

IQWiG Reports – Commission No. A16-45

**Sitagliptin/metformin
(type 2 diabetes mellitus) –**

**Benefit assessment according to §35a
Social Code Book V¹
(expiry of the decision)**

Extract

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³ Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
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)
POR	Peto odds ratio
RCT	randomized controlled trial
RR	relative risk
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination of sitagliptin/metformin. The pharmaceutical company (hereinafter referred to as “the company”) submitted a first dossier on the drug combination to be evaluated on 27 March 2013 for the early benefit assessment. 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 benefit assessment of the fixed combination of sitagliptin and metformin (hereinafter referred to as “sitagliptin/metformin”) was conducted according to the Summary of Product Characteristics (SPC) for the treatment of adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise in the following subindications.

- **Sitagliptin/metformin:** in patients in whom metformin monotherapy in the maximum tolerated dose does not provide adequate glycaemic control or those already being treated with the combination of sitagliptin and metformin.
- **Sitagliptin/metformin in combination with a sulfonylurea:** in patients in whom a combination of the maximum tolerated dose of both metformin and a sulfonylurea does not provide adequate glycaemic control.
- **Sitagliptin/metformin in addition to insulin:** in patients in whom a stable insulin dose and metformin alone does not provide adequate glycaemic control.

Following the G-BA’s subdivision of the therapeutic indication, the assessment was conducted for 3 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/metformin

Research question ^a	Therapeutic indication	ACT specified by the G-BA
A	Sitagliptin/metformin	Sulfonylurea (glibenclamide, glimepiride) ^b plus metformin
B	Sitagliptin/metformin plus sulfonylurea	Human insulin plus metformin <i>(note: treatment only with human insulin if metformin is not sufficiently effective)</i>
C	Sitagliptin/metformin plus insulin	Human insulin plus metformin <i>(note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)</i>
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. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics		

The assessment was conducted based on patient-relevant outcomes and on 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 A to C (sitagliptin/metformin, if applicable 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.

In addition, not all of the patients included in the study concurred with the target population of the present benefit assessment of the fixed combination of sitagliptin/metformin. Only about 82% of the patients included received treatment with metformin at the start of the study. The proportion of patients whose metformin dose concurred with the mandated dose of at least 1700 mg/day is unknown. The company also presented no analyses of a subpopulation on this.

Due to the size and the outcomes investigated (particularly cardiovascular events and all-cause mortality), the TECOS study and its limitations were assessed and described in detail in

benefit assessment A16-44 on sitagliptin (single agent), which is published at the same time as the present benefit assessment of the fixed combination.

Results

Research question A: sitagliptin/metformin

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

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

Study pool and study characteristics

Two studies, each of which compared sitagliptin/metformin versus glimepiride plus metformin (study P803 and study HARMONY 3), were available for the comparison of sitagliptin/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.

The HARMONY 3 study was a randomized, active-controlled, double-blind phase 3 study investigating the efficacy and safety of albiglutide in combination with metformin in comparison with sitagliptin, glimepiride and placebo (each in combination with metformin). The HARMONY 3 study was potentially relevant for the present benefit assessment. However, the company presented no analyses on the approval-compliant metformin dose of ≥ 1700 mg/day. Since the company did not sponsor the HARMONY 3 study, it cannot be assumed that this approach was results-driven. The company did not present valid data on the transferability of the results from the total population to the population of patients receiving metformin in the approval-compliant daily dose of ≥ 1700 mg.

Hence the underlying data in the present dossier were unchanged in comparison with the procedure for the first benefit assessment: No new analyses were presented on the known P803 study; analyses for the fixed combination of sitagliptin/metformin for the potentially relevant HARMONY 3 study were missing. Since, due to its duration, the HARMONY 3 study was primarily relevant for research question A1, its potential influence is addressed on the basis of the results on the sitagliptin single agent.

Results

The results of the P803 study were presented in detail in the first assessment of sitagliptin/metformin (Commission A13-03) and in the corresponding addendum (Commission A13-29). These resulted in a hint of lesser harm from sitagliptin/metformin for the outcome “symptomatic hypoglycaemia” and a hint of greater harm for the outcome “discontinuation due to adverse events (AEs)”. No hint of added benefit or greater harm of

sitagliptin/metformin in comparison with the ACT was shown for the further patient-relevant outcomes.

The result of the total population of the HARMONY 3 study was largely consistent with this. An exception was the outcome “discontinuation due to AEs”, for which the HARMONY 3 study showed no statistically significant difference between the treatment groups. Since in the total population of the HARMONY 3 study, only few and numerically fewer discontinuations due to AEs occurred under sitagliptin/metformin than under glimepiride plus metformin, it was also assumed for the fixed combination of sitagliptin/metformin that there is no disadvantage of sitagliptin/metformin versus the ACT regarding the outcome “discontinuation due to AEs”.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

On the basis of the results presented, the extent and probability of the added benefit of the drug combination of sitagliptin/metformin 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 \leq 50mg/dL) with a hint of lesser harm (extent: “considerable”).

Regarding mortality and micro- and macrovascular late complications, there was neither advantage nor disadvantage of the fixed combination of sitagliptin/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/metformin versus glimepiride plus metformin was “non-quantifiable”, but at most “considerable”.

Research question A2: sitagliptin/metformin versus glipizide plus metformin

Study pool and study characteristics

As in the first assessment, one study, in which sitagliptin/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.

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].

Results

The results on the added benefit were 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 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/metformin in comparison with glipizide plus metformin for the outcome “all-cause mortality”, as was the case in the first benefit assessment of sitagliptin/metformin. All events occurred in men. This again resulted in a hint of an added benefit of sitagliptin/metformin, 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 combination of sitagliptin/metformin 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/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/metformin in all-cause mortality.

Overall, there was therefore a hint of considerable added benefit of sitagliptin/metformin versus glipizide plus metformin for men. Because of the additional uncertainty, in women, the extent of added benefit of sitagliptin/metformin versus glipizide plus metformin 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/metformin versus glipizide plus 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/metformin.

Research question B: sitagliptin/metformin plus sulfonylurea

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

Research question C: sitagliptin/metformin plus insulin

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/metformin in combination with insulin 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 C. Hence there was no hint of an added benefit of sitagliptin/metformin in combination with insulin in comparison with the ACT; an added benefit is therefore not proven.

Extent and probability of added benefit – summary

Table 3 presents a summary of the extent and probability of the added benefit of sitagliptin/metformin.

Table 3: Sitagliptin/metformin – extent and probability of added benefit

Research question	Subindication	Comparator therapy	Extent and probability of added benefit
A1	Sitagliptin/metformin	Sulfonylurea (glibenclamide, glimepiride) plus metformin	Hint of an added benefit (extent “non-quantifiable”, at most “considerable”)
A2	Sitagliptin/metformin	Glipizide plus metformin ^a	<p><i>Treatment goal near-normal blood glucose levels:</i></p> <p>Men: hint of a considerable added benefit</p> <p>Women: hint of an added benefit (extent “non-quantifiable”, at most “considerable”)</p> <p><i>Other treatment goal:</i> added benefit not proven</p>
B	Sitagliptin/metformin plus sulfonylurea	Human insulin plus metformin (note: treatment only with human insulin if metformin is not sufficiently effective)	Added benefit not proven
C	Sitagliptin/metformin plus insulin	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
<p>a: According to the commission by the G-BA, studies of direct comparisons of sitagliptin/metformin versus glipizide plus metformin (research question A2) were additionally assessed. G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics</p>			

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

2.2 Research questions

The benefit assessment of the fixed combination of sitagliptin/metformin was conducted according to the SPC [3] for the treatment of adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise in the following subindications.

- **Sitagliptin/metformin:** in patients in whom metformin monotherapy in the maximum tolerated dose does not provide adequate glycaemic control or those already being treated with the combination of sitagliptin and metformin.
- **Sitagliptin/metformin in combination with a sulfonylurea:** in patients in whom a combination of the maximum tolerated dose of both metformin and a sulfonylurea does not provide adequate glycaemic control.
- **Sitagliptin/metformin in addition to insulin:** in patients in whom a stable insulin dose and metformin alone does not provide adequate glycaemic control.

Moreover, sitagliptin/metformin 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 3 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/metformin

Research question ^a	Therapeutic indication	ACT specified by the G-BA
A	Sitagliptin/metformin	Sulfonylurea (glibenclamide, glimepiride) ^b plus metformin
B	Sitagliptin/metformin plus sulfonylurea	Human insulin plus metformin <i>(note: treatment only with human insulin if metformin is not sufficiently effective)</i>
C	Sitagliptin/metformin plus insulin	Human insulin plus metformin <i>(note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)</i>
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. 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 question A. 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: combination of sitagliptin plus metformin
 - Research question A1: ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride] plus metformin)
 - Research question A2: 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 C. 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. In this benefit assessment, studies in which the patients had the possibility to optimize their treatment on an individual basis (including switching treatment type and regimen) were included.

The benefit assessment of sitagliptin/metformin was conducted according to the SPC [3] for the patient populations described above and the approval-compliant daily dosage of the fixed combination (sitagliptin: 100 mg; metformin: ≥ 1700 mg). This deviated from the company's approach, which did not limit the study inclusion to studies with the dosages mentioned.

The assessment was conducted based on patient-relevant outcomes and on 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 A to C (sitagliptin/metformin, if applicable 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.

In addition, not all of the patients included in the study concurred with the target population of the present benefit assessment of the fixed combination of sitagliptin/metformin. Only about 82% of the patients included received treatment with metformin at the start of the study. The proportion of patients whose metformin dose concurred with the mandated dose of at least 1700 mg/day is unknown. The company also presented no analyses of a subpopulation on this.

Overall, the presentations provided in the dossier were unsuitable to derive conclusions for the individual research questions of the present assessment. Irrespective of this, due to the size and the outcomes investigated (particularly cardiovascular events and all-cause mortality), the TECOS study was assessed and described in detail in Appendix A of benefit assessment A16-44 on sitagliptin (single agent) [7], which is published at the same time as the present benefit assessment of the fixed combination.

2.3 Research question A: sitagliptin/metformin

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 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/metformin versus the ACT specified by the G-BA (sulfonylurea [glibenclamide, glimepiride] plus metformin) and one study (P024) investigated the comparison of sitagliptin/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 [8]). 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 [9] and dulaglutide [10].

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/metformin. The analysis of the total population of the TECOS study was unsuitable for conclusions on research question A because, on the one hand, only a small part of the TECOS study concurred with the target population for research question A and, on the other, no comparison was conducted versus the ACT (see Section 2.2). Hence there were also no sufficient data on micro- and macrovascular late complications for research question A.

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

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

2.3.2.1 Study pool (research question A1)

The studies listed in Table 5 were included in the benefit assessment.

Table 5: 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

No analysis of the HARMONY 3 study for the fixed combination of sitagliptin/metformin

The HARMONY 3 study was a randomized, active-controlled, double-blind phase 3 study investigating the efficacy and safety of albiglutide in combination with metformin in comparison with sitagliptin, glimepiride and placebo (each in combination with metformin). 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. The study included adult patients with type 2 diabetes mellitus who, according to the inclusion criteria of the study, had received metformin for at least 12 weeks before the start of the study and whose metformin dose ≥ 1500 mg/day had been stable for at least 8 weeks.

The HARMONY 3 study was potentially relevant for the present benefit assessment. However, the company presented no analyses on the approval-compliant metformin dose of ≥ 1700 mg/day. Since the company did not sponsor the HARMONY 3 study, it cannot be assumed that this approach was results-driven.

The company did not present valid data on the transferability of the results from the total population to the population of patients receiving metformin in the approval-compliant daily dose of ≥ 1700 mg. The arguments put forward by the company in the dossier that general transferability can be assumed on the basis of the results for the studies P803 and P024 shown in addendum A13-29 [11] are inadequate. On the one hand, the P803 study was unsuitable to prove transferability already due to a major deviation in study duration (30 weeks [P803] versus 164 weeks [HARMONY 3]). On the other, the P024 study was not relevant for the present research question. Hence, as in the first assessment, only results from the P803 study were available for the fixed combination of sitagliptin/metformin.

Since, due to its duration, the HARMONY 3 study was primarily relevant for research question A1, its potential influence is addressed on the basis of the results on the sitagliptin single agent (dossier assessment A16-44) in the following sections. A detailed description of the HARMONY 3 study can be found in dossier assessment A16-44.

Underlying data of study P803 unchanged

The P803 study was already presented in the dossier from 27 March 2013 for the first benefit assessment of sitagliptin/metformin (see dossier assessment A13-03 [12] and the corresponding addendum A13-29 [11]). The company presented no different analyses on the P803 study in the present dossier.

A detailed description of the design and the results of the P803 study can be found in dossier assessment A13-02, in dossier assessment A13-03 and in the corresponding addendum A13-29 [8,11,12].

Summary

In summary, the underlying data in the present dossier were unchanged in comparison with the procedure for the first benefit assessment: No new analyses were presented on the known P803 study; analyses for the fixed combination of sitagliptin/metformin for the potentially relevant HARMONY 3 study were missing. Since, due to its duration, the HARMONY 3 study was primarily relevant for research question A1, its potential influence is addressed on the basis of the results on the sitagliptin single agent.

Section 2.3.2.4 contains a reference list for the studies included.

2.3.2.1.1 Study characteristics (research question A1)

See dossier assessment A13-02 [8] for the description of the study and intervention characteristics and of the risk of bias of the already known P803 study.

2.3.2.2 Results on added benefit (research question A1)

The results of the P803 study were presented in detail in the first assessment of sitagliptin/metformin (Commission A13-03 [12]) and in the corresponding addendum (Commission A13-29 [11]). These resulted in a hint of lesser harm from sitagliptin/metformin for the outcome “symptomatic hypoglycaemia” and a hint of greater harm for the outcome “discontinuation due to AEs”. No hint of added benefit or greater harm of sitagliptin/metformin in comparison with the ACT was shown for the further patient-relevant outcomes.

The result of the total population of the HARMONY 3 study was largely consistent with this. An exception was the outcome “discontinuation due to AEs”, for which the HARMONY 3 study showed no statistically significant difference between the treatment groups. Since in the total population of the HARMONY 3 study, only few and numerically fewer discontinuations due to AEs occurred under sitagliptin plus metformin than under glimepiride plus metformin [7], it was also assumed for the fixed combination of sitagliptin/metformin that there is no disadvantage of sitagliptin/metformin versus the ACT regarding the outcome “discontinuation due to AEs”.

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

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.

2.3.2.3.1 Assessment of added benefit at outcome level

As in the first assessment, a hint of lesser harm of sitagliptin/metformin in comparison with glimepiride plus metformin for the outcome “symptomatic hypoglycaemia” (blood glucose ≤ 50 mg/dL) remains from the assessment of the P803 study. On the basis of the results of the HARMONY 3 study it can be assumed that the hint of greater harm from sitagliptin/metformin for the outcome “discontinuation due to AEs” determined for the P803 study is not sufficiently robust.

No sufficient data were available on mortality and on micro- and macrovascular late complications.

2.3.2.3.2 Overall conclusion on added benefit

Table 6 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 6: Positive and negative effects from the assessment 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 ≤ 50 mg/dL) with a hint of lesser harm (extent: “considerable”).

Regarding mortality and micro- and macrovascular late complications, there was neither advantage nor disadvantage of the fixed combination of sitagliptin/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/metformin versus glimepiride plus metformin was “non-quantifiable”, but at most “considerable”.

This assessment deviates from that of the company, which derived proof of major added benefit of sitagliptin/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).

2.3.2.4 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: 08.09.2016]. 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, 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 [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, 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 [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>.

2.3.3 Research question A2: sitagliptin/metformin versus glipizide plus metformin

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

2.3.3.1 Study pool (research question A2)

2.3.3.1.1 Studies included

The study listed in Table 7 was included in the benefit assessment.

Table 7: Study pool – RCT, direct comparison: sitagliptin/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 study was already presented in the dossier from 27 March 2013 for the first benefit assessment of sitagliptin/metformin (see dossier assessment A13-03 [12] and the corresponding addendum A13-29 [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.

A detailed description of the design and the results of the P024 study can be found in dossier assessment A13-02, in dossier assessment A13-03 and in the corresponding addendum A13-29 [8,11,12].

Section 2.3.3.5 contains a reference list for the study included.

2.3.3.1.2 Study characteristics (research question A2)

See dossier assessment A13-02 [8] for the description of the study and intervention characteristics and of the risk of bias of the already known P024 study.

2.3.3.2 Results on added benefit (research question A2)

The results on the added benefit were presented in detail in the first assessment of sitagliptin. The results can also be found in Appendix B of dossier assessment A16-44 on sitagliptin [7]. 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 clinical study report (CSR), the first assessment of sitagliptin/metformin 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 relative risk (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 $\leq 1\%$ 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 [13], which was not the case in the present situation.

The results on all-cause mortality can be found in the following Table 8.

Table 8: Results (mortality) – RCT, direct comparison: sitagliptin/metformin vs. glipizide + metformin

Study Outcome category Outcome	Sitagliptin/metformin		Glipizide + metformin		Sitagliptin/metformin vs. glipizide + metformin RR [95% CI]; p-value
	N	Patients with event n (%)	N	Patients with event n (%)	
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 [14], the results on all-cause mortality presented in dossier assessment A13-02 [8] 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 [15]). 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/metformin in comparison with glipizide plus metformin for the outcome “all-cause mortality”, as was the case in the first benefit assessment of sitagliptin/metformin (A13-03). This again resulted in a hint of an added benefit of sitagliptin/metformin 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.

2.3.3.3 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”.

The following Table 9 shows the subgroup analyses on all-cause mortality by sex.

Table 9: Subgroups: outcome “all-cause mortality” by sex – RCT, direct comparison: sitagliptin/metformin vs. glipizide + metformin

Study Outcome Characteristic Subgroup	Sitagliptin/metformin		Glipizide + metformin		Sitagliptin/metformin vs. glipizide + metformin	
	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 [15]). 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.

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

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.

2.3.3.4.1 Assessment of added benefit at outcome level

The data presented in Section 2.3.3.2 resulted in a hint of an added benefit of the combination of sitagliptin/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 9). Furthermore, a hint of lesser harm for the outcomes “symptomatic hypoglycaemia”

(blood glucose \leq 50 mg/dL) and “severe hypoglycaemia”, each with considerable extent, for the total population remain unchanged from the first assessment.

2.3.3.4.2 Overall conclusion on added benefit

Table 10 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 10: Positive and negative effects from the assessment of the combination of sitagliptin/metformin compared with glipizide plus metformin

Positive effects	Negative effects
Hint of an added benefit for men – 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 \leq 50 mg/dL) and severe hypoglycaemia.

Regarding micro- and macrovascular late complications, there was neither advantage nor disadvantage of the combination of sitagliptin/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/metformin versus glipizide plus metformin for men. Because of the additional uncertainty, in women, the extent of added benefit of sitagliptin/metformin versus glipizide plus metformin 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/metformin versus glipizide plus 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/metformin.

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/metformin.

2.3.3.5 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 HbA_{1c} value. *Curr Med Res Opin* 2012; 28(8): 1281-1287.

Merck. A multicenter, double-blind, randomized study to evaluate the safety and efficacy of the addition of MK-0431 compared with sulfonylurea therapy in patients with type 2 diabetes with inadequate glycemic control on metformin monotherapy: study P024; clinical study report [unpublished]. 2006.

Merck. A multicenter, double-blind, randomized study to evaluate the safety and efficacy of the addition of MK-0431 compared with sulfonylurea therapy in patients with type 2 diabetes with inadequate glycemic control on metformin monotherapy: study P024; Zusatzanalysen [unpublished]. 2006.

Merck Sharp & Dohme. An investigational drug study in patients with type 2 diabetes mellitus (0431-024): full text view [online]. In: *ClinicalTrials.gov*. 25.08.2016 [Accessed: 08.09.2016]. URL: <https://clinicaltrials.gov/ct2/show/study/NCT00094770>.

Merck Sharp & Dohme. An investigational drug study in patients with type 2 diabetes mellitus (0431-024): study results [online]. In: *ClinicalTrials.gov*. 25.08.2016 [Accessed: 08.09.2016]. URL: <https://clinicaltrials.gov/ct2/show/results/NCT00094770>.

Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab* 2007; 9(2): 194-205.

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.

2.4 Research question B: sitagliptin/metformin plus sulfonyleurea

2.4.1 Information retrieval and study pool (research question B)

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

Sources of the company in the dossier:

- study list on 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/metformin plus sulfonyleurea 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/metformin. 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 (see Section 2.2). Hence there were also no sufficient data on micro- and macrovascular late complications for research question B.

The evidence base was therefore unchanged in comparison with the first assessment [12]. No relevant study was available for research question B.

2.4.2 Results on added benefit (research question B)

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

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

Since no relevant data were presented for the benefit assessment, there is no proof of an added benefit of the combination of sitagliptin/metformin plus sulfonyleurea. The company also claimed no added benefit for this research question.

2.5 Research question C: sitagliptin/metformin plus insulin

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 study was identified from the check.

The company included the P260 study of direct comparison in the assessment [16]. The study was unsuitable to derive conclusions on the added benefit of sitagliptin/metformin in combination with insulin 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/metformin. 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 (see Section 2.2). Hence there were also no sufficient data on micro- and macrovascular late complications for research question C.

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 glycosylated haemoglobin A1c (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 level⁵ ≥ 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.

Relevance of the study population for the present research question

According to the approval, only the subpopulation of patients who received at least 1700 mg/day metformin would be relevant for the present benefit assessment of the fixed combination of sitagliptin/metformin [3]. This applied to only 76% of the patients included in the P260 study. Besides the data of the total population, the company also presented data on the relevant subpopulation. Using subgroup analyses, it also tried to show that the data of the total population are transferable to the subpopulation. The approach of the company was methodologically inadequate, however, because its subgroup analysis did not consider the patients who received no metformin, but who nonetheless were part of the total population.

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 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 C.

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

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.

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.

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 [17]. 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/metformin in combination with insulin versus the ACT.

2.5.2 Results on added benefit (research question C)

No suitable data were available for research question C – sitagliptin/metformin in combination with insulin. There was no hint of an added benefit of sitagliptin/metformin in combination with insulin 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 suitable study was presented for the benefit assessment, an added benefit assessment of sitagliptin/metformin in combination with insulin versus the ACT specified by the G-BA was not proven. This deviates from the company’s assessment, which derived an indication of considerable added benefit.

2.6 Extent and probability of the added benefit – summary

An overview of the extent and probability of added benefit for the different subindications of sitagliptin/metformin in comparison with the relevant ACTs or versus glipizide plus

metformin is given in Table 11. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

Table 11: Sitagliptin/metformin – extent and probability of added benefit

Research question	Subindication	Comparator therapy	Extent and probability of added benefit
A1	Sitagliptin/metformin	Sulfonylurea (glibenclamide, glimepiride) plus metformin	Hint of an added benefit (extent “non-quantifiable”, at most “considerable”)
A2	Sitagliptin/metformin	Glipizide plus metformin ^a	<p><i>Treatment goal near-normal blood glucose levels:</i></p> <p>Men: hint of a considerable added benefit</p> <p>Women: hint of an added benefit (extent “non-quantifiable”, at most “considerable”)</p> <p><i>Other treatment goal:</i> added benefit not proven</p>
B	Sitagliptin/metformin plus sulfonylurea	Human insulin plus metformin (note: treatment only with human insulin if metformin is not sufficiently effective)	Added benefit not proven
C	Sitagliptin/metformin plus insulin	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/metformin versus glipizide plus metformin (research question A2) were additionally assessed. G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics			

This deviates from the approach of the company, which derived proof of major added benefit for sitagliptin/metformin and an indication of considerable added benefit for the combination of sitagliptin/metformin plus insulin.

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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