliflozin 5 mg + insulin (N = 271) ▪ dapagliflozin 10 mg + insulin (N = 270)[d] ▪ placebo + insulin (N = 272) Relevant subpopulation thereof[e]: ▪ dapagliflozin 5 mg + insulin (n = 127) ▪ placebo + insulin (n = 135)	▪ Screening: within 28 days before lead-in phase ▪ Lead-in phase: 8-week phase for the optimization of insulin treatment[f] ▪ Treatment phase: 52 weeks (24 weeks short-term therapy + 28 weeks long-term therapy) ▪ Follow-up: 4 weeks	148 centres in 13 countries: Argentina, Belgium, Canada, Chile, Germany, Japan, Netherlands, Poland, Russia, Sweden, Switzerland, United Kingdom, USA 7/2015–4/2018	Primary: change in HbA1c after 24 weeks Secondary: mortality, morbidity, health status, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin (continued)

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b: Exclusion criteria were, for example, history of type 2 diabetes mellitus, history of diabetic ketoacidosis (requiring medical intervention) and history of hospital admission for glycaemic control, each within 1 month prior to screening, or symptoms of poorly controlled diabetes.
c: Due to a randomization error, the number of randomized patients was increased by 55. The first 55 patients were excluded for the efficacy analyses.
d: The arm is not relevant for the assessment and is not shown in the next tables.
e: According to the approved therapeutic indication, use of dapagliflozin is only allowed in patients with BMI ≥ 27 kg/m² [3].
f: The optimization of insulin therapy was carried out at the physician's discretion on the basis of the blood glucose values measured by the patient and in accordance with the patient's individual needs and local guidelines.
AE: adverse event; BMI: body mass index; HbA1c: haemoglobin A1c; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin

Study	Intervention	Comparison
DEPICT 1	Dapagliflozin 5 mg (once daily irrespective of time, orally) + insulin (multiple daily injections [at least 3 times/day] or insulin pump therapy)[a] ▪ After the first dose of the study medication, a reduction of the insulin dose by up to 20% is recommended to reduce the risk of hypoglycaemia. This reduction was not obligatory and its time point and extent were at the physician's discretion[b]. ▪ In the course of the study, the insulin therapy could be adapted and optimized to the individual patient. The optimization of insulin therapy was carried out at the physician's discretion on the basis of the blood glucose values measured by the patient and in accordance with the patient's individual needs and local guidelines.	Placebo + +
	Concomitant interventions ▪ The company provided material for patient training. ▪ At the beginning of the lead-in phase, the patients received nutrition and exercise counselling (from qualified personnel) in accordance with ADA or comparative local guidelines. ▪ Patients were encouraged to follow the recommendations throughout the entire course of the study. **Prohibited concomitant treatment** ▪ antihyperglycaemic medication (in addition to the study medication and insulin) ▪ drugs to lower body weight ▪ newly applied systemic corticosteroid therapy lasting ≥ 5 days (inhaled and topical application were allowed) ▪ paracetamol-containing drugs during the use of a device for continuous blood glucose measurement and 24 hours before use of the device **Pretreatment** ▪ All patients had to be treated with insulin for at least 12 months, and ▫ the method of insulin administration (multiple daily injections or insulin pump therapy) had to be unchanged for at least 3 months prior to screening ▫ patients had to be on a total insulin dose of ≥ 0.3 IU/kg/day for at least 3 months prior to screening ▫ if on multiple daily injections, patients had to be on at least 3 injections per day	
DEPICT 2	See DEPICT 1	

a: Switching between multiple daily injections and insulin pump therapy in the course of the study was not allowed (exception: defect of the insulin pump). There was no exact specification regarding the type of insulin in the studies.
b: In case of a reduction of insulin, a retitration to the initial dose was to be aspired under close blood glucose monitoring (at least 4 blood glucose measurements per day in the first 2 weeks).
ADA: American Diabetes Association; IU: international units; RCT: randomized controlled trial; vs.: versus

Study design

The studies DEPICT 1 and DEPICT 2 have an identical study design (so-called twin studies) and are described jointly below. Both studies were double-blind, parallel, randomized and placebo-controlled. The aim of the studies was to investigate the efficacy and safety of dapagliflozin (5 mg and 10 mg) compared with placebo as an add-on therapy to insulin. Administration was in compliance with the SPC [3]. The studies had a multicentre design. The

studies included patients aged 18 years and older with type 1 diabetes mellitus who had been treated with insulin for at least 12 months (multiple daily injections or insulin pump therapy). At the beginning of treatment, the patients had to have an HbA1c between ≥ 7.5% and ≤ 10.5% and BMI ≥ 18 kg/m². Antihyperglycaemic medication (in addition to the study medication and insulin) was not allowed in the studies.

A total of 833[4] patients in the DEPICT 1 study and a total of 815 patients in the DEPICT 2 study were randomly allocated in a 1:1:1 ratio to the treatment arms of dapagliflozin (5 mg and 10 mg) and placebo, which were administered in addition to the existing individual insulin therapy. Stratification was according to the current use of continuous glucose monitoring (CGM) (yes/no), the method of insulin administration (multiple daily injections or insulin pump therapy) and baseline HbA1c (< 9.0%/≥ 9.0%). In both studies, only the treatment arm with the dapagliflozin dose of 5 mg, which is indicated for this therapeutic indication, in comparison with placebo is relevant for the benefit assessment.

Figure 1 is a schematic presentation of the (identical) design of the 2 studies DEPICT 1 and DEPICT 2.

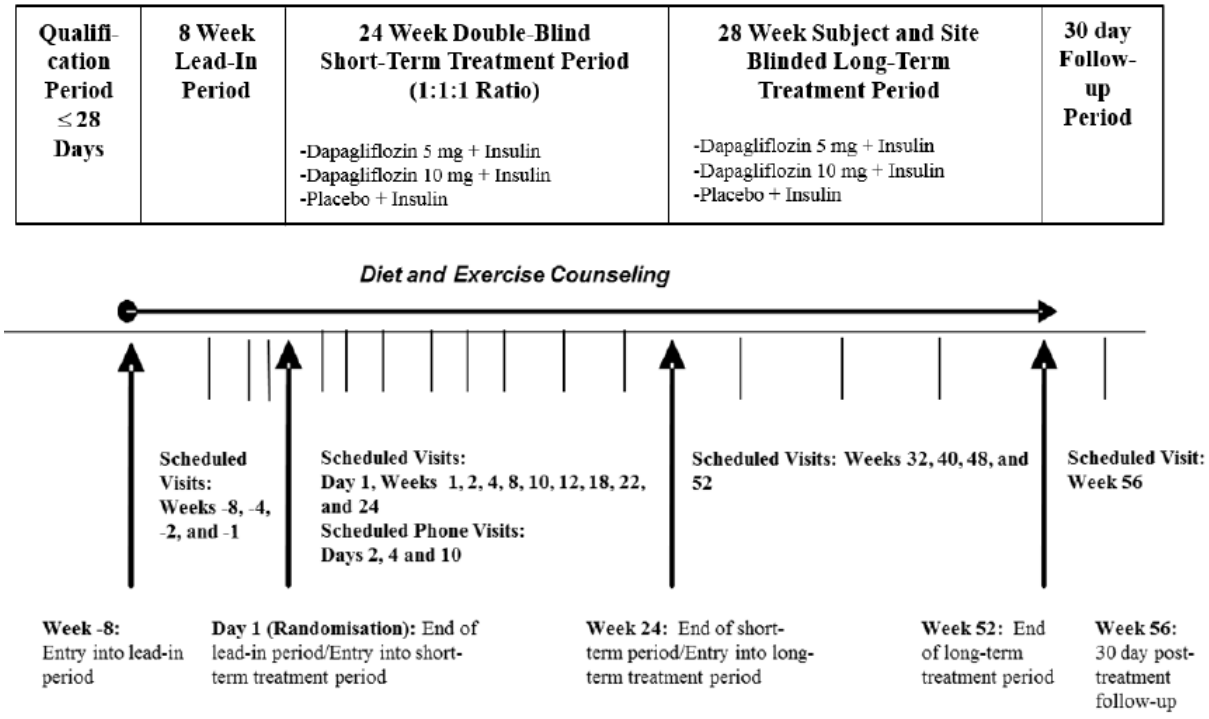

Figure 1: Design of the studies DEPICT 1 and DEPICT 2

[4] There was a randomization error for the first 55 patients included. Instead of a 1:1:1 ratio, these patients were erroneously randomized in a ratio of 1:2:0 to the treatment arms. The number of randomized patients was therefore increased by 55 (to a total of 833). The wrongly randomized 55 patients were excluded only for efficacy analyses, however. This randomization error was taken into account in the assessment of the outcome-specific risk of bias.

Eight weeks before randomization, the patients received an optimization of insulin treatment to improve their diabetes management (so-called lead-in phase). This 8-week optimization phase was relevant to ensure that the treatment effect of dapagliflozin versus placebo could not have been achieved by insulin adaptation alone. There was no exact specification regarding the type of insulin in the studies. It could be inferred from the study documents that the patients in the studies used both human insulin and insulin analogues. The optimization of insulin treatment was carried out at the physician's discretion on the basis of the blood glucose values measured by the patient and in accordance with the patient's individual needs and local guidelines. In addition, the patients were provided with training material. At the beginning of the lead-in phase, the patients additionally received nutrition and exercise counselling (from qualified personnel) in accordance with recommendations from the American Diabetes Association (ADA) or comparative local guidelines. The patients were encouraged to follow the recommendations throughout the entire course of the study. Each patient was also provided with a device for measuring blood glucose and ketone bodies and the patients were trained to use these devices.

During the lead-in phase, the insulin dose was increased by an average of 14.8% in the DEPICT 1 study and 19.1% in the DEPICT 2 study. This led to an average reduction in HbA1c levels of −0.262% (DEPICT 1) and −0.343% (DEPICT 2) at the end of the lead-in phase.

At the start of treatment, the study protocol recommended a reduction of the insulin dose by up to 20% to reduce the initial risk of hypoglycaemia. For the dapagliflozin arm, this concurs with the recommendation in the SPC [3]. For the comparator arm, however, this initially resulted in inadequate treatment as the dose was lowered despite optimized insulin therapy. However, the reduction potentially led to an underestimation of hypoglycaemic episodes and to an overestimation of HbA1c values in the comparator arm. The insulin reduction was not obligatory and its time point and extent were at the physician's discretion. Due to the blinding of the study medication and the group allocation, however, the investigators had to assume in principle, i.e. also for patients in the comparator arm, that there was additional blood glucose lowering by dapagliflozin. Accordingly, a relevant reduction of the mean insulin dose could be observed in the comparison arm directly at the start of the study, despite the preceding optimization phase (see Figure 2). In case of a reduction, a retitration to the initial dose was to be aspired under close blood glucose monitoring (at least 4 blood glucose measurements per day in the first 2 weeks).

Also in the further course of the study, the insulin treatment could be adapted and optimized to the individual patient according to the criteria mentioned above. In the comparator arms of both studies, the insulin dose increased again to the baseline value in the further course of the study after an initial reduction by an average of about 5 international units (IU) (equivalent to about 7% of the mean total insulin dose) (see exemplary Figure 2). The fact that the insulin dose in the course of the study did not rise above the baseline value at the start of treatment despite the possibility of optimizing insulin therapy indicates that insulin therapy had been sufficiently optimized in the lead-in phase.

Figure 4 **Change from baseline in total daily insulin over time – 52-week short-term + long-term treatment period (full analysis set)**

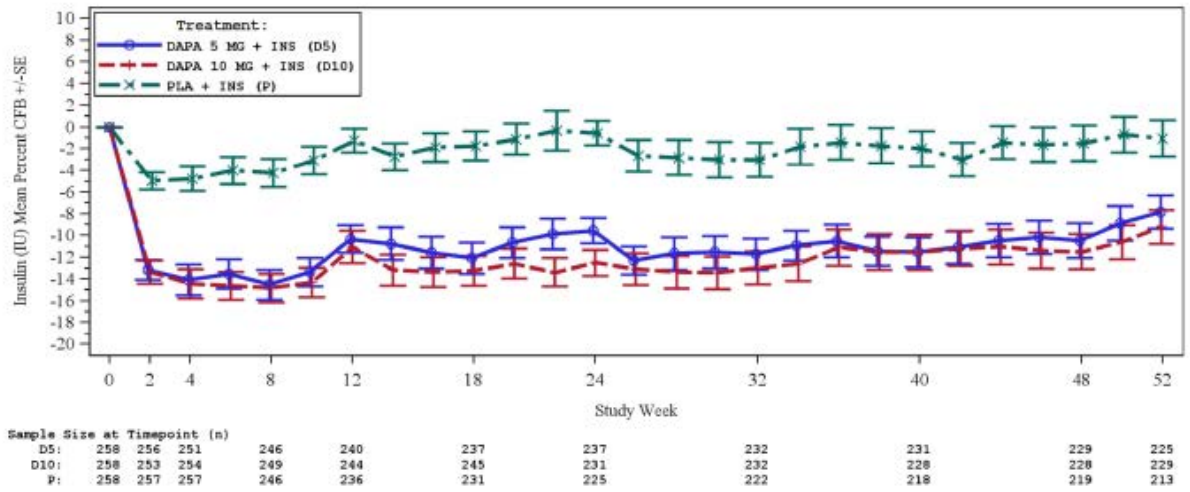

Figure 2: Insulin dose in the course of the study, DEPICT 1, total population

Based on the available data, it is assumed for the benefit assessment that insulin therapy was sufficiently optimized in the lead-in phase or in the further course of the study and that the ACT was therefore adequately implemented in the studies DEPICT 1 and DEPICT 2. The consequences of the insulin reduction in the comparator arm are considered in the assessment of the outcome-specific risk of bias.

Treatment duration in both studies was 52 weeks and was divided into a 24-week short-term therapy followed by a 28-week long-term therapy. The follow-up observation period was 4 weeks in each study. The assessment was conducted based on the results after 52 weeks.

Primary outcome in both studies was the change in HbA1c from baseline at week 24. Patient-relevant secondary outcomes were all-cause mortality and outcomes on morbidity as well as on AEs including episodes of hypoglycaemia and DKA. Outcomes on health-related quality of life were not investigated in the DEPICT studies.

Relevant subpopulation

In accordance with the approved therapeutic indication, the subpopulation within the studies DEPICT 1 and DEPICT 2 relevant for the benefit assessment comprises only patients with inadequately controlled type 1 diabetes mellitus as an adjunct to insulin with BMI ≥ 27 kg/m² [3].

In accordance with the approved therapeutic indication, the company presented results for the relevant subpopulation from both studies (patients with BMI ≥ 27 kg/m²), which were the basis for the present benefit assessment. The relevant subpopulation comprised about 58% (N = 299) of the patients of the total population in the DEPICT 1 study and about 48% (N = 262) in the DEPICT 2 study.

Table 8 shows the characteristics of the relevant subpopulation of the patients included in the studies DEPICT 1 and DEPICT 2.

Table 8: Characteristics of the study populations – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin

Study Characteristics Category	DEPICT 1		DEPICT 2	
	Dapagliflozin + insulin	Placebo + insulin	Dapagliflozin + insulin	Placebo + insulin
	Na = 145	Na = 154	Na = 127	Na = 135
Age [years], mean (SD)	46 (13)	45 (13)	43 (13)	45 (13)
Age classes, n (%)				
< 35 years	35 (24)	37 (24)	37 (29)	35 (26)
35 to < 50 years	49 (34)	56 (36)	44 (35)	45 (33)
≥ 50 years	61 (42)	61 (40)	46 (36)	55 (41)
Sex [F/M], %	57/43	47/53	60/40	54/46
Ethnicity, n (%)				
Caucasian	138 (95.2)	150 (97.4)	110 (86.6)	114 (84.4)
Other[b]	7 (4.8[c])	4 (2.6[c])	17 (13.4[c])	21 (15.6[c])
Body weight (kg), mean (SD)	90.90 (17.36)	94.05 (16.19)	91.59 (14.13)	91.57 (16.83)
BMI (kg/m²), mean (SD)	31.97 (5.16)	31.94 (4.06)	31.52 (4.08)	31.76 (4.45)
BMI (kg/m²), n (%)				
≤ 30	63 (43.4)	65 (42.2)	62 (48.8)	54 (40.0)
> 30	82 (56.6)	89 (57.8)	65 (51.2)	81 (60.0)
Renal function GFR (mL/min/1.73 m²), n (%)				
< 60	7 (4.8)	13 (8.4)	8 (6.3)	5 (3.7)
≥ 60 to < 90	82 (56.6)	73 (47.4)	60 (47.2)	73 (54.1)
≥ 90	56 (38.6)	68 (44.2)	59 (46.5)	57 (42.2)
Geographical region, n (%)				
North America	43 (29.7)	52 (33.8)	62 (48.8)	57 (42.2)
Latin America	7 (4.8)	6 (3.9)	16 (12.6)	13 (9.6)
Europe	81 (55.9)	94 (61.0)	36 (28.3)	49 (36.3)
Asia/Pacific	14 (9.7)	2 (1.3)	13 (10.2)	16 (11.9)
Disease duration: time between first diagnosis and randomization [years], mean (SD)	21.43 (12.10)	23.09 (12.43)	20.10 (10.30)	21.25 (11.68)
Baseline HbA1c, mean (SD)	8.51 (0.67)	8.42 (0.59)	8.35 (0.58)	8.39 (0.64)
HbA1c classes, n (%)				
< 8.0%	32 (22.1)	41 (26.6)	36 (28.3)	43 (31.9)
≥ 8.0% to < 9.0%	80 (55.2)	83 (53.9)	73 (57.5)	64 (47.4)
≥ 9.0%	33 (22.8)	30 (19.5)	18 (14.2)	28 (20.7)
Baseline insulin (IU/kg), mean (SD)	0.79 (0.64)	0.77 (0.28)	0.77 (0.28)	0.75 (0.25)
Method of insulin administration, n (%)				
MDI	83 (57.2)	89 (57.8)	69 (54.3)	79 (58.5)
CSII	62 (42.8)	65 (42.2)	58 (45.7)	56 (41.5)

(continued)

Table 8: Characteristics of the study populations – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin (continued)

Study Characteristics Category	DEPICT 1		DEPICT 2	
	Dapagliflozin + insulin	Placebo + insulin	Dapagliflozin + insulin	Placebo + insulin
	N[a] = 145	N[a] = 154	N[a] = 127	N[a] = 135
CGM use, n (%)				
Yes	42 (29.0)	46 (29.9)	46 (36.2)	35 (25.9)
No	103 (71.0)	108 (70.1)	81 (63.8)	100 (74.1)
Treatment discontinuation, n (%)	ND	ND	ND	ND
Study discontinuation, n (%)	ND	ND	ND	ND

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Including: black, Asian and other.
c: Institute's calculation.

BMI: body mass index; CGM: continuous glucose monitoring; CSII: continuous subcutaneous insulin infusion (insulin pump therapy); F: female; HbA1c: haemoglobin A1c; IU: international units; M: male; MDI: multiple daily injections; n: number of patients in the category; N: number of randomized patients of the relevant subpopulation; ND: no data; RCT. randomized controlled trial; SD: standard deviation; vs. versus

The patient characteristics for the relevant subpopulations are largely comparable both between the 2 treatment arms of the studies DEPICT 1 and DEPICT 2 and between the studies themselves. The mean age of the patients in both studies was about 45 years. The number of men and women was about the same in both studies; most patients were of Caucasian origin (DEPICT 1: about 95%, DEPICT 2: about 85%). Most patients were from Europe (DEPICT 1: about 60%, DEPICT 2: about 30%) and North America (DEPICT 1: about 30%, DEPICT 2: about 45%). In both studies, the average body weight was slightly over 90 kg and the average duration of the disease was over 20 years. The mean HbA1c value at baseline in both studies was about 8.5% and the mean initial insulin dose in both studies was about 0.77 IU/kg. In both studies, about 57% of the patients in both arms were treated with multiple daily injections of insulin (at least 3 times a day), and the remaining 43% received insulin pump therapy. In about one third of the patients in both studies, blood glucose levels were monitored using CGM. For the remaining 70% of the patients in the study without CGM, it remains unclear whether further optimization of insulin therapy would have been possible through the use of CGM. Overall, the evidence suggests a positive influence of CGM on the treatment of type 1 diabetes mellitus [4].

Some of the patients included in the DEPICT studies had a glomerular filtration rate (GFR) of < 60 mL/min, although, according to the SPC, treatment with dapagliflozin should not be initiated in these patients [3]. The company did not consider these patients when determining the patient numbers (see Chapter 3 of the full dossier assessment). It is unclear why the company did not take this into account when forming the relevant subpopulations for the benefit assessment. Since this only affected about 5.5% of the patients in the dapagliflozin arms of the 2 studies, there are no consequences for the benefit assessment.

There was no information on treatment and study discontinuations for the relevant subpopulation. Based on the available information for the total populations, it is not assumed that there was a relevant proportion of patients who discontinued treatment or the study in the subpopulation. Overall, a total of 84.4% (DEPICT 1) and 82.3% (DEPICT 2) of the randomized patients of the relevant treatment arms in the total population completed the study.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
DEPICT 1	Yes[a]	Yes	Yes	Yes	Yes	Yes	Low
DEPICT 2	Yes	Yes	Yes	Yes	Yes	Yes	Low

a: Initial randomization error in the first 55 patients due to a system error. These were excluded only for the efficacy analyses.
RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for both studies. This concurs with the company's assessment.

Limitations in the outcome-specific assessment of the risk of bias resulting from the randomization error for the DEPICT 1 study are described in Section 2.4.2 and in Section 2.7.4.2 of the full dossier assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - change in the mean HbA1c value (with the generally used relevance limit of 0.3 percentage points) and individual HbA1c reduction ≥ 0.5 percentage points as sufficiently valid surrogate for microvascular secondary complications
  - health status measured with the EQ-5D VAS
  - HFS-II Worry subscale
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - symptomatic confirmed hypoglycaemia (plasma glucose ≤ 54 mg/dL)
  - symptomatic confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dL)
  - severe hypoglycaemia
  - serious hypoglycaemia (PT, SAE)
  - diabetic ketoacidosis
  - genital infections (recorded with the company's prespecified PT list)
  - urinary tract infections (recorded with the company's prespecified PT list)
  - if applicable, further specific AEs/SAEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.4.3.2 of the full dossier assessment). The results on the change in body weight used by the company are only presented as supplementary information in this assessment.

Table 10 shows for which outcomes data were available in the studies included.

Table 10: Matrix of outcomes – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin

Study	Outcomes																
	All-cause mortality	**Change in HbA1c**	**HbA1c reduction ≥ 0.5 percentage points**	**Health status (EQ-5D VAS)**	**HFS-II (Worry subscale)**	**Health-related quality of life**	**SAEs**	**Discontinuation due to AEs**	**Symptomatic confirmed hypoglycaemia (plasma glucose ≤ 54 mg/dL)**	**Symptomatic confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dL)**	**Severe hypoglycaemia**	**Serious hypoglycaemia (PT, SAE)**	**Diabetic ketoacidosis**	**Genital infections[a]**	**Urinary tract infections[a]**	**Gastrointestinal disorders (SOC, AE)**	**Further specific SAEs**
DEPICT 1	Y	Y	Y	Y	No[b]	No[b]	Y	No[c]	No[d]	Y	No[e]	Y	(Y)[f]	Y	Y	Y	No[g]
DEPICT 2	Y	Y	Y	Y	Y	No[b]	Y	No[c]	No[d]	Y	No[e]	Y	(Y)[f]	Y	Y	Y	No[g]

a: Recorded with the company's prespecified PT list.
b: Outcome not recorded.
c: Discrepant information in the company's dossier (for reasons, see Section 2.7.4.3.2 of the full dossier assessment).
d: The company presents no analyses with the plasma glucose threshold of 54 mg/dL.
e: The operationalization presented by the company is unsuitable for an adequate representation of severe hypoglycaemia (for reasons, see Section 2.7.4.3.2 of the full dossier assessment).
f: The company only presents data on part of the observed DKAs (DKAs rated as definite DKAs by an independent adjudication committee). A complete assessment of the DKAs in the studies is not possible based on this operationalization (for reasons, see Section 2.7.4.3.2 of the full dossier assessment).
g: The results for SAEs at PT and SOC level are not available for the relevant subpopulation, so that an assessment of potentially relevant specific SAEs based on the study results is not possible.

AE: adverse event; DKA: diabetic ketoacidosis; EQ-5D: European Quality of Life-5 Dimensions; HbA1c: haemoglobin A1c; HFS-II: Hypoglycemia Fear Survey II; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus; Y: yes

2.4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin

Study		Outcomes																
	Study level	All-cause mortality	Change in HbA1c	HbA1c reduction ≥ 0.5 percentage points	Health status (EQ-5D VAS)	HFS-II (Worry subscale)	Health-related quality of life	SAEs	Discontinuation due to AEs	Symptomatic confirmed hypoglycaemia (plasma glucose ≤ 54 mg/dL)	Symptomatic confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dL)	Severe hypoglycaemia	Serious hypoglycaemia (PT, SAEs)	Diabetic ketoacidosis	Genital infections[a]	Urinary tract infections[a]	Gastrointestinal disorders (SOC, AE)	Further specific SAEs
DEPICT 1	L	H[b]	H[c]	H[c]	H[d]	–[e]	–[e]	H[b]	–[f]	–[g]	H[b, c]	–[h]	H[b, c]	H[b, i]	H[b]	H[b]	H[b]	–[j]
DEPICT 2	L	L	H[c]	H[c]	H[d]	H[d]	–[e]	L	–[f]	–[g]	H[c]	–[h]	H[c]	L[i]	L	L	L	–[j]

a: Recorded with the company's prespecified PT list.
b: 55 wrongly randomized patients were considered in the analysis (for reasons, see Section 2.7.4.2 of the full dossier assessment).
c: Due to the recommended reduction in insulin dose by up to 20% at the start of treatment, hypoglycaemic episodes are potentially underestimated and HbA1c values potentially overestimated in the comparator arm.
d: High proportion of patients not included in the analysis (> 10%) and large difference between the treatment groups (> 5 percentage points).
e: Outcome not recorded.
f: Discrepant information in the company's dossier (for reasons, see Section 2.7.4.3.2 of the full dossier assessment).
g: The company presents no analyses with the plasma glucose threshold of 54 mg/dL.
h: The operationalization presented by the company is unsuitable for a representation of severe hypoglycaemia (for reasons, see Section 2.7.4.3.2 of the full dossier assessment).
i: The assessment of the risk of bias refers to the operationalization of definite DKAs chosen by the company.
j: The results for SAEs at PT and SOC level are not available for the relevant subpopulation, so that an assessment of potentially relevant specific SAEs based on the study results is not possible.
AE: adverse event; DKA: diabetic ketoacidosis; EQ-5D: European Quality of Life-5 Dimensions; H: high; HbA1c: haemoglobin A1c; HFS-II: Hypoglycemia Fear Survey II; L: low; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias is described (if meaningful) jointly for the two studies DEPICT 1 and DEPICT 2.

For the DEPICT 2 study, the risk of bias for the results on the outcome "all-cause mortality" was rated as low, which concurs with the company.

In contrast to the assessment of the company, the risk of bias of the results of both operationalizations on the outcome "glycaemic control" (change in HbA1c and HbA1c reduction by ≥ 0.5 percentage points) was rated as high in both studies. This was due to the reduction in insulin dose by up to 20% at the start of treatment. This reduction was also recommended in the comparator arm, in which there should have been an optimal insulin dose after corresponding insulin adjustment in the lead-in phase. Consequently, HbA1c may have been increased by the inadequate reduction of the insulin dose, leading to potential overestimation of the effect for the outcome "HbA1c" in the comparator arm and to potential underestimation of the rates of hypoglycaemic episodes in the comparator arm.

The risk of bias of the results of the morbidity outcomes, measured with the HFS-II scale, and of health status, measured with the EQ-5D VAS, was rated as high due to missing values in both studies. This deviates from the assessment of the company, which rated the risk of bias of the results for these outcomes as low.

The DEPICT 1 study had the problem that there was a randomization error for the first 55 patients included. The company, however, excluded these wrongly randomized patients only for the evaluation of efficacy outcomes without further justification. A high risk of bias was therefore assumed in the DEPICT 1 study for all outcomes of the categories of mortality and side effects. This partly deviates from the assessment of the company, which only rated the results of the outcomes on AEs by SOC as having a high risk of bias, but with a different justification (see Section 2.7.4.2 of the full dossier assessment).

For the DEPICT 2 study, the risk of bias of the results on all outcomes of the category of side effects (except hypoglycaemic episodes, see above) was rated as low. This partly deviates from the assessment of the company, which rated the results of the outcomes on AEs by SOC as having a high risk of bias.

Further information on the assessment of the risk of bias can be found in Section 2.7.4.2 of the full dossier assessment.

2.4.3 Results

Table 12, Table 13 and Table 14 summarize the results on the comparison of dapagliflozin + insulin with placebo + insulin in patients with type 1 diabetes mellitus. Forest plots of the meta-analyses calculated by the Institute can be found in Appendix A of the full dossier assessment. Tables with the common AEs can be found in Appendix C of the full dossier assessment. Information on the common SAEs was not available for the relevant subpopulation, but is required for the present benefit assessment (see Section 2.7.4.3.2 of the full dossier assessment). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Data for the total study period (52 weeks) were included in the benefit assessment (see Section 2.7.4.3.3 of the full dossier assessment).

Table 12: Results (mortality, side effects) – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin

Outcome category Outcome Study	Dapagliflozin + insulin		Placebo + insulin		Dapagliflozin + insulin vs. placebo + insulin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality					
DEPICT 1	159	0 (0)	154	0 (0)	–
DEPICT 2	127	0 (0)	135	0 (0)	–
Total					–
Side effects					
AEs (supplementary information)					
DEPICT 1	*159*	*122 (76.7)*	*154*	*115 (74.7)*	–
DEPICT 2	*127*	*105 (82.7)*	*135*	*102 (75.6)*	–
SAEs					
DEPICT 1	159	19 (11.9)	154	16 (10.4)	1.15 [0.61; 2.15]; 0.662
DEPICT 2	127	13 (10.2)	135	9 (6.7)	1.54 [0.68; 3.47]; 0.302
Total[a]					1.29 [0.79; 2.13]; 0.310
Discontinuation due to AEs					
DEPICT 1	Discrepant information in the company's dossier[b]				–
DEPICT 2	Discrepant information in the company's dossier[b]				–
Total					–
Symptomatic confirmed hypoglycaemia (plasma glucose ≤ 54 mg/dL)					
DEPICT 1	No data presented				–
DEPICT 2	No data presented				–
Total					–
Symptomatic confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dL)					
DEPICT 1	159	128 (80.5)	154	114 (74.0)	1.09 [0.96; 1.23]; 0.174
DEPICT 2	127	112 (88.2)	135	110 (81.5)	1.08 [0.98; 1.20]; 0.131
Total[c]					1.09 [1.002; 1.18]; 0.045
Severe hypoglycaemia					
DEPICT 1	No usable data[d]				–
DEPICT 2	No usable data[d]				–
Total					–
Serious hypoglycaemia (PT, SAE)					
DEPICT 1	159	3 (1.9)	154	1 (0.6)	2.91 [0.31; 27.63]; 0.353
DEPICT 2	127	2 (1.6)	135	1 (0.7)	2.13 [0.20; 23.16]; 0.536
Total[a]					2.53 [0.49; 12.91]; 0.266

(continued)

Table 12: Results (mortality, side effects) – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin (continued)

Outcome category Outcome Study	Dapagliflozin + insulin N	 Patients with event n (%)	Placebo + insulin N	 Patients with event n (%)	Dapagliflozin + insulin vs. placebo + insulin RR [95% CI]; p-value
Side effects					
DKAs (all)[e]	No data for the relevant subpopulation				–
DKAs (possible)[e]	No data for the relevant subpopulation				–
DKAs (definite)[e]					
DEPICT 1	159	2 (1.3)	154	2 (1.3)	0.97 [0.14; 6.79]; 0.974
DEPICT 2	127	3 (2.4)	135	1 (0.7)	3.19 [0.34; 30.26]; 0.312
Total[a]					1.68 [0.41; 6.98]; 0.473
Genital infections[f]					
DEPICT 1	159	28 (17.6)	154	6 (3.9)	4.52 [1.93; 10.61]; < 0.001
DEPICT 2	127	15 (11.8)	135	6 (4.4)	2.66 [1.06; 6.64]; 0.036
Total[c]					3.61 [1.94; 6.72]; < 0.001
Urinary tract infections[f]					
DEPICT 1	159	16 (10.1)	154	10 (6.5)	1.55 [0.73; 3.31]; 0.258
DEPICT 2	127	16 (12.6)	135	10 (7.4)	1.70 [0.80; 3.61]; 0.166
Total[c]					1.62 [0.95; 2.77]; 0.075
Gastrointestinal disorders (SOC, AE)					
DEPICT 1	159	28 (17.6)	154	16 (10.4)	1.69 [0.96; 3.01]; 0.071
DEPICT 2	127	38 (29.9)	135	21 (15.6)	1.92 [1.20; 3.09]; 0.007
Total[c]					1.82 [1.26; 2.63]; 0.001
Specific SAEs	No usable data[g]				

a: Pooled analysis.
b: The information on the number of events for this outcome is contradictory within the company's dossier. The discrepant results are shown in Table 24, Appendix D, of the full dossier assessment as supplementary information.
c: Institute's calculation, meta-analysis with fixed effect (Mantel/Haenszel).
d: The operationalization presented by the company is unsuitable for an adequate representation of severe hypoglycaemia (for reasons, see Section 2.7.4.3.2 of the full dossier assessment).
e: The company presented only data on definite DKAs. A complete assessment of the DKAs in the studies is not possible based on this operationalization (for reasons, see Section 2.7.4.3.2 of the full dossier assessment).
f: Recorded with the company's prespecified PT list.
g: The results for SAEs at PT and SOC level are not available for the relevant subpopulation.
AE: adverse event; CI: confidence interval; DKA: diabetic ketoacidosis; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 13: Results (morbidity [HbA1c]) – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin

Outcome category Outcome Study	Dapagliflozin + insulin			Placebo + insulin			Dapagliflozin + insulin vs. placebo + insulin
	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	MD [95% CI]; p-value[b]
Morbidity							
Change in HbA1c[c]							
DEPICT 1	144	8.50 (0.67)	−0.34 (0.08)	153	8.42 (0.59)	0.08 (0.09)	−0.42 [−0.63; −0.22]; ND
DEPICT 2	126	8.35 (0.58)	−0.13 (0.07)	133	8.37 (0.63)	0.11 (0.07)	−0.24 [−0.42; −0.06]; ND
Total							−0.33 [−0.47; −0.19]; < 0.001
	N	Patients with event n (%)		N	Patients with event n (%)		RR [95% CI]; p-value
HbA1c reduction ≥ 0.5 percentage points[c]							
DEPICT 1	145	65 (44.8)		153	38 (24.8)		1.80 [1.30; 2.51]; < 0.001
DEPICT 2	126	48 (38.1)		133	24 (18.0)		2.11 [1.38; 3.23]; < 0.001
Total[d]							1.92 [1.48; 2.50]; < 0.001

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at the start of the study may be based on other patient numbers.
b: MMRM with treatment, baseline HbA1c, week, stratum, treatment x week, baseline HbA1c x week; for pooled analysis additionally the model terms study, treatment x study, week x study and treatment x week x study.
c: Sufficiently valid surrogate for microvascular late complications.
d: Institute's calculation, meta-analysis with fixed effect (Mantel/Haenszel).

CI: confidence interval; HbA1c: haemoglobin A1c; MD: mean difference; MMRM: mixed-effects model repeated measures; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; vs.: versus

Table 14: Results (morbidity, health-related quality of life) – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin

Outcome category Outcome Study	Dapagliflozin + insulin			Placebo + insulin			Dapagliflozin + insulin vs. placebo + insulin
	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	MD [95% CI]; p-value[b]
Morbidity							
EQ-5D VAS[c]							
DEPICT 1	143	76.50 (16.11)	3.84 (1.22)	144	76.42 (16.45)	1.25 (1.30)	2.59 [−0.33; 5.51]
DEPICT 2	118	65.21 (30.13)	10.76 (2.50)	116	69.89 (24.88)	4.11 (2.55)	6.64 [0.70; 12.59]
Total							4.87 [1.70; 8.04]; 0.003 Hedges' g [95% CI]: 0.24 [0.06; 0.42]
HFS-II (Worry subscale)[d]							
DEPICT 1	Outcome not recorded						
DEPICT 2	118	16.72 (11.89)	−0.24 (1.07)	115	16.52 (12.67)	−0.03 (1.11)	−0.21 [−2.72; 2.30]; 0.870
Supplementary information:							
Body weight (kg)							
DEPICT 1	145	90.90 (17.36)	−3.05 (0.378)		94.05 (16.19)	0.02 (0.39)	−3.06 [−4.10; −2.02]; < 0.001
DEPICT 2	127	91.59 (14.13)	−3.83 (0.44)		91.57 (16.83)	0.92 (0.46)	−4.71 [−5.89; −3.51]; < 0.001
Total							−3.89 [−4.67; −3.11]; < 0.001
Health-related quality of life	Outcome not recorded						

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at the start of the study may be based on other patient numbers.
b: MMRM with treatment, baseline HbA1c, week, stratum, treatment x week, baseline HbA1c x week; for pooled analysis additionally the model terms study, treatment x study, week x study and treatment x week x study.
c: A positive change from the start until the end of the study indicates improvement; a positive effect estimation indicates an advantage for the intervention.
d: A positive change from the start until the end of the study indicates deterioration (greater fear of the patient regarding hypoglycaemic episodes); a negative effect estimation indicates an advantage of the intervention.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HbA1c: haemoglobin A1c; HFS-II: Hypoglycemia Fear Survey II; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Based on the available data, at most proof, e.g. of an added benefit, can be determined for the outcomes "all-cause mortality", "SAEs" and the specific AEs (exception: hypoglycaemic episodes). Due to the high risk of bias in both studies, at most an indication, e.g. of an added benefit, can be determined for the following outcomes: health status (EQ-5D VAS), HbA1c as sufficiently valid surrogate for microvascular late complications, and hypoglycaemic episodes (see Section 2.7.4.2 of the full dossier assessment). Since the outcome "HFS-II (Worry subscale)" was only recorded in the DEPICT 2 study, and there was additionally a high risk of bias, at most a hint can be determined for this outcome.

Mortality

All-cause mortality

In both studies, no deaths occurred after 52 weeks. Hence, there was no statistically significant difference between dapagliflozin and insulin versus placebo and insulin for the outcome "all-cause mortality". This resulted in no hint of an added benefit of dapagliflozin and insulin versus insulin; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

HbA1c value as sufficiently valid surrogate for microvascular late complications

Two different operationalizations were used for the HbA1c value and considered jointly in the derivation of the added benefit.

Change in HbA1c

The meta-analysis produced a statistically significant difference in favour of dapagliflozin and insulin versus placebo and insulin for the change in HbA1c. However, the 95% CI of the effect is not completely outside the generally used relevance limit of 0.3 percentage points, which is also used by the regulatory authorities to assess a clinically relevant group difference [5-7]. It can therefore not be inferred that the effect was relevant.

HbA1c reduction ≥ 0.5 percentage points

The meta-analysis produced a statistically significant difference in favour of dapagliflozin and insulin versus placebo and insulin for the responder analysis HbA1c reduction ≥ 0.5 percentage points.

Summary

In summary, a relevant difference was shown in the reduction of HbA1c value in favour of dapagliflozin and insulin versus placebo and insulin on the basis of the responder analysis (reduction by 0.5 percentage points). Under consideration of the mean change in HbA1c, an irrelevant group difference cannot be excluded, but the direction of the effect is consistent with the results of the responder analysis. Overall, there is an indication of an added benefit of

dapagliflozin and insulin in comparison with insulin for the outcome “HbA1c” (as sufficiently valid surrogate outcome for microvascular late complications).

This concurs with the company’s assessment.

Health status (EQ-5D VAS)

The meta-analysis produced a statistically significant difference in favour of dapagliflozin and insulin versus placebo and insulin for the outcome “health status” measured with the EQ-5D VAS. However, the 95% CI of the standardized mean difference (Hedges’ g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect was relevant. This resulted in no hint of an added benefit of dapagliflozin and insulin in comparison with insulin; an added benefit is therefore not proven.

This concurs with the company’s assessment.

HFS-II (Worry subscale)

The outcome “HFS-II (Worry subscale)” was only recorded in the DEPICT 2 study. The study showed no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of dapagliflozin and insulin in comparison with insulin for the outcome “HFS-II (Worry subscale)”; an added benefit is therefore not proven.

This concurs with the company’s assessment.

Health-related quality of life

No outcomes of the outcome category “health-related quality of life” were investigated in the studies DEPICT 1 and DEPICT 2. This resulted in no hint of an added benefit of dapagliflozin and insulin in comparison with insulin in this outcome category; an added benefit is therefore not proven.

This concurs with the company’s assessment.

Side effects

Serious adverse events

The meta-analysis showed no statistically significant difference between dapagliflozin and insulin versus placebo and insulin for the outcome “SAEs”. This resulted in no hint of greater or lesser harm from dapagliflozin and insulin versus insulin; greater or lesser harm is therefore not proven.

This concurs with the company’s assessment.

Discontinuation due to adverse events

The information on the number of events for this outcome is partly contradictory within the company’s dossier (Module 4 A or Module 5, see Section 2.7.4.3.2 of the full dossier

assessment). The discrepant results are shown in Table 24, Appendix D, of the full dossier assessment as supplementary information. From the available documents, it is not possible to determine which event rates are correct. However, both event rates showed no statistically significant difference between dapagliflozin and insulin versus placebo and insulin in the meta-analysis. This resulted in no hint of greater or lesser harm from dapagliflozin and insulin versus insulin; greater or lesser harm is therefore not proven.

The result concurs with the assessment of the company, which used the event rates presented in Module 4 A of its dossier for its assessment.

Symptomatic, confirmed hypoglycaemia

For the outcome "symptomatic confirmed hypoglycaemia", results were only available for the plasma glucose threshold of 70 mg/dL. There were no analyses on the threshold value of 54 mg/dL.

The meta-analysis for symptomatic, confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dL) showed a statistically significant difference to the disadvantage of dapagliflozin and insulin. This effect was no more than marginal, however. This resulted in no hint of greater or lesser harm from dapagliflozin and insulin versus insulin; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Severe hypoglycaemia

The operationalization presented by the company is unsuitable for a representation of severe hypoglycaemia (for reasons, see Section 2.7.4.3.2 of the full dossier assessment).

This deviates from the approach of the company, which considered the results of the operationalization it had chosen and derived no greater or lesser harm for this outcome.

Serious hypoglycaemia (PT, SAE)

The meta-analysis showed no statistically significant difference between dapagliflozin and insulin versus placebo and insulin for the outcome "serious hypoglycaemia". This resulted in no hint of greater or lesser harm from dapagliflozin and insulin versus insulin; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Diabetic ketoacidosis

For the outcome "diabetic ketoacidosis", the company only presented results for the category "definite DKAs". The meta-analysis here showed no statistically significant difference between dapagliflozin and insulin versus placebo and insulin. Since relevant information on DKAs is

missing, no final conclusion can be drawn based on the data on definite DKAs alone (see also Section 2.7.4.3.2 of the full dossier assessment.

This deviates from the approach of the company, which considered only the analysis of "definite DKAs" in the assessment and derived no greater or lesser harm for this outcome.

Genital infections

The meta-analysis showed a statistically significant difference to the disadvantage of dapagliflozin and insulin versus placebo and insulin for the outcome "genital infections". This resulted in proof of greater harm from dapagliflozin and insulin in comparison with insulin.

This deviates from the assessment of the company insofar as the company only derived a marginal disadvantage of dapagliflozin and insulin without providing a concrete probability.

Urinary tract infections

The meta-analysis showed no statistically significant difference between dapagliflozin and insulin versus placebo and insulin for the outcome "urinary tract infections". This resulted in no hint of greater or lesser harm from dapagliflozin and insulin versus insulin; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Gastrointestinal disorders (SOC, AE)

The meta-analysis showed a statistically significant difference to the disadvantage of dapagliflozin and insulin versus insulin for the outcome "gastrointestinal disorders". This resulted in proof of greater harm from dapagliflozin and insulin in comparison with insulin.

This deviates from the assessment of the company insofar as the company only derived a marginal disadvantage of dapagliflozin and insulin without providing a concrete probability.

Specific serious adverse events

The results for SAEs at PT and SOC level were not available for the relevant subpopulation, so that an assessment of potentially relevant specific SAEs based on the study results was not possible.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present benefit assessment:

- age (< 35 years/≥ 35 years and < 50 years/≥ 50 years)
- sex (male/female)
- region (North America/Latin America/Europe/Asia)
- baseline HbA1c (< 9.0%/≥ 9.0%)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. For binary data, there must be 10 events in at least 1 subgroup. Subgroup analyses were available for all outcomes included.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 15 presents the subgroup results of dapagliflozin and insulin in comparison with placebo and insulin.

Table 15: Subgroups (side effects) – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin

Outcome **Characteristic**	**Dapagliflozin + insulin**		**Placebo + insulin**		**Dapagliflozin + insulin vs. placebo + insulin**	
Study **Subgroup**	**N**	**Patients with event** **n (%)**	**N**	**Patients with event** **n (%)**	**RR [95% CI]**	**p-value**
SAEs						
Region						
DEPICT 1						
North America	51	10 (19.6)	52	2 (3.8)	5.10 [1.17; 22.13]	0.030
Latin America	7	1 (14.3)	6	0 (0)	2.63 [0.13; 54.64]	0.533
Europe	87	5 (5.7)	94	14 (14.9)	0.39 [0.15; 1.03]	0.057
Asia/Pacific	14	3 (21.4)	2	0 (0)	1.40 [0.09; 20.65]	0.806
DEPICT 2						
North America	62	6 (9.7)	57	4 (7.0)	1.38 [0.41; 4.64]	0.604
Latin America	16	3 (18.8)	13	1 (7.7)	2.44 [0.29; 20.75]	0.415
Europe	36	3 (8.3)	49	4 (8.2)	1.02 [0.24; 4.28]	0.978
Asia/Pacific	13	1 (7.7)	16	0 (0)	3.64 [0.16; 82.62]	0.417
Total					Interaction:	0.041[a]
North America					2.58 [1.05; 6.32]	0.039
Latin America					2.50 [0.43; 14.37]	0.305
Europe					0.51 [0.23; 1.13]	0.098
Asia/Pacific					2.19 [0.30; 15.98]	0.440

a: Institute's calculation, meta-analysis with fixed effect (Mantel/Haenszel), p-value from Q test for heterogeneity.
CI: confidence interval; n: number of patients with (at least) one event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Side effects

Serious adverse events

The meta-analysis showed an effect modification by the characteristic "region" for the outcome "SAEs". There was a statistically significant difference to the disadvantage of dapagliflozin and insulin in comparison with placebo and insulin for patients from North America, whereas there was no statistically significant difference between the treatment groups for the remaining regions (Latin America, Europe, and Asia/Pacific).

Since there was no uniform and clearly interpretable picture for this outcome between the studies, the effect modification by the characteristic "region" for this outcome was not further considered. This concurs with the assessment of the company, which described the effect modification and classified it as not relevant to the conclusion.

2.5 Probability and extent of added benefit

The derivation of probability and extent of the added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 16).

It could not always be inferred from the dossier whether the outcomes considered in the present benefit assessment were serious/severe or non-serious/non-severe; moreover, the company's assessment was not always followed.

Determination of the outcome category for the outcome "HbA1c" (as sufficiently valid surrogate for the patient-relevant outcome "microvascular late complications")

The HbA1c value was used as sufficiently valid surrogate for the patient-relevant outcome "microvascular late complications" (see Section 2.7.4.3.2 of the full dossier assessment). Since microvascular late complications (e.g. blindness, amputations) are mostly serious, the outcome was allocated to the outcome category of severe/serious symptoms/late complications. This concurs with the company's assessment.

Determination of the outcome category for selected side effects

The specific AEs "genital infections" (company's prespecified PT list) and gastrointestinal disorders (SOC, AE) were allocated to the category of non-serious/non-severe side effects as the AEs included in these outcomes were mostly categorized as non-serious.

Table 16: Extent of added benefit at outcome level: dapagliflozin + insulin vs. placebo + insulin

Outcome category **Outcome**	**Dapagliflozin + insulin vs. placebo + insulin** **Proportion of events (%) or mean** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Change in HbA1c[c]	−0.34 to −0.13 vs. 0.08 to 0.11[d] MD: −0.33 [−0.47; −0.19]; < 0.001	Outcome category: "serious/severe symptoms/late complications" added benefit, extent: "non-quantifiable"
HbA1c reduction ≥ 0.5 percentage points[c]	38.1–44.8% vs. 18.0–24.8%[d] RR: 1.92 [1.48; 2.50]; < 0.001 RR[e]: 0.52 [0.40; 0.68] probability: "indication"	
EQ-5D VAS	3.84–10.76 vs. 1.25–4.11[d] MD: 4.87 [1.70; 8.04]; 0.003 Hedges' g: 0.24 [0.06; 0.42][f]	Lesser benefit/added benefit not proven
HFS-II (Worry subscale)	−0.24 vs. −0.03 MD: −0.21 [−2.72; 2.30]; 0.870	Lesser benefit/added benefit not proven
Health-related quality of life		
	No data presented	Lesser benefit/added benefit not proven
Side effects		
SAEs	10.2–11.9% vs. 6.7–10.4%[d] RR: 1.29 [0.79; 2.13]; 0.310	Greater/lesser harm not proven
Discontinuation due to AEs	Discrepant information in the company's dossier[g]	Greater/lesser harm not proven
Symptomatic confirmed hypoglycaemia (plasma glucose ≤ 54 mg/dL)	No data presented	
Symptomatic confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dL)	80.5–88.2% vs. 74.0–81.5%[d] RR: 1.09 [1.002; 1.18]; 0.045 RR[e]: 0.92 [0.85; 0.998]	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ greater/lesser harm not proven[i]
Severe hypoglycaemia	No usable data[h]	
Serious hypoglycaemia (PT, SAE)	1.6–1.9% vs. 0.6–0.7%[d] RR: 2.53 [0.49; 12.91]; 0.266	Greater/lesser harm not proven
DKAs (total)	No usable data	
DKAs (definite)[j]	1.3–2.4% vs. 0.7–1.3%[d] RR: 1.68 [0.41; 6.98]; 0.473	Greater/lesser harm not proven

(continued)

Table 16: Extent of added benefit at outcome level: dapagliflozin + insulin vs. placebo + insulin (continued)

Outcome category **Outcome**	**Dapagliflozin + insulin vs. placebo + insulin** **Proportion of events (%) or mean** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
Genital infections	11.8–17.6% vs. 3.9–4.4%[d] RR: 3.61 [1.94; 6.72]; < 0.001 RR[e]: 0.28 [0.15; 0.52] probability: "proof"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm extent: "considerable"
Urinary tract infections	10.1–12.6% vs. 6.5–7.4%[d] RR: 1.62 [0.95; 2.77]; 0.075	Greater/lesser harm not proven
Gastrointestinal disorders (SOC, AE)	17.6–29.9% vs. 10.4–15.6%[d] RR: 1.82 [1.26; 2.63]; 0.001 RR[e]: 0.55 [0.38; 0.79]; probability: "proof"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm extent: "considerable"
Specific SAEs	No usable data[k]	

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval (CI_u).
c: Sufficiently valid surrogate for microvascular late complications.
d: Minimum and maximum proportions of events or mean changes in each treatment arm in the included studies.
e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
g: The information on the number of events for this outcome is contradictory within the dossier. The discrepant results are shown in Table 24, Appendix D, of the full dossier assessment as supplementary information.
h: The operationalization presented by the company is unsuitable for an adequate representation of severe hypoglycaemia (for reasons, see Section 2.7.4.3.2 of the full dossier assessment).
i: The extent of the effect in this non-serious/non-severe outcome is no more than marginal.
j: The company presented only data on definite DKAs. A complete assessment of the DKAs in the studies is not possible based on this operationalization (for reasons, see Section 2.7.4.3.2 of the full dossier assessment).
k: The results for SAEs at PT and SOC level are not available for the relevant subpopulation, so that an assessment of potentially relevant specific SAEs based on the study results is not possible.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; DKA: diabetic ketoacidosis; EQ-5D: European Quality of Life-5 Dimensions; HbA1c: haemoglobin A1c; HFS-II: Hypoglycemia Fear Survey II; MD: mean difference (change from baseline); ND: no data; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 17: Positive and negative effects from the assessment of dapagliflozin + insulin in comparison with placebo + insulin

Positive effects	**Negative effects**
Serious/severe symptoms/late complications HbA1c[a]: indication of an added benefit – extent "non-quantifiable"	Non-serious/non-severe side effects ▪ genital infections: proof of greater harm – extent: "considerable" ▪ gastrointestinal disorders: proof of greater harm – extent: "considerable"
Data on severe hypoglycaemia, symptomatic confirmed hypoglycaemia (plasma glucose ≤ 54 mg/dL), DKAs (total) and specific SAEs are lacking.	
a: Sufficiently valid surrogate for microvascular late complications. DKA: diabetic ketoacidosis; HbA1c: haemoglobin A1c; SAE: serious adverse event	

In an incomplete data situation, the overall consideration showed 1 positive and 2 negative effects of dapagliflozin + insulin in comparison with placebo + insulin.

Overall, there is an indication of an added benefit for the outcome "change in HbA1c". For the HbA1c value as a sufficiently valid surrogate for microvascular late complications, however, there is no information available on the basis of which the extent of the added benefit could be determined (e.g. surrogate validation using the concept of a so-called surrogate threshold effect [1]). The extent of added benefit for this outcome can therefore not be quantified. This is offset by proof of greater harm of considerable extent for non-serious/non-severe side effects. For side effects, the data were not presented completely.

Overall, the added benefit of dapagliflozin and insulin versus insulin (human insulin and insulin analogues) is not proven in patients with type 1 diabetes mellitus and with BMI ≥ 27 kg/m², when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

The result of the assessment of the added benefit of dapagliflozin and insulin in comparison with insulin is summarized in Table 18.

Table 18: Dapagliflozin – probability and extent of added benefit

Therapeutic indication	ACT	Probability and extent of added benefit
Type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m², when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy	Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin aspart, insulin glulisine, insulin lispro)[a]	Added benefit not proven
a: The unchanged continuation of an inadequate therapy of type 1 diabetes mellitus, if there is still the option of optimizing insulin therapy, does not correspond to an ACT. The approvals and SPCs of the drugs of the ACT have to be considered. ACT: appropriate comparator therapy; BMI: body mass index; SPC: Summary of Product Characteristics		

The assessment described above deviates from that of the company, which overall derived proof of non-quantifiable added benefit.

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6 List of included studies

DEPICT 1

AstraZeneca. Dapagliflozin evaluation in patients with inadequately controlled type 1 diabetes (DEPICT 1): study details [online]. In: ClinicalTrials.gov. 13.09.2018 [Accessed: 13.05.2019]. URL: https://clinicaltrials.gov/ct2/show/NCT02268214.

AstraZeneca. Dapagliflozin evaluation in patients with inadequately controlled type 1 diabetes (DEPICT 1): study results [online]. In: ClinicalTrials.gov. 13.09.2018 [Accessed: 13.05.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02268214.

AstraZeneca. A multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 study to evaluate the efficacy and safety of dapagliflozin as an add-on to insulin therapy in subjects with type 1 diabetes mellitus [online]. In: EU Clinical Trials Register. [Accessed: 13.05.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-004674-97.

AstraZeneca. A multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 study to evaluate the efficacy and safety of dapagliflozin as an add-on to insulin therapy in subjects with type 1 diabetes mellitus: clinical trial results [online]. In: EU Clinical Trials Register. 08.09.2019 [Accessed: 13.05.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-004674-97/results.

AstraZeneca. A multicentre, randomised, double-blind, placebo-controlled, parallel group, phase 3 study to evaluate the efficacy and safety of dapagliflozin as an add-on to insulin therapy in subjects with type 1 diabetes mellitus: report for the 24-week short-term treatment period plus the 28-week long-term extension period: study MB102229; clinical study report [unpublished]. 2018.

AstraZeneca. A multicentre, randomised, double-blind, placebo-controlled, parallel group, phase 3 study to evaluate the efficacy and safety of dapagliflozin as an add-on to insulin therapy in subjects with type 1 diabetes mellitus: report for the 24-week short-term treatment period plus the 28-week long-term extension period: study MB102229; Zusatzanalysen [unpublished]. 2019.

Bristol-Myers Squibb. A multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 study to evaluate the efficacy and safety of dapagliflozin as an add-on to insulin therapy in subjects with type 1 diabetes mellitus [online]. In: Deutsches Register Klinischer Studien. [Accessed: 13.05.2019]. URL: http://www.drks.de/DRKS00009951.

Dandona P, Mathieu C, Phillip M, Hansen L, Griffen SC, Tschope D et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol 2017; 5(11): 864-876.

Dandona P, Mathieu C, Phillip M, Hansen L, Tschope D, Thoren F et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: the DEPICT-1 52-week study. Diabetes Care 2018; 41(12): 2552-2559.

European Medicines Agency. Forxiga, Edistride: joint CHMP and PRAC response assessment report; clinical-assessment of the responses to the CHMP/PRAC list of questions; procedure no. EMEA/H/C/WS1344 [unpublished]. 2018.

DEPICT 2

AstraZeneca. Dapagliflozin evaluation in patients with inadequately controlled type 1 diabetes (DEPICT 2): study details [online]. In: ClinicalTrials.gov. 05.03.2019 [Accessed: 13.05.2019]. URL: https://clinicaltrials.gov/ct2/show/NCT02460978.

AstraZeneca. Dapagliflozin evaluation in patients with inadequately controlled type 1 diabetes (DEPICT 2): study results [online]. In: ClinicalTrials.gov. 05.03.2019 [Accessed: 13.05.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02460978.

AstraZeneca. A multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 study to evaluate the efficacy and safety of dapagliflozin as an add-on to insulin therapy in subjects with type 1 diabetes mellitus: study two [online]. In: EU Clinical Trials Register. [Accessed: 13.05.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-004599-49.

AstraZeneca. A multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 study to evaluate the efficacy and safety of dapagliflozin as an add-on to insulin therapy in subjects with type 1 diabetes mellitus: study two; clinical trial results [online]. In: EU Clinical Trials Register. 03.04.2019 [Accessed: 13.05.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-004599-49/results.

AstraZeneca. A multicentre, randomised, double-blind, placebo-controlled, parallel group, phase 3 study to evaluate the efficacy and safety of dapagliflozin as an add-on to insulin therapy in subjects with type 1 diabetes mellitus: final 52-week clinical study report for the 24-week short-term treatment period plus the 28-week long-term extension period; study MB102230; clinical study report [unpublished]. 2018.

AstraZeneca. A multicentre, randomised, double-blind, placebo-controlled, parallel group, phase 3 study to evaluate the efficacy and safety of dapagliflozin as an add-on to insulin therapy in subjects with type 1 diabetes mellitus: final 52-week clinical study report for the 24-week short-term treatment period plus the 28-week long-term extension period; study MB102230; Zusatzanalysen [unpublished]. 2019.

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Please see full dossier assessment for full reference list.

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