IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.8 of the dossier assessment *Canagliflozin – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 June 2014). 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
CrCl	creatinine clearance
DPP	dipeptidyl-peptidase
eGFR	estimated glomerular filtration rate
GLP	glucagon-like peptide
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	haemoglobin A1c
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mITT	modified intention to treat
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug canagliflozin. 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 17 March 2014.

Research question

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

Monotherapy: in patients in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindications.

Combination therapy: as combination therapy with other blood-glucose lowering drugs including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Following the company's research questions in the dossier, the assessment was conducted separately for 5 research questions versus the ACT specified by the G-BA (see Table 2).

Table 2: Subindications considered in the benefit assessment, research questions and ACTs on canagliflozin

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

a: Subdivisions of the therapeutic indication according to the G-BA.
b: Designation corresponds to the coding in the company's dossier.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The research questions considered by the company do not cover the entire approved therapeutic indication of canagliflozin. The company noted in the dossier that further combination therapies are approved, but, referring to their low relevance for clinical practice, did not submit any corresponding modules.

Results

Research question A: canagliflozin monotherapy

The company identified no comparative study for the assessment of canagliflozin versus the ACT for research question A and claimed no added benefit.

Research question B: canagliflozin plus metformin

The company specified glimepiride plus metformin as comparator therapy in research question B, and thus followed the ACT specified by the G-BA (metformin plus sulfonylurea [glibenclamide, glimepiride]). However, it also defined a specific patient population for which treatment with sulfonylureas is approved according to the Summary of Product Characteristics (SPC), but not applicable from the company's point of view. The company named metformin plus sitagliptin as alternative comparator therapy for this patient population. In the present benefit assessment, the specific patient population named by the company is considered to be an irrelevant subpopulation in the therapeutic indication and is not considered further.

Comparison versus the ACT: canagliflozin plus metformin versus glimepiride plus metformin

The company presented the randomized 3-arm approval study DIA3009 sponsored by the company for the comparison versus the ACT. This study compared canagliflozin plus metformin with glimepiride plus metformin with all patients continuing their prior metformin therapy at a stable dose as concomitant treatment. Whereas the daily dose of canagliflozin was 100 mg and 300 mg and was not changed, glimepiride was to be titrated. After a starting dose of 1 mg/day, dose steps of 2, 4, and 6 mg/day and – if approved in the respective country – 8 mg/day were envisaged (dose levels 1 to 5) for titration in the glimepiride arm. To maintain blinding, the randomized study medication was also made available in the levels 1 to 5 for sham titration in both canagliflozin arms. Each level corresponded to 100 mg/day or 300 mg/day of canagliflozin. The dose level was to be increased if at least 50% of fasting plasma glucose measurements were above a target value of 110 mg/dL during the 2 weeks preceding the study visit/titration (at least 3 measurements were recommended). The interval between 2 dose level increases could be reduced to less than one week if a patient had higher blood glucose levels and the conditions for increasing the dose level were fulfilled. The dose level was not to be increased if, during the 2 weeks preceding the study visit, hypoglycaemias had occurred that, from the investigator's point of view, excluded an increase of the dose level.

Hence in the DIA3009 study, there were relevant differences between the treatment arms with regard to the specified target blood glucose levels and the therapeutic strategies determined by them: In the canagliflozin arms of the study, target blood glucose levels could not be aimed at by dose adaptation ("titration" to target levels was performed without dose changes and merely to maintain blinding) and fixed dosage was used. In the glimepiride arm, in contrast, titration was specified by an algorithm and orientated towards near-normal target levels. The substantial differences in blood-glucose lowering between the treatment groups in the first weeks of the study were apparently induced by the one-sided possibility of reaching target levels for glimepiride. The time course of the occurrence of the key outcomes of the DIA3009 study (hypoglycaemias) corresponded to the course of blood glucose lowering. The results of the DIA3009 study could not be used for assessing the added benefit of canagliflozin plus

metformin versus the ACT specified by the G-BA because it remained unclear whether the observed effects are attributable to the drugs or to the therapeutic strategy.

Further points in the DIA3009 study (e.g. use of canagliflozin in fixed doses of 100 or 300 mg/day and the unapproved glimepiride dose of 8 mg/day) are not discussed because they were not primarily relevant for the exclusion of the study.

Research question C: canagliflozin plus sulfonylurea

In research question C, the G-BA specified metformin plus sulfonylurea (glibenclamide, glimepiride) (note: if metformin is inappropriate according to the SPC, human insulin is to be used as treatment option) as ACT. The company followed the ACT, but claimed no added benefit, because it could not derive an added benefit from the DIA3010 study presented, neither using direct nor indirect comparisons. The DIA3010 study allowed no direct comparison of canagliflozin plus sulfonylureas versus metformin plus sulfonylureas. Indirect comparisons were therefore not possible because, according to the company, only 22 patients were treated with metformin plus sulfonylureas.

Research question D: canagliflozin plus metformin plus sulfonylurea

In research question D, the G-BA specified human insulin plus metformin (with the note that only human insulin is to be used if metformin is not sufficiently effective or not tolerated according to the SPC).

The company claimed no added benefit, because it could not derive an added benefit from the studies DIA3002 and DIA3010 presented, neither using direct nor indirect comparisons. Both studies allowed no direct comparison of canagliflozin plus metformin plus sulfonylureas versus human insulin plus metformin. The literature search conducted by the company resulted in no relevant studies with the necessary common comparator for the indirect comparisons.

Research question E: canagliflozin plus insulin (with or without oral antidiabetics)

The company identified no comparative study for the assessment of canagliflozin plus insulin (with or without oral antidiabetics) versus the ACT for research question E and claimed no added benefit.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug canagliflozin compared with the ACT is assessed as presented in Table 3.

Table 3: Canagliflozin – extent and probability of added benefit

Research question[a]	Subindication	ACT	Extent and probability of added benefit
A	Monotherapy with canagliflozin	Sulfonylurea (glibenclamide, **glimepiride**[b])	Added benefit not proven
B	Canagliflozin plus metformin	Metformin plus sulfonylurea (glibenclamide, **glimepiride**[b])	Added benefit not proven
C	Canagliflozin plus sulfonylurea	Metformin plus sulfonylurea (glibenclamide, **glimepiride**[b]) note: if metformin is inappropriate according to the SPC, human insulin is to be used as treatment option	Added benefit not proven
D	Canagliflozin plus metformin plus sulfonylurea	Human insulin plus metformin (note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)	Added benefit not proven
E	Canagliflozin plus insulin with or without additional oral antidiabetic	Human insulin plus metformin (note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)	Added benefit not proven

a: Designation corresponds to the coding in the company's dossier.
b: The comparator therapy chosen by the company is printed in **bold**.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The research questions considered by the company do not cover the entire approved therapeutic indication of canagliflozin. The company noted in the dossier that further combination therapies are approved, but, referring to their low relevance for clinical practice, did not submit any corresponding modules. An added benefit for these combination therapies is not proven.

The G-BA decides on the added benefit.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

2.2 Research questions

The aim of this report was to assess the added benefit of canagliflozin for the treatment of adults with type 2 diabetes mellitus in the following approved subindications:

Monotherapy: in patients in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindications.

Combination therapy: as combination therapy with other blood-glucose lowering drugs including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Following the company's research questions in the dossier, the assessment was conducted separately for 5 research questions versus the ACT specified by the G-BA. These are shown in Table 4.

Table 4: Subindications considered in the benefit assessment, research questions and ACTs on canagliflozin

Subindication[a]	**Research question of the company**[b]	**ACT specified by the G-BA**
Monotherapy when diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindications	A Monotherapy with canagliflozin	Sulfonylurea (glibenclamide, glimepiride)
Combination with another blood-glucose lowering drug (except insulin), when this, together with diet and exercise, does not provide adequate glycaemic control	B Canagliflozin plus metformin C Canagliflozin plus sulfonylurea	Metformin plus sulfonylurea (glibenclamide, glimepiride) (note: if metformin is inappropriate according to the SPC, human insulin is to be used as treatment option)
Combination with at least 2 other blood-glucose lowering drugs, when these, together with diet and exercise, do not provide adequate glycaemic control	D Canagliflozin plus metformin plus sulfonylurea	Metformin plus human insulin (note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)
Combination with insulin (with or without oral antidiabetic)	E Canagliflozin plus insulin (with or without oral antidiabetics)	Metformin plus human insulin (note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)
a: Subdivisions of the therapeutic indication according to the G-BA. b: Designation corresponds to the coding in the company's dossier. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics		

The research questions considered by the company do not cover the entire approved therapeutic indication of canagliflozin. The company itself noted in the dossier that further combination therapies are approved (e.g. dipeptidyl-peptidase [DPP] 4 inhibitors, alpha-glucosidase inhibitors and glucagon-like peptide (GLP) 1 agonists, as well as triple combinations containing only one drug from the group of metformin/sulfonylurea/insulin). Referring to an analysis of insurance data [3], the company pointed out the low relevance of these combinations for clinical practice. According to the company, there are no clinical data on the assessment of an added benefit of canagliflozin in the combinations mentioned. The company therefore submitted no modules on these combinations.

Research question A: canagliflozin monotherapy

The benefit assessment for canagliflozin monotherapy was conducted in comparison with the ACT (sulfonylureas [glibenclamide, glimepiride]) specified by the G-BA. The company followed this specification and chose glimepiride as ACT.

Research question B: canagliflozin plus metformin

For this research question, the G-BA specified metformin plus sulfonylurea (glibenclamide, glimepiride) as ACT with the note that human insulin is to be used as treatment option if metformin is inappropriate according to the SPC. The present assessment was conducted versus the ACT specified by the G-BA. The company followed this specification and chose metformin plus glimepiride as ACT.

However, the company additionally defined a specific patient population for which, from the company's point of view, treatment with sulfonylureas is not applicable. The company named sitagliptin plus metformin as ACT for this population. For the present benefit assessment, the patients who cannot be treated with sulfonylureas are considered to be a subpopulation in the therapeutic indication, which cannot be clearly defined. The patient population was therefore not considered.

Research question C: canagliflozin plus sulfonylurea

For this research question, the G-BA specified metformin plus sulfonylurea (glibenclamide, glimepiride) as ACT with the note that human insulin is to be used as treatment option if metformin is inappropriate according to the SPC. The present assessment was conducted versus the ACT specified by the G-BA. The company followed this specification and chose metformin plus glimepiride as ACT.

Research question D: canagliflozin plus sulfonylurea plus metformin

For this research question, the G-BA specified human insulin plus metformin with the note that only human insulin is to be used if metformin is not sufficiently effective or not tolerated according to the SPC. The present assessment was conducted versus the ACT specified by the G-BA. The company stated to follow the ACT, but the dossier contained contradictory information on the implementation of the ACT (insulin instead of human insulin). The

company disregarded the specific note by the G-BA (to use only human insulin if metformin is not sufficiently effective or not tolerated according to the SPC).

Research question E: combination therapy with insulin with or without additional oral antidiabetics

For this research question, the G-BA specified human insulin plus metformin with the note that only human insulin is to be used if metformin is not sufficiently effective or not tolerated according to the SPC. The present assessment was conducted versus the ACT specified by the G-BA. The company followed the specification of the G-BA.

Summary

In summary, the assessment of canagliflozin in the different approved subindications was conducted versus the respective ACTs specified by the G-BA. The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs) with a minimum duration of 24 weeks.

Further information about the research question can be found in Modules 3A to 3E, Sections 3.1, and in Modules 4A to E, Sections 4.2.1, of the dossier, and in Sections 2.9.2, 2.9.3, 2.9.4, 2.9.5 and 2.9.6 of the full dossier assessment.

2.3 Research question A: canagliflozin monotherapy

2.3.1 Information retrieval and study pool (research question A)

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on canagliflozin (studies completed up to 10 January 2014)
- bibliographical literature search on canagliflozin (last search on 22 January 2014)
- search in trial registries for studies on canagliflozin (last search on 13 January 2014)

The company did not identify any direct comparative studies or studies for an indirect comparison on canagliflozin in monotherapy versus the ACT specified by the G-BA.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4 A, Sections 4.2.2 and 4.2.3 of the dossier.

2.3.2 Results on added benefit (research question A)

The company presented no relevant data for the research question on canagliflozin in monotherapy. Hence the added benefit of canagliflozin in monotherapy versus the ACT specified by the G-BA is not proven.

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

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of canagliflozin in monotherapy in comparison with the ACT specified by the G-BA (sulfonylurea [glibenclamide, glimepiride]). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. The company claimed no added benefit for this research question.

Further information on the extent and probability of the added benefit can be found in Module 4A, Section 4.4 of the dossier.

2.3.4 List of included studies (research question A)

Not applicable as the company did not present any relevant studies in its dossier, from which an added benefit of canagliflozin in monotherapy versus the ACT (sulfonylurea [glibenclamide, glimepiride]) could be derived.

2.4 Research question B: canagliflozin plus metformin

2.4.1 Information retrieval and study pool (research question B)

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on canagliflozin (studies completed up to 10 January 2014)
- bibliographical literature search on canagliflozin (last search on 22 January 2014)
- search in trial registries for studies on canagliflozin (last search on 13 January 2014)

To check the completeness of the study pool:

- search in trial registries for studies on canagliflozin (last search on 27 March 2014)

This check produced no deviations from the study pool presented in the dossier.

From the steps of information retrieval mentioned, the company identified 2 studies in the relevant therapeutic indication (DIA3009 [4,5] and DIA3006 [6]). Both studies were unsuitable for the assessment of the added benefit of canagliflozin plus metformin in comparison with the ACT specified by the G-BA. The studies DIA3009 and DIA3006 are described below and the reasons for exclusion explained.

Description and reasons for exclusion of the studies DIA3009 and DIA3006

Study DIA3009

The DIA3009 study is presented in Table 5 and Table 6.

Table 5: Characteristics of the studies included – RCT, direct comparison: canagliflozin plus metformin vs. glimepiride plus metformin

Study	Study design	Population	Interventions, in each case in combination with metformin (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
DIA3009	RCT, double-blind, 3-arm, parallel	Adult patients with type 2 diabetes mellitus with inadequate glycaemic control under metformin monotherapy	Canagliflozin 100 mg (N = 483) canagliflozin 300 mg (N = 485) glimepiride (N = 484) Relevant subpopulation thereof[b]: canagliflozin 100 mg (n = 282) canagliflozin 300 mg (n = 276) glimepiride (n = 280)	Wash-out phase and titration to a stable metformin dose: 10 or 12 weeks[c] Single-blind placebo run-in phase: 2 weeks Randomized study treatment: 104 weeks Follow-up: 30 days after administration of the last dose of the randomized study medication Primary analysis after 52 weeks	157 study centres in 19 countries: Argentina, Bulgaria, Canada, Costa Rica, Denmark, Finland, Germany, India, Israel, Mexico, Norway, Philippines, Poland, Romania, Russia, Slovakia, South Korea, Ukraine, United States 8/2009 until 12/2011	Primary outcome: change in HbA1c (from baseline) after 52 weeks of treatment Secondary outcomes: health-related quality of life, hypoglycaemias, adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
b: According to the information provided by the company in Module 4B of the dossier. The company defined the relevant subpopulation as patients who received no loop diuretics, had an eGFR ≥ 60 mL/min/1.73m^2 or CrCl ≥ 60 mL/min on the day of randomization, received a maximum metformin dose of 3000 mg or no metformin XR until the study visit on the day of randomization.
c: Only for patients whose diabetes treatment had to be switched to fulfil the inclusion criteria for randomization. Depending on the prior therapy, the 12 weeks were divided into a period of up to 2 weeks of metformin dose titration and a 10-week phase with a stable metformin dose.
CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; HbA1c: haemoglobin A1c; N: number of randomized patients; n: relevant subpopulation; RCT: randomized controlled trial; vs.: versus; XR: retard formulation

Table 6: Characteristics of the interventions – RCT, direct comparison: canagliflozin plus metformin vs. glimepiride plus metformin

Study	Interventions	Comparison	Concomitant medication
DIA3009	Canagliflozin 100 mg/day canagliflozin 300 mg/day each in combination with metformin according to the conditions described in the column "Concomitant medication" each orally as individual dose before the first meal; sham titration to maintain blinding (dose levels 1 to 5)	Glimepiride in combination with metformin according to the conditions described in the column "Concomitant medication" orally once daily before the first meal *Titration, dose increase:* ▪ starting dose: 1 mg/day (dose level 1) ▪ dose increase during the course of the study was possible in the following steps: ▫ dose level 2: 2 mg/day ▫ dose level 3: 4 mg/day ▫ dose level 4: 6 mg/day ▫ dose level 5: 8 mg/day[a] ▪ depending on the approval in the respective country, 6 or 8 mg were specified as maximum dose[a] *Basis of decision on dose increase:* ▪ ≥ 50% of the fasting plasma glucose levels measured by the patients (≥ 3 measurements were recommended) > 110 mg/dL (> 6 mmol/L) during the 2 weeks preceding a study visit, and ▪ no hypoglycaemias in this period that, from the investigator's point of view, excluded a dose increase *Interval between 2 dose increases*: ▪ at least 2 weeks in general ▪ in patients with higher blood glucose levels, at the investigator's discretion, also shorter than 2 weeks (e.g. ≤ 1 week) if clinically indicated and conditions for dose increase were fulfilled ▪ longer if the patient required new advice on diet and exercise or if an increased risk of hypoglycaemia in case of dose increase was expected	▪ All antidiabetics used before the start of the study, with the exception of metformin, were discontinued. ▪ Each patient had to have inadequate glycaemic control under diet, exercise and metformin ≥ 2000 mg/day (or ≥ 1500 mg/day if higher doses were not tolerated) for at least 10 weeks before randomization. ▪ The metformin dose was to be maintained during the entire study. ▪ Other antidiabetics were not allowed. ▪ Systemic administration of glucocorticoids for more than 14 consecutive days was not allowed. ▪ Glycaemic rescue medication with pioglitazone[b]

(continued)

Table 6: Characteristics of the interventions – RCT, direct comparison: canagliflozin plus metformin vs. glimepiride plus metformin (continued)

Study	Interventions	Comparison	Concomitant medication
		Dose reduction/discontinuation of randomized study medication: ▪ in case of unexplainable severe or recurrent hypoglycaemias ▪ gradual reduction from one dose level to the next; direct reduction to dose level 1 possible if clinically indicated and at the investigator's discretion; discontinuation of medication was also allowed; if restarting medication after a discontinuation of 7 days was clinically inadequate, study participation could be stopped	

a: The maximum glimepiride dosage approved in Germany is 6 mg/day [7].
b: Only for patients at the highest approved dose level (6 or 8 mg/day); until week 26 depending on reaching different fasting plasma glucose levels; after week 26 depending on the HbA1c.
HbA1c: haemoglobin A1c; RCT: randomized controlled trial; vs.: versus

Study design

The DIA3009 study was a randomized, active-controlled, double-blind approval study sponsored by the company with a randomized study treatment of 104 weeks. Adult patients with type 2 diabetes mellitus were enrolled in whom no sufficient glycaemic control was achieved despite treatment with metformin at a stable dose of ≥ 2000 mg/day (≥ 1500 mg/day if higher doses were not tolerated) during at least 10 weeks (haemoglobin A1c [HbA1c] at the start of the run-in phase ≥ 7.0% and ≤ 9.5%, fasting plasma glucose level at the day of randomization > 110 mg/dL to ≤ 270 mg/dL).

The study included a 1-week screening phase, a wash-out phase with titration of the metformin dose during 10 or 12 weeks (2 weeks – if necessary – as titration phase and 10 weeks as stable metformin phase), a single-blind run-in phase of 2 weeks and a double-blind randomized treatment phase of 104 weeks. The patients were followed-up for 30 days after administration of the last dose of the randomized study medication. Patients who had already received metformin monotherapy at a stable dose for 12 weeks before screening did not have to undergo the wash-out phase.

1452 patients were randomly assigned in a ratio of 1:1:1 to one of the following 3 treatment arms: 100 mg/day canagliflozin (fixed dosage), 300 mg/day canagliflozin (fixed dosage) and glimepiride (titration was to depend on fasting plasma glucose level). 1450 of these 1452 patients received at least one dose of the randomized study medication (modified intention to treat [mITT] population). All patients continued their prior therapy with metformin at a stable dose as concomitant treatment. Other antidiabetics were not allowed.

Primary outcome of the study was the change in HbA1c after 52 weeks of treatment in comparison with the baseline value.

Assessment of the relevance of the study

Target population

For assessing the relevance of the study, it should first be explained that the company limited the population of the DIA3009 study to the target population of interest in accordance with specifications provided in the SPCs of canagliflozin and metformin.

The company defined the target population as those patients who received no loop diuretics, had an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2 or creatinine clearance (CrCl) ≥ 60 mL/min on the day of randomization, received a maximum metformin dose of 3000 mg and no retard formulation of metformin (not approved in Germany) until the study visit on the day of randomization.

Almost 200 patients per treatment arm were excluded from the study population because of this approach. Detailed information on the number of patients in the target population can be found in Table 7.

The company's approach to define the target population of the DIA3009 study is comprehensible.

Table 7: Number of patients in the DIA3009 study and in the target population

Population	**Canagliflozin 100 mg/day (N = 483) n (%)**	**Canagliflozin 300 mg/day (N = 485) n (%)**	**Glimepiride (N = 482) n (%)**
Study population according to Module 4B[a]	478	474	473
Target population[b]	282 (59.0)	276 (58.2)	280 (59.2)

a: In relation to the mITT population (patients for whom a baseline HbA1c and ≥ 1 HbA1c after randomization are available).
b: The number of patients originates from Module 4B. The percentages were calculated on the basis of the number of patients in the study population according to Module 4B.
HbA1c: haemoglobin A1c; mITT: modified intention to treat (patients who have received at least 1 dose of the randomized study medication); n: number of patients in the respective population; N: number of patients in the mITT population

Treatment regimen in the DIA3009 study

As described in the Section *Study design*, the patients either received 100 mg/day canagliflozin (fixed dosage), 300 mg/day canagliflozin (fixed dosage) or glimepiride (titration was to depend on fasting plasma glucose level) after randomization. The patients were required to continue taking their metformin dose from the stable phase of at least 10 weeks before randomization unchanged during the entire study duration (including the run-in phase).

After a starting dose of 1 mg/day, dose steps of 2, 4, and 6 mg/day and – if approved in the respective country – 8 mg/day were envisaged (referred to as "dose levels 1 to 5" in the study) for titration in the glimepiride arm. To maintain blinding, the randomized study medication was also made available in the levels 1 to 5 for sham titration in both canagliflozin arms. Each level of the fixed dosage corresponded to 100 mg/day or 300 mg/day of canagliflozin. The dose level was to be increased if at least 50% of fasting plasma glucose measurements were above a target value of 110 mg/dL during the 2 weeks preceding the study visit/titration (at least 3 measurements were recommended). The interval between 2 dose level increases could be reduced to less than one week if a patient had higher blood glucose levels and the conditions for increasing the dose level were fulfilled. The dose level was not to be increased if, during the 2 weeks preceding the study visit, hypoglycaemias had occurred that, from the investigator's point of view, excluded an increase of the dose level (see Table 6).

It can be inferred from these criteria that there were strict specifications for titration of glimepiride in the DIA3009 study. This became particularly evident in the specification of a concrete near-normal blood glucose level (fasting plasma glucose ≤ 110 mg/dL); especially as the dose was also to be increased for patients whose fasting plasma glucose levels were below 110 mg/dL, and thus in the normal range, in up to half of all measurements. No titration was

to be performed in case of hypoglycaemias that, from the investigator's point of view, excluded a dose increase.

The company compared the DIA study to the P803 sitagliptin study, which was used for a benefit assessment [8], and argued that the course of HbA1c of the 2 studies was comparable so that the DIA3009 study was also suitable for the benefit assessment. This assessment was not followed. The specifications for dose increase were less strict in the P803 study. No specific blood glucose level was determined as target value, for example. Dose titration was – based on blood glucose levels measured by the patient – at the investigator's discretion and was to be conducted according to his or her common practice. The overall goal was to increase the probability to achieve a target HbA1c level of ≤ 6.5%. Accordingly, in this study the reduction in HbA1c was less pronounced, and the differences in the course of the HbA1c between the treatment groups were smaller.

The assessment that the specifications for dose increase were rather strict in the DIA3009 study is also supported by the high proportion of patients who underwent dose increase or who reached the highest dose levels. Table 8 illustrates that the majority of the patients in the modified intention to treat (mITT) population of the DIA3009 study (between 75 and 84% in the 3 treatment arms) received the maximum dose levels 4 or 5, whereby this was a sham titration in the 2 canagliflozin arms. Approximately 75% of the patients in the glimepiride arm received the maximum dose levels.

It can also be assumed that most patients of the mITT population of the DIA3009 study were titrated to their highest dose levels in the study within the first weeks of the study, although titration in the DIA3009 study could be conducted during the entire course of the study. In the glimepiride arm, it took a median time of 13.0 weeks (minimum: 0.1 weeks, maximum: 89.4 weeks) until a patient reached the highest dose level (referring to titration up to week 104). The arithmetic mean was 19.4 weeks (standard deviation: 17.5 weeks) (see Table 8). There were no further data on the exact time course of the titration in the DIA3009 study.

As information on the titration was only available for the mITT population, the proportion of titrated patients and the time to titration in the target population remained unclear.

Table 8: Proportion of patients at the different dose levels (before use of glycaemic rescue medication) and time to reaching the highest dose level until week 104 in the mITT population of the DIA3009 study

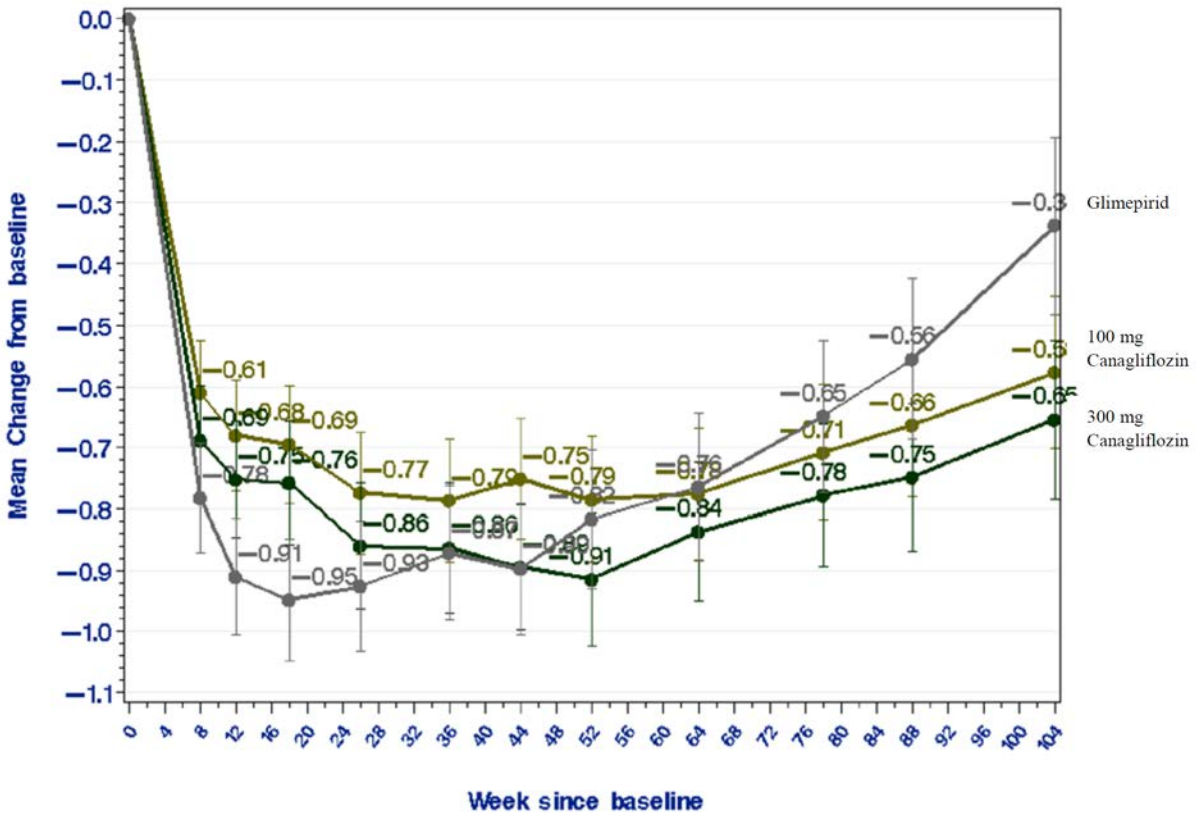
	Canagliflozin 100 mg/day (N = 483)	**Canagliflozin 300 mg/day (N = 485)**	**Glimepiride (N = 482)**
Dose level[a]	**n (%)**	**n (%)**	**n (%)**
dose level 1 (1 mg/day in the glimepiride arm)[b]	27 (5.6)	36 (7.4)	42 (8.7)
dose level 2 (2 mg/day in the glimepiride arm)[b]	26 (5.4)	39 (8.0)	36 (7.5)
dose level 3 (4 mg/day in the glimepiride arm)[b]	23 (4.8)	31 (6.4)	42 (8.7)
dose level 4 (6 mg/day in the glimepiride arm)[b]	214 (44.3)	196 (40.4)	200 (41.5)
dose level 5 (8 mg/day in the glimepiride arm)[b, c]	193 (40.0)	183 (37.7)	162 (33.6)
Time to reaching the highest dose level	**Weeks**	**Weeks**	**Weeks**
median (minimum, maximum)	12.6 (0.1; 98.4)	12.6 (0.1; 95.1)	13.0 (0.1; 89.4)
mean (SD)	17.9 (15.7)	18.2 (17.0)	19.4 (17.5)

a: The data refer to the events until week 104. The data until week 52 were only marginally different from these results. Percentages, Institute's calculation.
b: The canagliflozin dose was not changed (sham titration with double-blind study medication).
c: Dosage is not approved according to the SPC of glimepiride [7].
mITT: modified intention to treat (patients who have received at least 1 dose of the randomized study medication); n: number of patients per dose level; N: number of patients in the mITT population;
SD: standard deviation; SPC: Summary of Product Characteristics

It was clear from the treatment regimen of the DIA3009 study that titration with a blood-glucose lowering drug aimed at a target blood glucose level (fasting plasma glucose ≤ 110 mg/dL) was only possible in the glimepiride arm, but not in the canagliflozin arms. Hence the DIA3009 study constituted a comparison of 2 treatment regimens (therapeutic strategy + drug) and not of 2 drugs alone. It is therefore uncertain whether the effects observed in the study are attributable to the respective drugs used. They can also be caused by the different therapeutic strategies alone.

The courses of the HbA1c value of the DIA study support this assumption. Figure 1 shows the change in HbA1c value in the target population from the DIA3009 study after 104 weeks in comparison with the baseline value. There was no information on the handling of missing values. If one considers the time course of the change in HbA1c, a rapid decrease in HbA1c is evident under target-level directed treatment with glimepiride in the first weeks of the study. The minimum mean HbA1c value was reached after approximately 18 weeks.

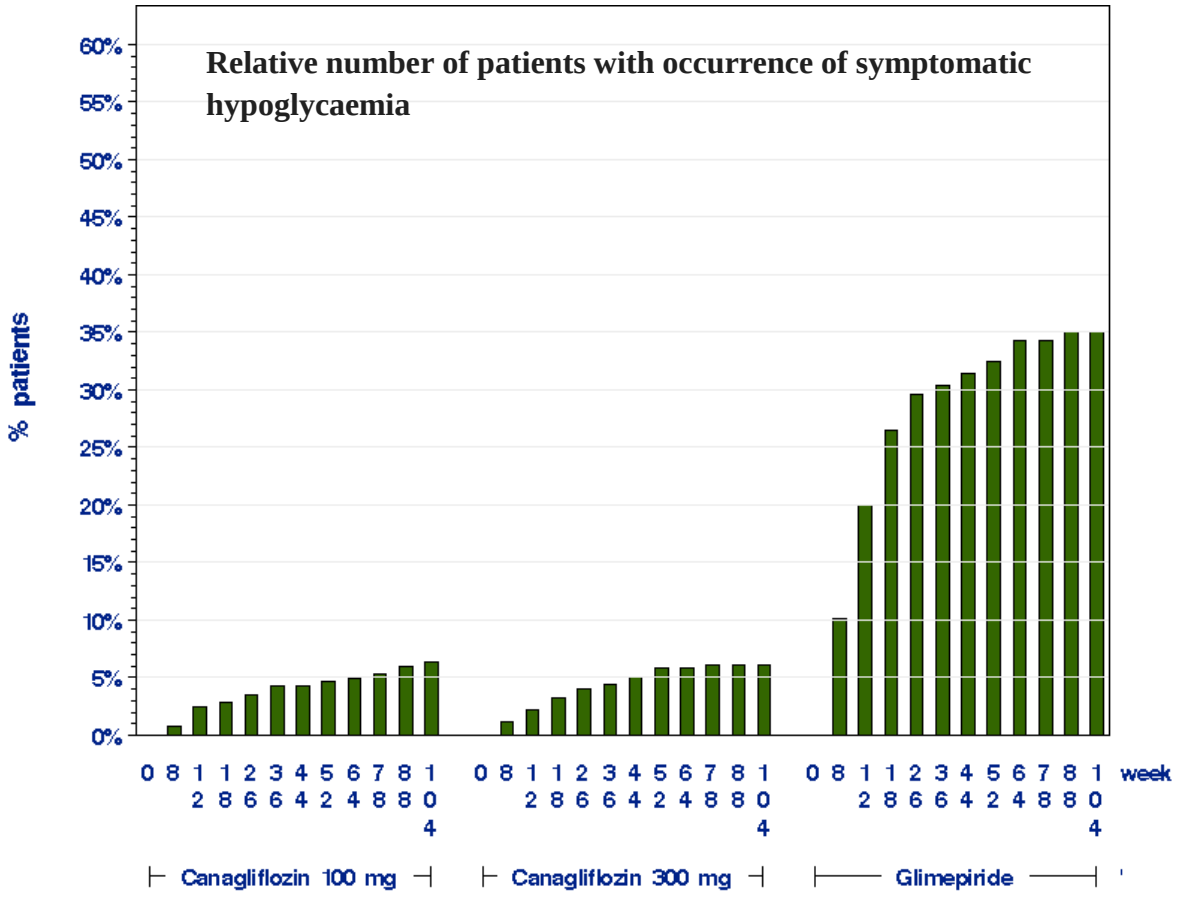
An initial decrease in HbA1c was also observed in the canagliflozin arms. In relation to the glimepiride arm it was markedly less pronounced, however. The difference between the 100 mg canagliflozin arm and the glimepiride arm was greatest after approximately 18 weeks (0.26 percentage points).



The analysis was based on the target population of the DIA3009 study. It was not clear from the information in Module 4B whether missing values were imputed and in how far patients with dose level 5 (8 mg glimepiride; unapproved dosage in Germany) were considered.

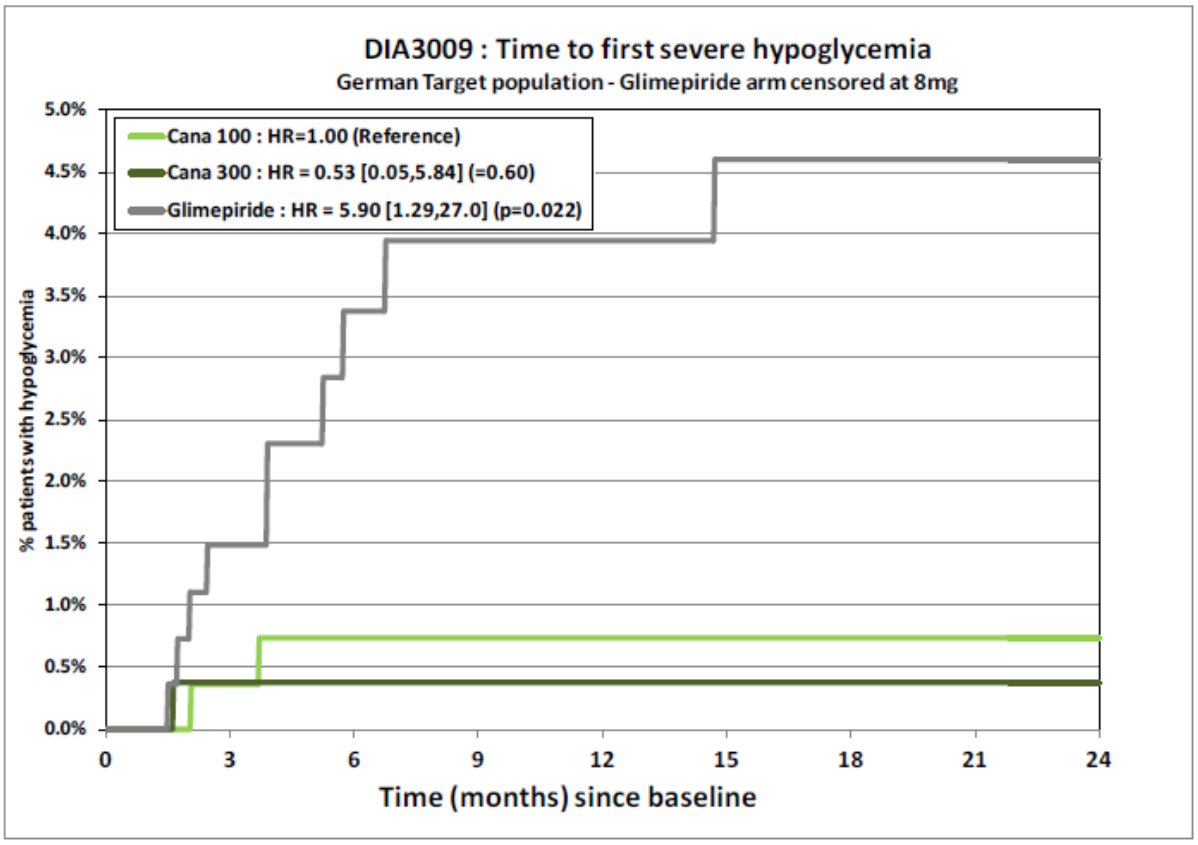
Figure 1: Change in HbA1c value in comparison with the baseline value in the target population in the 3009 study

As can be seen in Figure 2, the time course of the occurrence of symptomatic hypoglycaemias corresponds to the described course of blood-glucose lowering. The cumulative proportion of patients is presented in whom at least one symptomatic hypoglycaemia occurred, in each case in the treatment arms of the study in different week sections. A more detailed time course (e.g. in form of analyses under consideration of recurring hypoglycaemias in the time course) was not provided. In the glimepiride arm, symptomatic hypoglycaemia mainly occurred in the first 18 weeks. In the subsequent week sections, the percentage of additional patients with hypoglycaemias was lower in comparison with the preceding week section. Supporting this, with regard to severe hypoglycaemias, the first severe hypoglycaemia occurred within the first 5 months (approximately 20 weeks) in most patients, and only 2 patients had their first severe hypoglycaemia after month 6 (Figure 3). Overall, it can be inferred from the 2 figures that the difference in the occurrence of hypoglycaemias between the treatment groups was mainly caused by the first weeks of the study.



Symptomatic hypoglycaemias: hypoglycaemic events based on the question in the case report form: “Was the hypoglycaemia symptomatic?" The analysis was based on the target population from the DIA3009 study. It was not clear from the information in Module 4B in how far patients with dose level 5 (8 mg glimepiride; unapproved dosage in Germany) were considered.

Figure 2: Time course of the proportion of patients with symptomatic hypoglycaemias in the target population from the DIA3009 study



Severe hypoglycaemias: hypoglycaemic events requiring assistance of another individual or resulting in seizure or loss of consciousness. Assistance out of politeness was excluded from the operationalization of severe hypoglycaemia.

Figure 3: Time to the first severe hypoglycaemia in the target population of the DIA3009 study

Consideration of the approval status of canagliflozin and glimepiride

In the DIA3009 study canagliflozin was administered in 2 fixed doses: 100 mg/day and 300 mg/day. Dose changes were not envisaged in the course of the study. According to the specifications in the SPC, the recommended starting dose is exclusively 100 mg/day, however. In patients tolerating canagliflozin 100 mg once daily who have an eGFR $\geq$ 60 mL/min/1.73 m^2 or CrCl $\geq$ 60 mL/min and need tighter glycaemic control, the dose can be increased to 300 mg/day [9]. Hence the initial dose of 300 mg/day and the administration of 100 mg/day without the possibility of dose increase do not concur with the specifications in the SPC. This point is discussed by the company. As the study could not be used for the benefit assessment already for the reasons explained above, the company's rationale on the relevance of the 2 canagliflozin arms is not further commented on.

In the glimepiride arm of the study, over 30% of the patients received glimepiride in a dose of 8 mg/day, which is not approved in Germany (see Table 8). The company conducted different analyses to remove the possible bias caused by the 8 mg dose and present the robustness of

the results. As the study could not be used for the benefit assessment already for the reasons explained above, the company's rationale with regard to the different analyses is not further commented on.

In the DIA3009 study, the starting dose of glimepiride (1 mg/day) could be increased to 2 mg/day at first. Further titration was done in 2 mg steps. The SPC recommends a starting dose of 1 mg/day, which can be gradually increased depending on the glycaemic situation – at intervals of 1 to 2 weeks – to 2, 3 or 4 mg glimepiride daily (recommended maximum dose: 6 mg/day). It appears questionable whether a titration step of 2 mg instead of a possible dose increase of 1 mg is suitable for all patients. Furthermore it cannot be excluded that a dose of 3 mg/day or 5 mg/day would have been the required dose for adequate glycaemic control for some of the patients during the course of the titration. The company addressed the glimepiride titration scheme in Module 4B. This is not further commented on, however, because the study could not be used for the benefit assessment already for the reasons stated above.

Summary

In the DIA3009 study, there were relevant differences between the treatment arms with regard to the specified target blood glucose levels and the therapeutic strategies determined by them: In the canagliflozin arms of the study, target blood glucose levels were not aimed at ("titration" to target levels was performed without dose changes and merely to maintain blinding) and fixed dosage was used. In the glimepiride arm, in contrast, titration was specified by an algorithm and orientated towards near-normal target levels. The substantial differences in blood-glucose lowering between treatment groups were apparently induced by the one-sided possibility of reaching a target level for glimepiride. The time course of the occurrence of the key outcomes of the DIA3009 study (hypoglycaemias) corresponded to the course of blood glucose lowering. The results of the DIA3009 study could not be used for assessing the added benefit of canagliflozin plus metformin versus the ACT specified by the G-BA because it remained unclear whether the observed effects are attributable to the drugs or to the therapeutic strategy.

Study DIA3006

The DIA3006 study was a randomized, double-blind, 4-arm approval study sponsored by the company with a duration of 52 weeks. Adult patients with type 2 diabetes mellitus who did not achieve adequate glycaemic control despite metformin treatment were enrolled in the study. The study compared administration of canagliflozin (in the 2 dosages of 100 mg and 300 mg/day) with sitagliptin (100 mg/day) and with placebo with the patients in the placebo arm also receiving sitagliptin after 26 weeks. Metformin was to be maintained in a dose specified by the protocol in all 4 treatment arms during the entire course of the study.

The DIA3006 study allowed no conclusions on the comparison of canagliflozin with the ACT (sulfonylureas [glibenclamide, glimepiride]) and was therefore unsuitable for deriving an added benefit of canagliflozin plus metformin.

The exclusion of the DIA3006 study deviated from the company's approach. From the company's point of view, there is a specific patient population for which treatment with sulfonylureas is unsuitable because of the - from the company's point of view - increased risk of hypoglycaemia of the sulfonylureas. The company named sitagliptin plus metformin as alternative comparator therapy for this patient population. For the present benefit assessment however, patients who cannot be treated with sulfonylureas are considered to be an irrelevant subpopulation in the therapeutic indication (see Section 2.9.3.1 of the full dossier assessment).

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4 B, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.9.3.2.3.1 and 2.9.4.2.3.2 of the full dossier assessment.

2.4.2 Results on added benefit (research question B)

The company presented no relevant data for the research question on canagliflozin plus metformin. Hence the added benefit of canagliflozin plus metformin versus the ACT specified by the G-BA (metformin plus sulfonylurea [glibenclamide, glimepiride]) is not proven.

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

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of canagliflozin plus metformin in comparison with the ACT specified by the G-BA (metformin plus sulfonylurea [glibenclamide, glimepiride]). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This assessment deviates from that of the company.

The company claimed proof of considerable added benefit of canagliflozin plus metformin in comparison with metformin plus sulfonylurea. Moreover, the company claimed proof of a minor added benefit of canagliflozin plus metformin in comparison with its alternative comparator therapy (sitagliptin plus metformin) for the patient population for which, from the company's point of view, sulfonylurea is not an option.

Further information on the extent and probability of the added benefit can be found in Module 4B, Section 4.4 of the dossier, and in Section 2.9.3.2.8 of the full dossier assessment.

2.4.4 List of included studies (research question B)

Not applicable as the company did not present any relevant studies in its dossier, from which an added benefit of canagliflozin plus metformin versus the ACT (metformin plus sulfonylurea [glibenclamide, glimepiride]) could be derived.

2.5 Research question C: canagliflozin plus sulfonylurea

2.5.1 Information retrieval and study pool (research question C)

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on canagliflozin (studies completed up to 10 January 2014)
- bibliographical literature search on canagliflozin (last search on 22 January 2014)
- search in trial registries for studies on canagliflozin (last search on 13 January 2014)

The study pool of the company consisted of the DIA3010 study. This was a 3-arm approval study sponsored by the company with a study duration of 26 weeks (extension phase of 78 weeks). Patients with inadequate glycaemic control under existing antidiabetic treatment (with or without antidiabetic drugs) were enrolled. The study compared the administration of canagliflozin (100 mg/day or 300 mg/day) with placebo administration, in each case in addition to existing antidiabetic treatment. According to the company, 22 patients in the study were treated with a combination of canagliflozin or placebo and sulfonylureas.

The DIA3010 study allowed no comparison of canagliflozin plus sulfonylureas with metformin plus sulfonylureas. Hence the study was not used in the present benefit assessment to derive an added benefit of canagliflozin plus sulfonylureas versus the ACT specified by the G-BA using direct comparisons.

This concurs with the company's approach. The company presented the study and patient characteristics and the risk of bias at study level at first. However, in the further discussion it pointed out that it was a placebo-controlled study and stated the necessity of indirect comparisons. The company presented no indirect comparisons. It justified this by claiming that the number of patients in the target population in the study was too small to reach a sufficient statistical power. Referring to the assessment of dapagliflozin [10], it could not be expected from the point of view of the company to identify relevant studies on the ACT. The company claimed no added benefit for this research question.

The company's approach of information retrieval and specification of the study pool is commented on in Section 2.9.4.2.3 of the full dossier assessment.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4C, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.9.4.2.1 and 2.9.4.2.3 of the full dossier assessment.

2.5.2 Results on added benefit (research question C)

The company presented no relevant data for the research question on canagliflozin plus sulfonylurea. Hence the added benefit of canagliflozin plus sulfonylurea versus the ACT

specified by the G-BA (metformin plus sulfonylurea [glibenclamide, glimepiride]) is not proven.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4C, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier.

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

Since no relevant data were presented for the benefit assessment, there is no proof of an added benefit of canagliflozin plus sulfonylurea in comparison with the ACT specified by the G-BA (metformin plus sulfonylurea [glibenclamide, glimepiride]). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. The company claimed no added benefit for this research question.

Further information about the extent and probability of the added benefit can be found in Module 4C, Section 4.4 of the dossier, and in Section 2.9.4.2.8 of the full dossier assessment.

2.5.4 List of included studies (research question C)

Not applicable as the company did not present any relevant studies in its dossier, from which an added benefit of canagliflozin plus sulfonylurea versus the ACT (metformin plus sulfonylurea [glibenclamide, glimepiride]) could be derived.

2.6 Research question D: canagliflozin plus metformin plus sulfonylurea

2.6.1 Information retrieval and study pool (research question D)

The study pool of the assessment was compiled on the basis of the following information.

Sources of the company in the dossier:

- study lists on canagliflozin (studies completed up to 10 January 2014)
- bibliographical literature search on canagliflozin (last search on 22 January 2014)
- search in trial registries for studies on canagliflozin (last search on 13 January 2014)
- bibliographical literature search on the ACT (last search on 22 January 2014)
- search in trial registries for studies on the ACT (last search on 9 January 2014)

The study pool of the company consisted of the studies DIA3002 and DIA3010. The DIA3002 study was 3-arm approval study sponsored by the company with a study duration of 52 weeks. Patients with inadequate glycaemic control under prior therapy with metformin and sulfonylurea were enrolled. The study compared the administration of canagliflozin (100 mg/day or 300 mg/day) with placebo administration, in each case in addition to continued prior therapy with metformin plus sulfonylurea. A description of the DIA3010 study can be found under research question C (Section 2.5.1).

Both studies (DIA3002 and DIA3010) allowed no direct comparison of canagliflozin plus metformin plus sulfonylureas with human insulin plus metformin. Hence the 2 studies were not used in the present benefit assessment to derive an added benefit of canagliflozin plus metformin plus sulfonylureas versus the ACT specified by the G-BA using direct comparisons.

This concurs with the company's approach. The company presented the study and patient characteristics and the risk of bias at study level for both studies at first. However, in the further discussion it pointed out that these were placebo-controlled studies. It therefore stated the necessity of indirect comparisons. However, the literature search conducted by the company resulted in no relevant studies with the necessary common comparator. The company claimed no added benefit for this research question.

The company's approach of information retrieval and specification of the study pool is commented on in Section 2.9.5.2.3 of the full dossier assessment.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4D, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.9.5.2.1 and 2.9.5.2.3 of the full dossier assessment.

2.6.2 Results on added benefit (research question D)

The company presented no relevant data for the research question on canagliflozin plus metformin plus sulfonylurea. Hence the added benefit of canagliflozin plus metformin plus sulfonylurea versus the ACT specified by the G-BA (human insulin plus metformin [note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC]) is not proven.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4D, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier.

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

Since no relevant data were presented for the benefit assessment, there is no proof of an added benefit of canagliflozin plus metformin plus sulfonylurea in comparison with the ACT specified by the G-BA (human insulin plus metformin [note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC]). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This concurs with the company's result. The company claimed no added benefit for this research question.

Further information about the extent and probability of the added benefit can be found in Module 4D, Section 4.4 of the dossier, and in Section 2.9.5.2.8 of the full dossier assessment.

2.6.4 List of included studies (research question D)

Not applicable as the company did not present any relevant studies in its dossier, from which an added benefit of canagliflozin plus metformin plus sulfonylurea versus the ACT (human insulin plus metformin [treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC]) could be derived.

2.7 Research question E: canagliflozin plus insulin

2.7.1 Information retrieval and study pool (research question E)

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 canagliflozin (studies completed up to 10 January 2014)
- bibliographical literature search on canagliflozin (last search on 22 January 2014)
- search in trial registries for studies on canagliflozin (last search on 13 January 2014)

The company did not identify any direct comparative studies or studies for an indirect comparison on canagliflozin with insulin with or without additional oral antidiabetics versus the ACT specified by the G-BA. The company did not claim an added benefit for this research question.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4E, Sections 4.2.2 and 4.2.3 of the dossier.

2.7.2 Results on added benefit (research question E)

The company presented no relevant data for the research question on canagliflozin plus insulin with or without additional oral antidiabetic. Hence the added benefit of canagliflozin plus insulin with or without additional oral antidiabetic versus the ACT specified by the G-BA is not proven.

2.7.3 Extent and probability of added benefit (research question E)

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of canagliflozin plus insulin with or without additional oral antidiabetic in comparison with the ACT specified by the G-BA (human insulin plus metformin [treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC]). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. The company claimed no added benefit for this research question.

Further information on the extent and probability of the added benefit can be found in Module 4E, Section 4.4 of the dossier.

2.7.4 List of included studies (research question E)

Not applicable as the company did not present any relevant studies in its dossier, from which an added benefit of canagliflozin plus insulin with or without additional oral antidiabetic versus the ACT (human insulin plus metformin [note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC]) could be derived.

2.8 Extent and probability of added benefit – summary

An overview of the extent and probability of added benefit for the different subindications of canagliflozin in comparison with the relevant ACTs is given Table 9.

Table 9: Canagliflozin – extent and probability of added benefit

Research question[a]	Subindication	ACT	Extent and probability of added benefit
A	Monotherapy with canagliflozin	Sulfonylurea (glibenclamide, **glimepiride**[b])	Added benefit not proven
B	Canagliflozin plus metformin	Metformin plus sulfonylurea (glibenclamide, **glimepiride**[b])	Added benefit not proven
C	Canagliflozin plus sulfonylurea	Metformin plus sulfonylurea (glibenclamide, **glimepiride**[b]) note: if metformin is inappropriate according to the SPC, human insulin is to be used as treatment option	Added benefit not proven
D	Canagliflozin plus metformin plus sulfonylurea	Human insulin plus metformin (note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)	Added benefit not proven
E	Canagliflozin plus insulin with or without additional oral antidiabetic	Human insulin plus metformin (note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)	Added benefit not proven

a: Designation corresponds to the coding in the company's dossier.
b: The comparator therapy chosen by the company is printed in **bold**.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The research questions considered by the company do not cover the entire approved therapeutic indication of canagliflozin. The company noted in the dossier that further combination therapies are approved, but, referring to their low relevance for clinical practice, did not submit any corresponding modules. An added benefit for these combination therapies is not proven.

This assessment deviates from that of the company, which claimed proof of a considerable added benefit for the subindication of canagliflozin plus metformin (research question B). Moreover, for this subindication, the company claimed proof of a minor added benefit of canagliflozin plus metformin versus the alternative comparator therapy sitagliptin plus metformin chosen by the company for a population of patients for whom, from the company's point of view, sulfonylureas are unsuitable.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.1 [online]. 28 November 2013 [accessed: 7 February 2014]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. Sittig D, Friedel H. Therapiegruppen und Outcomes von Patienten mit T2DM: Analyse von Leistungsdaten eines Kollektivs von BKK-Versicherten [unpublished]. 2013.

4. Janssen Research & Development. A randomized, double-blind, 3-arm parallel-group, 2-year (104-week), multicenter study to evaluate the efficacy, safety, and tolerability of JNJ-28431754 100 mg and JNJ-28431754 300 mg compared with glimepiride in the treatment of subjects with type 2 diabetes mellitus not optimally controlled on metformin monotherapy: the CANTATA-SU trial (CANagliflozin Treatment And Trial Analysis Sulfonylurea); 52-week core double-blind period; protocol JNJ-28431754 DIA3009; phase 3; study DIA3009; clinical study report [unpublished]. 2012.

5. Janssen Research & Development. A randomized, double-blind, 3-arm parallel-group, 2-year (104-week), multicenter study to evaluate the efficacy, safety, and tolerability of JNJ-28431754 100 mg and JNJ-28431754 300 mg compared with glimepiride in the treatment of subjects with type 2 diabetes mellitus not optimally controlled on metformin monotherapy: the CANTATA-SU trial (CANagliflozin Treatment And Trial Analysis Sulfonylurea); 104-week double-blind treatment phase; 28431754DIA3009; study DIA3009; clinical study report [unpublished]. 2013.

6. Janssen Research & Development. A randomized, double-blind, placebo- and active-controlled, 4-arm, parallel-group, multicenter study to evaluate the efficacy, safety, and tolerability of JNJ-28431754 (canagliflozin) compared with sitagliptin and placebo in the treatment of subjects with type 2 diabetes mellitus with inadequate glycemic control on metformin monotherapy (52-week double-blind phase): the CANTATA-D trial (CANagliflozin Treatment and Trial Analysis - DPP-4 Inhibitor comparator trial); protocol 28431754DIA3006; phase 3; study DIA3006; clinical study report [unpublished]. 2012.

7. Ratiopharm. Glimepirid-ratiopharm 1 mg/2 mg/3 mg Tabletten: Fachinformation [online]. July 2013 [accessed: 6 February 2014]. URL: http://www.fachinfo.de.

8. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Sitagliptin: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A13-02 [online]. 27 June 2013 [accessed: 5 July 2013]. (IQWiG-Berichte; Volume 175). URL: https://www.iqwig.de/download/A13-02_Sitagliptin_Nutzenbewertung-35a-SGB-V.pdf.

9. Janssen. Invokana 100 mg Filmtabletten, Invokana 300 mg Filmtabletten: Fachinformation [online]. November 2013 [accessed: 15 May 2014]. URL: http://www.fachinfo.de.

10. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dapagliflozin: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A12-18 [online]. 13 February 2013 [accessed: 18 March 2013]. (IQWiG-Berichte; Volume 155). URL: https://www.iqwig.de/download/A12-18_Dapagliflozin_Nutzenbewertung_35a-SGB-V.pdf.

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