IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Dapagliflozin (type 2 diabetes mellitus) –

Benefit assessment according to §35a Social Code Book V[1] (new scientific findings)

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Dapagliflozin (Diabetes mellitus Typ 2) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 March 2018). 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
ACT	appropriate comparator therapy
AE	adverse event
DPP-4	dipeptidyl peptidase-4
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLP-1	Glucagon-Like-Peptide-1
HbA1c	haemoglobin A1c
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NVL	National Care Guideline (Nationale VersorgungsLeitlinie; NVL)
SPC	Summary of Product Characteristics
RCT	Randomized controlled Trial (randomisierte kontrollierte Studie)
SGB	Sozialgesetzbuch (Social Code Book)
SGLT-2	Sodium Glucose Co-Transporter 2

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 pharmaceutical company (hereinafter referred to as "the company") submitted a first dossier of the drug to be evaluated on 15 December 2012 for the early benefit assessment. The company now requested a new benefit assessment for a subindication – i.e. an add-on combination therapy with metformin – because of new scientific findings. The assessment was based on a dossier compiled by the pharmaceutical company. The dossier was sent to IQWiG on 21 December 2017.

Research question

The aim of this report was to assess the added benefit of dapagliflozin for the treatment of adult patients with type 2 diabetes mellitus in comparison with the appropriate comparator therapy (ACT) in the following approved therapeutic indication:

- Dapagliflozin in combination with metformin (dapagliflozin + metformin): in patients in whom monotherapy with metformin together with diet and exercise does not provide adequate glycaemic control.

The assessment was conducted in comparison with the G-BA's ACT. This ACT is shown in Table 2.

Table 2: Research question of the benefit assessment of dapagliflozin in type 2 diabetes mellitus

Subindication	ACT[a]
Dapagliflozin + metformin	▪ **Metformin + sulfonylurea** (glibenclamide or glimepiride)[b] or ▪ Metformin + empagliflozin or ▪ Metformin + liraglutide[c]
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: According to the commission by the G-BA, studies of direct comparisons versus glipizide are to be additionally assessed. c: Liraglutide in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for operationalization, see study protocol [1]). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

In its choice of the comparator therapy, the company followed the G-BA's specification and chose metformin + sulfonylurea from the options. It additionally described that it also considered studies in comparison with the sulfonylurea glipizide. Glipizide is not approved in

Germany. According to the G-BA's commission, the comparison versus glipizide is also considered and outlined in an individual research question.

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.

Results

The company identified the following RCTs for the assessment of the added benefit of dapagliflozin in adult patients with type 2 diabetes mellitus:

- for the comparison of dapagliflozin + metformin vs. glimepiride + metformin: study D1689C00014 (study DapaZu); this study was conducted after the first dossier assessment on dapagliflozin and submitted by the company for the present dossier assessment for the first time,
- for the comparison of dapagliflozin + metformin vs. glipizide + metformin: study D1690C00004; this study was already the subject of the first dossier assessment on dapagliflozin.

No added benefit of dapagliflozin in comparison with the ACT could be derived from the two studies.

Dapagliflozin + metformin vs. glimepiride + metformin

DapaZu study

The DapaZu study is a randomized, active-controlled, double-blind phase 4 study. Adult patients between 18 and 74 years with type 2 diabetes mellitus in whom no sufficient glycaemic control was achieved despite treatment with metformin at a stable maximum tolerated dosage of ≥ 1500 mg/day and who had a glycosylated haemoglobin A1c (HbA1c) value between ≥ 7.5% and ≤ 10.5% in the inclusion phase were included in the study.

The study consisted of a 2-week inclusion phase, a treatment phase of 52 weeks and a follow-up phase of 3 weeks.

314 patients were randomized to the dapagliflozin arm and 313 patients to the glimepiride arm (each in addition to metformin). After randomization, the patients received either a fixed dose of 10 mg/day dapagliflozin or a start dose of 1 mg/day glimepiride, each in addition to placebo, to blind the assignment to the individual study arms. At each visit, the investigator could increase the glimepiride dose by 1 mg/day up to a maximum dose of 6 mg/day (at an interval of at least 2 weeks). In addition, all patients received a stable metformin dose of ≥ 1500 mg/day that had been ongoing before study inclusion.

The primary outcome of the study was the change in HbA1c after 52 weeks of treatment. The aim was to show the non-inferiority of dapagliflozin versus glimepiride (each in addition to

metformin) regarding the change of the HbA1c values from the start of the study to treatment week 52. The non-inferiority boundary was determined a priori at 0.30 percentage points.

Results on hypoglycaemic events not interpretable

The results of the DapaZu study described above on the outcome "hypoglycaemia" are not interpretable. This is primarily due to the concrete blood-glucose lowering approach in the control group (active titration with glimepiride with regular up-titration up to a dose of 6 mg/day) in connection with the resulting clear differences in blood-glucose lowering (no non-inferiority of dapagliflozin during the course of the study). The individually specified blood glucose treatment goals were achieved less frequently under dapagliflozin, whereby the specification of the treatment goals on the basis of the documents presented by the company also remained unclear.

Besides the fact that the differences in the achievement of the target levels in the individual study arms restrict the interpretability of the results on hypoglycaemias, the question was then whether the specified targets were reasonable at all. If so, treatment particularly with dapagliflozin would have been inadequate (in about 80% of the patients). If not, this would imply overtreatment in the comparator arm, since titration was oriented towards these inadequate treatment goals.

Supplementary consideration of the results of the DapaZu study

If, irrespective of the issues mentioned above, the results of the DapaZu study are considered in detail, they altogether show no advantage of dapagliflozin versus glimepiride. A lower rate of non-severe hypoglycaemic events on the one side is accompanied by more genital infections, urinary tract infections as well as more discontinuations due to adverse events on the other.

Dapagliflozin + metformin vs. glipizide + metformin

Study D1690C00004

The study D1690C00004 is a randomized, double-blind and active-controlled approval study on the comparison of dapagliflozin+metformin with glipizide+metformin. The company already presented this study for the first assessments of dapagliflozin as single agent (A12-18 and A13-18) and as fixed combination with metformin (A14-07); it is extensively described in the related documents. In its justification on the benefit assessment decisions for dapagliflozin and for the fixed combination dapagliflozin/metformin, the G-BA explained in detail why study D1690C00004 is unsuitable for a derivation of an added benefit of dapagliflozin. The company's newly presented dossier did not provide new findings.

Summary

The data presented by the company provided 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 presents a summary of the probability and extent of the added benefit of dapagliflozin.

Table 3: Dapagliflozin – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Dapagliflozin + metformin	▪ **Metformin + sulfonylurea** (glibenclamide or glimepiride)[b] or ▪ Metformin + empagliflozin or ▪ Metformin + liraglutide[c]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: According to the G-BA's commission, studies of direct comparisons versus glipizide are to be additionally assessed.
c: Liraglutide in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for operationalization, see study protocol [1]).
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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 [2,3].

2.2 Research question

The aim of this report was to assess the added benefit of dapagliflozin for the treatment of adult patients with type 2 diabetes mellitus in comparison with the ACT in the following approved therapeutic indication:

- Dapagliflozin in combination with metformin (dapagliflozin + metformin): in patients in whom monotherapy with metformin together with diet and exercise does not provide adequate glycaemic control.

Dapagliflozin is approved both as monotherapy and in combination with other blood-glucose lowering drugs. These indications are not subject of the present assessment.

The assessment was conducted in comparison with the G-BA's ACT. This ACT is shown in Table 4.

Table 4: Research question of the benefit assessment of dapagliflozin in type 2 diabetes mellitus

Subindication	**ACT**[a]
Dapagliflozin + metformin	▪ **Metformin + sulfonylurea** (glibenclamide or glimepiride)[b] or ▪ Metformin + empagliflozin or ▪ Metformin + liraglutide[c]
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: According to the commission by the G-BA, studies of direct comparisons versus glipizide are to be additionally assessed. c: Liraglutide in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for operationalization, see study protocol [1]). ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

In its choice of the comparator therapy, the company followed the G-BA's specification and chose metformin + sulfonylurea from the options. It additionally described that it also considered studies in comparison with the sulfonylurea glipizide. Glipizide is not approved in Germany. According to the G-BA's commission, the comparison versus glipizide is also considered and outlined in an individual research question.

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. 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 (status: 17 October 2017)
- bibliographical literature search on dapagliflozin (last search on 17 October 2017)
- search in trial registries for studies on dapagliflozin (last search on 16 October 2017)

To check the completeness of the study pool:

- search in trial registries for studies on dapagliflozin (last search on 11 January 2018)

The check identified no additional relevant study.

The company identified the following RCTs for the assessment of the added benefit of dapagliflozin in adult patients with type 2 diabetes mellitus:

- for the comparison of dapagliflozin + metformin vs. glimepiride + metformin: study D1689C00014 (study DapaZu) [4-6]; this study was conducted after the first dossier assessment on dapagliflozin (dossier assessment A12-18 and the corresponding addendum A13-18) and submitted by the company for the present dossier assessment for the first time,
- for the comparison of dapagliflozin + metformin vs. glipizide + metformin: study D1690C00004 [7]; this study was already the subject of the first dossier assessment on dapagliflozin.

Both RCTs are presented in Table 5.

Table 5: Study pool of the company – RCT, direct comparison: dapagliflozin+metformin vs. sulfonylurea + metformin

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
D1689C00014 (DapaZu[b])	No	Yes	No
D1690C00004	Yes	Yes	No
a: Study sponsored by the company. b: Hereinafter, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

No added benefit of dapagliflozin in comparison with the ACT could be derived from the two studies included by the company. This is justified in detail below.

Dapagliflozin + metformin vs. glimepiride + metformin

DapaZu study

Study characteristics

Table 6 and Table 7 describe the DapaZu study.

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
DapaZu	RCT, double-blind, parallel	Adult patients (18 to 74 years) with type 2 diabetes mellitus and HbA1c of ≥ 7.5% to 10.5% with prior metformin treatment of ≥ 1500 mg/day for at least 8 months	▪ Dapagliflozin + placebo (for saxagliptin + glimepiride) + metformin (N = 314) ▪ Glimepiride + placebo (for dapagliflozin + saxagliptin) + metformin (N = 313) ▪ Dapagliflozin + saxagliptin + placebo (for glimepiride) + metformin (N = 312)[c]	screening: 1 week Inclusion phase: 2 weeks Treatment phase: 52 weeks Follow-up: 3 weeks[b]	194 study centres in Germany, Slovak Republic, Hungary, Poland and Czech Republic 09/2015-03/2017	Primary: change in HbA1c after 52 weeks of treatment Secondary: morbidity, hypoglycaemia, health-related quality of life, side effects

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively contain information on relevant available outcomes from the information provided by the company in Module 4A of the dossier.
b: Applies to adverse events (up to and including 4 days in case of AE and at most 30 days in case of SAEs after administration of the last dose of the study medication).
c: The arm is not relevant for the assessment and is no longer shown in the following tables.
AE: adverse event; HbA1c: haemoglobin A1c; N: number of randomized patients; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

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

Study	Intervention	Comparison
DapaZu	▪ Dapagliflozin 10 mg; once daily, orally + metformin ≥ 1500 mg/day[a], orally, at current dosage + placebo for saxagliptin + placebo for glimepiride	▪ Glimepiride (start dose 1 mg, titration up to 6 mg), once daily, orally, + metformin ≥ 1500 mg/day, orally, at current dosage Placebo for dapagliflozin + placebo for saxagliptin *Titration/dose increase of glimepiride* starting dose: 1 mg/day Dose increase by 1 mg every 2 weeks up to a maximum dose of 6 mg/day was possible. Individual target level, a fasting plasma glucose (FPG) target level of about 110 mg/dl was recommended. Dose reduction was allowed.
	Prior and concomitant medication *Pretreatment* Pretreatment for at least 8 weeks before the start of the study with metformin ≥ 1500 mg/day or in a maximum tolerated dose *Non-permitted concomitant treatment* ▪ Sulfonylureas, pioglitazone, rosiglitazone, GLP-1 receptor agonists, dipeptidyl-peptidase (DPP) 4 and sodium dependent glucose co-transporter (SGLT2) inhibitors, loop diuretics ▪ further test medication ▪ systemic glucocorticoids (equivalent to ≥ 10 mg/day prednisolone, orally) ≥ 5 days (inhalation and topical application was allowed) ▪ over-the-counter drugs for weight reduction *As-needed medication* Glycaemic rescue medication with insulin was allowed within a defined range of FPG or HBA1c threshold values for a total of 14 days and for up to 7 consecutive days: ▪ weeks 0 to 12 (after visit 2 and including visit 8): FPG > 240 mg/dl (13.3 mmol/l) ▪ weeks 12 to 24 (after visit 8 and including visit 9): FPG > 200 mg/dl (11.1 mmol/l) ▪ weeks 24 to 52 (after visit 9 and including visit 12): HbA1c > 8.0%	

DPP-4: dipeptidyl peptidase-4; FPG: Fasting Plasma Glucose; GLP-1: Glucagon-Like-Peptide-1; HbA1c: haemoglobin A1c; RCT: randomized controlled trial; SGLT2: Sodium Glucose Co-Transporter 2; vs.: versus

The DapaZu study is a randomized, active-controlled, double-blind phase 4 study. Adult patients between 18 and 74 years with type 2 diabetes mellitus in whom no sufficient glycaemic control was achieved despite treatment with metformin at a stable maximum tolerated dosage of ≥ 1500 mg/day and who had an HbA1c value between ≥ 7.5% and ≤ 10.5% in the inclusion phase were included in the study. All patients should have received metformin at a stable dosage of ≥ 1500 mg/day for at least 8 weeks before inclusion.

The study consisted of a 2-week inclusion phase, a treatment phase of 52 weeks and a follow-up phase of 3 weeks.

A total of 939 patients were randomly assigned to the 3 study arms dapagliflozin, glimepiride as well as dapagliflozin + saxagliptin (each in addition to metformin). In the 2 study arms relevant for the present assessment, 314 patients were randomly allocated to the dapagliflozin arm, and 313 patients to the glimepiride arm.

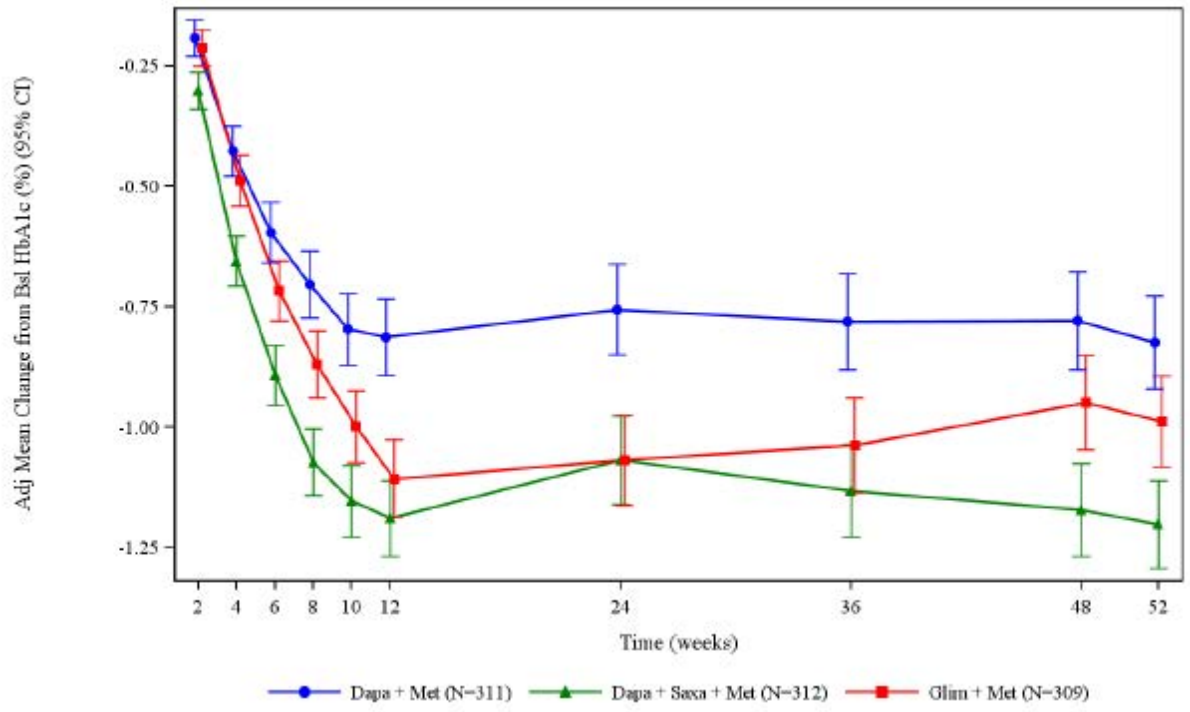
After randomization, the patients received either a fixed dose of 10 mg/day dapagliflozin or a starting dose of 1 mg/day glimepiride, each in addition to placebo, to blind the assignment to the individual study arms. At each visit, the investigator could increase the glimepiride dose by 1 mg/day up to a maximum dose of 6 mg/day (at an interval of at least 2 weeks). In addition, all patients received a stable metformin dose of ≥ 1500 mg/day that had been ongoing before study inclusion. Hyperglycaemic rescue medication with insulin was allowed in addition to the randomized study medication and metformin within the defined glucose threshold values after the maximum glimepiride dose (6 mg/day) or glimepiride-placebo dose had been reached (see Table 7).

The primary outcome of the study was the change in HbA1c after 52 weeks of treatment. The aim was to show the non-inferiority of dapagliflozin versus glimepiride (each in addition to metformin) regarding the change of the HbA1c values from the start of the study to treatment week 52. The non-inferiority boundary was determined a priori at 0.30 percentage points.

Results on hypoglycaemic events not interpretable

The results of the DapaZu study described above on the outcome “hypoglycaemia” are not interpretable. This is primarily due to the concrete blood-glucose lowering approach in the control group (active titration with glimepiride with regular up-titration up to a dose of 6 mg/day) in connection with the resulting clear differences in blood-glucose lowering (no non-inferiority of dapagliflozin during the course of the study). The individually specified blood glucose treatment goals were achieved less frequently under dapagliflozin, whereby the specification of the treatment goals on the basis of the documents presented by the company also remained unclear.

Figure 1 shows the change of the HbA1c values during the 52-week treatment phase, and Table 8 presents the values including the mean differences over the entire course of the study.



The green curve describes the course of the HbA1c values in a study arm which is not relevant for the present assessment (dapagliflozin + saxagliptin + metformin). HbA1c values after administration of the rescue medication or treatment discontinuation were not considered in presented curves. MMRM analysis of the ITT population.

Figure 1: Adjusted mean changes of the HbA1c values in the course of the DapaZu study

Table 8: HbA1c values and mean differences in the course of the study

Treatment week	Dapagliflozin + metformin		Glimepiride + metformin		Dapagliflozin + metformin vs. glimepiride + metformin
	N[a]	HbA1c mean[b, c] (SD)	N[a]	HbA1c mean[b, c] (SD)	MD [95% CI][b, c]
Week 2	309	8.08 (0.74)	305	8.09 (0.80)	0.02 [-0.03; 0.07]
Week 4	309	7.83 (0.74)	305	7.81 (0.82)	0.06 [-0.01; 0.14]
Week 6	309	7.65 (0.73)	305	7.56 (0.81)	0.12 [0.03; 0.21]
Week 8	309	7.55 (0.76)	305	7.38 (0.81)	0.17 [0.07; 0.26]
Week 10	309	7.45 (0.78)	305	7.27 (0.82)	0.20 [0.10; 0.31][d]
Week 12	309	7.44 (0.79)	305	7.16 (0.84)	0.29 [0.18; 0.41][d]
Week 24	309	7.48 (0.83)	305	7.18 (0.92)	0.31 [0.18; 0.44][d]
Week 36	309	7.39 (0.84)	305	7.17 (0.90)	0.26 [0.12; 0.40][d]
Week 48	309	7.27 (0.75)	305	7.11 (0.81)	0.17 [0.03; 0.31][d]
Week 52	309	7.21 (0.67)	305	7.05 (0.74)	0.16 [0.03; 0.2986]
HbA1c values including data after administration of a rescue medication or treatment discontinuation					
Week 52	310	7.39 (0.81)	306	7.21 (0.85)	0.18 [0.06; 0.31]

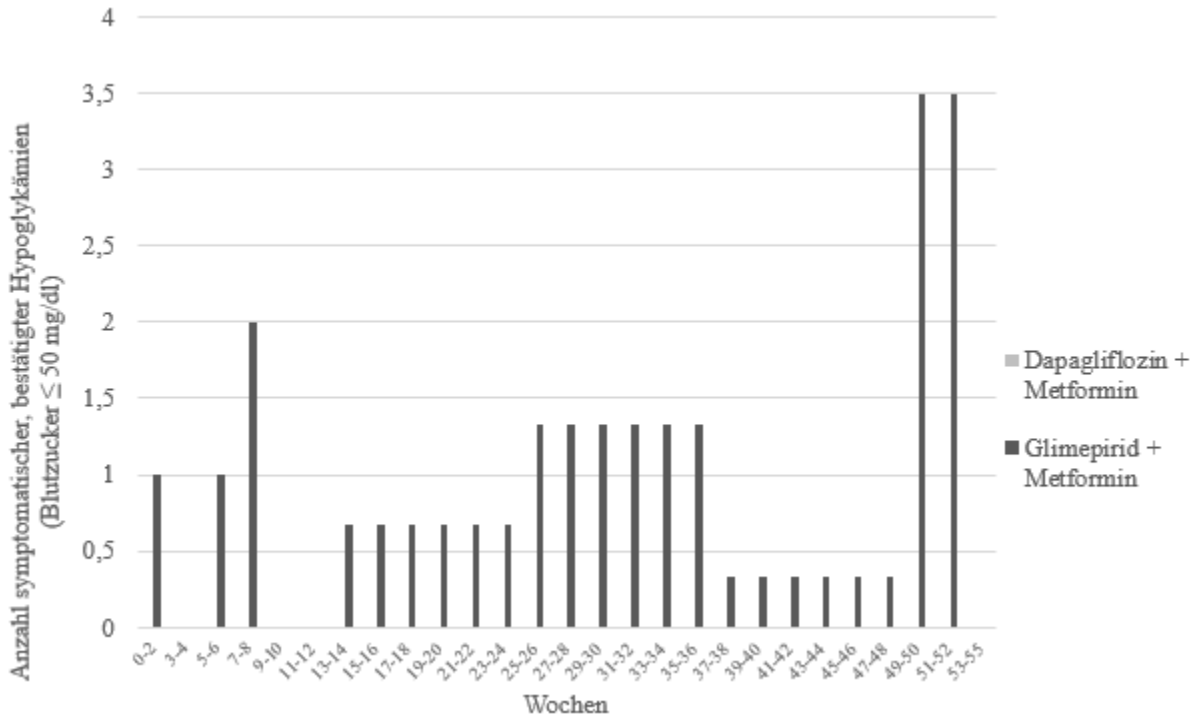
a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Unless stated otherwise, MMRM analysis of the ITT population.
c: No consideration of HbA1c values after administration of the rescue medication or treatment discontinuation. HbA1c values in the course of the study including data after administration of a rescue medication were only available at week 52.
d: The upper limit of the 95% CI was above the non-inferiority boundary of 0.3 percentage points.
CI: confidence interval; HbA1c: haemoglobin A1c; ITT: Intention to treat; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Considering the time course of the changes of the HbA1c values, a decrease of the HbA1c values was observed in both study arms, which, however, was clearly stronger under the target-level directed treatment with glimepiride. The greatest difference (0.31 percentage points) was shown at week 24 (see Table 8). The non-inferiority of dapagliflozin, based on the non-inferiority boundary of 0.3 percentage points determined by the company itself, was not reached during the major part of the study (week 10 to week 48 or week 52, depending on the type of the analysis).

Thereby, the treatment strategy in the glimepiride arm followed a titration scheme which was not appropriate and did not comply with the specifications of the Summary of Product Characteristics (SPC). As described above, the glimepiride dose could be increased to at most 6 mg/day during the course of the study. The SPC of glimepiride describes this dosage to be the maximum recommended dosage. However, the stepwise titration is described only up to a dose of 4 mg/day. According to the SPC, daily doses higher than 4 mg glimepiride improve the effect only in individual cases [8]. This implies a titration scheme permitting titration up to the maximum daily dose of 6 mg based on an individual consideration, but not including titration of dosages above 4 mg/day as regular titration step to be an adequate measure.

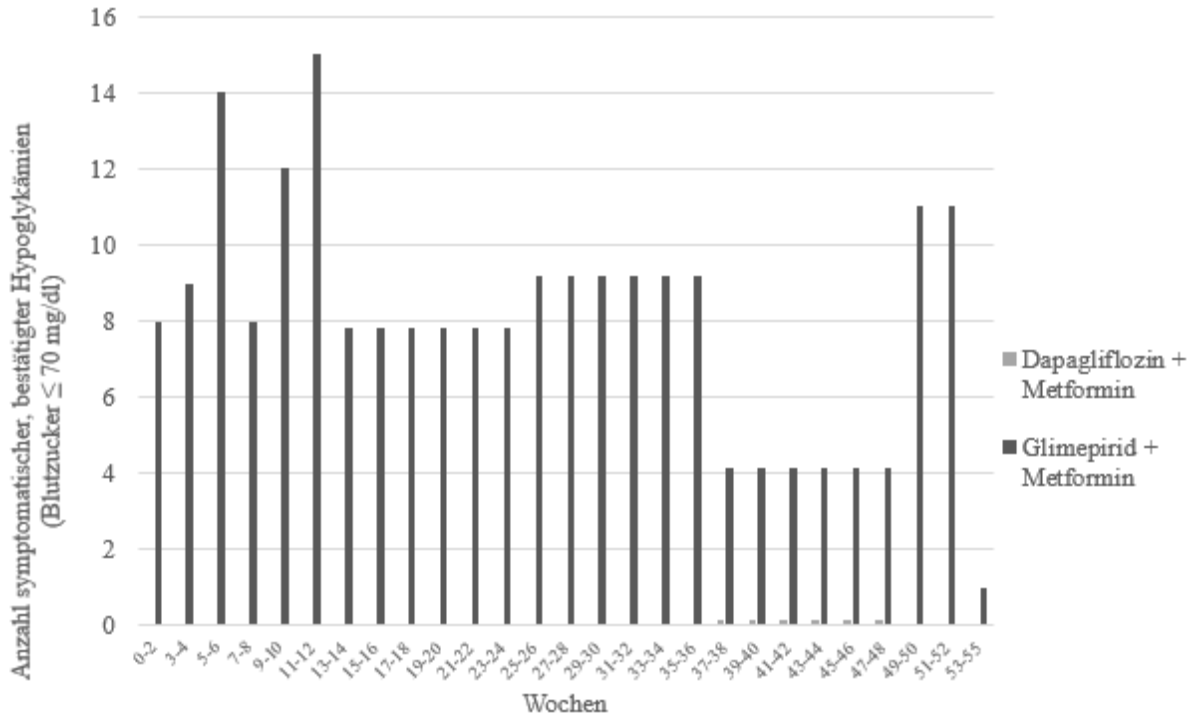
However, in the DapaZu study, titration steps to dosages > 4 mg glimepiride/day (5 or 6 mg/day) were possible for all patients; these titration steps had the same relevance as titration steps to the dosages ≤ 4 mg/day. Administration of rescue medication was only allowed after the maximum dose of 6 mg/day glimepiride or glimepiride placebo had been reached. As early as at treatment week 8, almost one fifth (18.3%) of the patients in the glimepiride arm received glimepiride doses > 4 mg/day. At the end of the study after 52 weeks, the proportion of patients was 64% and the mean daily dose was 4.7 mg (median: 6 mg). Thus, the titration applied in the DapaZu study did evidently not restrict the administration of glimepiride doses above 4 mg/day to individual cases, on the contrary, this was the normal case. This was neither appropriate, nor did it correspond to the approval of glimepiride. It should be additionally noted that – before conducting the study – the G-BA had indicated that up-titration of a product which is to be titrated must be performed according to the approval and to the general state of knowledge as well as under consideration of an individual benefit-risk assessment [9,10]. With the DapaZu study, the company did not fulfil this criterion.

Administration of high glimepiride doses is also reflected by the occurrence of symptomatic hypoglycaemic events. The DapaZu study did not involve the occurrence of severe hypoglycaemic events, however, during the entire course of the study symptomatic confirmed hypoglycaemic events (blood glucose level ≤ 50 or 70 mg/dl) occurred clearly more often in the glimepiride arm (see Figure 2 and Figure 3, only one confirmed symptomatic hypoglycaemic event ≤ 70 mg/dl was observed in the dapagliflozin + metformin arm).



Information at 2-week intervals are only available up to week 12. Between weeks 13 and 48, the number of hypoglycaemic events was reported per 12 weeks, and between weeks 49 and 52 per 4 weeks. Here, the average number of hypoglycaemic events is indicated per 2 weeks for these periods. As an exception, the last bar illustrates 3 weeks.

Figure 2: Number of symptomatic confirmed hypoglycaemias (blood-glucose level ≤ 50 mg/dl)



Information at 2-week intervals are only available up to week 12. Between weeks 13 and 48, the number of hypoglycaemic events was reported per 12 weeks, and between weeks 49 and 52 per 4 weeks. Here, the average number of hypoglycaemic events is indicated per 2 weeks for these periods. As an exception, the last bar illustrates 3 weeks.

Figure 3: Number of confirmed symptomatic hypoglycaemias (blood-glucose level ≤ 70 mg/dl)

Specification of individual treatment target values is intransparent

The company explained having considered the consultation by the G-BA when planning the DapaZu study [9,10]. In the consultation indicated by the company, the G-BA explained that the individualized HbA1c targets in the study were to be agreed upon with the patients under consideration of several aspects such as age or comorbidities as well as after balancing of benefit (risk reduction with regard to diabetes-related secondary diseases) and risk (e.g. for confirmed hypoglycaemic events). The type of the used substance should also be considered when specifying the targets. Titration of the comparator therapy should take place in accordance with these individual treatment target values and not on the basis of a uniform target value specified for all patients. These criteria concur with the recommendations of the National Care Guideline (Nationale VersorgungsLeitlinie [NVL]) for the treatment of type 2 diabetes [11].

It was not clear from the information presented by the company whether the described aspects from the consultation by the G-BA had been sufficiently implemented in the DapaZu study. According to the study documents, individual treatment goals for HbA1c and FPG were agreed upon with all patients. However, the study documents do not provide information on the criteria on which the specification of the target values were to be based. Nor does the information address the specified target values or the question of whether these values differed among the individual patients. At the same time, it is shown that an FPG target value of 110 mg/dl was

regularly recommended for the specification of the target values, which aimed at near-normal blood glucose levels.

The available data consistently suggested that the HbA1c target values in the DapaZu study did not differ notably from an HbA1c < 7%, since the number of patients who had reached an HbA1c < 7% at week 52 (68 [20.3%] vs. 107 [33.9%]) deviated only marginally from the number of patients who had reached their individual treatment goal (70 [21.6%] vs. 117 [37.8%]). However, data on the overlapping of these 2 analyses are missing.

Besides the fact that the differences in the achievement of the target levels restrict the interpretability of the results on hypoglycaemic events, the question was then whether these targets were reasonable at all. If so, treatment particularly with dapagliflozin would have been inadequate (in about 80% of the patients). If not, this would imply overtreatment in the comparator arm, since titration was oriented towards these inadequate treatment goals.

Supplementary consideration of the results of the DapaZu study

If, irrespective of the issues mentioned above, the results of the DapaZu study (see Appendix A of the full dossier assessment) are considered in detail, they altogether show no advantage of dapagliflozin versus glimepiride. A lower rate of non-severe hypoglycaemic events on the one side is accompanied by more genital infections, urinary tract infections as well as more discontinuations due to adverse events on the other.

Dapagliflozin + metformin vs. glipizide + metformin

Study D1690C00004

The study D1690C00004 is a randomized, double-blind and active-controlled approval study on the comparison of dapagliflozin+metformin with glipizide+metformin. The company already presented this study for the first assessment of dapagliflozin as single agent (A12-18 and A13-18) [12] and as fixed combination with metformin (A14-07) [13]; it is extensively described in the related documents.

In its justification on the benefit assessment decisions for dapagliflozin and for the fixed combination dapagliflozin/metformin, the G-BA explained in detail why study D1690C00004 was unsuitable for a derivation of an added benefit of dapagliflozin [14,15]. Since study D1690C00004 already ended in 2013, the data pertaining to a study duration of 208 weeks presented by the company for the present benefit assessment were already available for the first assessment of the fixed combination dapagliflozin/metformin. As found in the first assessment of the fixed combination dapagliflozin/metformin, these data do not change the assessment of the uninterpretability of study D1690C00004.

2.4 Results on added benefit

The data presented by the company provided 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

The result of the assessment of the added benefit of dapagliflozin in comparison with the ACT is summarized in Table 9.

Table 9: Dapagliflozin – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Dapagliflozin + metformin	▪ **Metformin + sulfonylurea** (glibenclamide or glimepiride)[b] or ▪ Metformin + empagliflozin or ▪ Metformin + liraglutide[c]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: According to the commission by the G-BA, studies of direct comparisons versus glipizide are to be additionally assessed.
c: Liraglutide in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for operationalization, see study protocol [1]).
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no suitable data for the benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-65-dapagliflozin-type-2-diabetes-mellitus-benefit-assessment-according-to-35a-social-code-book-v-new-scientific-findings.8836.html.