IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-44

Sitagliptin (type 2 diabetes mellitus) –

Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

Extract

[1] Translation of Sections 2.1 to 2.8 of the dossier assessment *Sitagliptin (Diabetes mellitus Typ 2) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung)* (Version 1.0; Status: 30 September 2016). 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
BMI	body mass index
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycosylated haemoglobin A1c
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
POR	Peto odds ratio
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
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 sitagliptin. The pharmaceutical company (hereinafter referred to as "the company") submitted a first dossier of the drug to be evaluated on 27 March 2013 for the early benefit assessment. This dossier was assessed in dossier assessment A13-02. In this procedure, by decision of 1 October 2013, the G-BA limited its decision until 1 October 2015. By decision of 19 February 2015, this limitation period was prolonged until 1 July 2016. The assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 4 July 2016.

Research question

The aim of this report was to assess the added benefit of sitagliptin for the treatment of adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise in the following approved subindications:

- **Monotherapy with sitagliptin:** in patients for whom metformin is inappropriate due to contraindications or intolerance.
- **Sitagliptin in combination with metformin:** in patients in whom metformin monotherapy does not provide adequate glycaemic control.
- **Sitagliptin in combination with a sulfonylurea:** in patients in whom monotherapy with the maximum tolerated dose of a sulfonylurea does not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- **Sitagliptin in combination with a sulfonylurea and metformin:** in patients in whom dual therapy with these drugs does not provide adequate glycaemic control.
- **Sitagliptin in addition to insulin** (with or without metformin): in patients in whom a stable insulin dose does not provide adequate glycaemic control.

Following the G-BA's subdivision of the therapeutic indication, the assessment was conducted for 5 research questions versus the appropriate comparator therapy (ACT) specified by the G-BA. These are shown in Table 2.

Table 2: Research questions of the benefit assessment of sitagliptin

Research question[a]	**Subindication**	**ACT specified by the G-BA**
A	Monotherapy with sitagliptin	Sulfonylurea (glibenclamide, glimepiride)[b]
B	Sitagliptin plus metformin	Sulfonylurea (glibenclamide, glimepiride)[b] plus metformin
C	Sitagliptin plus sulfonylurea	Human insulin plus sulfonylurea (glibenclamide, glimepiride[c], if applicable treatment only with human insulin)
D	Sitagliptin 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)*
E	Sitagliptin plus insulin (with or without metformin)	Human insulin plus metformin *(note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)*

a: Designation corresponds to the coding in the company's dossier.
b: According to the commission by the G-BA, studies of direct comparisons versus glipizide are to be additionally assessed.
c: The company did not provide any studies for this therapeutic indication so that a possible additional assessment of studies of direct comparisons versus glipizide (in combination with human insulin) is not relevant.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

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

Study TECOS

In its dossier, the company also presented the results of the study TECOS. The TECOS study was a randomized, controlled, double-blind study investigating cardiovascular outcomes in patients with type 2 diabetes mellitus and established vascular disease. The study compared treatment with sitagliptin in addition to existing antidiabetic therapy versus "standard diabetes treatment". In research questions B to E (sitagliptin in combination with other antidiabetic therapies), the company described the results of the total population of the TECOS study. The company did not provide analyses relating to the research questions. However, due to the design of the TECOS study it is questionable whether analyses of the TECOS study relating to research questions would be meaningfully interpretable. Overall, the presentations provided in the dossier were unsuitable to derive conclusions for the individual research questions of the present assessment.

Results

Research question A: sitagliptin monotherapy

The added benefit was assessed versus the ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride]) (research question A1) and, additionally, versus glipizide (research question A2) in this assessment in 2 separate research questions.

Research question A1: sitagliptin versus sulfonylurea (glibenclamide, glimepiride)

As in the first assessment, the company included one study of direct comparison (P251) for research question A1. This study was unsuitable for the assessment of the added benefit because it can be assumed that the majority of the patients enrolled did not fulfil the criteria of the approval of sitagliptin (intolerance or contraindication to metformin).

This resulted in no hint of an added benefit of sitagliptin monotherapy in comparison with the ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride]); an added benefit is therefore not proven.

Research question A2: sitagliptin versus glipizide

The company used a total of 3 studies of direct comparisons versus glipizide for research question A2: P010 (including both extension phases P010-10 and P010-20), P063 and P073. The company had presented all 3 studies already for the first assessment. The 2 studies P010 and P073 had not been relevant for the benefit assessment. Of the 3 studies mentioned, only a subpopulation of study P063 had been relevant. This also applied to the present benefit assessment.

Hence, the same study was available for the present research question as in the first assessment. In the meantime, however, the approval of metformin had been changed insofar as metformin is only contraindicated in creatinine clearance < 45 mL/min. As a result, the circle of patients for whom sitagliptin monotherapy is an option had narrowed accordingly. This also concerns the size of the subpopulation of the P063 study relevant for the present assessment. However, the company only presented the analysis of the P063 study known from the first assessment, although a different analysis would have been required due to the changed approval of metformin. This approach was inconsistent because the company considered the changed approval for the calculation of the patient numbers; and it was also inadequate because this influenced the result of the benefit assessment to a potentially relevant degree due to the low numbers of events. Overall, there were therefore no interpretable data for research question A2.

Hence the added benefit of sitagliptin in monotherapy is not proven.

Research question B: combination of sitagliptin plus metformin

The added benefit was assessed in comparison with the ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride] plus metformin) (research question B1) and,

additionally, versus glipizide plus metformin (research question B2) in this assessment in 2 separate research questions.

Research question B1: sitagliptin plus metformin versus sulfonylurea (glibenclamide, glimepiride) plus metformin

Study pool and study characteristics

Two studies, each of which compared sitagliptin plus metformin versus glimepiride plus metformin (study P803 and study HARMONY 3) were available for the comparison of sitagliptin plus metformin versus the ACT specified by the G-BA. The company had already presented the P803 study for the first assessment; the HARMONY 3 study, which was not conducted by the company itself, was published after completion of the first assessment.

In principle, both studies were relevant for the present research question. Due to the substantially longer duration of the HARMONY 3 study (156 weeks plus 8 weeks follow-up) versus the P803 study (30 weeks), the HARMONY 3 study was primarily used for the derivation of the added benefit of sitagliptin in combination with metformin versus the ACT specified by the G-BA (sulfonylurea [glibenclamide, glimepiride] plus metformin). The P803 study was used as additional information for assessing the certainty of conclusions at outcome level.

The HARMONY 3 study was a randomized, active-controlled, double-blind phase 3 study. Adult patients with type 2 diabetes mellitus were enrolled in whom no sufficient glycaemic control was achieved despite treatment with metformin at a stable dosage of ≥ 1500 mg (or maximum tolerated dosage < 1500 mg/day) and who had a glycosylated haemoglobin A1c (HbA1c) value between 7% and 10% at the last visit in the stabilization phase. Before screening, all patients had to have received metformin for at least 12 weeks and at a stable dosage for at least 8 weeks of this period.

A total of 1049 patients were randomly assigned in a ratio of 3:3:3:1 to the 4 treatment arms albiglutide, glimepiride, sitagliptin and placebo (each with metformin).

Treatment regimen

After randomization, the patients either received a fixed dose of 100 mg/day sitagliptin or a dose of 2 mg/day glimepiride, which could be continued with a masked increase to 4 mg/day starting from week 4. All patients additionally received ≥ 1500 mg/day metformin.

Hence not all dosing options of glimepiride according to the Summary of Product Characteristics (SPC) were available. The patients could not start with the lowest starting dose of 1 mg, and it was not possible to administer titration steps of 1 mg. The dosage could also not be increased to the maximum dosage of up to 6 mg. Hence there was no treatment optimized for the individual patient by using the options of an approval-compliant use of glimepiride. The HARMONY 3 study could be used for the benefit assessment of sitagliptin, however, because, overall, there was approval-compliant use of glimepiride with the use of

2 mg and 4 mg dosages. Due to the uncertainties, at most “hints” of an added benefit could be derived from the HARMONY 3 study.

Risk of bias

The risk of bias at study level was rated as low for the HARMONY 3 study.

Results

Mortality and morbidity

With few events overall, there was no statistically significant difference between the treatment groups for the outcomes “all-cause mortality” and “cardiac and cerebral events” in the HARMONY 3 study. The outcome “health status” was not recorded in the HARMONY 3 study. In the first assessment, no statistically significant difference between the treatment arms was shown in the P803 study for this outcome. An added benefit of sitagliptin plus metformin in comparison with glimepiride plus metformin is not proven for these outcomes.

Health-related quality of life

No usable data on health-related quality of life were available in either of the 2 studies. Hence there was no hint of an added benefit of the combination of sitagliptin plus metformin in comparison with the ACT sulfonylurea (glibenclamide, glimepiride) plus metformin. An added benefit for this outcome is therefore not proven.

Side effects

Regarding side effects, the picture was mixed: In the HARMONY 3 study, there was no statistically significant difference between the treatment groups regarding severe hypoglycaemia, pancreatitis, renal function disorder, treatment discontinuation due to adverse events (AEs) and serious adverse events (SAEs). There was a statistically significant difference in favour of sitagliptin plus metformin versus glimepiride plus metformin for symptomatic hypoglycaemia with a blood glucose threshold of ≤ 70 mg/dL. The result of the P803 study was consistent with the one of the HARMONY 3 study; there was also a statistically significant advantage of sitagliptin plus metformin versus glimepiride plus metformin for symptomatic hypoglycaemia with a blood glucose level of ≤ 50 mg/dL. Overall, there was a hint of lesser harm from sitagliptin plus metformin for the outcome “symptomatic hypoglycaemia”.

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 sitagliptin compared with the ACT is assessed as follows:

Overall, a positive effect remains. This was shown in the outcome category "non-serious/non-severe side effects" for confirmed symptomatic hypoglycaemia (blood glucose ≤ 70mg/dL) with a hint of lesser harm (extent: "considerable").

Regarding mortality and micro- and macrovascular late complications, the HARMONY 3 study showed neither advantage nor disadvantage of the combination of sitagliptin plus metformin versus glimepiride plus metformin. However, the HARMONY 3 study, as the P803 study, was not designed to investigate these outcomes. Hence no sufficient data were available for this also in this reassessment. As a result, the extent of the added benefit of sitagliptin versus glimepiride was "non-quantifiable", but at most "considerable".

Research question B2: sitagliptin plus metformin versus glipizide plus metformin

Study pool and study characteristics

As in the first assessment, one study, in which sitagliptin plus metformin was compared with glipizide plus metformin, was available for this research question (study P024).

See dossier assessment A13-02 for the description of the study and intervention characteristics and of the risk of bias of the already known P024 study.

Results

The results on the added benefit are presented in detail in the first assessment of sitagliptin. As in the first assessment, there was a statistically significant difference between the treatment arms for the 3 outcomes "all-cause mortality", "symptomatic hypoglycaemia" (blood glucose ≤ 50 mg/dL) and "severe hypoglycaemia".

The company presented a new analysis on the outcome "all-cause mortality" for the present benefit assessment because it had been criticized already during the procedure on the first dossier assessment that one of the deaths had been observed in an unsystematic follow-up. These corrected results (8 instead of 9 reported deaths [1 under sitagliptin and 7 under

[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). 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). For further details see [1,2].

glipizide]) from the regular follow-up observation period of the P024 study were therefore used for the present assessment.

Despite the changed data, there was a statistically significant difference in favour of sitagliptin in comparison with glipizide for the outcome "all-cause mortality", as was the case in the first benefit assessment of sitagliptin. All events occurred in men. This again resulted in a hint of an added benefit of sitagliptin, which is limited to the subgroup of men, for the outcome "all-cause mortality". This assessment was based on few events overall observed in the study.

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

On the basis of the results presented, the extent and probability of the added benefit of the drug sitagliptin compared with the ACT is assessed as follows:

In summary, only positive effects remain at outcome level. These consist of a hint of non-quantifiable added benefit in all-cause mortality (only for men) and a hint of lesser harm with considerable extent both for symptomatic hypoglycaemia (blood glucose ≤ 50 mg/dL) and severe hypoglycaemia.

Regarding micro- and macrovascular late complications, there was neither advantage nor disadvantage of the combination of sitagliptin plus metformin versus glipizide plus metformin. However, the P024 study was not designed to investigate these outcomes. Hence there were still no sufficient data on these outcomes. This led to additional uncertainty, particularly for women. In men, there was still an advantage of sitagliptin in all-cause mortality.

Overall, there was therefore a hint of considerable added benefit of sitagliptin versus glipizide for men. Because of the additional uncertainty, in women, the extent of added benefit of sitagliptin versus glipizide is "non-quantifiable", but not more than "considerable" on the basis of the available data.

Due to the treatment directed towards a consistent near-normal target level, the conclusions in both cases (men and women) are limited to patients in whom near-normal levels of blood glucose are aimed at.

In summary, there is a hint of a considerable added benefit in men and a hint of a non-quantifiable added benefit in women of sitagliptin versus glipizide in combination with metformin. In both cases, this added benefit is limited to patients in whom near-normal blood glucose levels are aimed at. For patients without such a treatment goal, there is no proof of added benefit of sitagliptin.

Research question C: combination of sitagliptin plus sulfonylurea

As in the first assessment, the company identified no study on the combination of sitagliptin plus sulfonylurea versus the ACT. Hence the added benefit of sitagliptin plus sulfonylurea is not proven.

Research question D: combination of sitagliptin plus metformin plus sulfonylurea

As in the first assessment, the company identified no study on the combination of sitagliptin plus metformin plus sulfonylurea versus the ACT. Hence the added benefit of sitagliptin plus metformin plus sulfonylurea is not proven.

Research question E: sitagliptin plus insulin (with or without metformin)

The company included the P260 study of direct comparison in the assessment. The study was unsuitable to derive conclusions on the added benefit of sitagliptin in combination with insulin (with or without metformin) in comparison with the ACT because the patients in the comparator arm received no meaningful escalation of their insulin therapy. Despite known inadequate previous insulin therapy, the ongoing basal insulin therapy was continued in some of the patients. In other patients, forced treatment switching to a basal insulin resulted in treatment de-escalation.

There were therefore no suitable data for research question E. Hence there was no hint of an added benefit of sitagliptin in combination with insulin (with or without metformin) in comparison with the ACT; an added benefit is therefore not proven.

Extent and probability of added benefit – summary

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

Table 3: Sitagliptin – extent and probability of added benefit

Research question	Subindication	Comparator therapy	Extent and probability of added benefit
A1	Monotherapy with sitagliptin	Sulfonylurea (glibenclamide, glimepiride)	Added benefit not proven
A2	Monotherapy with sitagliptin	Glipizide[a]	Added benefit not proven
B1	Sitagliptin plus metformin	Sulfonylurea (glibenclamide, glimepiride) plus metformin	Hint of an added benefit (extent "non-quantifiable", at most "considerable")
B2	Sitagliptin plus metformin	Glipizide plus metformin[a]	*Treatment goal near-normal blood glucose levels:* Men: hint of a considerable added benefit Women: hint of added benefit (extent "non-quantifiable", at most "considerable") *Other treatment goal:* added benefit not proven
C	Sitagliptin plus sulfonylurea	Human insulin plus sulfonylurea (glibenclamide, glimepiride, if applicable treatment only with human insulin)	Added benefit not proven
D	Sitagliptin plus metformin plus sulfonylurea	Human insulin plus metformin (note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)	Added benefit not proven
E	Sitagliptin plus insulin (with or without metformin)	Human insulin plus metformin (note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)	Added benefit not proven

a: According to the commission by the G-BA, studies of direct comparisons of sitagliptin versus glipizide (research question A2) and sitagliptin plus metformin versus glipizide plus metformin (research question B2) were additionally assessed.

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

Study TECOS

In its dossier, the company also presented the results of the total population of the TECOS study on the research question B to E. The TECOS study was a randomized, controlled, double-blind study investigating cardiovascular outcomes in patients with type 2 diabetes mellitus and established vascular disease. The study compared treatment with sitagliptin in

addition to existing antidiabetic therapy versus "standard diabetes treatment". In research questions B to E (sitagliptin in combination with other antidiabetic therapies), the company described the results of the total population of the TECOS study. The company did not provide analyses relating to the research questions. However, due to the design of the TECOS study it is questionable whether analyses of the TECOS study relating to research questions would be meaningfully interpretable. Overall, the TECOS study was unsuitable to derive conclusions for the individual research questions of the present assessment.

In summary, the TECOS study had the following limitations:

- The presentations in the dossier allowed no conclusions on the added benefit of sitagliptin for the individual research questions and corresponding ACTs because the company presented no analyses on them. Due to the treatment in the comparator group, it is questionable whether such analyses would be meaningfully interpretable.
- Similarly, no conclusions can be drawn in comparison with "standard treatment" because the study was conducted at a multinational and multicontinental level so that no uniform "standard treatment" can be assumed. There were no regional analyses to be able to make a valid evaluation of potential differences in antidiabetic care as well as on the drug treatment of cardiovascular risk factors.
- There were also no regional analyses for most outcomes considered. Hence it was not clear from the presentations that the results of the TECOS study can be transferred to the German health care context, as was postulated by the company.
- Due to the HbA1c inclusion criterion of 6.5% to 8%, it is also questionable whether a majority of the patients in the TECOS study required escalation of their antidiabetic therapy at all, according to current standards. Add-on therapy with sitagliptin is only approved in patients with inadequate glycaemic control (and, correspondingly, required escalation of their antidiabetic therapy), however, so that the TECOS study was largely conducted outside the current approval of sitagliptin and is therefore not relevant for treatment in the framework of the approval.
- It could also not be seen that patients with inadequate blood glucose and blood pressure control already at the start of the study received adequate escalation of their treatment in the course of the study.
- The TECOS study was unsuitable to draw conclusions on the monotherapy with sitagliptin because sitagliptin monotherapy was not investigated in the TECOS study.

Results from the TECOS study

Overall, the results of the TECOS study for the use of sitagliptin versus placebo, each in addition to antidiabetic "standard treatment", showed

- no disadvantage of sitagliptin regarding all-cause mortality as well as cardiovascular morbidity and mortality

- no advantage of sitagliptin regarding all-cause mortality as well as cardiovascular morbidity and mortality
- a disadvantage of sitagliptin for the outcome “retinopathy”
- At the same time, no conclusions can be drawn for the outcomes “symptomatic confirmed hypoglycaemia” and “severe hypoglycaemia” because there were no analyses in a valid operationalization.

There was a statistically significant result in favour of sitagliptin for the outcome “hospitalization due to hyperglycaemia”. This supported the observation, according to which no adequate antihyperglycaemic treatment was ensured in the comparator arm because blood sugar imbalances were more common than in the sitagliptin arm.

2.2 Research questions

The aim of this report was to assess the added benefit of sitagliptin for the treatment of adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise in the following approved subindications:

- **Monotherapy with sitagliptin:** in patients for whom metformin is inappropriate due to contraindications or intolerance.
- **Sitagliptin in combination with metformin:** in patients in whom metformin monotherapy does not provide adequate glycaemic control.
- **Sitagliptin in combination with a sulfonylurea:** in patients in whom monotherapy with the maximum tolerated dose of a sulfonylurea does not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- **Sitagliptin in combination with a sulfonylurea and metformin:** in patients in whom dual therapy with these drugs does not provide adequate glycaemic control.
- **Sitagliptin in addition to insulin** (with or without metformin): in patients in whom a stable insulin dose does not provide adequate glycaemic control.

Moreover, sitagliptin is also approved in combination with glitazones [3]. However, glitazones are excluded from prescription [4]. This subindication was therefore not considered in the benefit assessment.

Following the G-BA's subdivision of the therapeutic indication, the assessment was conducted for 5 research questions versus the ACT specified by the G-BA. These are shown in Table 4.

Table 4: Research questions of the benefit assessment of sitagliptin

Research question[a]	**Subindication**	**ACT specified by the G-BA**
A	Monotherapy with sitagliptin	Sulfonylurea (glibenclamide, glimepiride)[b]
B	Sitagliptin plus metformin	Sulfonylurea (glibenclamide, glimepiride)[b] plus metformin
C	Sitagliptin plus sulfonylurea	Human insulin plus sulfonylurea (glibenclamide, glimepiride[c], if applicable treatment only with human insulin)
D	Sitagliptin 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)*
E	Sitagliptin plus insulin (with or without metformin)	Human insulin plus metformin *(note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)*

a: Designation corresponds to the coding in the company's dossier.
b: According to the commission by the G-BA, studies of direct comparisons versus glipizide are to be additionally assessed.
c: The company did not provide any studies for this therapeutic indication so that a possible additional assessment of studies of direct comparisons versus glipizide (in combination with human insulin) is not relevant.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

Regarding the ACT, the company generally followed the G-BA's specifications for all research questions.

It additionally described that it also considered studies in comparison with the sulfonylurea glipizide for research questions A and B. According to the G-BA commission, these were also taken into account in the present assessment and considered in an individual research question.

- Research question A: monotherapy with sitagliptin
  - Research question A1: ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride])
  - Research question A2: glipizide
- Research question B: combination of sitagliptin plus metformin
  - Research question B1: ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride] plus metformin)
  - Research question B2: glipizide plus metformin

As glipizide is no longer approved in Germany, the SPC that was last valid in Germany was applied [5]. This was from the year 2000. The current SPC from Austria [6], where glipizide is still approved, was additionally used to also take into account the approval-compliant use of glipizide according to current knowledge.

The company regarded intensified blood-glucose lowering therapy to be required for the patients included in research question E. It stated that it considered treatments with optimization of the insulin therapy for the individual patient as ACT. The company did not provide a complete presentation of the different options, but only described that it considered them to include, among other things, an insulin dose increase while maintaining the ongoing insulin therapy strategy. Studies in which the patients had the possibility to optimize their treatment on an individual basis (including switching treatment type and regimen) were included in this benefit assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. 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.

Study TECOS

In its dossier, the company also presented the results of the study TECOS. The TECOS study was a randomized, controlled, double-blind study investigating cardiovascular outcomes in patients with type 2 diabetes mellitus and established vascular disease. The study compared treatment with sitagliptin in addition to existing antidiabetic therapy versus "standard diabetes treatment". In research questions B to E (sitagliptin in combination with other antidiabetic therapies), the company described the results of the total population of the TECOS study. The company did not provide analyses relating to the research questions. However, due to the design of the TECOS study it is questionable whether analyses of the TECOS study relating to research questions would be meaningfully interpretable. Overall, the presentations provided in the dossier were unsuitable to derive conclusions for the individual research questions of the present assessment. Due to the size and the outcomes investigated (particularly cardiovascular events and all-cause mortality), the TECOS study is described in Appendix A of the full dossier assessment irrespective of this.

2.3 Research question A: sitagliptin monotherapy

2.3.1 Information retrieval (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 sitagliptin (status: 1 April 2016)
- bibliographical literature search on sitagliptin (last search on 23 May 2016)
- search in trial registries for studies on sitagliptin (last search on 4 April 2016)

To check the completeness of the study pool:

- search in trial registries for studies on sitagliptin (last search on 13 July 2016)

No studies other than the ones cited by the company in the dossier were identified from this check.

The company identified 4 studies of direct comparisons from the steps of information retrieval mentioned: P010 [7] (including both extension phases P010-10 and P010-20), P251 [8], P063 [9] and P073 [10]. One study (P251) investigated the comparison of sitagliptin versus the ACT specified by the G-BA (sulfonylurea [glibenclamide, glimepiride]), and 3 studies (P010, P063 and P073) investigated the comparison of sitagliptin versus glipizide. All 4 studies had already been presented in the first dossier on sitagliptin (dossier assessment A13-02 [11]).

2.3.2 Research question A1: sitagliptin versus sulfonylurea (glibenclamide, glimepiride)

As in the first assessment, the data presented by the company were unsuitable to draw conclusions on the added benefit of sitagliptin monotherapy.

The company included the study P251 in its benefit assessment. This was a randomized, active-controlled study on the comparison of sitagliptin with glimepiride with a 30-week treatment duration in older patients with type 2 diabetes mellitus. As already explained in detail in the first assessment of sitagliptin, the study was unsuitable to draw conclusions on the added benefit of sitagliptin in monotherapy because it can be assumed that the majority of the patients enrolled did not fulfil the conditions of the approval of sitagliptin, i.e. intolerance or contraindication to metformin [11].

The theoretical considerations regarding possible transferability to the approved population put forward by the company also could not rectify this. The company presented no data supporting these considerations (see Section 2.9.3.2.3.2 of the full dossier assessment).

Overall, as in the first assessment, there were no relevant data for the assessment of the added benefit of sitagliptin monotherapy versus the ACT (glibenclamide, glimepiride).

A detailed presentation of study P251 and of the reasons for the lacking relevance in the present research question can be found in the first assessment [11], as well as regarding the company's arguments put forward in the present dossier in Section 2.9.2.2.3.2 of the full dossier assessment.

2.3.2.1 Results on added benefit (research question A1)

As in the first assessment, the company presented no relevant study for the assessment of the added benefit of sitagliptin in monotherapy versus the ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride]) in the dossier. Hence there was no hint of an added benefit of sitagliptin monotherapy; an added benefit is therefore not proven.

2.3.2.2 Extent and probability of added benefit (research question A1)

Since, as in the first assessment, no relevant study for the assessment of the added benefit of sitagliptin monotherapy versus the ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride]) was presented, there was no hint of an added benefit of sitagliptin versus the ACT specified by the G-BA (sulfonylurea [glibenclamide, glimepiride]). This deviates from the assessment of the company, which additionally included 3 studies on the comparison of sitagliptin with glipizide and overall derived proof of a considerable added benefit versus sulfonylureas.

2.3.3 Research question A2: sitagliptin versus glipizide

Only the comparison of sitagliptin monotherapy versus glipizide is considered in this section.

2.3.3.1 Study pool (research question A2)

The company used a total of 3 studies of direct comparisons versus glipizide: P010 (including both extension phases P010-10 and P010-20), P063 and P073. The company had presented all 3 studies already for the first assessment. The 2 studies P010 and P073 had not been relevant for the benefit assessment (see dossier assessment A13-02 [11]). Of the 3 studies mentioned, only a subpopulation of study P063 had been relevant. This also applied to the present benefit assessment.

Hence, the same study was available for the present research question as in the first assessment. Since in the meantime the approval of metformin had been changed, however, the same subpopulation of study P063 could not be used for the current benefit assessment. This is further explained below.

2.3.3.1.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: sitagliptin vs. glipizide

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
P063	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial			

See dossier assessment A13-02 [11] for a description of the study and intervention characteristics of the already known P063 study.

Relevant subpopulation: change of the approval of metformin

The approval of sitagliptin monotherapy is limited to patients for whom metformin monotherapy is not an option, either due to an intolerance or due to a contraindication [3]. There are contraindications to metformin for patients with renal failure or renal function disorder [12]. Since only patients with moderate or severe renal function disorder were included in the study P063, this study potentially covered part of the target population for sitagliptin monotherapy. Since glipizide is contraindicated for patients with severe renal function disorder, these patients could not be taken into account for the benefit assessment, as was the case in the first assessment. The remaining patients were those with moderate renal function disorder for whom metformin is not an option according to the SPC.

In the first dossier assessment A13-02, the total subpopulation of patients with moderate renal function disorder from study P063 was used for the benefit assessment. This comprised patients with a creatinine clearance between 30 mL/min and 50 mL/min. At the time point of the first assessment, these patients had a contraindication to the use of metformin. In the meantime, however, the SPC of metformin had been updated insofar as metformin is only contraindicated in creatinine clearance < 45 mL/min [13]. As a result, the circle of patients for whom sitagliptin is an option had narrowed accordingly. This also concerns the size of the subpopulation of the P063 study relevant for the present assessment. The company also described the changes to the approval status of metformin in Module 3 A to estimate the relevant patient numbers. It did not consider this characteristic for the benefit assessment, however. The company's approach was therefore inconsistent and inadequate for the benefit assessment.

This change of the subpopulation had a potential influence on the result because, for the only outcome for which the first assessment had shown a statistically significant result (symptomatic hypoglycaemia), this result had only been caused by few events and the effect had been no more than marginal [11]. The conclusion on the outcome "all-cause mortality" even depended on one single event: In the commenting procedure to the first assessment, the company had selectively corrected the allocation to the relevant subpopulation for one single patient in the control arm. The corresponding result was statistically significant in favour of sitagliptin [14], whereas on the basis of the information provided in the clinical study report (CSR) of study P063, the result was not statistically significant [11,15]. In the present dossier, the company presented the statistically significant result in favour of sitagliptin.

Summary

In summary, the company only presented the analysis of the P063 study known from the first assessment, although a different analysis would have been required due to the changed approval of metformin. This approach was inconsistent because it considered the changed approval for the calculation of the patient numbers; and it was also inadequate because this influenced the result of the benefit assessment to a potentially relevant degree due to the low numbers of events. Overall, there were therefore no interpretable data for research question A2.

2.3.3.2 Results on added benefit (research question A2)

The company presented no interpretable data for the assessment of the added benefit of sitagliptin monotherapy versus glipizide for research question A2. Hence there was no hint of an added benefit of sitagliptin monotherapy; an added benefit is therefore not proven.

2.3.3.3 Extent and probability of added benefit (research question A2)

Since the company presented no interpretable data for the assessment of the added benefit of sitagliptin monotherapy versus glipizide, there was no hint of an added benefit of sitagliptin versus glipizide. The overall assessment deviates substantially from that of the company. The

company claimed proof of a considerable added benefit for the entire subindication of monotherapy with sitagliptin versus sulfonylureas as a group.

Additional information: results from the TECOS study

In research questions B to E (sitagliptin in combination with other antidiabetic therapies), the company described the results of the total population of the TECOS study. The company did not provide analyses relating to the research questions. However, due to the design of the TECOS study it is questionable whether analyses of the TECOS study relating to research questions would be meaningfully interpretable.

The TECOS study was unsuitable to draw conclusions on the monotherapy with sitagliptin because sitagliptin monotherapy was not investigated in the TECOS study. Hence the evidence base for patients who, due to contraindications or intolerance to metformin, have to switch to a different monotherapy was also not improved by the TECOS study.

2.3.3.4 List of included studies

P063

Arjona Ferreira JC, Marre M, Barzilai N, Guo H, Golm GT, Sisk CM et al. Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes and moderate-to-severe chronic renal insufficiency. Diabetes Care 2013; 36(5): 1067-1073.

Merck. A multicenter, randomized, double-blind study to evaluate the efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes mellitus and chronic renal insufficiency who have inadequate glycemic control [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 23.05.2016]. URL: https://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.html.

Merck. A multicenter, randomized, double-blind study to evaluate the efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes mellitus and chronic renal insufficiency who have inadequate glycemic control; study P063; clinical study report [unpublished]. 2011.

Merck Sharp & Dohme. A multicenter, randomized, double-blind study to evaluate the efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes mellitus and chronic renal insufficiency who have inadequate glycemic control [online]. In: EU Clinical Trials Register. [Accessed: 08.09.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2007-003548-32.

Merck Sharp & Dohme. Sitagliptin versus glipizide in participants with type 2 diabetes mellitus and chronic renal insufficiency (MK-0431-063 AM1): full text view [online]. In: ClinicalTrials.gov. 27.04.2016 [Accessed: 25.04.2016]. URL: https://clinicaltrials.gov/ct2/show/study/NCT00509262.

Merck Sharp & Dohme. Sitagliptin versus glipizide in participants with type 2 diabetes mellitus and chronic renal insufficiency (MK-0431-063 AM1): study results [online]. In: ClinicalTrials.gov. 27.04.2015 [Accessed: 08.09.2016]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00509262.

2.4 Research question B: combination of sitagliptin plus metformin

2.4.1 Information retrieval (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 sitagliptin (status: 1 April 2016)
- bibliographical literature search on sitagliptin (last search on 23 May 2016)
- search in trial registries for studies on sitagliptin (last search on 4 April 2016)

To check the completeness of the study pool:

- search in trial registries for studies on sitagliptin (last search on 13 July 2016)

No additional relevant study was identified from the check.

The company identified 3 studies of direct comparisons from the steps of information retrieval mentioned: HARMONY 3, P803 and P024. Two of these studies investigated the comparison of sitagliptin plus metformin versus the ACT specified by the G-BA (sulfonylurea [glibenclamide, glimepiride] plus metformin) and one study (P024) investigated the comparison of sitagliptin plus metformin versus glipizide plus metformin. The studies P803 and P024 had already been presented for the first benefit assessment of sitagliptin (see Commission A13-02 [11]). The multi-arm study HARMONY 3, which was not sponsored by the company, had already been assessed in the dossier assessments of the drugs albiglutide [16] and dulaglutide [17].

The company presented an analysis of the total population of the TECOS study as additional information, but claimed not to have used it for the derivation of an added benefit of sitagliptin. The analysis of the total population of the TECOS study was unsuitable for conclusions on research question B because, on the one hand, only a small part of the TECOS study concurred with the target population for research question B and, on the other, no comparison was conducted versus the ACT. Hence there were also no sufficient data on micro- and macrovascular late complications for research question B (see Appendix A of the full dossier assessment).

2.4.2 Research question B1: sitagliptin plus metformin versus sulfonylurea (glibenclamide, glimepiride) plus metformin

Only the comparison of sitagliptin plus metformin versus the ACT specified by the G-BA (sulfonylurea [glibenclamide, glimepiride]) is considered in this section.

2.4.2.1 Study pool (research question B1)

2.4.2.1.1 Studies included

The studies listed in Table 6 were included in the benefit assessment.

Table 6: Study pool of the company – RCT, direct comparison: sitagliptin + metformin vs. glimepiride + 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)
HARMONY 3	No	No	Yes
P803	No	Yes	No
a: Study for which the company was sponsor. RCT: randomized controlled trial; vs.: versus			

In principle, both studies were relevant for the present research question. Due to the substantially longer duration of the HARMONY 3 study (156 weeks plus 8 weeks follow-up) versus the P803 study (30 weeks), the HARMONY 3 study was primarily used for the derivation of the added benefit of sitagliptin in combination with metformin versus the ACT specified by the G-BA (sulfonylurea [glibenclamide, glimepiride] plus metformin). The P803 study was used as additional information for assessing the certainty of conclusions at outcome level. No meta-analysis was conducted because of the notably different observation periods and the different therapeutic strategies in the comparator arm.

Section 2.4.2.5 contains a reference list for the studies included.

2.4.2.1.2 Study characteristics (research question B1)

Table 7 and Table 8 describe the HARMONY 3 study used for the benefit assessment. The corresponding information on the already known study P803 regarding study design, treatment regimen and study population can be found in dossier assessment A13-02 [11].

Table 7: Characteristics of the included study HARMONY 3 – RCT, direct comparison: sitagliptin + 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]
HARMONY 3	RCT, double-blind, parallel, placebo- and active-controlled	Adult patients with type 2 diabetes mellitus with HbA1c of 7.0% to 10.0% with prior metformin treatment ≥ 1500 mg/day for ≥ 3 months	Each in combination with metformin: ▪ sitagliptin (N = 313) ▪ glimepiride (N = 317) ▪ albiglutide (N = 315)[b] ▪ placebo (N = 104)[b]	▪ Lead-in phase: 4 weeks ▪ Treatment phase: 156 weeks ▪ Follow-up phase: ▪ 8 weeks	289 study centres in 10 countries 2/2009–3/2013	Primary: change in HbA1c after 104 weeks of treatment Secondary: mortality, morbidity hypoglycaemia, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: The arm is not relevant for the assessment and is no longer shown below.
AE: adverse event; HBA1c: glycosylated haemoglobin A1c; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 8: Characteristics of the interventions – RCT, direct comparison: sitagliptin + metformin vs. glimepiride + metformin

Study	Intervention	Comparison	Concomitant medication
HARMONY 3	Sitagliptin (100 mg), once daily, orally + metformin (≥ 1500 mg/day), orally, at current dosage + placebo for glimepiride, once daily, orally *Discontinuation of randomized study medication:* discontinuation in case of severe or repeated hypoglycaemia	Glimepiride, once daily, orally + metformin (≥ 1500 mg/day), orally, at current dosage + placebo for sitagliptin, once daily, orally[a] *Titration, dose increase of glimepiride* ▪ starting dose: 2 mg/day ▪ dose increase (week 4 to 143) to 4 mg/day possible	▪ *OAD treatment* ▫ pretreatment at least 12 weeks before screening with metformin ≥ 1500 mg/day (or maximum tolerated dosage < 1500 mg/day for at least 8 weeks before randomization) at a stable dosage for at least 8 weeks ▪ *As-needed medication:* ▫ glycaemic rescue medication was allowed within a defined range of glucose levels

a: The patients in both arms additionally received once weekly subcutaneous administration of an albiglutide placebo.
HbA1c: glycosylated haemoglobin A1c; OAD: oral antidiabetic; RCT: randomized controlled trial; vs.: versus

Study HARMONY 3

Study design

The HARMONY 3 study was a randomized, active-controlled, double-blind phase 3 study. Adult patients with type 2 diabetes mellitus were enrolled in whom no sufficient glycaemic control was achieved despite treatment with metformin at a stable dosage of ≥ 1500 mg/day (or maximum tolerated dosage < 1500 mg/day) and who had an HbA1c value between 7% and 10% at the last visit in the stabilization phase. Before screening, all patients had to have received metformin for at least 12 weeks and at a stable dosage for at least 8 weeks of this period.

The study consisted of a 4-week stabilization phase, a treatment phase of 156 weeks and a follow-up phase of 8 weeks. One interim analysis was planned per protocol after all patients had reached at least week 104.

A total of 1049 patients were randomly assigned in a ratio of 3:3:3:1 to the 4 treatment arms albiglutide, glimepiride, sitagliptin and placebo (each with metformin). Randomization was stratified by HbA1c value (< 8.0% versus ≥ 8.0%), history of myocardial infarction (yes versus no) and age (< 65 versus ≥ 65 years). In the 2 study arms relevant for the present assessment, 313 patients were randomly allocated to the sitagliptin arm, and 317 patients to the glimepiride arm.

The primary outcome of the study was the change in HbA1c after 104 weeks.

Treatment regimen

After randomization, the patients either received a fixed dose of 100 mg/day sitagliptin or a dose of 2 mg/day glimepiride, which could be continued with a masked increase to 4 mg/day starting from week 4. All patients additionally received ≥ 1500 mg/day metformin. Hyperglycaemic rescue medication of investigator's choice was allowed in addition to the randomized study medication and background therapy within defined glucose thresholds. Patients who had received a dose increase of the study medication had to have received this higher dose for at least 4 weeks before they could be administered hyperglycaemic rescue medication.

The starting dose of glimepiride in the HARMONY 3 study was 2 mg/day and could be increased once to a masked dose of 4 mg from week 4 after randomization. An HbA1c value above 7.5% was the condition for a dose increase from week 12. According to the SPC of glimepiride, in patients in whom no adequate metabolic control is achieved on their maximum daily dose of metformin alone, treatment is initiated with a low dose, which is then gradually increased up to the maximum daily dose of 6 mg depending on the metabolic control aimed at [18]. In the HARMONY 3 study, doses of 1 mg, 3 mg, 5 mg, and 6 mg were not available. The patients could not start with the lowest starting dose of 1 mg, and it was not possible to administer titration steps of 1 mg. The dosage could also not be increased to the maximum dosage of up to 6 mg. Instead of stepwise dose increase, only one single dose increase by

2 mg could be performed. Hence there was no treatment optimized for the individual patient by using the options of an approval-compliant use of glimepiride. The HARMONY 3 study could be used for the benefit assessment of sitagliptin, however, because, overall, there was approval-compliant use of glimepiride with the use of 2 mg and 4 mg dosages.

Figure 1 shows the change in HbA1c value in comparison with the baseline value up to week 164 in the HARMONY 3 study. Missing values were imputed with the last observation carried forward (LOCF) value.

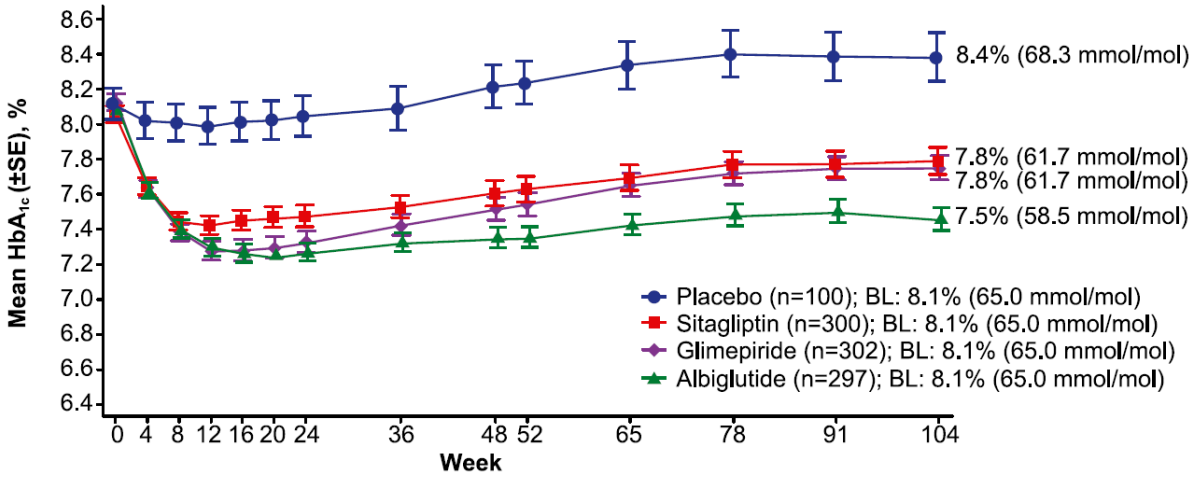

Figure 1: Change in HbA1c value in comparison with the baseline value up to week 164 in the HARMONY 3 study [17]

Overall, the picture of the HbA1c courses was largely consistent in the 2 treatment arms sitagliptin plus metformin and glimepiride plus metformin. The maximum difference in HbA1c between the 2 treatment arms was approximately 0.2 percentage points (read from the graph).

Since the available documents on HARMONY 3 provide no information on the time courses of the hypoglycaemia or other patient-relevant outcomes (cerebral or cardiac events) for the sitagliptin plus metformin and the glimepiride plus metformin arms, an uncertainty remains regarding the influence of the glimepiride treatment regimen. As already presented in the dossier assessments on albiglutide [16] and dulaglutide [17], the HARMONY 3 study was considered to be interpretable despite the limitations described.

Study population

Table 9 shows the characteristics of the patients in the HARMONY 3 study. See dossier assessment A13-02 [11] for the characteristics of the study populations of the already known P803 study.

Table 9: Characteristics of the study populations – RCT, direct comparison: sitagliptin + metformin vs. glimepiride + metformin

Study Characteristics Category	**Sitagliptin + metformin**	**Glimepiride + metformin**
HARMONY 3	N = 302	N = 307
Age [years], mean (SD)	54 (10)	54 (10)
Sex [F/M], %	54/46	49/51
Body weight [kg], mean (SD)	90.3 (19.1)	91.8 (20.4)
BMI [kg/m^2], mean (SD)	32.5 (5.4)	32.5 (5.5)
Duration of diabetes [years], mean (SD)	5.8 (4.7)	6.0 (4.7)
Duration of diabetes [years], n (%)		
< 3 years	96 (31.8)	99 (32.2)
≥ 3 to ≤ 7 years	118 (39.1)	102 (33.2)
> 7 years	88 (29.1)	106 (34.5)
HbA1c value [%], mean (SD)	8.1 (0.8)	8.1 (0.8)
HbA1c value [%], n (%)		
< 8%	160 (53.0)	146 (47.6)
≥ 8%	142 (47.0)[c]	161 (52.4)
Ethnicity, n (%)[a]		
White[b]	226 (74.6)[c]	229 (74.1)[c]
Non-white[d]	77 (25.4)[c]	80 (25.9)[c]
Treatment discontinuation, n (%)	112 (35.8)	116 (36.6)
Study discontinuation, n (%)	62 (19.8)[e]	61 (19.2)[e]

a: Patients could be allocated to more than one category.
b: This group included white (white/Caucasian/European heritage) and white (Arab/North African heritage).
c: Institute's calculation.
d: This group included black (African American/African heritage) and other non-white (native Americans/Alaskans, Asian – central/South Asian heritage, Asia – East Asian heritage, Asia – Japanese heritage, Asia – South East Asian heritage).
e: Furthermore, 1 vs. 2 patients (sitagliptin vs. glimepiride) did not complete the follow-up phase, although they received the study treatment until the end.
BMI: body mass index; F: female; HbA1c: glycosylated haemoglobin A1c; M: male; n: proportion of patients in the category; N: number of patients who received at least one dose of the study medication (safety population); RCT: randomized controlled trial; SD: standard deviation; vs.: versus

There was no important difference between the treatment arms regarding age, sex, body weight, body mass index (BMI), diabetes duration, number of treatment discontinuations and study discontinuations. The mean age of patients was 54 years and mean disease duration with type 2 diabetes mellitus was 6 years. Approximately the same proportion of men and women were included in the 2 study arms. The mean HbA1c value in the 2 study arms was 8.1% at the start of the study, and under 8% in approximately 50% of the patients at the start of the study. Regarding ethnicity, the proportion of whites (about 75%) was notably larger than the proportion of non-whites. 35.8% of the patients in the sitagliptin arm and 36.6% of

the patients in the glimepiride arm, thus approximately one third of the patients in both arms, discontinued treatment. Approximately 20% of the patients in both study arms discontinued the study.

Risk of bias at study level

Table 10 shows the risk of bias of the HARMONY 3 study at study level.

Table 10: Risk of bias at study level – RCT, direct comparison: sitagliptin + metformin vs. glimepiride + metformin

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
HARMONY 3	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for the HARMONY 3 study. This concurs with the company's assessment.

2.4.2.2 Results on added benefit (research question B1)

2.4.2.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.9.3.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - cardiac morbidity
  - cerebral morbidity
  - health status
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - symptomatic hypoglycaemia (blood glucose ≤ 54 mg/dL; blood glucose ≤ 70 mg/dL)
  - severe hypoglycaemia
  - renal function disorder
  - pancreatitis

The choice of patient-relevant outcomes deviated from the choice of the company, which considered cardiac and cerebral morbidity not as separate outcomes, but only as a composite outcome “severe cardiovascular events”. The results on the overall rate of AEs and on the change in body weight used by the company are only presented as additional information in this assessment. In addition, the change in HbA1c is presented as supplementary information. A detailed explanation on the inclusion of outcomes can be found in Section 2.9.3.2.4.3 of the full dossier assessment.

Table 11 shows for which outcomes of the included HARMONY 3 study data were available.

Table 11: Matrix of outcomes – RCT, direct comparison: sitagliptin + metformin vs. glimepiride + metformin

Study	Outcomes											
	All-cause mortality	Cardiac morbidity[a]	Cerebral morbidity[a]	Health status (EQ-5D VAS)	Health-related quality of life	Serious adverse events	Discontinuation due to adverse events	Symptomatic hypoglycaemia (blood glucose ≤ 54 mg/dL)	Symptomatic hypoglycaemia (blood glucose ≤ 70 mg/dL)	Severe hypoglycaemia	Renal function disorder[a]	Pancreatitis[a]
HARMONY 3	Yes	Yes	Yes	No[b]	No[c]	Yes	Yes	–[d]	Yes	Yes	Yes	Yes

a: Consideration of the following events (MedDRA coding): cardiac morbidity: "cardiac disorders" (SOC, SAEs without deaths), cerebral morbidity: "nervous system disorders" (SOC, SAEs without deaths), renal function disorder: "renal and urinary disorders" (SOC, SAEs without deaths), pancreatitis: "pancreatitis" (PT).
b: This outcome was only recorded in the P803 study.
c: The outcome was not recorded in the study.
d: The outcome was recorded in the study, but not published.
MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.4.2.2.2 Risk of bias

Table 12 shows the risk of bias for the outcomes of the HARMONY 3 study.

Table 12: Risk of bias at study and outcome level – RCT, direct comparison: sitagliptin + metformin vs. glimepiride + metformin

Study	Study level	Outcomes											
		All-cause mortality	Cardiac morbidity	Cerebral morbidity	Health status (EQ-5D VAS)	Health-related quality of life	Serious adverse events	Discontinuation due to adverse events	Symptomatic hypoglycaemia (blood glucose ≤ 54 mg/dL)	Symptomatic hypoglycaemia (blood glucose ≤ 70 mg/dL)	Severe hypoglycaemia	Renal function disorder	Pancreatitis
HARMONY 3	L	L	L	L	–[a]	–[b]	L	L	–[c]	H[d]	H[d]	L	L

a: This outcome was only recorded in the P803 study.
b: The outcome was not recorded in the study.
c: The outcome was recorded in the study, but not published.
d: Due to the uncertainties regarding the use of glimepiride assessed as having a high risk of bias (see Section 2.4.2.1.2).
EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

The determination of the risk of bias at outcome level deviates from that of the company.

The risk of bias was rated as low for all outcomes except the hypoglycaemia outcomes. The high risk of bias for these outcomes resulted from the uncertainties on the use of glimepiride in the study (see Section 2.4.2.1.2). This deviates from the assessment of the company, which rated the risk of bias as low also for the hypoglycaemia outcomes.

Detailed reasons for the assessment of the risk of bias can be found in Section 2.9.3.2.4.2 of the full dossier assessment.

2.4.2.2.3 Results

Table 13 and Table 14 contain the results of the HARMONY 3 study on the comparison of sitagliptin plus metformin versus glimepiride plus metformin. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations. See dossier assessment A13-02 [11] for the results of the already known P803 study.

The tables contain results on the overall rate of AEs, on the change in body weight and on the HbA1c as additional information.

Table 13: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: sitagliptin + metformin vs. glimepiride + metformin

Study Outcome category Outcome	Sitagliptin + metformin		Glimepiride + metformin		Sitagliptin + metformin vs. glimepiride + metformin
	N	Patients with event n (%)	N	Patients with event n (%)	RR/Peto OR[a] [95% CI]; p-value[b]
HARMONY 3 (164 weeks)					
Mortality					
All-cause mortality	302	2 (0.7)	307	6 (2.0)	0.37 [0.09; 1.49]; 0.212
Morbidity					
Cardiac morbidity	302	5 (1.7)	307	5 (1.6)	1.02[c] [0.30; 3.48]; > 0.999[c]
Cerebral morbidity	302	1 (0.3)	307	2 (0.7)	0.52[c] [0.05; 5.03]; 0.683[c]
Health status	Outcome not recorded in the HARMONY 3 study[d]				
Health-related quality of life					
	Outcome not recorded				
Side effects					
AEs[e] (supplementary information)	302	251 (83.1)	307	261 (85.0)	–
SAEs[e]	302	32 (10.6)	307	36 (11.7)	0.90 [0.58; 1.42]; 0.712
Discontinuation due to AEs[e]	302	13 (4.3)	307	17 (5.5)	0.78 [0.38; 1.57]; 0.533
Symptomatic hypoglycaemia					
blood glucose ≤ 54 mg/dL[f]	302	ND	307	24 (7.8)	NC
blood glucose ≤ 70 mg/dL	302	9 (3.0)	307	66 (21.5)	0.14 [0.07; 0.27]; < 0.001
Severe hypoglycaemia	302	1 (0.3)	307	1 (0.3)	1.02 [0.06; 16.29]; > 0.999
Renal function disorder	302	0 (0)	307	1 (0.3)	0.34[c] [0.01; 8.28]; 0.515
Pancreatitis[g,h]	302	0 (0)	307	0 (0)	NC

(continued)

Table 13: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: sitagliptin + metformin vs. glimepiride + metformin (continued)

a: Peto OR provided in event numbers ≤ 1% in at least one cell and when the observed Peto OR depending on the respective group size ratio and a 1.1 times tolerated deviation was between the maximum effect sizes indicated in Table III [19].
b: Unconditional exact test (CSZ method according to [20]).
c: Institute's calculation.
d: Results from the P803 study available for this outcome. There is no statistically significant difference between the treatment arms.
e: Hypoglycaemic events were also recorded here.
f: Events up to at least week 104 without consideration of the observations under and after rescue medication.
g: Module 4 B of the dossier indicates 0 vs. 1 events for "pancreatitis". The CSR indicates 0 vs. 0 events for the MedDRA PT "pancreatitis" and 0 vs. 1 events for the MedDRA PT "pancreatitis acute". It cannot be inferred from the information provided by the company in Module 4 B of the dossier, which PT it referred to.
h: According to the CSR, there were 3 events (1 vs. 2) documented and assessed by an independent committee as possible "pancreatitis". However, the results from this assessment are not presented in a comprehensible way in the CSR (corresponding result tables are not available). According to the information provided in the full publication, the 2 cases under glimepiride according to this assessment were not pancreatitis [21]; the assessment result for the one case in the sitagliptin arm is not available.

AE: adverse event; CI: confidence interval; CSR: clinical study report; CSZ: convexity, symmetry, z score; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with event; N: number of analysed patients; ND: no data; OR: odds ratio; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 14: Results (supplementary outcomes: body weight and HbA1c) – RCT, direct comparison: sitagliptin + metformin vs. glimepiride + metformin

Study **Outcome category** **Outcome**	**Sitagliptin + metformin**			**Glimepiride + metformin**			**Sitagliptin + metformin vs. glimepiride + metformin**
	N[a]	**Values at start of study mean (SD)**	**Change at end of study mean[b] (SE)**	**N[a]**	**Values at start of study mean (SD)**	**Change at end of study mean[b] (SE)**	**MD[b,c] [95% CI]; p-value**
HARMONY 3 (104 weeks)							
Supplementary outcomes							
Body weight (kg)	300	90.4 (19.0)	-0.9 (0.2)	302	91.9 (20.5)	1.2 (0.2)	-2.0 [-2.7; -1.4]; < 0.001
HbA1c (%)	See Figure 1 for information on the change in HbA1c value in the course of the study						
	297	8.1 (0.8)	-0.3 (0.1)	299	8.1 (0.8)	-0.4 (0.1)	0.08 [-0.10; 0.26]; 0.381

a: LOCF analysis of the ITT population.
b: Adjusted by region, previous myocardial infarctions, age category and baseline HbA1c; for body weight additionally by baseline body weight.
c: It is unclear where the values on the mean differences come from; the information cannot be found in the CSR.

CI: confidence interval; CSR: clinical study report; HbA1c: haemoglobin A1c; ITT: intention to treat; LOCF: last observation carried forward; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

Mortality

All-cause mortality

There was no statistically significant difference between sitagliptin plus metformin and glimepiride plus metformin for the outcome “all-cause mortality”. Hence there was no hint of an added benefit of sitagliptin plus metformin in comparison with the ACT sulfonylurea (glibenclamide, glimepiride) plus metformin. An added benefit for this outcome is therefore not proven. This deviates from the assessment of the company, which derived proof of an added benefit versus sulfonylureas as a group for the outcome “all-cause mortality”.

Morbidity

Cardiac and cerebral morbidity

There was no statistically significant difference between sitagliptin plus metformin and glimepiride plus metformin for the outcomes “cardiac and cerebral morbidity”. Hence there was no hint of an added benefit of sitagliptin plus metformin in comparison with the ACT sulfonylurea (glibenclamide, glimepiride) plus metformin. An added benefit for these outcomes is therefore not proven. It should be noted that the HARMONY 3 study was not designed to investigate cardiovascular outcomes.

The assessment of the added benefit for these outcomes deviates from that of the company, which derived an indication of an added benefit versus sulfonylureas as a group on the basis of the composite outcome “severe cardiovascular events”. However, it only derived this conclusion from the results on the P024 study from the comparison of sitagliptin plus metformin versus glipizide plus metformin. As described in Section 2.9.3.2.4 of the full dossier assessment, the company presented no analyses on this outcome for the HARMONY 3 study, claiming that there was no operationalization for the outcome “severe cardiovascular events” comparable with the studies P803 and P024. As in the first assessment [11], cardiac and cerebral events are considered as separate outcomes in the present benefit assessment. Furthermore, the results based on the System Organ Classes (SOCs) presented for the HARMONY 3 study were not consistent with the explanations of the company.

Health status

Health status was not recorded in the HARMONY 3 study. In the first assessment, there was no statistically significant difference between the treatment arms in the P803 study for this outcome. Hence there was no hint of an added benefit of the combination of sitagliptin plus metformin in comparison with the ACT sulfonylurea (glibenclamide, glimepiride) plus metformin. An added benefit for this outcome is therefore not proven.

This concurs with the assessment of the company, which, deviating from this, allocated this outcome to health-related quality of life.

Health-related quality of life

No usable data on health-related quality of life were available in either of the 2 studies. Hence there was no hint of an added benefit of the combination of sitagliptin plus metformin in comparison with the ACT sulfonylurea (glibenclamide, glimepiride) plus metformin. An added benefit for this outcome is therefore not proven. This concurs with the company's assessment.

Side effects

Serious adverse events and discontinuation due to adverse events

There were no statistically significant differences between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". Hence there was no hint of greater or lesser harm of the combination of sitagliptin plus metformin in comparison with the ACT sulfonylurea (glibenclamide, glimepiride) plus metformin. An added benefit for this outcome is therefore not proven. This concurs with the company's assessment.

Severe hypoglycaemia

One severe hypoglycaemic event occurred in each of the 2 treatment groups. Hence there was no hint of greater or lesser harm of the combination of sitagliptin plus metformin in comparison with the ACT sulfonylurea (glibenclamide, glimepiride) plus metformin. An added benefit for severe hypoglycaemia is therefore not proven.

This deviates from the assessment of the company, which derived proof of lesser harm of sitagliptin versus sulfonylureas as a group for this outcome.

Symptomatic hypoglycaemia (blood glucose ≤ 54 mg/dL and ≤ 70 mg/dL)

Only results on a blood glucose threshold of ≤ 70 mg/dL were available for the outcome "symptomatic hypoglycaemia". Analyses on hypoglycaemia with a lower blood glucose threshold (≤ 54 mg/dL) were not published for the HARMONY 3 study and were therefore not presented by the company. This would have been principally preferable because they have a higher validity due to the lower blood glucose threshold.

There was a statistically significant difference in favour of sitagliptin plus metformin versus glimepiride plus metformin for symptomatic hypoglycaemia with a blood glucose threshold of ≤ 70 mg/dL. An estimation was conducted to check whether sitagliptin has an advantage over glimepiride regarding symptomatic hypoglycaemia with a blood glucose level ≤ 54 mg/dL. This was based on the 24 symptomatic hypoglycaemic events (in 104 weeks) with a blood glucose level ≤ 54 mg/dL reported for the glimepiride arm, which were known from the dossier assessment on the drug albiglutide [16] and which were contained in the company's dossier. This was therefore the minimum of the events occurred under glimepiride. In a worst case consideration, this number was compared with the 9 cases of symptomatic hypoglycaemia with a blood glucose level ≤ 70 mg/dL in the sitagliptin arm (maximum of the events occurred under sitagliptin with a blood glucose level ≤ 54 mg/dL). This analysis

produced a statistically significant result in favour of sitagliptin (relative risk [RR] of 0.38 [0.18; 0.81], p = 0.009). In the present case, the lack of data on the blood glucose threshold ≤ 54 mg/dL did therefore not raise doubts about the conclusions on symptomatic hypoglycaemia based on the data on the blood glucose threshold ≤ 70 mg/dL.

The result of the P803 study was consistent with the one of the HARMONY 3 study; there was also a statistically significant advantage of sitagliptin plus metformin versus glimepiride plus metformin for symptomatic hypoglycaemia with a blood glucose level of ≤ 50 mg/dL. In the present situation, the results of the P803 study were unsuitable to improve the certainty of results, however. The hypoglycaemia outcomes of both studies had a high risk of bias, which additionally was caused by the same uncertainties. Different treatment regimens with titration of the sulfonylurea to a target level versus a fixed sitagliptin dose in the intervention arm were used in both studies. In addition, the use of glimepiride in the HARMONY 3 study was limited, as described above.

Overall, there was a hint of lesser harm of sitagliptin plus metformin in comparison with the ACT sulfonylurea (glibenclamide or glimepiride) plus metformin for the outcome "symptomatic hypoglycaemia".

This deviates from the assessment of the company, which derived proof of lesser harm of sitagliptin versus sulfonylureas as a group for the outcome "symptomatic hypoglycaemia" with a blood glucose threshold ≤ 70 mg/dL.

Renal function disorder and pancreatitis

Renal function disorder occurred in no patient in the sitagliptin arm and in one patient in the glimepiride arm. Pancreatitis did not occur in any treatment arm. Hence there were no hints of greater or lesser harm of the combination of sitagliptin plus metformin in comparison with the ACT sulfonylurea (glibenclamide or glimepiride) plus metformin. An added benefit for these outcomes is therefore not proven. This concurs with the company's assessment.

2.4.2.3 Subgroups and other effect modifiers

Due to the limited data availability of the HARMONY 3 study, the company presented no subgroup analyses for this. In the first assessment of sitagliptin, no relevant effect modifications were identified for the present research question on the basis of the P803 study. The operationalization of the subgroup analyses by the regions Germany and rest of the world for the P803 study newly submitted by the company was regarded unsuitable (see Section 2.9.3.2.4.3 of the full dossier assessment). No statistically significant and relevant differences were shown for this operationalization either.

This concurs with the assessment of the company, which also identified no relevant effect modifiers.

2.4.2.4 Extent and probability of added benefit (research question B1)

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

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

2.4.2.4.1 Assessment of added benefit at outcome level

The data presented in Section 2.4.2.2 resulted in a hint of lesser harm for the combination of sitagliptin plus metformin in comparison with the ACT sulfonylurea (glibenclamide or glimepiride) plus metformin for symptomatic hypoglycaemia with a blood glucose threshold ≤ 70 mg/dL).

The extent of the respective added benefit at outcome level was estimated from these results (see Table 15).

Table 15: Extent of added benefit at outcome level: combination sitagliptin + metformin vs. glimepiride + metformin

Outcome category **Outcome**	**Sitagliptin + metformin vs. glimepiride + metformin** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	2 (0.7) vs. 6 (2.0) 0.37 [0.09; 1.49] p = 0.212[c]	Lesser benefit/added benefit not proven
Morbidity		
Cardiac morbidity	5 (1.7) vs. 5 (1.6) 1.02 [0.30; 3.48] p > 0.999[c]	Lesser benefit/added benefit not proven
Cerebral morbidity	1 (0.3) vs. 2 (0.7) Peto OR: 0.52 [0.05; 5.03] p = 0.683[c]	Lesser benefit/added benefit not proven
Health status	Outcome not recorded in the HARMONY 3 study[d]	Lesser benefit/added benefit not proven
Health-related quality of life		
	Outcome not recorded	
Side effects		
Overall rate of SAEs	32 (10.6) vs. 36 (11.7) 0.90 [0.58; 1.42] p = 0.712[c]	Greater/lesser harm not proven
Treatment discontinuations due to AEs	13 (4.3) vs. 17 (5.5) 0.78 [0.38; 1.57] p = 0.533[e]	Greater/lesser harm not proven
Symptomatic hypoglycaemia (blood glucose ≤ 70 mg/dL)	9 (3.0) vs. 66 (21.5) 0.14 [0.07; 0.27] p < 0.001[c, f] probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
Severe hypoglycaemia	1 (0.3) vs. 1 (0.3) Peto OR: 1.02 [0.06; 16.29] p > 0.999[c]	Greater/lesser harm not proven
Renal function disorder	0 (0) vs. 1 (0.3) 0.34 [0.01; 8.28] p = 0.515[c]	Greater/lesser harm not proven
Pancreatitis	0 (0.0) vs. 0 (0) Not calculated[c]	Greater/lesser harm not proven

(continued)

Table 15: Extent of added benefit at outcome level: combination sitagliptin + metformin vs. glimepiride + metformin (continued)

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Results consistent with study P803.
d: Results from the P803 study available for this outcome. There is no statistically significant difference between the treatment arms.
e: Results inconsistent with study P803 regarding direction of effect and significance (probability: hint of greater harm, extent: "considerable"): 10 (sitagliptin) vs. 2 (glimepiride) patients had events in the P803 study. This resulted in an RR of 3.86 [1.24: 12.05] and a p-value of 0.020. Due to the substantially longer study duration of the HARMONY 3 study, no greater harm can be assumed despite the resulting inconsistency, however.
f: The P803 study recorded symptomatic hypoglycaemic events with a blood glucose level ≤ 50 mg/dL and ≤ 70 mg/dL. Analogous to the company's approach, symptomatic hypoglycaemic events with a blood glucose level ≤ 50 mg/dL were used for the derivation of the added benefit at outcome level of the P803 study. Due to the lower blood-glucose threshold, these have higher validity.
AE: adverse event; CI: confidence interval; CI_u: upper limit of the CI; MD: mean difference; OR: odds ratio; RR: relative risk; SAE: serious adverse event; vs.: versus

2.4.2.4.2 Overall conclusion on added benefit

Table 16 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of the combination of sitagliptin + metformin compared with glimepiride + metformin

Positive effects	**Negative effects**
Hint of lesser harm – extent: "considerable" (non-serious/non-severe side effects: symptomatic hypoglycaemia)	–
No sufficient data were available on mortality and on micro- and macrovascular late complications.	

Overall, a positive effect remains. This was shown in the outcome category "non-serious/non-severe side effects" for confirmed symptomatic hypoglycaemia (blood glucose ≤ 70mg/dL) with a hint of lesser harm (extent: "considerable").

Regarding mortality and micro- and macrovascular late complications, the HARMONY 3 study showed neither advantage nor disadvantage of the combination of sitagliptin plus metformin versus glimepiride plus metformin. However, the HARMONY 3 study, as the P803 study, was not designed to investigate these outcomes. Hence no sufficient data were available for this also in this reassessment.

As a result, the extent of the added benefit of sitagliptin versus glimepiride was "non-quantifiable", but at most "considerable".

This assessment deviates from that of the company, which derived proof of major added benefit of sitagliptin plus metformin on the basis of the joint consideration of the studies HARMONY 3, P803 (comparison with glimepiride plus metformin) and P024 (comparison with glipizide plus metformin).

Additional information: results from the TECOS study

The company presented an analysis of the total population of the TECOS study as additional information, but claimed not to have used it for the derivation of an added benefit of sitagliptin. The company did not provide analyses relating to the research questions, however. However, due to the design of the TECOS study it is questionable whether analyses of the TECOS study relating to research questions would be meaningfully interpretable.

The analysis of the total population of the TECOS study was unsuitable for conclusions on research question B also because only 30% of the patients included were receiving monotherapy with metformin at the start of the study, thus concurring with the target population of research question B. The results of the TECOS study for the use of sitagliptin versus placebo, each in addition to antidiabetic "standard treatment", showed

- no disadvantage of sitagliptin regarding all-cause mortality as well as cardiovascular morbidity and mortality
- no advantage of sitagliptin regarding all-cause mortality as well as cardiovascular morbidity and mortality
- a disadvantage of sitagliptin for the outcome "retinopathy"
- At the same time, no conclusions can be drawn for the outcomes "symptomatic confirmed hypoglycaemia" and "severe hypoglycaemia" because there were no analyses in a valid operationalization.

2.4.2.5 List of included studies

HARMONY 3

Ahrén B, Johnson SL, Stewart M, Cirkel DT, Yang F, Perry C et al. HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. Diabetes Care 2014; 37(8): 2141-2148.

GlaxoSmithKline. Efficacy and safety of albiglutide in treatment of type 2 diabetes: full text view [online]. In: ClinicalTrials.gov. 12.05.2016 [Accessed: 08.09.2016]. URL: https://clinicaltrials.gov/show/NCT00838903.

GlaxoSmithKline. A randomized, double-blind, placebo- and active-controlled, parallel-group, multicenter study to determine the efficacy and safety of albiglutide when used in combination with metformin compared with metformin plus sitagliptin, metformin plus glimepiride, and metformin plus placebo in subjects with type 2 diabetes mellitus [online]. In: EU Clinical Trials Register. [Accessed: 08.092016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-007660-41.

GlaxoSmithKline. Efficacy and safety of albiglutide in treatment of type 2 diabetes: study results [online]. In: ClinicalTrials.gov. 12.05.2016 [Accessed: 08.09.2016]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00838903.

GlaxoSmithKline. A randomized, double-blind, placebo and active-controlled, parallel-group, multicenter study to determine the efficacy and safety of albiglutide when used in combination with metformin compared with metformin plus sitagliptin, metformin plus glimepiride, and metformin plus placebo in subjects with type 2 diabetes mellitus: year 3 report; study GLP112753; clinical study report [online]. In: GlaxoSmithKline Clinical Study Register. 25.02.2016 [Accessed: 08.09.2016]. URL: http://www.gsk-clinicalstudyregister.com/files/112753/5255/gsk-112753-clinical-study-report-redact.pdf.

P803

Arechavaleta R, Seck T, Chen Y, Krobot KJ, O'Neill EA, Duran L et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab 2011; 13(2): 160-168.

Merck. A phase III, multicenter, double-blind, randmoized study to evaluate the safety and efficacy of the addition of sitagliptin compared with the addition of glimepiride in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 19.05.2016]. URL: https://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.html.

Merck. A phase III, multicenter, double-blind, randmoized study to evaluate the safety and efficacy of the addition of sitagliptin compared with the addition of glimepiride in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin [online]. In: EU Clinical Trials Register. [Accessed: 08.09.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-000145-35.

Merck. A phase III, multicenter, double-blind, randomized study to evaluate the safety and efficacy of the addition of sitagliptin compared with the addition of glimepiride in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin: study P803; clinical study report [unpublished]. 2010.

Merck. A phase III, multicenter, double-blind, randomized study to evaluate the safety and efficacy of the addition of sitagliptin compared with the addition of glimepiride in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin: study P803; Zusatzanalysen [unpublished]. 2009.

Merck Sharp & Dohme. A study to test the safety and efficacy of sitagliptin compared to glimepiride in patients with type 2 diabetes on a stable dose of metformin (0431-803)(COMPLETED): full text view [online]. In: ClinicalTrials.gov. 23.03.2015 [Accessed: 03.05.2016]. URL: https://clinicaltrials.gov/show/NCT00701090.

Merck Sharp & Dohme. A study to test the safety and efficacy of sitagliptin compared to glimepiride in patients with type 2 diabetes on a stable dose of metformin (0431-803)(COMPLETED): study results [online]. In: ClinicalTrials.gov. 23.03.2015 [Accessed: 08.09.2016]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00701090.

2.4.3 Research question B2: sitagliptin plus metformin versus glipizide plus metformin

Only the comparison of the combination of sitagliptin plus metformin versus glipizide plus metformin is considered in this section.

2.4.3.1 Study pool (research question B2)

2.4.3.1.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 17: Study pool – RCT, direct comparison: combination of sitagliptin plus metformin vs. glipizide plus 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)
P024	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial			

The P024 study was already presented in the dossier from 26 March 2013 for the first benefit assessment of sitagliptin (see dossier assessment A13-02 [11]). In its dossier from 30 June 2016, the company presented a new analysis on the outcome “all-cause mortality” of the data already presented in the dossier from 26 March 2013.

Section 2.4.3.5 contains a reference list for the studies included.

2.4.3.1.2 Study characteristics (research question B2)

See dossier assessment A13-02 [11] for the description of the study and intervention characteristics and of the risk of bias of the already known P024 study.

2.4.3.2 Results on added benefit (research question B2)

The results on the added benefit are presented in detail in the first assessment of sitagliptin. The results can also be found in Appendix B of the full present dossier assessment. In the first assessment, there was a statistically significant difference between the treatment arms for the 3 outcomes “all-cause mortality”, “symptomatic hypoglycaemia” (blood glucose ≤ 50 mg/dL) and “severe hypoglycaemia”.

Hereinafter, the results on the outcome “all-cause mortality” are shown, for which the company presented a new analysis.

Risk of bias for the outcome “all-cause mortality”

As in dossier assessment A13-02, the risk of bias for the outcome “all-cause mortality” was rated as low. This concurs with the company’s assessment.

Changed data for the outcome "all-cause mortality"

The change in data for the outcome "all-cause mortality" refers to the company's specification of the deaths occurred under glipizide. According to the information provided in the CSR, the first assessment of sitagliptin reported 8 deaths under glipizide and 1 death under sitagliptin. It was already criticized during the procedure on the first dossier assessment that the CSR described one of the deaths under glipizide as suicide that occurred 41 days after completion of the study. This death originated from an unsystematic follow-up based on a decision by the investigator.

For the present assessment, 8 reported deaths (1 under sitagliptin and 7 under glipizide) from the regular follow-up observation period of the P024 study were therefore used.

Results

Deviating from the company, the RR and not the Peto odds ratio (POR) is shown as effect measure for all-cause mortality. To use the POR, further conditions besides event numbers ≤ 1% in at least one treatment group have to be met. Among other factors, the observed POR depending on the respective group size ratio and a 1.1 times tolerated deviation has to lie between the maximum effect sizes indicated in Table III in Brockhaus 2014 [19], which was not the case in the present situation.

The results on all-cause mortality can be found in the following Table 18.

Table 18: Results (mortality) – RCT, direct comparison: sitagliptin + metformin vs. glipizide + metformin

Study Outcome category Outcome	Sitagliptin + metformin		Glipizide + metformin		Sitagliptin + metformin vs. glipizide + metformin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
P024 (104 weeks)					
Mortality					
All-cause mortality	588	1 (0.2)	584	7 (1.2)[a]	0.14 [0.02; 1.15][b] 0.033[c]

a: According to the explanations in the justification on the G-BA decision on the benefit assessment of sitagliptin from 1 October 2013 [22], the results on all-cause mortality presented in dossier assessment A13-02 [11] have been corrected: sitagliptin: 1 (0.2) vs. glipizide: 8 (1.4). Discrepancies resulted from the fact that the CSR described one suicide that occurred 41 days after completion of the study.
b: Institute's calculation.
c: Unconditional exact test (CSZ method according to [20]).
CI: confidence interval; CSR: clinical study report; CSZ: convexity, symmetry, z score; G-BA: Federal Joint Committee; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Mortality

All-cause mortality

Despite the changed data, there was a statistically significant difference in favour of sitagliptin in comparison with glipizide for the outcome "all-cause mortality", as was the case in the first benefit assessment of sitagliptin (A13-02). This again resulted in a hint of an added benefit of sitagliptin for the outcome "all-cause mortality". This assessment was based on few events overall observed in the study. Using a joint consideration of all studies versus sulfonylurea, the company also derived an added benefit for all-cause mortality.

2.4.3.3 Subgroups and other effect modifiers

As in the first assessment, the subgroup analysis on all-cause mortality is presented according to sex in the present benefit assessment because all deaths occurred in the subgroup of men. In its new dossier, the company additionally presented data on possible effect modifications by region. It considered an influence of the effects between Germany and the rest of the world in each case. It would be more meaningful, however, to pool countries with a comparable health care situation to estimate a potential effect modification by the characteristic "region" (see Section 2.9.3.2.4.3 of the full dossier assessment). However, there was no effect modification by region.

The following Table 19 shows the subgroup analyses on all-cause mortality by sex.

Table 19: Subgroups: outcome "all-cause mortality" by sex – RCT, direct comparison: sitagliptin + metformin vs. glipizide + metformin

Study Outcome	Sitagliptin + metformin		Glipizide + metformin		Sitagliptin + metformin vs. glipizide + metformin	
Characteristic Subgroup	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]	p-value[b]
P024 (104 weeks)						
All-cause mortality						
Sex						
Men	336	1 (0.3)	358	7 (2.0)	0.15 [0.02; 1.23][c]	0.042[c]
Women	252	0 (0)	226	0 (0)	NC	NC
					Interaction:	NC

a: All patients as treated (APaT population).
b: Unconditional exact test (CSZ method according to [20]).
c: Institute's calculation.
CI: confidence interval; CSZ: convexity, symmetry, z score; n: number of patients with event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; RR: relative risk; vs.: versus

As in the first assessment, the test for interaction could not be conducted for the outcome "all-cause mortality" for the effect modifier "sex" because all events only occurred in men. There was an advantage for men in the sitagliptin group, which was statistically significant. Since no

conclusion can be drawn on the effect in women because no events occurred in the 2 treatment arms in the subgroup of women, as in the first assessment, the conclusion on added benefit regarding all-cause mortality is limited to the subgroup of men.

2.4.3.4 Extent and probability of added benefit (research question B2)

The derivation of extent and probability of added benefit at outcome level is shown below under consideration of the new data on all-cause mortality, taking into account the various outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.4.3.4.1 Assessment of added benefit at outcome level

The data presented in Section 2.4.3.2 resulted in a hint of an added benefit of the combination of sitagliptin plus metformin in comparison with glipizide plus metformin for the outcome "all-cause mortality" in the subgroup of men. The extent of added benefit is non-quantifiable because the upper limit of the confidence interval of the effect estimate includes 1 (see Table 19). Furthermore, a hint of lesser harm for the outcomes "symptomatic hypoglycaemia" (blood glucose ≤ 50 mg/dL) and "severe hypoglycaemia", each with considerable extent, for the total population remain unchanged from the first assessment.

2.4.3.4.2 Overall conclusion on added benefit

Table 20 summarizes the results included in the overall consideration on the extent of added benefit under inclusion of the data already known from the first assessment and the newly submitted data on all-cause mortality.

Table 20: Positive and negative effects from the assessment of the combination of sitagliptin plus metformin compared with glipizide plus metformin

Positive effects	**Negative effects**
Sex: men Hint of an added benefit – extent: "non-quantifiable" (all-cause mortality)	—
Hint of lesser harm – extent: "considerable" (non-serious/non-severe side effects: symptomatic hypoglycaemia)	
Hint of lesser harm – extent: "considerable" (serious/severe AEs: severe hypoglycaemias)	
No sufficient data were available on micro- and macrovascular late complications.	

Overall, only positive effects remain at outcome level on the basis of the available and evaluable results. These consist of a hint of non-quantifiable added benefit in all-cause mortality (only for men) and a hint of lesser harm with considerable extent both for symptomatic hypoglycaemia (blood glucose ≤ 50 mg/dL) and severe hypoglycaemia.

Regarding micro- and macrovascular late complications, there was neither advantage nor disadvantage of the combination of sitagliptin plus metformin versus glipizide plus metformin. However, the P024 study was not designed to investigate these outcomes. Hence there were still no sufficient data on these outcomes. This led to additional uncertainty, particularly for women. In men, there was still an advantage of sitagliptin in all-cause mortality.

Overall, there was therefore a hint of considerable added benefit of sitagliptin versus glipizide for men. Because of the additional uncertainty, in women, the extent of added benefit of sitagliptin versus glipizide is "non-quantifiable", but not more than "considerable" on the basis of the available data.

Due to the treatment directed towards a consistent near-normal target level, the conclusions in both cases (men and women) are limited to patients in whom near-normal levels of blood glucose are aimed at.

In summary, there is a hint of a considerable added benefit in men and a hint of a non-quantifiable added benefit in women of sitagliptin versus glipizide in combination with metformin. In both cases, this added benefit is limited to patients in whom near-normal blood glucose levels are aimed at. For patients without such a treatment goal, there is no proof of added benefit of sitagliptin.

The overall assessment deviates substantially from that of the company. The company claimed proof of a major added benefit for the total population of the therapeutic indication "sitagliptin plus metformin".

Additional information: results from the TECOS study

The company presented an analysis of the total population of the TECOS study as additional information, but claimed not to have used it for the derivation of an added benefit of sitagliptin. The company did not provide analyses relating to the research questions, however. However, due to the design of the TECOS study it is questionable whether analyses of the TECOS study relating to research questions would be meaningfully interpretable.

The analysis of the total population of the TECOS study was unsuitable for conclusions on research question B also because only 30% of the patients included were receiving monotherapy with metformin at the start of the study, thus concurring with the target population of research question B. The results of the TECOS study for the use of sitagliptin versus placebo, each in addition to antidiabetic "standard treatment", showed

- no disadvantage of sitagliptin regarding all-cause mortality as well as cardiovascular morbidity and mortality
- no advantage of sitagliptin regarding all-cause mortality as well as cardiovascular morbidity and mortality
- a disadvantage of sitagliptin for the outcome “retinopathy”
- At the same time, no conclusions can be drawn for the outcomes “symptomatic confirmed hypoglycaemia” and “severe hypoglycaemia” because there were no analyses in a valid operationalization.

2.4.3.5 List of included studies

P024

Krobot KJ, Ferrante SA, Davies MJ, Seck T, Meininger GE, Williams-Herman D et al. Lower risk of hypoglycemia with sitagliptin compared to glipizide when either is added to metformin therapy: a pre-specified analysis adjusting for the most recently measured HbA1c value. Curr Med Res Opin 2012; 28(8): 1281-1287.

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Seck T, Nauck M, Sheng D, Sunga S, Davies MJ, Stein PP et al. Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study. Int J Clin Pract 2010; 64(5): 562-576.

Seck TL, Engel SS, Williams-Herman DE, McCrary Sisk C, Golm GT, Wang H et al. Sitagliptin more effectively achieves a composite endpoint for A1C reduction, lack of hypoglycemia and no body weight gain compared with glipizide. Diabetes Res Clin Pract 2011; 93(1): e15-e17.

2.5 Research question C: combination of sitagliptin 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 sitagliptin (status: 1 April 2016)
- bibliographical literature search on sitagliptin (last search on 23 May 2016)
- search in trial registries for studies on sitagliptin (last search on 4 April 2016)

To check the completeness of the study pool:

- search in trial registries for studies on sitagliptin (last search on 13 July 2016)

No relevant studies were identified from this check. The company also identified no relevant study for a comparison of the combination of sitagliptin plus sulfonylurea versus the ACT specified by the G-BA. The company presented an analysis of the total population of the TECOS study as additional information, but claimed not to have used it for the derivation of an added benefit of sitagliptin. The analysis of the total population of the TECOS study was unsuitable for conclusions on research question C because, on the one hand, only a small part of the TECOS study concurred with the target population for research question C and, on the other, no comparison was conducted versus the ACT. Hence there were also no relevant data on long-term cardiovascular morbidity and mortality for research question C.

The evidence base was therefore unchanged in comparison with the first assessment [11]: No relevant study was available for research question C.

2.5.2 Results on added benefit (research question C)

The company presented no relevant data for research question C. Hence there was no hint of an added benefit of the combination of sitagliptin plus sulfonylurea for adults with type 2 diabetes mellitus in comparison with the ACT. An added benefit is therefore not proven.

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 the combination of sitagliptin plus sulfonylurea. The company also claimed no added benefit for this research question.

2.6 Research question D: combination of sitagliptin 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 list on sitagliptin (status: 1 April 2016)
- bibliographical literature search on sitagliptin (last search on 23 May 2016)
- search in trial registries for studies on sitagliptin (last search on 4 April 2016)

To check the completeness of the study pool:

- search in trial registries for studies on sitagliptin (last search on 13 July 2016)

No relevant studies were identified from this check. The company also identified no relevant study for a comparison of the combination of sitagliptin plus sulfonylurea plus metformin versus the ACT specified by the G-BA. The company presented an analysis of the total population of the TECOS study as additional information, but claimed not to have used it for the derivation of an added benefit of sitagliptin. The analysis of the total population of the TECOS study was unsuitable for conclusions on research question D because, on the one hand, only a small part of the TECOS study concurred with the target population for research question D and, on the other, no comparison was conducted versus the ACT. Hence there were also no relevant data on long-term cardiovascular morbidity and mortality for research question D.

The evidence base was therefore unchanged in comparison with the first assessment [11]: No relevant study was available for research question D.

2.6.2 Results on added benefit (research question D)

The company presented no relevant data for research question D. Hence there was no hint of an added benefit of the combination of sitagliptin plus sulfonylurea plus metformin for adults with type 2 diabetes mellitus in comparison with the ACT. An added benefit is therefore not proven.

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 the combination of sitagliptin plus sulfonylurea plus metformin. The company also claimed no added benefit for this research question.

2.7 Research question E: combination of sitagliptin 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 sitagliptin (status: 1 April 2016)
- bibliographical literature search on sitagliptin (last search on 23 May 2016)
- search in trial registries for studies on sitagliptin (last search on 4 April 2016)

To check the completeness of the study pool:

- search in trial registries for studies on sitagliptin (last search on 13 July 2016)

No relevant study was identified from the check.

The company included the P260 study of direct comparison in the assessment [23]. The study was unsuitable to derive conclusions on the added benefit of sitagliptin in combination with insulin (with or without metformin) in comparison with the ACT because the patients in the comparator arm received no meaningful escalation of their insulin therapy. This is explained in detail in the following sections.

Furthermore, the company presented an analysis of the total population of the TECOS study as additional information, but claimed not to have used it for the derivation of an added benefit of sitagliptin. The analysis of the total population of the TECOS study was unsuitable for conclusions on research question E because, on the one hand, only a small part of the TECOS study concurred with the target population for research question E and, on the other, no comparison was conducted versus the ACT. Hence there were also no relevant data on long-term cardiovascular morbidity and mortality for research question E.

Characteristics of study P260

The P260 study was a multicentre, randomized, double-blind, placebo-controlled study sponsored by the company with a treatment duration of 24 weeks. The study included adult patients with type 2 diabetes mellitus who have inadequate glycaemic control despite ongoing treatment with insulin (with or without metformin or sulfonylurea). Patients with HbA1c $\geq 7.5\%$ and $\leq 11.0\%$ and, with additional pretreatment with a sulfonylurea, HbA1c $\geq 7.5\%$ and $\leq 10.0\%$ were eligible for inclusion in the study. Any ongoing prior therapy with a sulfonylurea was discontinued in a 2-week wash-out phase. In addition, all patients were treated with insulin glargine irrespective of their prior insulin therapy. When switching from administration twice daily to once daily, the insulin dose was reduced to 70% to 80% of their prior dose. This was followed by a 2-week placebo run-in phase.

The patients were randomized to additional treatment with sitagliptin 100 mg/day or placebo while continuing their insulin therapy with insulin glargine. Any ongoing stable metformin therapy before the start of the study (at a stable dose of ≥ 1500 mg/day for at least 10 weeks) was also continued. This dose was also maintained during the treatment phase.

During the 24-week treatment phase, from week 2 the patients were "encouraged" to independently titrate their evening dose of insulin to a target level according to a specified algorithm based on self-measured glucose levels. This was a morning fasting plasma glucose level[5] ≥ 72 mg/dL and ≤ 100 mg/dL.

The primary outcome of the study was the change in insulin dose after 24 weeks of treatment. Patients were stratified by the use of metformin and/or a sulfonylurea at the time point of screening.

A total of 660 patients were randomly assigned in a ratio of 1:1 to the 2 treatment arms.

Insulin pretreatment

There was no information since when patients had been receiving insulin therapy. According to the inclusion criteria, however, patients had been treated for at least 10 weeks either with a mixed insulin (with > 70% basal insulin), an intermediate-acting insulin or a long-acting insulin at a stable dose between 15 and 150 units/day. The mean HbA1c value at the start of the study was about 8.8%. This information suggests that the patients in the study were mainly patients who were not at the beginning of their insulin therapy and who had inadequate glycaemic control under the existing therapy. Hence patients in the P260 study concurred with the present research question E.

No treatment escalation in the comparator arm

Whereas the patients in the P260 study received an intensification of their therapy by the administration of sitagliptin in addition to basal insulin (with or without metformin) in the intervention arm, treatment escalation was not mandated in the comparator arm, although treatment escalation would have been required. Treatment with basal insulin (insulin glargine, with or without metformin) was continued in some of the patients, partially with algorithmic reduction of the insulin dose, although the glycaemic control was already inadequate. Some of the patients even had treatment "de-escalation": Based on the available information, before study inclusion > 20% (17% in addition to metformin) of the patients had received mixed insulin, and thus a conventional insulin treatment strategy. Before the start of the study, this treatment was switched to basal insulin therapy with once-daily administration of insulin in the evening. Furthermore, 28% of the patients included had been treated with a sulfonylurea in addition to insulin (26% in addition to insulin and metformin). This was discontinued before the start of the study.

[5] It was not clear from the CSR whether this referred to fasting plasma glucose or fasting blood glucose. Both terms were used as synonyms. Hereinafter, the term "fasting plasma glucose" is used.

The company's assessment that the individual intensification of the insulin treatment by increase of the basal insulin possible in the study constituted a meaningful implementation of the ACT for the research question was not followed. In contrast to the company's description, this also does not concur with the therapeutic strategy of an intensified insulin therapy as the one implemented in the AWARD 4 study in the assessment of dulaglutide [24]. On the contrary, the aim was to achieve blood-glucose lowering to near-normal levels with a basal insulin alone in patients with known inadequate insulin therapy, which is not medically meaningful.

Summary

In summary, despite known inadequate previous insulin therapy, the ongoing basal insulin therapy was continued in some of the patients in the comparator arm of study P260. In other patients, forced treatment switching to a basal insulin resulted in treatment de-escalation. Overall, the P260 study was unsuitable for the assessment of sitagliptin versus the ACT.

2.7.2 Results on added benefit (research question E)

No suitable data were available for research question E – sitagliptin in combination with insulin (with or without metformin). Hence there was no hint of an added benefit of sitagliptin in combination with insulin (with or without metformin) in comparison with the ACT; an added benefit is therefore not proven.

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

Since no suitable study was presented for the benefit assessment, an added benefit assessment of sitagliptin in combination with insulin (with or without metformin) versus the ACT specified by the G-BA was not proven. This deviates from the assessment of the company, which derived an indication of a considerable added benefit for sitagliptin in combination with insulin (with or without metformin).

2.8 Extent and probability of added benefit - summary

An overview of the extent and probability of added benefit for the different subindications of sitagliptin in comparison with the relevant ACTs or versus glipizide/glipizide plus metformin is given below. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

Table 21: Sitagliptin – extent and probability of added benefit

Research question	Subindication	Comparator therapy	Extent and probability of added benefit
A1	Monotherapy with sitagliptin	Sulfonylurea (glibenclamide, glimepiride)	Added benefit not proven
A2	Monotherapy with sitagliptin	Glipizide[a]	Added benefit not proven
B1	Sitagliptin plus metformin	Sulfonylurea (glibenclamide, glimepiride) plus metformin	Hint of an added benefit (extent "non-quantifiable", at most "considerable")
B2	Sitagliptin plus metformin	Glipizide plus metformin[a]	*Treatment goal near-normal blood glucose levels:* men: hint of a considerable added benefit women: hint of added benefit (extent "non-quantifiable", at most "considerable") *Other treatment goal:* added benefit not proven
C	Sitagliptin plus sulfonylurea	Human insulin plus sulfonylurea (glibenclamide, glimepiride, if applicable treatment only with human insulin)	Added benefit not proven
D	Sitagliptin plus metformin plus sulfonylurea	Human insulin plus metformin (note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)	Added benefit not proven
E	Sitagliptin plus insulin (with or without metformin)	Human insulin plus metformin (note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)	Added benefit not proven

a: According to the commission by the G-BA, studies of direct comparisons of sitagliptin versus glipizide (research question A2) and sitagliptin plus metformin versus glipizide plus metformin (research question B2) were additionally assessed.

This deviates from the approach of the company, which derived proof of considerable added benefit for the monotherapy with sitagliptin, proof of major added benefit for the combination of sitagliptin plus metformin, and an indication of considerable added benefit for the combination with insulin (with or without metformin).

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

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Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a16-44-sitagliptin-benefit-assessment-according-to-35a-social-code-book-v.7522.html.