IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A13-02

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

Extract

[1] Translation of Sections 2.1 to 2.8 of the dossier assessment "Sitagliptin – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 27 June 2013). 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Sitagliptin – Benefit assessment according to § 35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
27 March 2013

Internal Commission No.:
A13-02

Address of publisher:
Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Andreas Fritsche, Institute for Diabetes Research and Metabolic Diseases, University Hospital Tübingen, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

IQWiG employees involved in the dossier assessment:[2]

- Katrin Nink
- Lars Beckmann
- Gertrud Egger
- Wolfram Groß
- Elke Hausner
- Helmut Hörn
- Thomas Kaiser
- Stefan K. Lhachimi
- Regine Potthast
- Wiebke Sieben
- Min Zhou

Keywords: sitagliptin, diabetes mellitus – type 2, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ANCOVA	analysis of covariance
BfArM	*Bundesinstitut für Arzneimittel und Medizinprodukte* (Federal Institute for Drugs and Medical Devices)
CI	confidence interval
CT	conventional insulin treatment
eGFR	estimated glomerular filtration rate
EQ-5D	European Quality of Life-5 Dimensions
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
HbA1c	haemoglobin A1c
ICT	intensified conventional insulin treatment
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
MedDRA	Medical Dictionary of Regulatory Activities
OAD	oral antidiabetic drug
OR	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
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug sitagliptin. The benefit assessment formed part of the assessment of the established drug market of gliptins, which was commissioned by the G-BA on 7 June 2012. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 27 March 2013.

Research question

The benefit assessment of sitagliptin was conducted according to the approval for the following therapeutic indication: treatment of adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise.

Within this therapeutic indication, different subindications for the use of sitagliptin and thus different research questions result from the type of prior treatment.

The G-BA specified an appropriate comparator therapy (ACT) for each of the different subindications. This benefit assessment concurs with the G-BA's specifications.

Table 2: Subindications and ACT for sitagliptin

Research question[a]	**Subindication**	**ACT**
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, if applicable only treatment 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)
E	Sitagliptin plus insulin (with or without metformin)	Human insulin plus metformin (note: only 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, direct comparative studies versus glipizide were to be additionally assessed.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

Deviations by the company

The company included studies with sulfonylureas without limitation to the drugs specified by the G-BA in the following subindications: **monotherapy with sitagliptin** (research question A), **combination of sitagliptin plus metformin** (research question B) and **combination of sitagliptin plus sulfonylurea** (research question C). According to the commission by the G-BA, direct comparative studies versus glipizide were additionally assessed. These kinds of studies were presented for the research questions A and B and assessed separately (research question A2 and B2).

In the subindication "sitagliptin plus insulin with or without metformin" (research question E), the company defined conventional insulin treatment (CT), intensified conventional insulin treatment (ICT) and insulin dose increase as comparator therapies. This constituted an appropriate specification of the ACT. Different insulin treatment regimens may be medically reasonable to optimize treatment for the individual patient. Studies in which the patients had the option to optimize their treatment on an individual basis (including switching treatment type and treatment regimen) were included in this benefit assessment.

Results

The assessment was based on patient-relevant outcomes. Direct comparative randomized controlled trials (RCTs) were included in the assessment.

Monotherapy with sitagliptin

The added benefit was assessed in comparison with 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

No relevant study was available for the research question A1.

The company included 1 direct comparative study (P251) and 11 RCTs for an indirect comparison for the research question A1. These studies were unsuitable for assessing the added benefit for several reasons: mainly because the patients in the studies did not fulfil the criteria of the approval of sitagliptin (intolerance or contraindication to metformin), the 2 treatment arms differed too much with regards to their haemoglobin A1c (HbA1c) values, the study duration was too short, or the dosages administered did not comply with the approval.

Research question A2

The company included 3 direct comparative studies versus glipizide (P063, P010 and P073) for the research question A2. The study P010 was not relevant for the assessment 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). The study P073 was not relevant because patients with severe renal impairment were enrolled for whom the use of the

comparator glipizide is not approval-compliant. Hence the study P063 remains. However, only a subpopulation of this study was relevant (patients with moderate renal impairment).

The study P063 was a randomized, active-controlled, double-blind approval study sponsored by the company with a study period of 54 weeks. It included patients aged 30 years or older with type 2 diabetes mellitus with moderate (30 ml/min ≤ estimated glomerular filtration rate [eGFR] < 50 ml/min) or severe (eGFR < 30 ml/min) renal impairment.

Patients were enrolled when their HbA1c value was between 7% and 9% 2 weeks before randomization. If patients had received prior antidiabetic treatment, this was washed out with diet and exercise during the run-in phase, which lasted up to 14 weeks. The randomization of the patients to the 2 treatment arms was stratified according to the patients' renal status as well as to prior cardiovascular disorders and cardiac failure. 426 patients were randomized (213 to the sitagliptin arm and 213 to the glipizide arm). The relevant subpopulation of the patients with moderate renal impairment comprised 71% of the total study population in the study P063.

The patients received either a fixed dose of 50 mg sitagliptin/day or glipizide at a starting dose of 2.5 mg/day. Glipizide could be up-titrated to a maximum dose of 20 mg/day. The criteria for the titration included a consistent target level for fasting blood glucose (120 mg/dl) under consideration of the risk of hypoglycaemia. Despite the different therapeutic strategies used, the overall picture of the courses of HbA1c was largely similar in the 2 treatment groups of the study P063. The results of the study P063 could therefore be interpreted, but they can only be transferred to patients for whom near-normal levels of blood glucose are aimed at. Further uncertainties resulted from the discrepancies between the courses of HbA1c and fasting plasma glucose and missing data on courses for the relevant subpopulation of patients with moderate renal impairment. Hence, at most "hints" of an added benefit could be derived from the study P063.

With few events overall, there was no statistically significant difference between the treatment groups in all-cause mortality or in cardiac and cerebral events. An added benefit of sitagliptin in comparison with glipizide is not proven for these outcomes.

Data on health-related quality of life were not recorded in the study P063. An added benefit of sitagliptin in comparison with glipizide is not proven for this outcome.

There was a statistically significant advantage of sitagliptin for confirmed symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl). Since the upper limit of the 95% confidence interval (CI) was above 0.9, and this was a non-serious adverse event (AE), not more than a marginal advantage of sitagliptin versus glipizide can be derived from this.

There was no statistically significant difference between the treatment groups for the individual outcomes in the category "AEs". Greater or lesser harm from sitagliptin in comparison with glipizide is therefore not proven.

Overall, there are neither positive nor negative effects of sitagliptin versus glipizide. The effect with regards to non-serious hypoglycaemias was not more than marginal. No sufficient data were available on micro- and macrovascular late complications. An added benefit of sitagliptin versus glipizide is therefore not proven for the subpopulation of patients with moderate renal impairment in whom near-normal levels of blood glucose are aimed at. No relevant data were available for the remaining target population of sitagliptin monotherapy. The added benefit of sitagliptin versus glipizide for the total target population is therefore not proven.

The overall assessment deviates considerably 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.

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

One study, in which sitagliptin plus metformin was compared with glimepiride plus metformin, was available for this research question (study P803).

The study P803 was a randomized, active-controlled, double-blind study sponsored by the company with a duration of 30 weeks. Adult patients with type 2 diabetes mellitus were enrolled in whom no sufficient glycaemic control was achieved despite treatment with metformin at a stable dose of ≥ 1500 mg/day during at least 12 weeks (HbA1c ≥ 6.5% and ≤ 9.0%).

1035 patients were randomly assigned in a ratio of 1:1, 516 patients to the sitagliptin plus metformin arm and 519 patients to the glimepiride plus metformin arm. In some 70% of the patients, the HbA1c value was below 8% at the start of the study, and more than 20% of the patients had an HbA1c value of < 7%.

After randomization, the patients either received a fixed dose of 100 mg/day sitagliptin or they started with 1 mg/day glimepiride (starting dose) and a placebo of the respective other drug. The patients were required to continue taking their metformin dose from their prior treatment or from the stable phase of at least 12 weeks before the start of the study during the entire study duration (including the run-in phase).

During a period of 18 weeks, the glimepiride dose could be up-titrated to a maximum dose of 6 mg/day at the investigator's discretion and depending on the blood glucose levels measured by the patient. The daily dose could be increased to 2 mg first and then in steps of 1 or 2 mg.

The overall goal of the dose titration was to maximize the probability to achieve a target HbA1c value of ≤ 6.5%. The dose could be reduced any time to avoid hypoglycaemias. Despite the different therapeutic strategies used, the overall picture of the courses of HbA1c was largely similar in the 2 treatment groups of the study P803. The results of the study P803 could therefore be interpreted, but they can only be transferred to patients for whom near-normal levels of blood glucose are aimed at. Further uncertainties resulted from missing data on the time course of hypoglycaemias and the up-titration of glimepiride in 2-mg steps for some patients (20% maximum). Hence, at most "hints" of an added benefit could be derived from the study P803.

With few events overall, there was no statistically significant difference between the treatment groups in all-cause mortality, cardiac and cerebral events and health-related quality of life. An added benefit of sitagliptin plus metformin in comparison with glimepiride plus metformin is not proven for these outcomes.

Regarding AEs, the picture was mixed: There was no statistically significant difference in severe hypoglycaemias, pancreatitis, renal impairment and serious adverse events (SAEs). There was a statistically significant advantage of sitagliptin plus metformin versus glimepiride plus metformin for confirmed symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl). This led to a hint of lesser harm from sitagliptin plus metformin. There was a statistically significant disadvantage of sitagliptin plus metformin for treatment discontinuation due to AEs. This led to a hint of greater harm from the combination of sitagliptin plus metformin in comparison with glimepiride plus metformin.

Overall, positive and negative effects remain at outcome level. A hint of lesser harm (extent: "considerable") is offset by a hint of greater harm (extent: "minor"). Hence there are opposing conclusions on AEs, which overall result in a hint of a minor added benefit. There was neither an advantage nor a disadvantage of the combination of sitagliptin plus metformin versus glimepiride plus metformin regarding micro- and macrovascular late complications. No sufficient data were available on these outcomes, however. This led to an additional uncertainty. The extent of added benefit of sitagliptin versus glimepiride is therefore "non-quantifiable", but not more than "minor" on the basis of the available data.

Overall, there is a hint of a minor added benefit of the combination of sitagliptin plus metformin versus glimepiride plus metformin for patients in whom near-normal levels of blood glucose are aimed at. For patients without such a treatment goal, there is no proof of added benefit of sitagliptin.

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

Research question B2

One study, in which sitagliptin plus metformin was compared with glipizide plus metformin, was available for this research question (study P024).

The study P024 was a randomized, active-controlled, double-blind approval study sponsored by the company with a duration of 104 weeks. It was conducted to investigate patients with inadequate glycaemic control despite treatment with ≥ 1500 mg/day metformin (HbA1c ≥ 6.5% to ≤ 10.0%).

1172 patients were randomly assigned in a ratio of 1:1, 588 patients to the sitagliptin plus metformin arm and 584 patients to the glipizide plus metformin arm. About 65% of the patients had an HbA1c value of below 8% at the start of the study. Patients who had received metformin monotherapy, metformin combination therapy or no antidiabetic treatment before enrolment were included. Depending on the treatment and the HbA1c value at enrolment, the patients underwent a treatment algorithm aimed at achieving a patient population with inadequate glycaemic control despite monotherapy with metformin at a dose of ≥ 1500 mg a day. However, it was unsuitable to guarantee that only patients with inadequate glycaemic control despite maximum tolerated dose of metformin were enrolled and treated. Patients who had not received prior antidiabetic therapy or less than 50% of the maximum approved dose of metformin were also enrolled. There was no information on the proportion of these patient populations.

After randomization, the patients either received a fixed dose of 100 mg sitagliptin a day or glipizide at a starting dose of 5 mg/day and a placebo of the respective other drug. During the treatment duration, the patients were requested not to change their daily metformin dose.

The starting dose of 5 mg glipizide (+ placebo) could be increased over a period of 18 weeks. The first dose increase was possible after 3 weeks, further dose increases could be made at 3-week intervals. If, at the doctor's discretion, the patient benefited from faster up-titration, this could also be done at shorter intervals (≥ 1 week). The dose was increased in steps of 5 mg/day. The glipizide dose was only to be increased if the fasting blood glucose was > 110 mg/dl on the day of the study visit and in the week before, if no hypoglycaemias had occurred since the last dose increase and if, at the investigator's discretion, the dose increase did not put the patient at risk of hypoglycaemias. The dose could be reduced any time to avoid hypoglycaemias. Despite the different therapeutic strategies used, the overall picture of the courses of HbA1c was largely similar in the 2 treatment groups of the study P024. The results of the study P024 could therefore be interpreted, but they can only be transferred to patients for whom near-normal levels of blood glucose are aimed at. Further uncertainties resulted from missing data on the time course of hypoglycaemias and the uncertainty about how many patients received a maximum tolerated dose of metformin without achieving adequate glycaemic control. Hence, at most "hints" of an added benefit could be derived from the study P024.

There was a statistically significant difference between sitagliptin plus metformin and glipizide plus metformin in all-cause mortality. A total of 8 deaths occurred under glipizide (1.4%), and 1 death under sitagliptin (0.2%). All events occurred in men. This led to a hint of an added benefit of sitagliptin plus metformin in comparison with glimepiride plus metformin for all-cause mortality in men.

With few events overall, there was no statistically significant difference between the treatment groups in cardiac and cerebral events. An added benefit of sitagliptin plus metformin in comparison with glipizide plus metformin is not proven for these outcomes.

Data on health-related quality of life were not recorded in the study P024. An added benefit of the combination of sitagliptin plus metformin in comparison with glipizide plus metformin is not proven for this outcome.

There were fewer symptomatic hypoglycaemias (confirmed by a measured blood glucose level of ≤ 50 mg/dl) and fewer severe hypoglycaemias under sitagliptin plus metformin than under glipizide plus metformin. These results were statistically significant. This led to a hint of lesser harm from the combination of sitagliptin plus metformin in comparison with glipizide plus metformin for these 2 outcomes.

There was no statistically significant difference between treatment with sitagliptin plus metformin and glipizide plus metformin regarding the following AEs; pancreatitis, renal impairment, SAEs and treatment discontinuation due to AEs. An added benefit of the combination of sitagliptin plus metformin in comparison with glipizide is not proven for these outcomes.

Overall, only positive effects of sitagliptin remain at outcome level. These consist of a hint of major added benefit in all-cause mortality (only for men) and a hint of lesser harm with considerable extent both for symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl) and severe hypoglycaemias. There was neither an advantage nor a disadvantage of the combination of sitagliptin plus metformin versus glipizide plus metformin regarding micro- and macrovascular late complications. No sufficient data were available on these outcomes, however. This led to an additional uncertainty. It does not seem appropriate, however, to question the advantage in all-cause mortality observed in men because of this. Therefore, there is an overall hint of a major added benefit of sitagliptin versus glipizide in 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. For patients without such a treatment goal, there is no proof of added benefit of sitagliptin.

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

Combination of sitagliptin plus sulfonylurea

The company identified no study on the combination of sitagliptin plus sulfonylurea versus the ACT.

Combination of sitagliptin plus metformin plus sulfonylurea

The company identified no study on the combination of sitagliptin plus metformin plus sulfonylurea versus the ACT.

Sitagliptin plus insulin (with or without metformin)

In its assessment, the company included the study Hong 2012, in which the additional administration of sitagliptin in comparison with an insulin dose increase on the basis of an ongoing insulin treatment and additional oral antidiabetic treatment was investigated. The study was unsuitable for the benefit assessment because a relevant proportion of the patients did not receive approval-compliant treatment. Concomitant medication with other OADs that were not approved in this combination was administered to a major extent. There were no analyses for the patients treated according to the approval.

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

Based on the results presented, the extent and probability of an added benefit of the drug sitagliptin is assessed as follows:

[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 1-3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

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	*Treatment goal near-normal blood glucose levels:* hint of a minor added benefit *Other treatment goal:* added benefit not proven
B2	Sitagliptin plus metformin	Glipizide plus metformin[a]	*Treatment goal near-normal blood glucose levels:* men: hint of a major added benefit women: hint of an added benefit (extent "non-quantifiable", not more than "considerable") *Other treatment goal:* added benefit not proven
C	Sitagliptin plus sulfonylurea	Human insulin plus sulfonylurea (glibenclamide, glimepiride, if applicable only treatment 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 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, direct comparative studies of sitagliptin versus glipizide (research question A2) and sitagliptin plus metformin versus glipizide plus metformin (research question B2) were additionally assessed.			

It should also be noted that the data on late complications (particularly on the prevention of micro- and macrovascular events) presented by the company were insufficient. The prevention of micro- and macrovascular late complications is an important goal in the treatment of patients with type 2 diabetes mellitus. It is not comprehensible that such data for sitagliptin are still lacking. At the time of this assessment, sitagliptin has already been approved throughout Europe for more than 6 years (since March 2007). The gliptin

saxagliptin, which was approved considerably later (in October 2009), these data are apparently already available and will be presented shortly. Long-term data on sitagliptin are to be available in 2015 at the earliest.

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

2.2 Research questions

The benefit assessment of sitagliptin 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:

- **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.

The G-BA specified an ACT for each of the different subindications. These are shown in Table 4.

Table 4: Subindications and ACT for 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 only treatment 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)
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, direct comparative studies versus glipizide were to be additionally assessed.
c: The company did not provide any studies for this subindication so that a possible additional assessment of direct comparative studies versus glipizide (in combination with human insulin) was not relevant.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

Research question A: monotherapy with sitagliptin

The G-BA specified sulfonylureas (glibenclamide, glimepiride) as ACT for this subindication. According to the commission by the G-BA, direct comparative studies versus glipizide were to be additionally assessed. In this benefit assessment, the added benefit of sitagliptin monotherapy was therefore assessed in comparison with the following comparator therapies:

- Research question A1: ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride])
- Research question A2: glipizide

The company claimed to concur with the G-BA's specification on the ACT. Nevertheless, it included studies with sulfonylureas without limitation to the drugs defined by the G-BA (see Section 2.9.2.1 of the full dossier assessment).

The valid SPC of glibenclamide or glimepiride was used for answering the question whether these drugs were administered according to their approval [5,6]. As glipizide is no longer approved in Germany, the SPC that was last valid in Germany was obtained from the Federal Institute for Drugs and Medical Devices (BfArM) and applied [7]. This was from the year 2000. The current SPC from Austria [8], where glipizide is still approved, was additionally used to also take into account the approval-compliant use of glipizide according to current knowledge.

Research question B: combination of sitagliptin plus metformin

The G-BA specified sulfonylureas (glibenclamide, glimepiride) plus metformin as ACT for this subindication. According to the commission by the G-BA, direct comparative studies versus glipizide were to be additionally assessed. In this benefit assessment, the added benefit of sitagliptin plus metformin was therefore assessed in comparison with the following comparator therapies:

- Research question B1: ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride] plus metformin)
- Research question B2: glipizide plus metformin

Regarding the ACT, the company claimed to concur with the G-BA's specification. Nevertheless, the company included studies with sulfonylureas without limitation to the drugs defined by the G-BA, and did not conduct a separate assessment of the added benefit versus the G-BA's ACT and glipizide (but versus sulfonylureas as a whole) (see Section 2.9.3.1 of the full dossier assessment).

The valid SPC of glibenclamide or glimepiride was used for answering the question whether these drugs were administered according to their approval [5,6]. For glipizide, the SPC that was last valid in Germany [7] as well as the current SPC from Austria [8] were also used for question B.

Research question C: combination of sitagliptin plus sulfonylurea

The G-BA specified human insulin plus sulfonylurea (glibenclamide, glimepiride, if applicable treatment only with human insulin) as ACT for this subindication. The company claimed to concur with the G-BA's specification on the ACT. Nevertheless, it included studies with sulfonylureas without limitation to the drugs defined by the G-BA in its research question.

Research question D: combination of sitagliptin plus metformin plus sulfonylurea

The G-BA specified human insulin plus metformin (treatment only with human insulin if metformin is not sufficiently effective) as ACT for this subindication. This was in accordance with the company's approach.

Research question E: combination of sitagliptin plus insulin

The G-BA specified human insulin plus metformin (if applicable only human insulin if metformin is not tolerated according to the SPC or not sufficiently effective) as ACT for this subindication. Regarding the ACT, the company defined CT, ICT and insulin dose increase as comparator therapies. This constituted an appropriate specification of the ACT. Different insulin treatment regimens may be medically advisable to optimize treatment for the individual patient. Studies in which the patients had the option to optimize their treatment on an individual basis (including switching treatment type and regimen) were included in this benefit assessment.

Summary

In summary, the assessment of sitagliptin in the different subindications was conducted versus the ACTs specified by the G-BA. For the research questions A (sitagliptin) and B (sitagliptin plus metformin), the added benefit versus glipizide (A2) and versus glipizide plus metformin (B2) was also assessed. The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs) with a minimum duration of 24 weeks.

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

2.3 Research question A: monotherapy with sitagliptin

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 lists on sitagliptin monotherapy (studies completed up to 1 February 2013)
- Bibliographical literature search on sitagliptin monotherapy (last search on 25 February 2013 – cut-off date 1 February 2013)

- Search in trial registries for studies on sitagliptin monotherapy (last search on 1 February 2013)
- Bibliographical literature search on sulfonylureas (last search on 27 February 2013 – cut-off date 1 February 2013)
- Search in trial registries for studies on sulfonylureas (last search on 1 February 2013)

The Institute's own search:

- Bibliographical literature search on gliptins to check the search results of the company (last search on 19 March 2013)
- Search in trial registries for studies on gliptins to check the search results of the company (last search on 21 March 2013)

No additional studies were identified in the Institute's search.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4A, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.9.2.2 and 2.9.2.4.1 of the full dossier assessment.

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

The data presented by the company were unsuitable to draw conclusions on the added benefit of sitagliptin monotherapy. This is justified below.

Direct comparison

The company included the study P251 in its benefit assessment. This was a company-sponsored, randomized, active-controlled, double-blind study with a 30-week treatment duration for the comparison of sitagliptin with glimepiride. It was conducted in adult patients aged between 65 and 85 years with type 2 diabetes mellitus who had either received no anti-hyperglycaemic treatment or had inadequate glycaemic control (HbA1c between 7.0% and 9.0%) after discontinuation of this treatment in the run-in phase.

The study was unsuitable for the assessment of the added benefit. According to the inclusion criteria of the study 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). Intolerance to metformin was no inclusion criterion for the study. However, 35 patients (7.3% of 480 randomized patients) with moderate renal impairment (a contraindication to metformin) participated in the study. But there were considerable differences in glycaemic control between the sitagliptin and the glimepiride arm of this subpopulation (sitagliptin arm: 7.93% [mean value]; glimepiride arm: 7.56% [mean value]). This difference became larger in the end of the study (sitagliptin arm: 8.00% [mean value]; glimepiride arm: 7.22% [mean value]) so that the relevant outcomes could no longer be interpreted. For this reason, the data of the subgroup of patients with moderate renal impairment were not used for the assessment.

A comprehensive presentation of the study P251 and the reasons for exclusion from the assessment can be found in Appendix A of the full dossier assessment.

Indirect comparison

The company presented a simple adjusted indirect comparison of sitagliptin versus sulfonylureas in addition to the presentation of the direct comparative study. The company chose placebo as common comparator. The company presented 11 studies for the adjusted indirect comparison. On the sitagliptin side, the company included 5 studies that compared sitagliptin versus placebo. On the sulfonylurea side, it included 6 studies. In these studies, glibenclamide or glimepiride was also compared with placebo.

However, all 11 studies included by the company were unsuitable for answering the present research question (see Table 5). It can be assumed that the majority of the patients enrolled in the 11 studies did not fulfil the criteria of the approval of sitagliptin (intolerance or contraindication to metformin). Some of the studies were also unsuitable for the assessment because they lasted less than 24 weeks (studies P023, P040, Garber 2002 and Schade 1998) or because the sulfonylurea was not used in compliance with its approval (Johnston 1998, Schade 1998, Hoffmann 1994, Kovacevic 1997 and Segal 1997).

A comprehensive presentation of the studies of the indirect comparison and the reasons for exclusion can be found in Appendix A of the full dossier assessment.

Table 5: Overview of the reasons for exclusion of the studies – indirect comparison: research question A1, sitagliptin vs. sulfonylurea (glibenclamide, glimepiride)

Study	Reasons for exclusion			
	Population	Study duration	Approved maximum dose of sulfonylurea exceeded	Titration of sulfonylurea lacking or not compliant with approval
Sitagliptin vs. placebo				
P021	●			
P023	●	●		
P036	●			
P040	●	●		
P047	●			
Sulfonylurea (glimepiride or glibenclamide) vs. placebo				
Garber 2002	●	●		
Hoffmann 1994	●			●
Johnston 1998	●		●	
Kovacevic 1997	●			●
Schade 1998	●	●	●	
Segal 1997	●			●

Summary

Overall, no relevant data were available for assessing the added benefit of the monotherapy with sitagliptin versus the ACT (glibenclamide, glimepiride), neither for a direct, nor for an indirect comparison.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4A, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.9.2.4.1 and 2.9.2.4.2 of the full dossier assessment.

2.3.2.1 Results on added benefit (research question A1)

No relevant studies were available for the research question "monotherapy with sitagliptin", neither for a direct, nor for an indirect comparison. Hence the added benefit of sitagliptin versus the ACT specified by the G-BA (sulfonylureas [glibenclamide, glimepiride]) is not proven.

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

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of sitagliptin versus the ACT specified by the G-BA (sulfonylurea [glibenclamide, glimepiride]). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This deviates from the company's assessment, which additionally included 3 studies on the comparison of sitagliptin with glipizide and derived a proof of a considerable added benefit versus sulfonylureas as a whole.

Further information about the extent and probability of the added benefit can be found in Module 4A, Section 4.4 of the dossier, and in Section 2.9.2.9 of the full dossier assessment.

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 direct comparative studies versus glipizide: P010 (including the 2 extension phases P010-10 and P010-20), P063 and P073. This approach was not accepted. Only a subpopulation of the study P063 was used for this research question.

The studies P010 and P073 were not relevant for the assessment. The patients investigated in the study P010 did not concur with the approval population of sitagliptin monotherapy. According to the inclusion criteria of the study 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). Intolerance or contraindication to metformin was no inclusion criterion for the study.

The study P073 was also unsuitable for the assessment of the added benefit. Patients with severe renal impairment have a contraindication to metformin so that patients were enrolled in this study for whom sitagliptin monotherapy is approved. But for patients with severe renal impairment, the use of the comparator glipizide is not compliant with the approval. As the company itself stated, glipizide has not been approved in Germany since the year 2007. The SPC of glipizide current in Austria was therefore used to be able to take into account current approved knowledge on the use of glipizide. According to this SPC, glipizide is contraindicated in patients with severe renal impairment [8]. A comprehensive presentation of the studies P010 and P073 and of the reasons for exclusion can be found in Appendix A of the full dossier assessment.

2.3.3.1.1 Studies included

The approval study included in the benefit assessment is listed in the following table.

Table 6: 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; vs.: versus			

Section 2.3.3.4 contains a reference list for the study included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4A, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.9.2.4.1 and 2.9.2.4.2 of the full dossier assessment.

2.3.3.1.2 Study characteristics

Table 7 and Table 8 describe the study used for the benefit assessment.

Table 7: Characteristics of the studies included – RCT, direct comparison: sitagliptin vs. glipizide

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
P063	RCT, double-blind, parallel, active-controlled, multicentre, double-dummy	Patients ≥ 30 years with type 2 diabetes mellitus and inadequate glycaemic control (HbA1c value between ≥ 7.0% and ≤ 9%) under diet and exercise alone and with moderate to severe renal impairment (eGFR < 50 ml/min), no dialysis treatment expected during the course of the study	Sitagliptin 25 mg/day or 50 mg/day[b] (N = 213) Glipizide 2.5–20 mg/day (N = 213) Relevant subpopulation: patients with moderate renal impairment: Sitagliptin 50 mg/day (n = 149) Glipizide 2.5–20 mg/day (n = 154)	Diet and exercise run-in phase: up to 14 weeks Placebo run-in: 2 weeks Randomized treatment: 54 weeks	177 study centres in Asia, Europe, South America, United States of America Oct 2007 – Mar 2011	Primary: change in the HbA1c value in comparison with baseline value after 54 weeks, hypoglycaemias, AEs

a: Primary outcomes contain information without consideration of the relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for the present benefit assessment.

b: Dosage of sitagliptin in compliance with approval according to renal status of the patients.

AE: adverse event; eGFR: estimated glomerular filtration rate; N: Number of randomized patients; n: relevant subpopulation; RCT: randomized controlled trial; vs.: versus

Table 8: Characteristics of the interventions – RCT, direct comparison: sitagliptin vs. glipizide

Study	Sitagliptin	Glipizide	Concomitant medication
P063	**Relevant subpopulation: moderate renal impairment (30ml/min ≤ eGFR < 50ml/min):** sitagliptin (50 mg/day) + glipizide placebo (dose increase and reduction as in the glipizide verum arm)	Glipizide (5-20mg/day) + sitagliptin placebo Glipizide: *Titration, dose increase* ▪ Starting dose: 2.5 mg once a day before breakfast. ▪ Starting from week 2, possible up-titration in 4 steps to a maximum of 4 tablets (of 5 mg each; maximum dose: 20 mg) a day, at intervals of at least 2 weeks. With 10 mg or more, the dose was distributed to 2 administrations a day. *Basis of decision on up-titration* ▪ Up-titration was conducted at the investigator's discretion and based on the following criteria: Fasting and preprandial fingerstick blood glucose value (from the week prior to the visit) ≥ 120 mg/dl, and ▪ The patient had no hypoglycaemia or symptoms that, in the investigator's assessment, were signs of hypoglycaemia since the last visit. ▪ The investigator could also titrate independent from these criteria if he or she deemed this clinically appropriate. *Titration, dose reduction* ▪ If hypoglycaemias were suspected, dose reduction was possible at any time. Glipizide was discontinued if hypoglycaemias continued to occur under the minimum dose of 2.5 mg. Increasing the dose again was possible if this seemed clinically appropriate.	All antidiabetics used before the beginning of the study were discontinued. Before randomization, patients received a diet and fitness programme of up to 14 weeks. Insulin as rescue medication for inadequate glycaemic control.

eGFR: estimated glomerular filtration rate; RCT: randomized controlled trial; vs.: versus

The study P063 was a randomized, active-controlled, double-blind approval study sponsored by the company with a study period of 54 weeks. It included patients aged 30 years or older with type 2 diabetes mellitus with moderate (30 ml/min ≤ estimated glomerular filtration rate [eGFR] < 50 ml/min) or severe (eGFR < 30 ml/min) renal impairment.

The study included a 1-week screening period, a phase of up to 14 weeks with diet and exercise and the wash-out of OADs, a 2-week placebo run-in phase, and a treatment phase of 54 weeks.

The patients were enrolled when their HbA1c value was between 7% and 9% 2 weeks before randomization. If the patients had received prior antidiabetic treatment, this was washed out with diet and exercise during a run-in phase, which lasted up to 14 weeks.

The randomization of the patients to the 2 treatment arms was stratified according to the patients' renal status as well as to prior cardiovascular disorders and cardiac failure. Primary outcome of the study was the change in HbA1c value, which was not a patient-relevant outcome for the benefit assessment, however.

Relevant subpopulation

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 (see Section 2.3). There are contraindications to metformin for patients with chronic renal failure or renal impairment (creatinine clearance < 60 ml/min). Since only patients with moderate or severe renal impairment were included in the study P063, this study covered part of the target population for sitagliptin monotherapy.

Only patients with moderate renal impairment and hence only a subpopulation of the study P063 could be considered in this assessment because glipizide is contraindicated in patients with severe renal impairment. The relevant subpopulation of the patients with moderate renal impairment comprised about 72% of the total study population in the study P063. In the outcomes considered by the company in Module 4A, the company also presented the results on patients with moderate and severe renal impairment separately. The information below refers to the relevant subpopulation.

Treatment regimen

After randomization, the patients in the study P063 received either a fixed dose of 50 mg sitagliptin/day or glipizide at a starting dose of 2.5 mg/day.

The starting dose of 2.5 mg glipizide/day could be up-titrated at the investigator's instigation at an interval of at least 2 weeks in 4 steps to a maximum dose of 20 mg/day. With a dose of 10 mg/day or more, the dose was distributed to 2 administrations a day. The criteria for the titration are presented in Table 8 and include a consistent target level for fasting blood glucose (120 mg/dl) under consideration of the risk of hypoglycaemia.

It was clear from the treatment regimen of the study P063 that titration with a blood-glucose lowering drug to a specified consistent target level (fasting blood glucose < 120 mg/dl) was only possible in the glipizide group, but not in the sitagliptin group. In the sitagliptin group, titration was conducted with the glipizide placebo. Hence the study P063 constituted a

comparison of 2 treatment regimens and not of 2 drugs. Moreover, it should be noted that the target blood glucose level specified was low (fasting blood glucose < 120 mg/dl). A consistent target value of 120 mg/dl for the included patients with existing renal disorder is a target value aiming at near-normal blood glucose levels.

It is particularly necessary to consider the course of HbA1c in the study to assess the influence of the different treatment regimens on the effect observed in the study. Figure 1 shows the change in HbA1c (adjusted mean values) during the 54-week treatment phase of the study. Missing values were replaced with the last observation carried forward (LOCF). The figure refers to the total population of study P063. There were no such data for the relevant subpopulation of patients with moderate renal impairment.

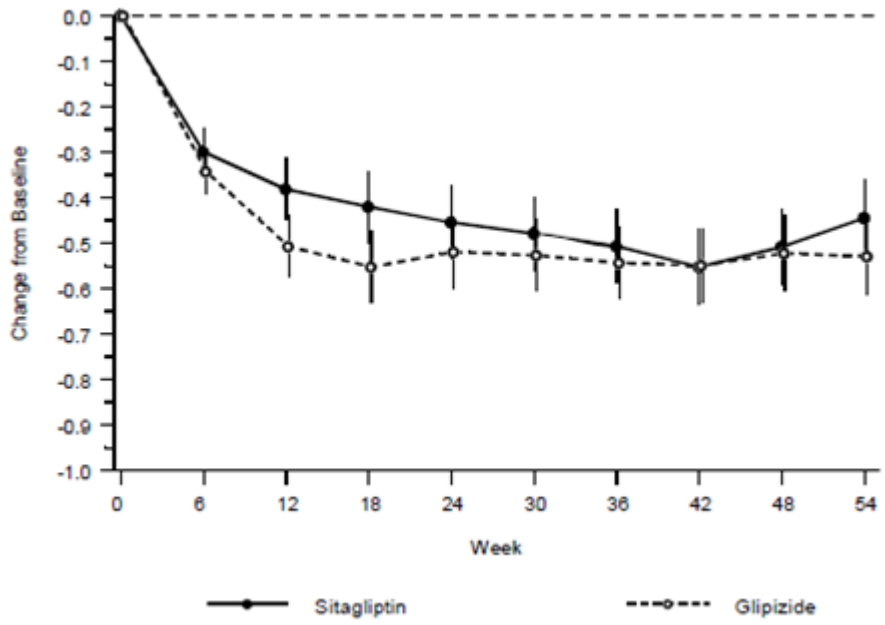


Figure refers to the total study population (least squares estimate from analysis of covariance (ANCOVA) model adjusted for treatment, renal impairment, prior therapy and HbA1c at baseline).

Figure 1: Change in HbA1c value (adjusted mean value) according to treatment groups in the course of the study (full analysis set, LOCF)

Considering the time course, there was a rapid decrease in HbA1c in both treatment arms. This was parallel in the first 6 weeks. In weeks 6 to 18, the decrease was slightly more pronounced in the glipizide arm than in the sitagliptin arm. In weeks 12 to 18, the difference between the arms was at its maximum, but, in a rough estimate based on the figure, at no more than 0.15 percentage points. In the further course of the study, the curves approached each other again. According to the clinical study report, there was a difference of 0.09% 95% CI [−0.13; 0.30] at the end of the study after 54 weeks.

In Figure 1, despite the different therapeutic strategies used, the overall picture of the courses of HbA1c was largely similar in the 2 treatment groups of the study P063. This is not necessarily the case in studies with different treatment regimens in the treatment groups. In the studies described in the dossier assessment of linagliptin (study 1218.20) [9] and in the addendum to the assessment of the fixed combination saxagliptin/metformin (study D1680L00002) [10] for example, HbA1c decrease was considerably more pronounced in the sulfonylurea arms with a treatment directed towards target levels than in the comparator arms (linagliptin or saxagliptin) without specified target levels after the first 16 or 24 weeks. In both studies, up-titrations of the sulfonylurea were conducted as soon as the patients reached a fasting glucose value of > 110 mg/dl. The requirements in the study P063 were less strict both with regards to the target fasting glucose value of < 120 mg/dl and with regards to the requirements the investigator had to follow.

In contrast to the other studies mentioned above, there was a noticeable difference between the courses of the HbA1c value and the fasting plasma glucose in the study P063. This is shown in Figure 2 below.

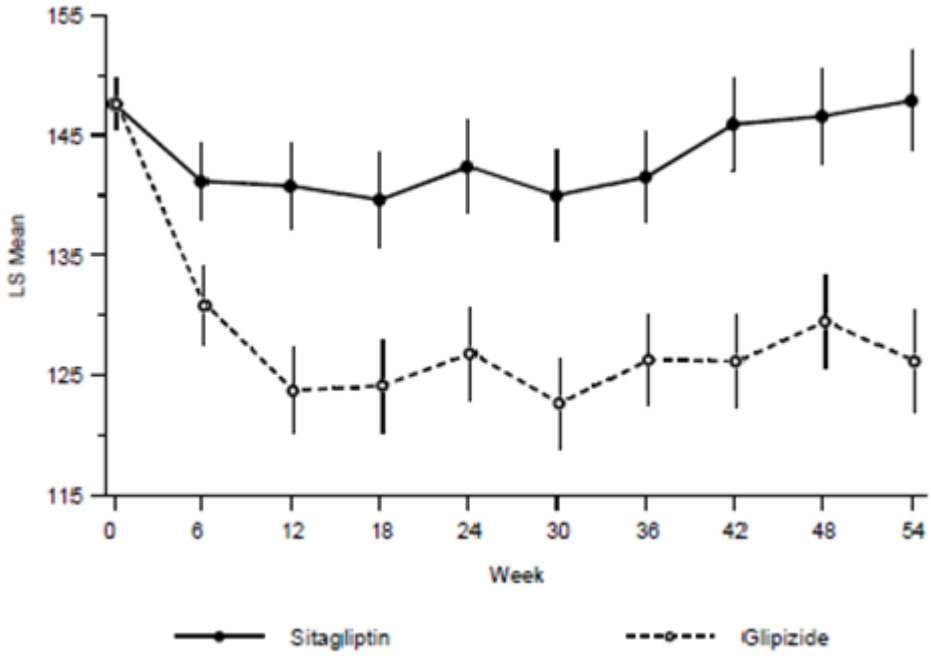


Figure refers to the total study population (least squares estimate from ANCOVA model adjusted for treatment, renal impairment, prior therapy and HbA1c at baseline).

Figure 2: Fasting plasma glucose (mg/dl; adjusted mean value) according to treatment groups in the course of the study (full analysis set, LOCF)

In contrast to the course of HbA1c (Figure 1), the course of fasting plasma glucose shows noticeable differences between the treatment groups for the total population in the entire study period. No data were available for the relevant subpopulation of the study. It could not be excluded that the differences observed can be explained by the different treatment strategies.

The time course of these events has to be considered to be able to assess if the different therapeutic strategies of the sitagliptin and the glipizide arm, particularly during the titration phase in the beginning of the study, influenced the risk of hypoglycaemia or the occurrence of other outcomes. There is no information on the time course of the hypoglycaemias for study P063, however. There was no noticeable increase in serious cardiac and cerebral events or deaths during the titration phase of the sulfonylurea (Figure 3, Figure 4 and Figure 5). Furthermore, the mean HbA1c value in study P063 was above 7% in the entire study period and thus higher than in the studies on linagliptin and saxagliptin mentioned above so that the missing time courses for the hypoglycaemias did not result in a downgrading of the certainty of results.

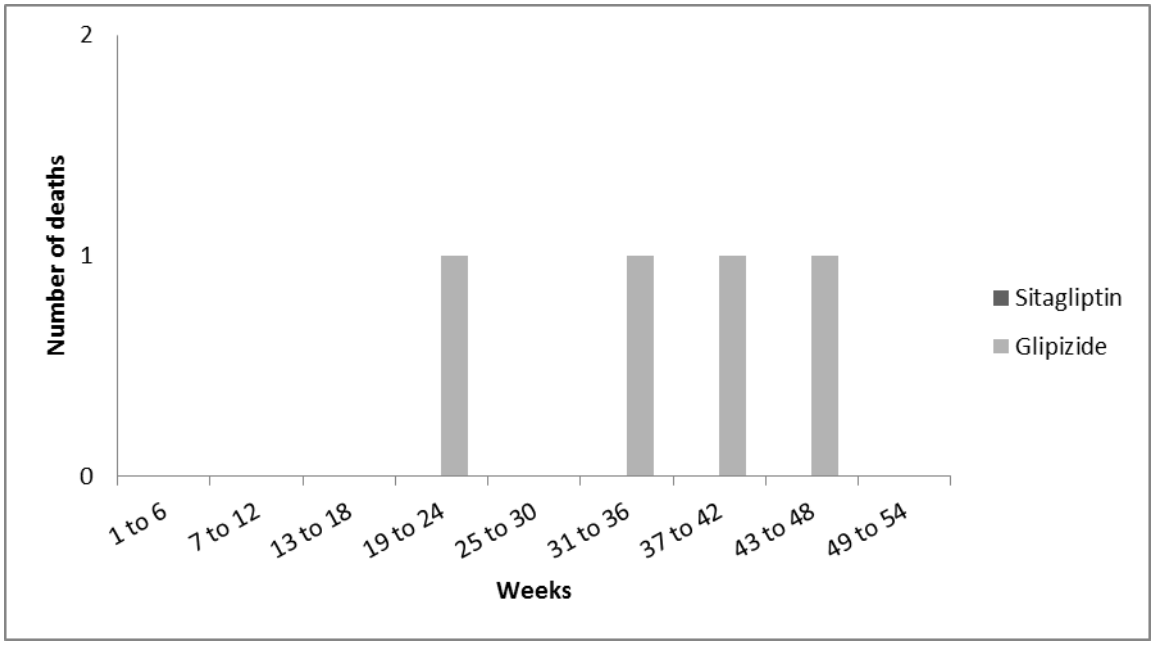
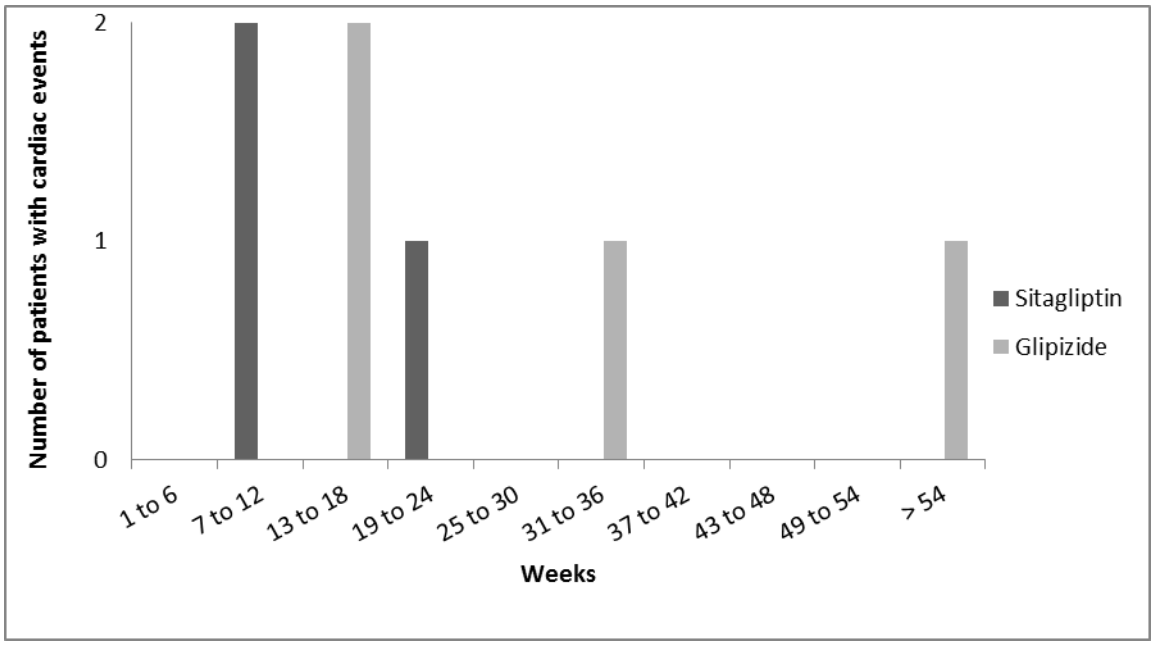
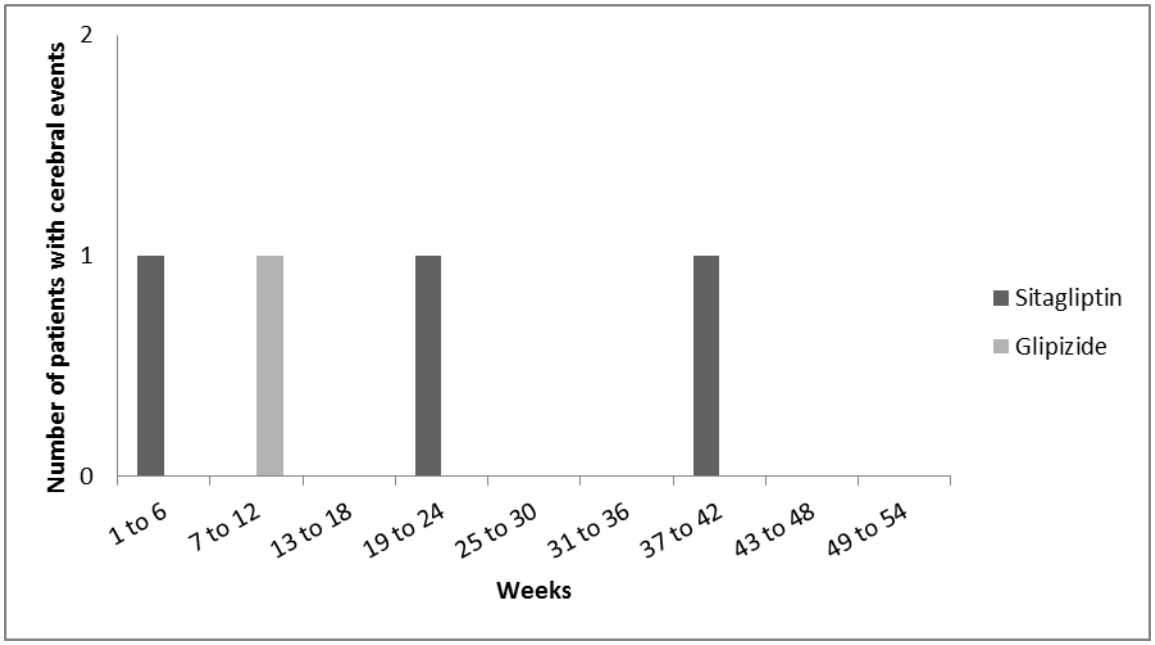


Figure 3: Time course of deaths in patients with moderate renal impairment in the study P063 (sitagliptin versus glipizide)



Presentation of cardiac events operationalized as SAEs from the System Organ Class (SOC) "cardiac disorders" (according to the Medical Dictionary for Regulatory Activities [MedDRA])

Figure 4: Time course of cardiac events in patients with moderate renal impairment in the study P063



Presentation of cerebral events operationalized as SAEs from the SOC "cardiac disorders" (according to the Medical Dictionary for Regulatory Activities [MedDRA])

Figure 5: Time course of cardiac events in patients with moderate renal impairment in the study P063

Consequences for study inclusion and assessment

There are no indications that the different therapeutic strategies in study P063 had such a considerable impact that an interpretation of the study for the comparison of the 2 drugs was not possible.

The study P063 was considered to be relevant for assessing the added benefit of sitagliptin versus glipizide.

Uncertainties resulted from:

- discrepancies in the courses of HbA1c and fasting plasma glucose,
- missing data on courses for the relevant subpopulation of patients with moderate renal impairment.

The uncertainties described resulted in a downgrading of the certainty of results of the study P063.

Moreover, the results from the study P063 can only be transferred to patients who are suitable for blood-glucose lowering to near-normal levels.

Characteristics of the study population

There was no information on the characteristics of the relevant subpopulation of patients with moderate renal impairment in the dossier – with the exception of the HbA1c value at the start of the study. This would have been advisable, however, because differences in factors such as age, duration of disease or glycaemic control would have to be expected in comparison with patients with severe renal impairment, i.e. patients with an advanced stage of disease.

Table 9 shows the characteristics of the patients in the study included for the total population.

Table 9: Characteristics of the study population – RCT, direct comparison: sitagliptin vs. glipizide (total population)

Study Characteristic Category	Sitagliptin	Glipizide
P063		
N	211	212
Age [years]: mean (SD)	64.2 (10.7)	64.2 (9.4)
Sex f/m [%]	62.1/37.9	57.5/42.5
Body weight (kg): mean (SD)	70.1 (16.4)	70.5 (15.1)
BMI (kg/m²): mean (SD)	27.0 (5.0)	26.9 (4.5)
Duration of diabetes [years]: mean (SD)	10.9 (7.6)	11.2 (8.0)
HbA1c value at start of study [%]: mean (SD)[a]	7.84 (0.79)	7.94 (0.74)
HbA1c value at start of study [%]: [n (%)]		
< 7.0	18 (8.5)	9 (4.2)
≥ 7.0 to < 8.0	104 (49.3)	111 (52.4)
≥ 8.0 to < 9.0	71 (33.6)	77 (36.3)
≥ 9.0	17 (8.1)	15 (7.1)
Ethnicity [n (%)]		
Caucasian	63 (29.9)	62 (29.2)
Asian	114 (54.0)	121 (57.1)
Black/Afro-American	4 (1.9)	5 (2.4)
Other	30 (14.2)[a]	24 (11.3)[b]

a: Data for relevant subpopulation.
b: Institute's calculation.
BMI: Body Mass Index; f: female; HbA1c: haemoglobin A1c; m: male; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

For the total population, there were no important differences between the treatment groups. HbA1c (long-term marker for the average blood glucose level) had a mean value of 7.8% and 7.9% at the start of the study, both in the total population and in the relevant subpopulation. More than half of the patients had an HbA1c value of below 8% at the start of the study. According to current knowledge, for part of the patients one cannot assume inadequate glycaemic control that would have required intensified therapy.

Risk of bias at study level

Table 10 shows the risk of bias at study level.

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

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			
P063	yes	yes	yes	yes	yes	yes	low
RCT: randomized controlled trial; vs.: versus							

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

Further information on study design, study populations and the risk of bias at study level can be found in Module 4A, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and in Appendix 4-G of the dossier, and in Sections 2.9.2.5.1, 2.9.2.5.2 and Appendix A of the full dossier assessment.

2.3.3.2 Results on added benefit (research question A2)

The following patient-relevant outcomes were considered in this assessment (for reasons and operationalization, see Section 2.9.2.5.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - cardiac morbidity
  - cerebral morbidity
- Health-related quality of life
- Adverse events
  - hypoglycaemias (interpretation in connection with change in HbA1c value over time)
    - symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)
    - severe hypoglycaemias
  - pancreatitis
  - renal impairment
  - start of dialysis
  - overall rate of SAEs
  - treatment discontinuations due to AEs

The choice of patient-relevant outcomes deviated from that of the company. The company did not consider cardiac and cerebral morbidity as separate outcomes, but as a combined outcome "severe cardiovascular events" without presenting the individual components. Moreover, the outcomes "renal impairment", "start of dialysis" and "pancreatitis" were included in this assessment. These outcomes were not predefined by the company. 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. A detailed explanation can be found in Section 2.9.2.5.3 of the full dossier assessment.

Table 11 shows for which outcomes of the studies included data were available.

Table 11: Matrix of outcomes – RCT, direct comparison: sitagliptin vs. glipizide

Study	Outcomes										
	All-cause mortality	Cardiac morbidity	Cerebral morbidity	Health-related quality of life	Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)	Severe hypoglycaemias	Pancreatitis	Renal impairment	Start of dialysis	SAEs	Treatment discontinuation due to AEs
P063	yes	yes[a]	yes[a]	–[b]	yes	yes	yes[c]	yes[d]	yes[e]	yes	yes

a: Used by the company by means of a combined outcome of cardiac and cerebral events. Operationalized in this assessment using SAEs of the MedDRA SOC "cardiac disorders" and "nervous system disorders".
b: Outcome not recorded in the study P063.
c: Operationalized using the Preferred Term "pancreatitis" according to MedDRA. No predefined outcome of the company.
d: Operationalized using the SAEs of the MedDRA SOC "renal and urinary disorders".
d: Additionally included.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class (according to MedDRA); vs.: versus

Although there were data on most outcomes, the results, particularly on micro- and macrovascular late complications, were insufficient due to the size and duration of the study.

Risk of bias

Table 12 shows the risk of bias for these outcomes.

Table 12: Risk of bias at study and outcome level – RCT, direct comparison: research question A, sitagliptin vs. glipizide

Study	Study level	Outcomes										
		All-cause mortality	Cardiac morbidity	Cerebral morbidity	Health-related quality of life	Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)	Severe hypoglycaemias	Pancreatitis	Renal impairment	Start of dialysis	SAEs	Treatment discontinuation due to AEs
P063	l	l	h[a]	h[a]	–[b]	h[c]	h[c]	h[d]	h[d]	l	l	l

a: Deviating from the company, by approximation operationalized in this assessment using SAEs of the MedDRA SOC "cardiac disorders" and "nervous system disorders". No predefined benefit outcome, therefore high risk of bias due to limited data availability.
b: Outcome was not recorded.
c: Information on time course of hypoglycaemias is lacking. Influence of different therapeutic strategies could not be estimated, therefore high risk of bias.
d: By approximation operationalized using the SAEs of the MedDRA SOC "renal and urinary disorders" and "pancreatitis". No predefined benefit outcome, therefore high risk of bias due to limited data availability.
AE: adverse event; h: high; HbA1c: haemoglobin A1c; l: low; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class (according to MedDRA); vs.: versus

The assessment of the risk of bias at outcome level deviated from the company's assessment as follows:

- Since the company did not cite them as separate or predefined outcomes in Module 4A, it did not assess the risk of bias for the following outcomes: cardiac morbidity, cerebral morbidity, renal impairment, start of dialysis and pancreatitis. Because of the limited data availability, the risk of bias was rated as high for cardiac morbidity, cerebral morbidity, renal impairment and pancreatitis.
- The company rated the risk of bias as low for symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl) and for severe hypoglycaemias. Deviating from this assessment, the risk of bias was rated as high because of the lack of information on the time course of the hypoglycaemias.

Furthermore, the uncertainties described in Section 2.3.3.1 are to be additionally considered.

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4A, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Sections 2.9.2.5.2 and 2.9.2.5.3 of the full dossier assessment.

Results

Table 13 summarizes the results on the comparison of sitagliptin monotherapy with glipizide. The data from the company's dossier were supplemented, where necessary, by the Institute's own calculations.

The odds ratio (OR) offers a good approximation of the relative risk (RR) in low numbers of events. Hence in event rates of ≤ 1% (in at least one cell), the Peto OR instead of the RR was calculated as effect measure and used for the assessment.

Due to lacking or unsuitable data in Module 4A, the outcomes "cardiac morbidity", "cerebral morbidity" and "renal impairment" could only be considered by approximation using non-fatal SAEs of the corresponding MedDRA SOCs. The outcome "pancreatitis" was assessed using the MedDRA Preferred Term "pancreatitis". The data on the outcome "start of dialysis" were taken from the information on the monitoring of renal function.

Table 13: Results (dichotomous outcomes) – RCT, direct comparison: research question A, sitagliptin vs. glipizide (study P063, monotherapy with sitagliptin, relevant subpopulation)

Study Outcome category Outcome	Sitagliptin		Glipizide		Sitagliptin vs. glipizide
	N	Patients with events n (%)	N	Patients with events n (%)	RR/Peto OR[a] [95% CI]; p-value[b]
P063					
Mortality					
All-cause mortality	149	0 (0)	154	4 (2.6)[d]	0.14 [0.02; 0.98][c,d] 0.051
Morbidity					
Cardiac morbidity[e]	149	3 (2.0)	154	4 (2.6)	0.78 [0.18; 3.40][d] 0.808[d]
Cerebral morbidity[f]	149	3 (2.0)	154	1 (0.6)	3.1 [0.33; 29.48][d] 0.312[d]
Health-related quality of life	Not recorded				
AEs					
Hypoglycaemias					
Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)	149	4 (2.7)	154	13 (8.4)	0.32 [0.11; 0.95]; 0.030[d]
Severe hypoglycaemias	149	3 (2.0)	154	3 (1.9)	1.03 [0.21; 5.04]; > 0.999[d]
HbA1c change	See Figure 1 for information on the course of HbA1c change. Uncertainties resulted from the discrepancies in the courses of HbA1c and fasting plasma glucose.				
Pancreatitis	149	0 (0)	154	0 (0)	n.c.
Renal impairment[g]	149	1 (0.7)	154	2 (1.3)	0.53 [0.05; 5.12][d] 0.605[d]
Start of dialysis	149	0 (0)	154	0 (0)	n.c.
Overall rate AEs[h]	149	111 (74.5)	154	113 (73.4)	
Overall rate SAEs[h]	149	27 (18.1)	154	25 (16.2)	1.12 [0.68; 1.83]; 0.711[d]
Treatment discontinuation due to AEs[h]	149	9 (6.0)	154	11 (7.1)	0.85 [0.36; 1.98]; 0.762[d]
Supplementary outcome "body weight"					
Body weight in kg after week 54	Not presented in the present report[i]				

(continued)

Table 13: Results (dichotomous outcomes) – RCT, direct comparison: research question A, sitagliptin vs. glipizide (study P063, monotherapy with sitagliptin, relevant subpopulation) (continuation)

a: Peto OR provided instead of RR in event numbers ≤ 1% in at least one cell.
b: Institute's calculation, unconditional exact test (CSZ method according to [11]).
c: The discrepancy between p-value (exact) and CI (asymptotic) is due to different calculation methods.
d: Institute's calculation.
e: Serious cardiac events. MedDRA SOC “cardiac disorders”, without deaths.
f: Serious cerebral events. MedDRA SOC “nervous system disorders”, without deaths.
g: Serious renal events. MedDRA SOC “renal and urinary disorders”, without deaths.
h: Hypoglycaemic events were also recorded here.
i: Only analysis without replacement of missing values available. Because the proportion of patients who were not considered in the analysis was > 30% in the sitagliptin arm, the data are not presented.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; FPG: fasting plasma glucose; HbA1c: haemoglobin A1c; MedDRA: Medical Dictionary for Regulatory Activities; N: number of analysed patients; n: number of patients with event; n.c.: not calculated; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class (according to MedDRA); vs.: versus

Mortality

All-cause mortality

Treatment with sitagliptin did not result in a statistically significant difference for the relevant subpopulation of patients with moderate renal impairment in comparison with glipizide for all-cause mortality. This assessment was based on few events overall observed in the study. The company did also not derive a statistically significant advantage of sitagliptin for the outcome "all-cause mortality".

Morbidity

Cardiac and cerebral morbidity

For cardiac and cerebral events (both operationalized as SAEs without deaths of the respective MedDRA SOC), there were only few events and no statistically significant differences between the treatment arms. An added benefit of the monotherapy with sitagliptin versus glipizide is therefore not proven for the subpopulation of patients with moderate renal impairment for cardiac and cerebral morbidity.

Overall, the data availability on morbidity only allows to draw very limited conclusions on the comparison of sitagliptin and glipizide. Recording patient-relevant outcomes on diabetic late complications was not a goal.

The company did also not derive an added benefit for cardiac and cerebral morbidity. Deviating, it considered all studies jointly versus sulfonylurea and used a different operationalization of the outcome – as a combined outcome without presenting the individual components.

Health-related quality of life

No data on health-related quality of life were recorded in the study P063.

Adverse events

Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)

There was a statistically significant advantage of the treatment arm with sitagliptin for confirmed symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl). Since the upper limit of the CI was above 0.9, and this was a non-serious AE, not more than a marginal advantage of sitagliptin versus glipizide could be derived from this [2].

This assessment deviated from that of the company. From the joint consideration of the studies P251 (comparison with glimepiride) and P063, the company derived a statistically significant advantage for the relevant subpopulation with the upper limit of the CI being below 0.9. In the overall consideration of all studies (P010, P063 and P073 in comparison with glipizide, P251 in comparison with glimepiride) over all subpopulations, it derived proof of a considerable added benefit of sitagliptin versus sulfonylureas as a whole.

Severe hypoglycaemias

There were only 3 patients with severe hypoglycaemic events in each of the 2 treatment arms. An advantage of sitagliptin versus glipizide could not be derived from this.

This assessment partly deviated from that of the company. From the joint consideration of the studies P251 (comparison with glimepiride) and P063, the company did also not derive a statistically significant advantage for the relevant subpopulation. But in the overall consideration of all studies (P010, P063 and P073 in comparison with glipizide, P251 in comparison with glimepiride), it derived proof of a major added benefit of sitagliptin versus sulfonylureas as a whole.

Serious adverse events

Treatment with sitagliptin did not result in a statistically significant difference in comparison with glipizide for SAEs. However, hypoglycaemias, which were also recorded as specific outcome, were also recorded as SAEs. Overall, this applied to 3 patients in the glipizide arm and to 0 patients in the sitagliptin arm. An analysis without the 3 cases under glipizide was conducted to investigate whether there was a disadvantage of sitagliptin versus glipizide with regards to other SAEs than hypoglycaemias (worst-case scenario). This also resulted in a non-statistically significant difference between the treatment groups (RR 1.27 [0.76; 2.12], p = 0.482).

Greater or lesser harm from the monotherapy with sitagliptin in comparison with glipizide is therefore not proven for SAEs.

Treatment discontinuation due to adverse events

Treatment with sitagliptin did not result in a statistically significant difference in comparison with glipizide for discontinuations due to AEs. However, hypoglycaemias were also recorded in this outcome. Overall, this applied to 2 patients in the glipizide arm and to 0 patients in the sitagliptin arm. It was unclear whether the 2 patients of the glipizide arm belonged to the relevant subpopulation. Without these 2 patients, the event rate would be almost identical in the 2 treatment groups (about 6% each).

Greater or lesser harm from the monotherapy with sitagliptin than from glipizide is therefore not proven for treatment discontinuations due to AEs.

Renal impairment, start of dialysis and pancreatitis

Treatment with sitagliptin did not result in a statistically significant difference in comparison with glipizide for renal impairment, start of dialysis and pancreatitis. Greater or lesser harm from the combination of sitagliptin plus metformin in comparison with glimepiride plus metformin is not proven for renal impairment and pancreatitis.

The company did not include these 3 outcomes.

Subgroups

Subgroup analyses for the potential effect modifiers "age" (< 65 years versus ≥ 65 years, predefined age strata of the study P063) and "sex" (male versus female) were included in the benefit assessment. The subgroup analyses of the hypoglycaemias presented by the company were not considered because they were only based on the adjusted event-based (c-log-log regression), and not on the patient-based analysis (see Section 2.9.2.5.3 of the full dossier assessment).

Table 14 presents the subgroup analyses for which there was proof or indication of an interaction.

Table 14: Subgroups: outcomes according to age, RCT, direct comparison: sitagliptin vs. glipizide

Study Outcome Characteristic Subgroup	Sitagliptin N[a]	Sitagliptin Patients with events n (%)	Glipizide N[a]	Glipizide Patients with events n (%)	Sitagliptin vs. glipizide RR/Peto OR[b] [95% CI]	Sitagliptin vs. glipizide p-value[c]
P063						
Treatment discontinuation due to AEs						
Age						
< 65 years	67	4 (6.0)	77	1 (1.3)	4.60 [0.53; 40.13]	0.135
≥ 65 years	82	5 (6.1)	77	10 (13.0)	0.47 [0.17; 1.31]	0.145
					Interaction:	0.062[d]
SAE						
Age						
< 65 years	67	13 (19.4)	77	8 (10.4)	1.87 [0.82; 4.23]	0.131
≥ 65 years	82	14 (17.1)	77	17 (22.1)	0.77 [0.41; 1.46]	0.530
					Interaction:	0.095[d]
Cerebral morbidity[e]						
Sex						
Men	99	3 (3.0)[f]	93	1 (1.1)[f]	2.82 [0.3; 26.62]	0.504
Women	50	0 (0)	61	0 (0)	n.c.	n.c.
					Interaction:	n.c.

a: All patients as treated.
b: Peto OR provided instead of RR in event numbers ≤ 1% in at least one cell.
c: Unconditional exact test (CSZ method according to [11]).
d: Institute's calculation, Cochran's Q test.
e: Data from narratives of the SAEs.
f: Institute's calculation of the percentages.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; n. c.: not calculated; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

There was an indication for the effect modifier "age" for each of the outcomes "SAEs" and "treatment discontinuation due to AEs". However, these effects were not statistically significant for the relevant subpopulation or for the individual age groups. For both outcomes, there was a numerical advantage of sitagliptin for patients ≥ 65 years, whereas there was a numerical advantage of glipizide for the group of patients aged under 65 years.

For the outcome "cerebral events", the test for interaction could not be calculated for the effect modifier "sex" because all events only occurred in men. For men, there was a numerical disadvantage of sitagliptin, which was not statistically significant for the total population or for the subgroups of men.

The results of the subgroup analyses according to age and sex did not lead to a change in the overall conclusion and are not considered any further.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Sections 2.9.2.5.2 and 2.9.2.5.3 of the full dossier assessment.

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

The derivation of extent and probability of added benefit is presented below for the monotherapy with sitagliptin versus glipizide. Only conclusions on part of the target population (patients with moderate renal impairment) could be drawn from the available documents. There was no information on the total target population.

The derivation of extent and probability of added benefit is presented at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in Appendix A of Benefit Assessment A11-02 [2].

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.

2.3.3.3.1 Assessment of added benefit at outcome level

The data availability presented in Section 2.3.3.2 did not result in proof of an added benefit of or lesser harm from the monotherapy of sitagliptin versus glipizide for the subpopulation of patients with moderate renal impairment. The results at outcome level are presented in Table 15 below.

Table 15: Extent of added benefit at outcome level: sitagliptin vs. glipizide

Outcome category **Outcome**	**Sitagliptin vs. glipizide** **Patients (%) with event** **Effect estimates [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0 (0) vs. 4 (2.6) Peto OR: 0.14 [0.02; 0.98] p = 0.051[c]	Lesser benefit/added benefit not proven
Morbidity		
Cardiac morbidity	3 (2.0) vs. 4 (2.6) RR: 0.78 [0.18; 3.40] p = 0.808	Lesser benefit/added benefit not proven
Cerebral morbidity	3 (2.0) vs. 1 (0.6) Peto OR: 3.1 [0.33; 29.48] p = 0.312	Lesser benefit/added benefit not proven
AEs		
SAEs	27 (18.1) vs. 25 (16.2) RR: 1.12 [0.68; 1.83] p = 0.711	Greater/lesser harm not proven
Discontinuation due to AE	9 (6.0) vs. 11 (7.1) RR: 0.85 [0.36; 1.98] p = 0.762	Greater/lesser harm not proven
Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)	4 (2.7) vs. 13 (8.4) RR: 0.32 [0.11; 0.95] p = 0.030	Outcome category: non-serious/non-severe AEs CI_o > 0.90 greater/lesser harm not proven
Severe hypoglycaemias	3 (2.0) vs. 3 (1.9) RR: 1.03 [0.21; 5.04] p > 0.999	Greater/lesser harm not proven
Renal impairment	1 (0.7) vs. 2 (1.3) Peto OR: 0.53 [0.05; 5.12] p = 0.605	Greater/lesser harm not proven
Start of dialysis	0 (0) vs. 0 (0) Peto OR: n.c.	Greater/lesser harm not proven
Pancreatitis	0 (0) vs. 0 (0) Peto OR: n.c.	Greater/lesser harm not proven

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_o.
c: The discrepancy between p-value (exact) and CI (asymptotic) is due to different calculation methods.
AE: adverse event; CI: confidence interval; CI_o: upper limit of the CI; n.c.: not calculated; OR: odds ratio; RR: relative risk; SAE: serious adverse event; vs.: versus

2.3.3.3.2 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 sitagliptin compared with glipizide

Positive effects	Negative effects
No sufficient data were available on micro- and macrovascular late complications.	

There are neither positive nor negative effects of sitagliptin versus glipizide. The effect with regards to non-serious hypoglycaemias was not more than marginal. No sufficient data were available on micro- and macrovascular late complications. An added benefit of sitagliptin versus glipizide is therefore not proven for the subpopulation of patients with moderate renal impairment in whom near-normal levels of blood glucose are aimed at. No relevant data were available for the remaining target population of sitagliptin monotherapy. The added benefit of sitagliptin versus glipizide for the total target population is therefore not proven.

The overall assessment deviates considerably from that of the company. The company claimed proof of a considerable added benefit versus sulfonylureas as a group for the entire subindication of monotherapy with sitagliptin.

2.3.3.4 List of included studies

P063

1. Arjona JCF, 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 2012; 36(5): 1067-1073.

2. 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.

3. Merck. 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. 22 May 2012 [accessed: 06 June 2012]. URL: http://www.clinicaltrials.gov/ct2/show/study/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 plus metformin (studies completed up to 1 February 2013)
- Bibliographical literature search on sitagliptin plus metformin (last search on 25 February 2013 – cut-off date 1 February 2013)
- Search in trial registries for studies on sitagliptin plus metformin (last search on 1 February 2013)

The Institute's own search:

- Bibliographical literature search on gliptins to check the search results of the company (last search on 19 March 2013)
- Search in trial registries for studies on gliptins to check the search results of the company (last search on 21 March 2013)

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

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4B, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.9.3.2 and 2.9.3.4.1 of the full dossier assessment.

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

2.4.2.1 Studies included

The study listed in Table 17 was included in the benefit assessment.

Table 17: Study pool - RCT, direct comparison: combination of sitagliptin plus metformin vs. glimepiride 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)
P803	no	yes	no
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The company also included the study P803 in its benefit assessment. In addition, the company used a further study. This was study P024 on the comparison of the combination of sitagliptin plus metformin versus glipizide plus metformin. The company assessed the added benefit versus sulfonylureas as a whole on the basis of the meta-analytical evaluation of these 2 studies.

The study P024 is considered in a separate research question (research question B2) in this dossier assessment.

Section 2.4.2.5 contains a reference list for the study included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4B, Section 4.3.1.1 of the dossier, and in Sections 2.9.3.4.1 and 2.9.3.4.2 of the full dossier assessment.

2.4.2.2 Study characteristics (research question B1)

Table 18 and Table 19 describe the study used for the benefit assessment.

Table 18: Characteristics of the studies included – RCT, direct comparison: combination of sitagliptin plus metformin vs. glimepiride plus metformin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
P803	RCT, double-blind, double-dummy, parallel	Patients (≥ 18 years) whose type 2 diabetes mellitus cannot be adequately controlled with metformin at a dose of ≥ 1500 mg/day (HbA1c value ≥ 6.5% and ≤ 9.0%)	Sitagliptin 100 mg/day in combination with metformin ≥ 1500 mg/day (N = 516) Glimepiride 1 to 6 mg/day in combination with metformin ≥ 1500 mg/day (N = 519)	Screening period: 2 weeks Run-in: 2 weeks Treatment: 30 weeks Telephone follow-up 2 weeks after the end of treatment	Asia Pacific (4 countries), Europe (9 countries), Central and South America (9 countries) Jun 2008 – Oct 2009	Primary: change in HbA1c value Secondary: health-related quality of life hypoglycaemias AEs

a: Primary outcomes contain information without consideration of the relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for the present benefit assessment.

AE: adverse event; HbA1c: haemoglobin A1; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 19: Characteristics of the interventions – RCT, direct comparison: combination of sitagliptin plus metformin vs. glimepiride plus metformin

Study	Intervention	Comparison	Concomitant medication
P803	Sitagliptin 100 mg/day + glimepiride placebo (dose increase as in the glimepiride verum arm)	Sitagliptin placebo + glimepiride *Titration, dose increase* Starting dose: 1 mg/day glimepiride During a period of 18 weeks, the daily dose could be increased to 2 mg first and then in steps of 1 or 2 mg (maximum dose: 6 mg/day). It was unclear at what time the glimepiride dose could be increased for the first time and at which intervals subsequent titration was to be done. *Basis of decision on up-titration* The dose increase was conducted on the basis of the blood glucose levels measured by the patient and at the investigator's discretion. The goal of the dose titration was to maximize the probability to achieve a target HbA1c value of ≤ 6.5%. *Titration, dose reduction* The dose could be reduced any time to avoid hypoglycaemias.	Stable metformin dose (≥ 1500 mg/day) over at least 12 weeks before the start of the study. The metformin dose was not to be changed during the entire study. Other anti-hyperglycaemic drugs were not allowed.
HbA1c: haemoglobin A1c; RCT: randomized controlled trial; vs.: versus			

Study design

The study P803 was an active-controlled, double-blind RCT with a duration of 30 weeks. Adult patients with type 2 diabetes mellitus were enrolled in whom no sufficient glycaemic control was achieved despite treatment with metformin at a stable dose of ≥ 1500 mg/day during at least 12 weeks (HbA1c ≥ 6.5% and ≤ 9.0%).

The study included a 2-week screening period and a 2-week run-in period, a 30-week treatment phase as well as a telephone follow-up 2 weeks after the end of the treatment. The patients received placebo and metformin during the run-in period.

1035 patients were randomly assigned in a ratio of 1:1, 516 patients to the sitagliptin plus metformin arm and 519 patients to the glimepiride plus metformin arm.

The change in HbA1c value was the primary outcome of the study.

Treatment regimen

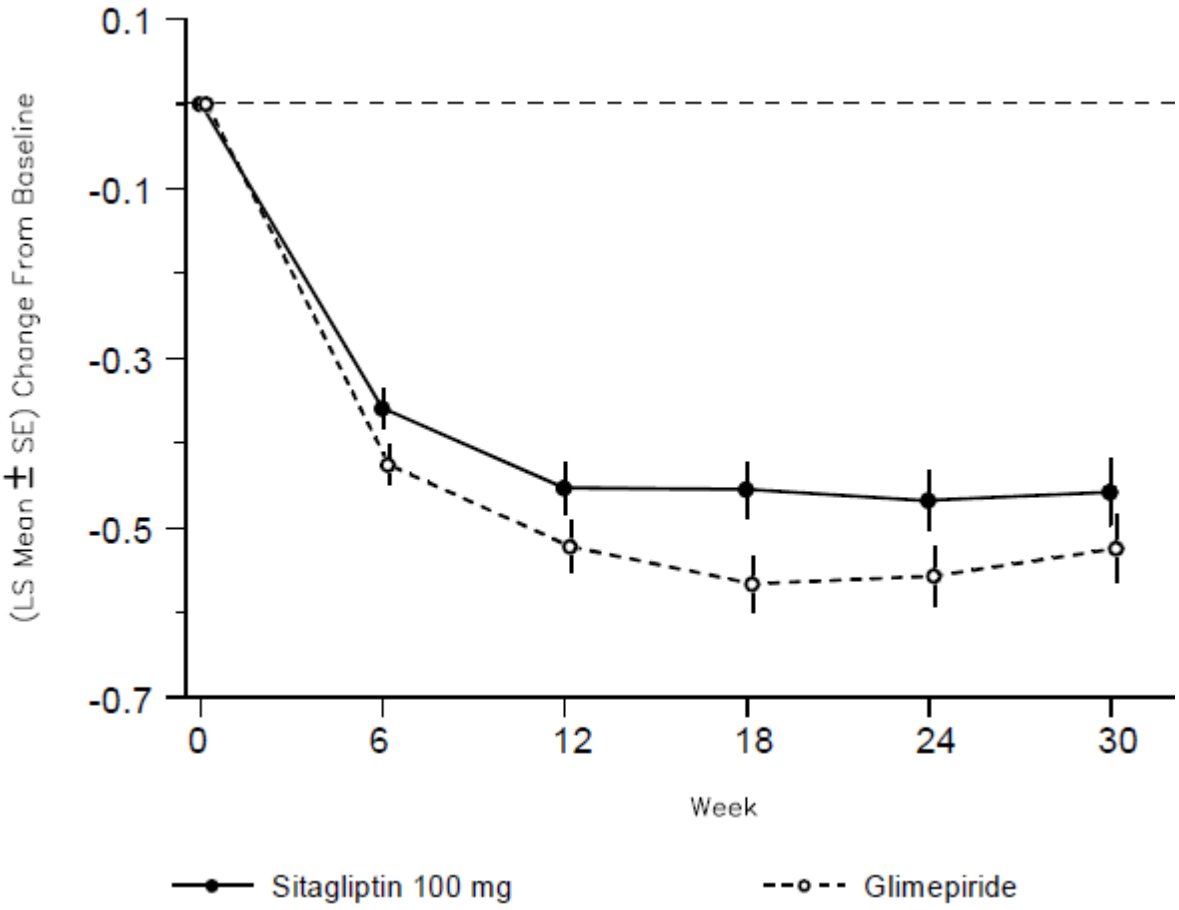
After randomization, the patients either received a fixed dosage of 100 mg/day sitagliptin or they started with 1 mg/day glimepiride (starting dose) and a placebo of the respective other drug. The patients were required to continue taking their metformin dose from the stable phase of at least 12 weeks before the start of the study unchanged during the entire study duration (including the run-in phase).

The starting dose of 1 mg glimepiride (+ placebo) was chosen in the study to minimize the risk of hypoglycaemias. During a period of 18 weeks, the glimepiride dose could be up-titrated to a maximum dose of 6 mg/day depending on the blood glucose levels measured by the patient. The daily dose could be increased to 2 mg first and then in steps of 1 or 2 mg (see Table 19). According to the SPC [6], the up-titration in steps of 2 mg glimepiride, which was allowed in the study, is not envisaged. The study could still be used because it was apparent from the available documents that the titration steps for dose increase were conducted in accordance with the approval (1 mg) in at least 80% of the patients. This was unclear for the rest of the patients so that the proportion of patients with a dose titration that was not compliant with the approval (2 mg) was not more than 20%. The overall goal of the dose titration was to maximize the probability to achieve the target HbA1c value of $\leq 6.5\%$ recommended by the International Diabetes Federation and the American Association of Clinical Endocrinologists [12].

It was clear from the treatment regimen of the study P803 that titration with a blood-glucose lowering drug aimed at a target blood glucose level (HbA1c value $\leq 6.5\%$) was only possible in the glimepiride arm, but not in the sitagliptin arm. In the sitagliptin arm, titration was conducted with the glimepiride placebo. Hence the study P803 constituted a comparison of 2 treatment regimens and not of 2 drugs. In addition, it should be noted that the specified target blood glucose (glimepiride dosage aimed at an HbA1c value $\leq 6.5\%$) was very low. In contrast to studies with linagliptin [9] or saxagliptin/metformin [13], no concrete target fasting blood glucose levels were specified, and the specifications for dose increases and reductions were less strict.

It is particularly necessary to consider the course of HbA1c in the study to assess whether the effects observed in the study were attributable to the drugs used or whether they were caused by different therapeutic strategies.

Figure 6 shows the change in HbA1c (mean values estimated with the least squares method) during the 30-week treatment phase of the study. Missing values were replaced with LOCF.



The mean values and standard errors of the changes were estimated according to the least squares method with missing values being replaced by the last available measurement (LOCF).

Figure 6: Course of changes in the HbA1c value in the study P803 after randomization (sitagliptin plus metformin vs. glimepiride plus metformin, full analysis set, LOCF)

Considering the time course of the change in HbA1c value, there was a rapid decrease in HbA1c in both treatment arms. This was nearly parallel in the first 6 weeks. In the further course, the lowering of the HbA1c value was slightly more pronounced in the glimepiride arm than in the sitagliptin arm. The difference between the arms was at its maximum in week 18, but was at a maximum of about 0.13 percentage points at this point (rough estimate based on Figure 6). In the end of the study, the courses of HbA1c of both treatment groups approached each other and the difference was not statistically significant [95% CI] of 0.07% [−0.02; 0.16]. Different results for the 2 treatment arms resulted solely from the responder analyses contained in the available documents. It was shown that statistically significantly more patients achieved the target HbA1c value of 6.5% or were below it in the glimepiride arm than in the sitagliptin arm (sitagliptin arm: 19.3% of the patients, glimepiride arm: 26.5% of the patients); RR [95% CI]: 0.73 [0.58; 0.91], p = 0.006).

In Figure 6, however, the overall picture of the courses of HbA1c was largely similar in the 2 treatment arms[5]. This is not necessarily the case when different treatment regimens are followed in the treatment arms. In the studies with linagliptin [9] and saxagliptin/metformin [10] (studies 1218.20 and D1680L00002), HbA1c decreases were considerably more pronounced in the sulfonylurea arm with a treatment directed towards target levels than in the comparator arm (linagliptin or saxagliptin) without specified target levels. According to the available documents, the requirements in the study P803 were less strict, however. Dose titration was – based on the blood glucose levels measured by the patient – at the doctor's discretion and to be conducted according to his or her usual practice. The overall goal was to increase the probability to achieve a target HbA1c level of ≤ 6.5%. In the studies 1218.20 and D1680L00002, up-titration of the sulfonylurea was conducted as long as the patients still had a fasting glucose value of ≥ 110 mg/dl. The maximum difference in HbA1c value between the gliptin and the sulfonylurea arm in the study P803 was considerably below the difference observed for linagliptin or saxagliptin. It was unclear whether this resulted from the specifications for glimepiride titration, which were less strict, or from a greater blood-glucose lowering effect of sitagliptin versus linagliptin or saxagliptin. Eventually, however, this led to the results of the study P803 being interpretable and usable for the benefit assessment of sitagliptin.

Independent from this, the time course of these events was crucial for the interpretation of the results on hypoglycaemias and on cardio- and cerebrovascular events because the HbA1c value changed over the course of the study. No such data were available for hypoglycaemias in the study P803. There was no noticeable increase in the outcomes "serious cardiac events", "serious cerebral events" or "deaths" during the titration phase of the sulfonylurea (see Figure 7 to Figure 9). Overall, no correlation could therefore be established between the time course of the occurrence of patient-relevant events and the lowering of blood-glucose.

[5] In contrast to study P063 (research question A2), there was no noticeable difference between the courses on HbA1c value and on fasting plasma glucose. The course of fasting plasma glucose is therefore not presented.

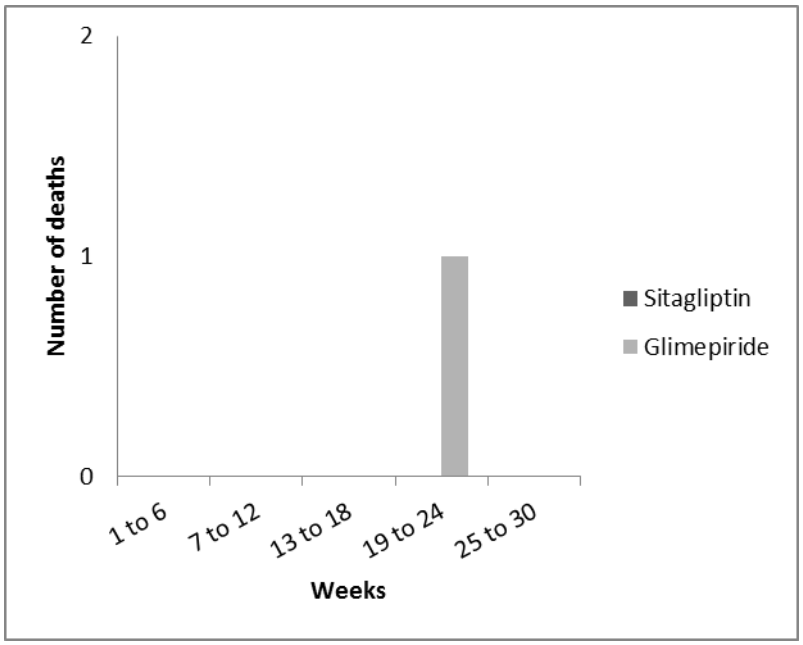
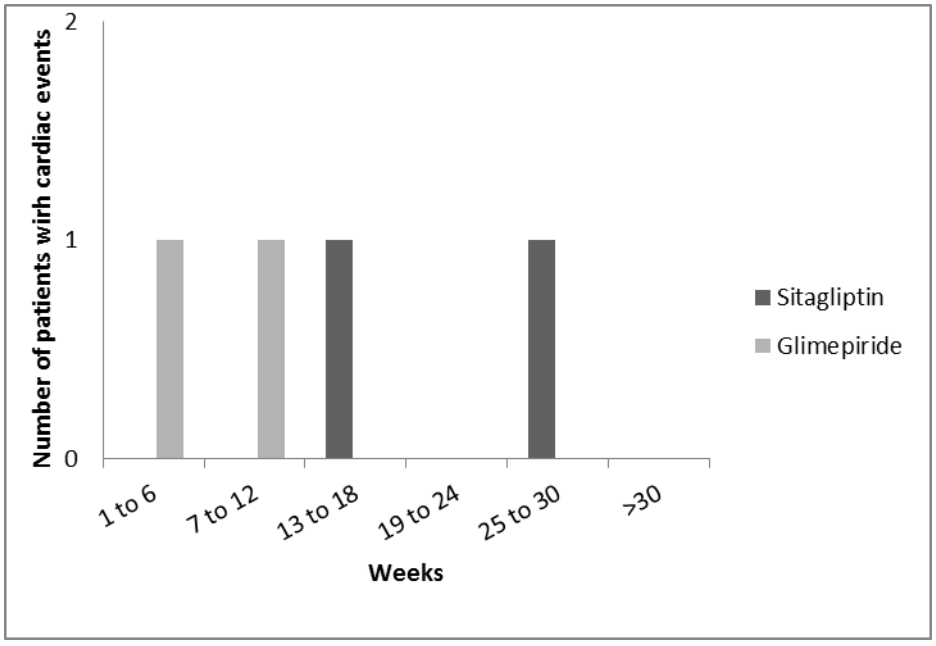
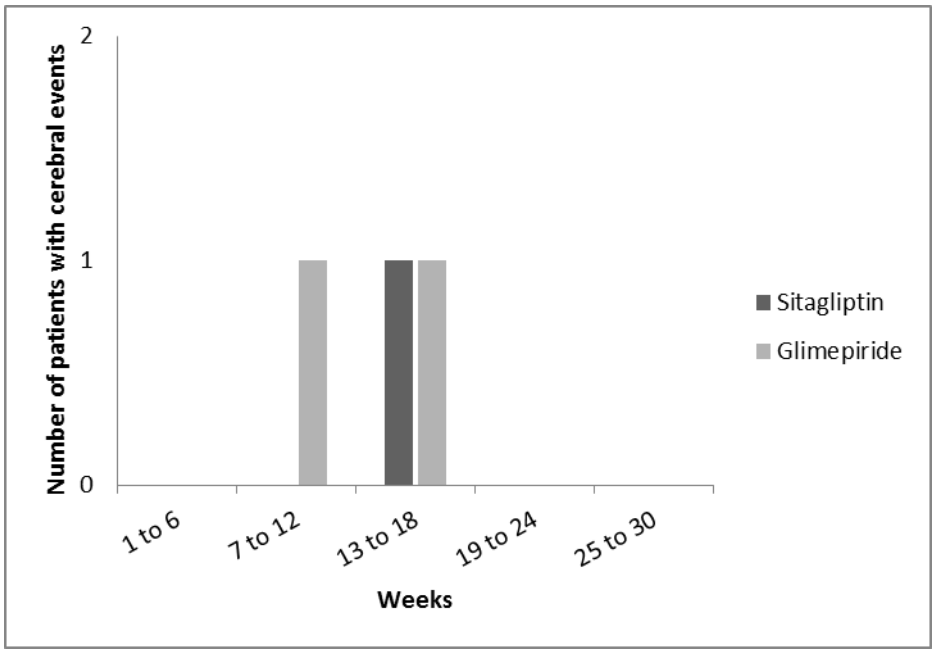


Figure 7: Time course of deaths in the study P803 (sitagliptin plus metformin vs. glimepiride plus metformin)



Presentation of cardiac events operationalized as SAEs from the SOC "cardiac disorders" (according to MedDRA)

Figure 8: Time course of cardiac events in the study P803 (sitagliptin plus metformin vs. glimepiride plus metformin)



Presentation of cerebral events operationalized as SAEs from the SOC "nervous system disorders" (according to MedDRA)

Figure 9: Time course of cerebral events in the study P803 (sitagliptin plus metformin vs. glimepiride plus metformin)

Consequences for study inclusion and assessment

There were no indications that the different therapeutic strategies in the study P803 had major impact. It was unclear whether this resulted solely from the specifications for glimepiride titration, which were less strict compared with the ones in studies with linagliptin or saxagliptin, or also from a greater blood-glucose lowering efficacy of sitagliptin versus linagliptin or saxagliptin. Eventually, however, this led to the results of the study P803 being interpretable and usable for the benefit assessment of sitagliptin.

Uncertainties regarding the overview of the evidence resulted from:

- missing data on the time course of the hypoglycaemias
- a possible up-titration of glimepiride in 2 mg steps, which is not compliant with the approval, in part of the patients (20% maximum)

The uncertainties described resulted in a downgrading of the certainty of results of the study P803.

Characteristics of the study population

Table 20 shows the characteristics of the patients in the study P803.

Table 20: Characteristics of the study populations – RCT, direct comparison: sitagliptin plus metformin vs. glimepiride plus metformin

Study Characteristic Category	Sitagliptin plus metformin	Glimepiride plus metformin
P803		
N	516	519
Age [years]: mean (SD)	56.3 (9.7)	56.2 (10.1)
Sex f/m [%]	45.0/55.0	46.2/53.8
Body weight (kg): mean (SD)	80.6 (15.2)	82.0 (16.7)
BMI (kg/m²): mean (SD)	29.7 (4.5)	30.2 (4.4)
Duration of diabetes [years]: mean (SD)	6.8 (4.6)	6.7 (4.8)
HbA1c value at start of study [%]: mean (SD)	7.50 (0.7)	7.51 (0.8)
HbA1c value at start of study [%]: [n (%)]		
< 7.0	114 (22.1)	126 (24.3)
≥ 7.0 to < 8.0	280 (54.3)	254 (48.9)
≥ 8.0 to < 9.0	107 (20.7)	115 (22.2)
≥ 9.0	15 (2.9)	24 (4.6)
Daily metformin dose [mg]: mean (SD)	no data	no data
Ethnicity [n (%)]		
Caucasian	297 (57.6)	298 (57.4)
Asian	109 (21.1)	111 (21.4)
Black/Afro-American	6 (1.2)	6 (1.2)
Other	104 (20.2)[a]	104 (20.0)[a]

a: Institute's calculation.
BMI: Body Mass Index; f: female; m: male; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

There were no important differences regarding patients' characteristics between the treatment arms. The mean value of HbA1c at the start of the study was 7.5% in both arms of the full analysis set. In some 70% of the patients, the HbA1c value was below 8% at the start of the study, and more than 20% of the patients even had an HbA1c value of < 7%. Based on current findings, it can therefore not be assumed for a large part of the patients that they had inadequate glycaemic control that would have needed intensified treatment.

Risk of bias at study level

Table 21 shows the risk of bias at study level.

Table 21: Risk of bias at study level – RCT, direct comparison: combination of sitagliptin plus 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			
P803	yes	yes	yes	yes	yes	yes	low
RCT: randomized controlled trial; vs.: versus							

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

Further information about the study design, study populations and risk of bias at the study level can be found in Module 4, Sections 4.3.1.2.1 and 4.3.1.2.2, and Appendix 4-G of the dossier, and in Sections 2.9.3.5.1 and 2.9.3.5.2 of the full dossier assessment.

2.4.2.3 Results on added benefit (research question B1)

The following patient-relevant outcomes were considered in this assessment (for reasons and operationalization, see Section 2.9.3.5.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - cardiac morbidity
  - cerebral morbidity
- Health-related quality of life
- Adverse events
  - hypoglycaemias (interpretation in connection with change in HbA1c over time)
    - symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)
    - severe hypoglycaemias
  - pancreatitis
  - renal impairment
  - overall rate of SAEs
  - treatment discontinuations due to AEs

The choice of patient-relevant outcomes deviated from that of the company. The company did not consider cardiac and cerebral morbidity as separate outcomes, but as a combined outcome without presenting the individual components. Moreover, the outcomes "renal impairment" and "pancreatitis" were included in this assessment. Both outcomes were not predefined by the company. 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. A detailed explanation on the inclusion of outcomes can be found in Section 2.9.3.5.3 of the full dossier assessment.

Table 22 shows for which outcomes data were available in the study P803.

Table 22: Matrix of outcomes – RCT, direct comparison: combination of sitagliptin plus metformin vs. glimepiride plus metformin

Study	Outcomes									
	All-cause mortality	Cardiac morbidity	Cerebral morbidity	Health-related quality of life	Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)	Severe hypoglycaemias	Pancreatitis	Renal impairment	SAEs	Treatment discontinuation due to AEs
P803	yes	yes[a]	yes[a]	yes[b]	yes	yes	yes[c]	yes[d]	yes	yes

a: Used by the company by means of a combined outcome of cardiac and cerebral events. Operationalized in this assessment using non-fatal SAEs of the MedDRA SOC "cardiac disorders" and "nervous system disorders".
b: Recorded in the study using the EQ-5D.
c: Operationalized using the Preferred Term "pancreatitis" according to MedDRA. No predefined outcome of the company.
d: Operationalized using non-fatal SAEs of the MedDRA SOC "renal and urinary disorders". No predefined outcome of the company.
AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term according to MedDRA; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class according to MedDRA; vs.: versus

Although there were data on most outcomes, the results, particularly on micro- and macrovascular late complications, were insufficient due to the size and duration of the study.

Table 23 shows the risk of bias for these outcomes.

Table 23: Risk of bias at study level – RCT, direct comparison: combination of sitagliptin plus metformin vs. glimepiride plus metformin

Study		Outcomes									
	Study level	All-cause mortality	Cardiac morbidity	Cerebral morbidity	Health-related quality of life	Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)	Severe hypoglycaemias	Pancreatitis	Renal impairment	SAEs	Treatment discontinuation due to AEs
P803	l	l	h[a]	h[a]	l	h[b]	h[b]	h[c]	h[a]	l	l

a: By approximation post-hoc operationalized using the MedDRA SOC.
b: Time course of the hypoglycaemias not presented.
c: By approximation post-hoc operationalized using the MedDRA PT.
h: high; l: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: MedDRA Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class according to MedDRA; vs.: versus

The assessment of the risk of bias at outcome level deviated from the company's assessment as follows:

- Since the company did not cite them as separate or predefined outcomes, it did not assess the risk of bias for cardiac morbidity, cerebral morbidity, renal impairment and pancreatitis.
- The company rated the risk of bias as low for symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl) and for severe hypoglycaemias. The risk of bias was rated as high for this assessment, however, because there was no information on the time course.

Further information about the choice of outcome and risk of bias at the outcome level can be found in Module 4B, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier, and in Sections 2.9.3.5.2 and 2.9.3.5.3 of the full dossier assessment.

Table 24, Table 25 and Table 26 summarize the results on the comparison of the combination "sitagliptin plus metformin" with "glimepiride plus metformin". The data from the company's dossier were supplemented, where necessary, by the Institute's own calculations. The tables contain results on the overall rate of AEs and on the change in body weight as additional information.

The OR offers a good approximation of the RR in low numbers of events. Hence in event rates of ≤ 1% (in at least one cell), the Peto OR instead of the RR was calculated as effect measure and used for the assessment.

Due to lacking or unsuitable data in Module 4B, the outcomes "cardiac morbidity", "cerebral morbidity" and "renal impairment" could only be considered by approximation using non-fatal SAEs of the corresponding MedDRA SOCs. The outcome "pancreatitis" was assessed using the MedDRA Preferred Term "pancreatitis".

Table 24: Results (dichotomous outcomes) – RCT, direct comparison: sitagliptin plus metformin vs. glimepiride plus metformin

Study Outcome category Outcome	Sitagliptin plus metformin		Glimepiride plus metformin		Sitagliptin plus metformin vs. glimepiride plus metformin
	N[a]	Patients with events n (%)	N[a]	Patients with events n (%)	RR/Peto-OR[b] [95% CI]; p-value[c]
P803					
Mortality					
All-cause mortality	516	0 (0)	518	1 (0.2)	0.14 [0.00; 6.85]; > 0.999
Morbidity					
Cardiac morbidity[d]	516	2 (0.4)	518	2 (0.4)	1.00 [0.14; 7.15]; > 0.999[e]
Cerebral morbidity[f]	516	1 (0.2)	518	2 (0.4)	0.51 [0.05; 4.96]; 0.584[e]
AEs					
Hypoglycaemias					
Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)	516	3 (0.6)	518	33 (6.4)	0.18 [0.09; 0.35]; < 0.001[e]
Severe hypoglycaemias	516	1 (0.2)	518	3 (0.6)	0.37 [0.05; 2.62]; 0.624[e]
HbA1c change	See Figure 6 for information on the change in HbA1c value in the course of the study.				
Pancreatitis	516	1 (0.2)	518	0 (0)	7.42 [0.15; 373.83]; 0.499[e]
Renal impairment[g]	516	0 (0)	518	0 (0)	n.c.
Overall rate AEs[h]	516	244 (47.3)	518	291 (56.2)	n.c.
Overall rate SAEs[h]	516	16 (3.1)	518	11 (2.1)	1.46 [0.68; 3.12]; 0.338[e]
Treatment discontinuation due to AEs[h]	516	10 (1.9)	518	2 (0.4)	3.86 [1.24; 12.05]; 0.020

a: All randomized patients according to the allocated treatment arm.
b: Peto OR provided in event numbers ≤ 1% in at least one cell.
c: Fisher's exact test.
d: Serious cardiac events. MedDRA SOC “cardiac disorders”, without deaths.
e: Institute's calculation.
f: Serious cerebral events. MedDRA SOC “nervous system disorders”, without deaths.
g: Serious renal events. MedDRA SOC “renal and urinary disorders”, without deaths.
h: Hypoglycaemias were also recorded here, with hypoglycaemias occurring neither in the SAEs nor in the treatment discontinuations due to AEs.
AE: adverse event; CI: confidence interval; HbA1c: haemoglobin A1c; MedDRA: Medical Dictionary for Regulatory Activities; N: Number of analysed patients; n: number of patients with event; n.c.: not calculated; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class according to MedDRA; vs.: versus

Table 25: Results (continuous outcomes) – RCT, direct comparison: sitagliptin plus metformin vs. glimepiride plus metformin

Study Outcome category Outcome	Sitagliptin plus metformin			Glimepiride plus metformin			Sitagliptin plus metformin vs. glimepiride plus metformin
	N[a]	Values at start of study mean (SD)	Change at end of study mean (SD)	N[a]	Values at start of study mean (SD)	Change at end of study mean (SD)	ΔLSM[b] [95% CI]; p-value[c]
P803							
Health-related quality of life							
EQ-5D (VAS)	488	82.1 (13.7)	83.8 (13.7)	493	80.6 (15.4)	83.5 (13.8)	-0.5 [-1.9; 1.0]; 0.514
Supplementary outcome "body weight"							
Body weight							
Change in body weight at week 30	465	80.6 (15.2)	-0.8 (3.0)	461	82.2 (16.8)	1.2 (2.8)	-2.0 [-2.3; -1.6]; < 0.001

a: Unless stated otherwise, LOCF analysis of the ITT population. Includes all patients according to their randomization who received at least one dose of the study medication and for whom a baseline and at least one further measurement were available.
b: Adjusted for country and baseline value.
c: Cochran-Mantel-Haenszel test.

ΔLSM: difference calculated with the least squares method; EQ-5D: European Quality of Life-5 Dimensions; ITT: intention to treat; CI: confidence interval; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Mortality

All-cause mortality

There was only 1 death (under glimepiride) in the study P803. An added benefit of the combination of sitagliptin plus metformin in comparison with glimepiride plus metformin is not proven for all-cause mortality.

This assessment deviated from that of the company. From the joint consideration of the studies P803 (comparison with glimepiride plus metformin) and P024 (comparison with glipizide plus metformin), the company derived proof of an added benefit versus sulfonylureas as a group for this outcome.

Morbidity

Cardiac morbidity

2 cardiac events occurred in each of the 2 treatment groups; the difference was not statistically significant. An added benefit of the combination of sitagliptin plus metformin in comparison with glimepiride plus metformin is not proven for cardiac morbidity.

This assessment deviated from that of the company. The company used a combined outcome of cardiac and cerebral events and, from the joint consideration of the studies P803 (comparison with glimepiride plus metformin) and P024 (comparison with glipizide plus metformin), derived proof of an added benefit versus sulfonylureas as a group for this outcome.

Cerebral morbidity

2 cerebral events occurred under glimepiride, and 1 under sitagliptin. The difference was not statistically significant. An added benefit of the combination of sitagliptin plus metformin in comparison with glimepiride plus metformin is not proven for cerebral morbidity.

This deviated from the company, which did not include this outcome separately in its benefit assessment.

Health-related quality of life

European Quality of Life-5 Dimensions (visual analogue scale)

There was no statistically significant difference between treatment with sitagliptin plus metformin and glimepiride plus metformin regarding the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D). An added benefit of the combination of sitagliptin plus metformin in comparison with glimepiride plus metformin is not proven for health-related quality of life.

This assessment concurred with that of the company, which also derived no added benefit for health-related quality of life.

Adverse events

Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)

There were fewer symptomatic hypoglycaemias (confirmed by a measured blood glucose level of ≤ 50 mg/dl) under sitagliptin plus metformin than under glimepiride. The result was statistically significant. This led to a hint of lesser harm from the combination of sitagliptin plus metformin in comparison with glimepiride plus metformin for symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl).

This assessment deviated from that of the company. From the joint consideration of the studies P803 (comparison with glimepiride plus metformin) and P024 (comparison with glipizide plus metformin), the company derived proof of an added benefit versus sulfonylureas as a group for this outcome.

Severe hypoglycaemias

1 severe hypoglycaemia occurred under sitagliptin, and 3 under glimepiride. The difference was not statistically significant. Greater or lesser harm from the combination of sitagliptin plus metformin in comparison with glimepiride plus metformin is not proven for severe/serious hypoglycaemias.

This assessment deviated from that of the company. From the joint consideration of the studies P803 (comparison with glimepiride plus metformin) and P024 (comparison with glipizide plus metformin), the company derived proof of an added benefit versus sulfonylureas as a group for this outcome.

Overall rate of serious adverse events

There was no statistically significant difference between treatment with sitagliptin plus metformin and glimepiride plus metformin regarding the overall rate of SAEs. Greater or lesser harm from the combination of sitagliptin plus metformin in comparison with glimepiride plus metformin is not proven for the overall rate of SAEs.

This assessment concurred with that of the company, which also derived no added benefit for the overall rate of SAEs.

Treatment discontinuations due to adverse events

Treatment with sitagliptin plus metformin in comparison with glimepiride plus metformin resulted in statistically significantly more patients with treatment discontinuation due to AEs. This led to a hint of greater harm from the combination of sitagliptin plus metformin in comparison with glimepiride plus metformin for the overall rate of AEs that led to treatment discontinuation.

This assessment deviated from that of the company, which "did not conduct a rating of the overview of the evidence" in the 2 studies "because of the different directions of the effects".

Pancreatitis and renal impairment

1 pancreatitis occurred under sitagliptin, and none under glimepiride. Renal impairment did not occur in any of the 2 treatments. Greater or lesser harm from the combination of sitagliptin plus metformin in comparison with glimepiride plus metformin is not proven for pancreatitis and renal impairment.

This assessment deviated from that of the company, which did not include these outcomes.

Subgroups

Subgroup analyses for the potential effect modifiers "age" (< 65 years versus ≥ 65 years, predefined age strata of the study P803) and "sex" (male versus female) were included in the benefit assessment.

Table 26 presents the subgroup analyses for which there was proof or indication of an interaction.

Table 26: Subgroups: outcomes according to sex and age, RCT, direct comparison: combination of sitagliptin plus metformin vs. glimepiride plus metformin

Study Outcome Characteristic Subgroup	Sitagliptin		Glimepiride		Sitagliptin vs. glimepiride	
	N[a]	Patients with events n (%)	N[a]	Patients with events n (%)	RR/Peto-OR[b] [95% CI]	p-value
P803						
Cardiac events[c]						
Age						
< 65 years	411	0 (0)	406	2 (0.5)[d]	0.13 [0.01; 2.14]	0.162
≥ 65 years	105	2 (1.9)[d]	112	0 (0)	7.97 [0.49; 128.51]	0.150
					Interaction:	0.041[e]
Treatment discontinuations due to AEs						
Sex						
Men	284	7 (2.5)	278	0 (0)	7.39 [1.67; 32.78]	0.009
Women	232	3 (1.3)	240	2 (0.8)	1.55 [0.27; 9.01]	0.645
					Interaction:	0.184[e]

a: All randomized patients according to the allocated treatment arm.
b: Peto OR provided instead of RR in event numbers ≤ 1% in at least one cell.
c: Data from the patient listings: non-fatal SAEs of the MedDRA SOC "cardiac disorders".
d: Institute's calculation of percentage.
e: Institute's calculation, Cochran's Q test.

AE: adverse event; CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; N: Number of analysed patients; n: number of patients with event; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class according to MedDRA; vs.: versus

There was proof of an interaction for the outcome of cardiac events for the potential effect modifier "age" in the study P803. However, the effects were not statistically significant at the level of the 2 age groups (< 65 years; ≥ 65 years). No different conclusions on added benefit could therefore be derived for the 2 age groups for this outcome. There was an indication of an interaction for the outcome "treatment discontinuations due to AEs" for the potential effect modifier "sex". Since there were no interactions for other outcomes on AEs and there was only an indication, but not a proof of an effect modification for treatment discontinuations due to AEs, it could not be excluded that this indication was an artefact. Hence no different conclusions were derived on the added benefit for men and women.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4B, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Sections 2.9.3.5.2 and 2.9.3.5.3 of the full dossier assessment.

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 Appendix A of Benefit Assessment A11-02 [2].

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 added benefit.

2.4.2.4.1 Assessment of added benefit at outcome level

The data availability presented in Section 2.4.2.3 resulted in a hint of lesser harm from the combination of sitagliptin plus metformin in comparison with glimepiride plus metformin for the outcome "symptomatic hypoglycaemias" (blood glucose ≤ 50 mg/dl) and a hint of greater harm for the outcome "treatment discontinuations due to AEs". The extent of the respective added benefit at outcome level was estimated from these results (see Table 27).

Table 27: Extent of added benefit at outcome level: combination of sitagliptin plus metformin vs. glimepiride plus metformin

Outcome category **Outcome**	**Combination of sitagliptin plus metformin vs. glimepiride plus metformin** **Patients (%) with event/ patient days** **Effect estimates [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0 (0) vs. 1 (0.2) Peto OR: 0.14 [0.00; 6.85] p > 0.999	Greater harm/added benefit not proven
Morbidity		
Cardiac morbidity	2 (0.4) vs. 2 (0.4) Peto OR: 1.00 [0.14; 7.15] p > 0.999	Added benefit not proven
Cerebral morbidity	1 (0.2) vs. 2 (0.4) Peto OR: 0.51 [0.05; 4.96] p = 0.584	Added benefit not proven
Health-related quality of life		
EQ-5D, VAS	Means: 83.8 mm vs. 83.5 mm ΔLSM: -0.5 [-1.9; 1.0] p = 0.514	Added benefit not proven

(continued)

Table 27: Extent of added benefit at outcome level: combination of sitagliptin plus metformin vs. glimepiride plus metformin (continuation)

Outcome category **Outcome**	**Combination of sitagliptin plus metformin vs. glimepiride plus metformin** **Patients (%) with event/ patient days** **Effect estimates [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
AEs		
Overall rate of SAEs	16 (3.1) vs. 11 (2.1) RR: 1.46 [0.68; 3.12] p = 0.338	Greater/lesser harm not proven
Treatment discontinuations due to AEs	10 (1.9) vs. 2 (0.4) RR: 0.26 [0.08; 0.81] p = 0.020 Probability: "hint"	Outcome category: non-serious/non-severe AEs $0.80 \leq CI_o < 0.9$ greater harm, extent: "minor"
Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)	3 (0.6) vs. 33 (6.4) Peto OR: 0.18 [0.09; 0.35] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs[c] $CI_o < 0.80$ lesser harm, extent: "considerable"
Severe hypoglycaemias	1 (0.2) vs. 3 (0.6) Peto OR: 0.37 [0.05; 2.62] p = 0.624	Greater/lesser harm not proven
Renal impairment	0 (0) vs. 0 (0) Peto OR: not calculated p = not calculated	Greater/lesser harm not proven
Pancreatitis	1 (0.2) vs. 0 (0) Peto OR: 7.42 [0.15; 373.83] p = 0.499	Greater/lesser harm not proven

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_o.
c: These were SAEs in 5 out of 10 treatment discontinuations in the sitagliptin arm, and in 0 out of 2 treatment discontinuations in the glipizide arm. The treatment discontinuations were therefore classified as "non-serious".

ΔLSM: difference calculated with the least squares method; AE: adverse event; CI: confidence interval; CI_o: upper limit of CI; EQ-5D: European Quality of Life-5 Dimensions; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.2.4.2 Overall conclusion on added benefit

Table 28 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 28: Positive and negative effects from the assessment of the combination of sitagliptin plus metformin compared with glimepiride plus metformin

Positive effects	**Negative effects**
Hint of lesser harm – extent: "considerable" (non-serious/non-severe AEs: symptomatic hypoglycaemias)	Hint of greater harm - extent "minor" (non-serious/non-severe AEs: treatment discontinuations due to AEs)
No sufficient data were available on micro- and macrovascular late complications.	
AE: adverse event	

Overall, positive and negative effects remain at outcome level. On the one hand, there is a hint of lesser harm (extent: "considerable"), on the other there is a hint of greater harm (extent: "minor"). Hence there are opposing conclusions on AEs, which overall result in a hint of a minor added benefit.

There was neither an advantage nor a disadvantage of the combination of sitagliptin plus metformin versus glimepiride plus metformin regarding micro- and macrovascular late complications. No sufficient data were available on these outcomes, however. This led to an additional uncertainty. The extent of added benefit of sitagliptin versus glimepiride is therefore "non-quantifiable", but not more than "minor" on the basis of the available data.

Overall, there is a hint of a minor added benefit of the combination of sitagliptin plus metformin versus glimepiride plus metformin for patients in whom near-normal levels of blood glucose are aimed at. For patients without such a treatment goal, there is no proof of added benefit of sitagliptin.

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

2.4.2.5 List of included studies

P803

1. 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.

2. 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; supplemental statistical analysis [unpublished]. 2009.

3. 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]. 2009.

4. Merck. 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. 17 December 2010 [accessed: 13 June 2013]. URL: http://www.clinicaltrials.gov/ct2/show/NCT00701090.

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

2.4.3.1 Studies included

The study listed in Table 29 was included in the benefit assessment.

Table 29: 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; vs.: versus			

The company used the study P024 to assess the added benefit of the combination of sitagliptin plus metformin versus sulfonylureas (without limitation to specific drugs) plus metformin. Accordingly, it drew the conclusions on added benefit based on the joint consideration of the 2 studies P803 (comparison with glimepiride) and P024 (comparison with glipizide), which it identified for its research question.

The study P803 is considered in a separate research question (research question B1) in this dossier assessment.

Section 2.4.3.5 contains a reference list for the study included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4B, Section 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections 2.9.3.4.1 and 2.9.3.4.2 of the full dossier assessment.

2.4.3.2 Study characteristics (research question B2)

Table 30 and Table 31 describe the study used for the benefit assessment.

Table 30: Characteristics of the studies included – RCT, direct comparison: combination of sitagliptin plus metformin vs. glipizide plus metformin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
P024	RCT, double-blind, double-dummy, parallel	Patients (≥ 18 years and ≤ 78 years) whose type 2 diabetes mellitus cannot be adequately controlled with metformin at a dose of ≥ 1500 mg/day (HbA1c value ≥ 6.5% and ≤ 10.0%)	Sitagliptin 100 mg/day in combination with metformin ≥ 1500 mg/day (N = 588) Glipizide 5 to 20 mg/day in combination with metformin ≥ 1500 mg/day (N = 584)	Screening: 1 week Period of treatment with a stable metformin dose (metformin monotherapy ≥ 1500 mg/day) up to 16 weeks Placebo run-in: 2 weeks Treatment: 104 weeks Telephone follow-up 2 weeks after the end of treatment	Europe (20 countries), USA/Puerto Rico, other continents (14 countries) Oct 2004 – May 2007	Primary: change in HbA1c value Secondary: health-related quality of life hypoglycaemias AEs

a: Primary outcomes contain information without consideration of the relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for the present benefit assessment.

AE: adverse event; HbA1c: haemoglobin A1; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 31: Characteristics of the interventions – RCT, direct comparison: combination of sitagliptin plus metformin vs. glipizide plus metformin

Study	Intervention	Comparison	Concomitant medication
P024	sitagliptin 100 mg/day + glipizide placebo (dose increase as in the glipizide verum arm)	Sitagliptin placebo + glipizide *Titration, dose increase* ▪ Starting dose: 5 mg/day ▪ The dose could be increased in steps of 5 mg/day over 18 weeks. Maximum dose: 20 mg/day ▪ First dose increase: 3 weeks after randomization, then usually every 3 weeks; the interval could be reduced to 1 week if the patient, at the investigator's discretion, benefited from faster up-titration; last dose increase at week 18 (maximum dose: 20 mg/day) *Basis of decision on up-titration* ▪ Fasting fingerstick blood glucose value on the day of the study visit was ≥ 110 mg/dl AND ▪ all fasting and preprandial fingerstick blood glucose values in the week before the study visit were ≥ 110 mg/dl AND ▪ no hypoglycaemic event since the last dose increase AND, at the doctor's discretion, a dose increase does not pose a risk of hypoglycaemias for the patient. *Titration, dose reduction* During the entire study duration, the glipizide dose could be reduced to avoid hypoglycaemias.	All antidiabetics used before the start of the study, with the exception of metformin, were discontinued. In the run-in phase, each randomized patient presented proof of inadequate glycaemic control under diet, exercise and metformin ≥ 1500 mg/day. This metformin dose was maintained during the entire study. Other anti-hyperglycaemic drugs were not allowed.
RCT: randomized controlled trial; vs.: versus			

Study design and patients

Study P024 was a randomized, active-controlled, double-blind approval study sponsored by the company. It was conducted to investigate patients with inadequate glycaemic control despite treatment with ≥ 1500 mg/day metformin. Patients with an HbA1c value of ≥ 6.5% and ≤ 10.0% were eligible for inclusion in the study.

The study comprised a 1-week screening period, a phase for stabilization of the metformin dose of up to 16 weeks, a 2-week phase with placebo and stable metformin administration as well as a treatment phase of 104 weeks.

The patient collective was recruited during the screening phase from several patient populations:

- Patients under metformin monotherapy at a dose of ≥ 1500 mg/day with an HbA1c value of ≥ 6.5% and ≤ 10.0% (Group 1)
- Patients under metformin monotherapy at a dose of ≥ 1500 mg/day with an HbA1c value of > 10.0% (Group 2)
- Patients under metformin monotherapy at a dose of < 1500 mg/day or monotherapy with another oral antidiabetic drug (OAD) with an HbA1c value of ≥ 6.5% (Group 3)
- Patients under metformin therapy in combination with another OAD with an HbA1c value of ≥ 5.5% and ≤ 10% (Group 4)
- Patients who do not receive antidiabetic treatment with an HbA1c value of > 7.5% (Group 5)

Patients of Group 1 went directly from the screening phase to the placebo run-in phase. The individual metformin dose of these patients was maintained during the entire course of the study.

The stabilization phase of the metformin dose was envisaged for the patients of Groups 2 to 5. The current dose of metformin was adjusted during this study period. For patients with combination therapy, the concomitant drugwas discontinued and washed out in patients with combination therapy. Patients without prior antidiabetic therapy or with a daily metformin dose of less than 1500 mg, received up-titration to a daily dose of at least 1500 mg.

The algorithm used to select patients and to find the dose of metformin was aimed at including a patient population with inadequate glycaemic control despite monotherapy with metformin at a dose of ≥ 1500 mg a day. It was unsuitable to guarantee that only patients with inadequate glycaemic control despite maximum tolerated dose of metformin were enrolled and then treated, however.

1172 patients were randomly assigned in a ratio of 1:1, 588 patients to the sitagliptin plus metformin arm and 584 patients to the glipizide plus metformin arm.

Primary outcome of the study was the change in HbA1c value, which was not a patient-relevant outcome for the benefit assessment, however.

Treatment regimen

After randomization, the patients either received a fixed dose of 100 mg sitagliptin/day or glipizide at a starting dose of 5 mg/day and a placebo of the respective other drug. The patients were requested not to change their daily metformin dose during the treatment duration.

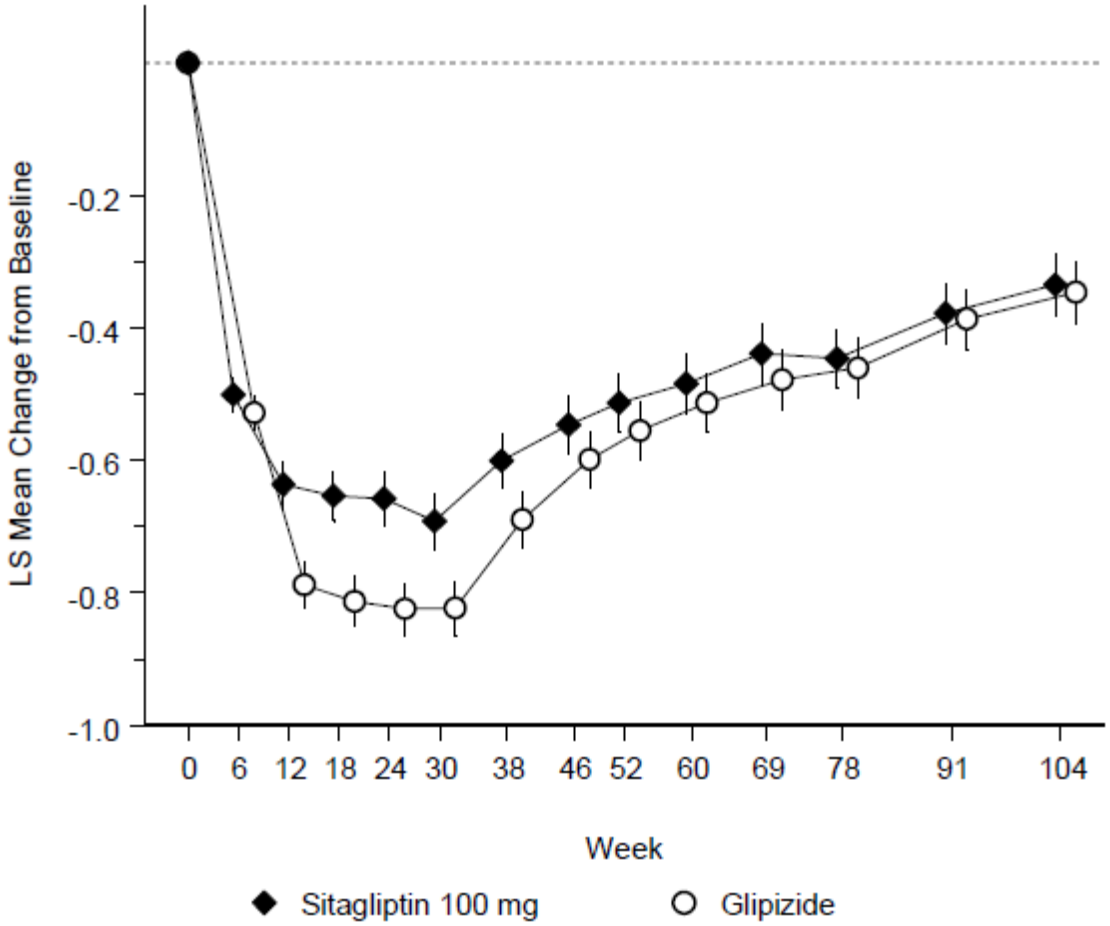
The starting dose of 5 mg glipizide (+ placebo) could be increased over a period of 18 weeks. The first dose increase was possible after 3 weeks, further dose increases were possible at 3-week intervals.

The criteria for the titration are presented in Table 31 and include a consistent target level for fasting blood glucose (110 mg/dl) under consideration of the risk of hypoglycaemia.

It was clear from the treatment regimen of the study P024 that titration with a blood-glucose lowering drug to a specified consistent target level (fasting blood glucose < 110 mg/dl) was only possible in the glipizide arm, but not in the sitagliptin arm. In the sitagliptin arm, titration was conducted with the glipizide placebo. Hence the study P024 constituted a comparison of 2 treatment regimens and not of 2 drugs. Additionally, it should be noted that the target blood glucose level specified was very low (fasting blood glucose < 110 mg/dl). Because of the study results on blood-glucose lowering to the near-normal level [14], current guidelines recommend blood-glucose lowering to the near-normal level only after an individual balancing of benefits and risks, and in principle target levels should be agreed upon under consideration of individual circumstances [15-17]. A consistent target level of fasting plasma glucose of < 110 mg/dl is a target level that corresponds to blood-glucose lowering to near-normal levels.

It is particularly necessary to consider the course of HbA1c value in the study to assess in how far the effects observed in the study were attributable to the different therapeutic strategies.

Figure 10 shows the change in HbA1c (mean values estimated with the least squares method) during the 104-week treatment phase of the study. Missing values were replaced with LOCF.



Displayed are the mean values and standard errors of the changes, which were estimated according to the least squares method with missing values being replaced by the last available measurement (LOCF).

Figure 10: Course of changes in the HbA1c value after randomization (sitagliptin plus metformin vs. glipizide plus metformin)

Considering the time course of the change in HbA1c value, there was a rapid decrease in HbA1c in both treatment arms. This was nearly parallel in the first 6 weeks. In the further course, the lowering of the HbA1c value was slightly more pronounced in the glipizide arm. The difference between the treatment arms was at its maximum in week 24, but was at a maximum of about 0.17 percentage points at this point (rough estimate based on Figure 10). From the middle of the study, the curves approached each other again. At the end of the study after 104 weeks, there was a difference, which was not statistically significant, of [95% CI] 0.01% [−0.08; 0.10]. A responder analysis at the end of the study for the response criterion "HbA1c < 6.5%" showed no differences between the 2 arms for the total population (sitagliptin 21.2%, glipizide 20.0%).

Similarly to the study P803, the overall picture of the courses of HbA1c was largely similar in the 2 treatment arms of the study P024[6]. As already described in Section 2.3.3.1.2 (research question A2), this is not necessarily the case when different treatment regimens are followed in the treatment arms. This can be seen in the studies on linagliptin [9] and saxagliptin/metformin [10] mentioned in Sections 2.3.3.1.1 and 2.4.2.1. As in the linagliptin study, titration to a consistent target fasting blood glucose level of ≤ 110 mg/dl was also conducted in the study P024. But this strict specification was linked to the condition that any hypoglycaemic events that had occurred since the last dose increase as well as the investigator's assessment of the risk of hypoglycaemia had to be considered. Hence the titration was less strict than in the study on linagliptin mentioned. In addition, as in the study P803 (research question B1), the efficacy of sitagliptin on the HbA1c value was shown to be greater in the study P024 than the one of linagliptin in the study 1218.20. The maximum differences between the gliptin and the sulfonylurea arm were smaller in the study P024 than in the linagliptin study, and they were never in a range of the linagliptin or of the saxagliptin/metformin study.

The time course of these events was considered to be able to assess for the study P024 if the 2 different strategies, particularly during the titration phase in the beginning of the study, influenced the risk of hypoglycaemia or the occurrence of other outcomes. No such data were available for the outcome "hypoglycaemias" in the study P024. There was no noticeable increase in the outcomes "serious cardiac events", "serious cerebral events" or "deaths" during the titration phase of glipizide (see Figure 11 to Figure 13).

When interpreting the time courses, it has to be considered that only 65% of the patients in the sitagliptin arm and 69% of the patients in the glipizide arm were still in the study after week 52. Only 43 and 45% of the patients completed the study until week 104. Overall, no correlation could be established between the time course of the occurrence of patient-relevant events and the lowering of blood-glucose. It remained unclear, however, whether the conclusions on mortality and on cardiac and cerebral morbidity also applied to hypoglycaemias.

[6] In contrast to study P063 (research question A2), there was no noticeable difference between the courses on HbA1c value and on fasting plasma glucose. The course of fasting plasma glucose is therefore not presented.

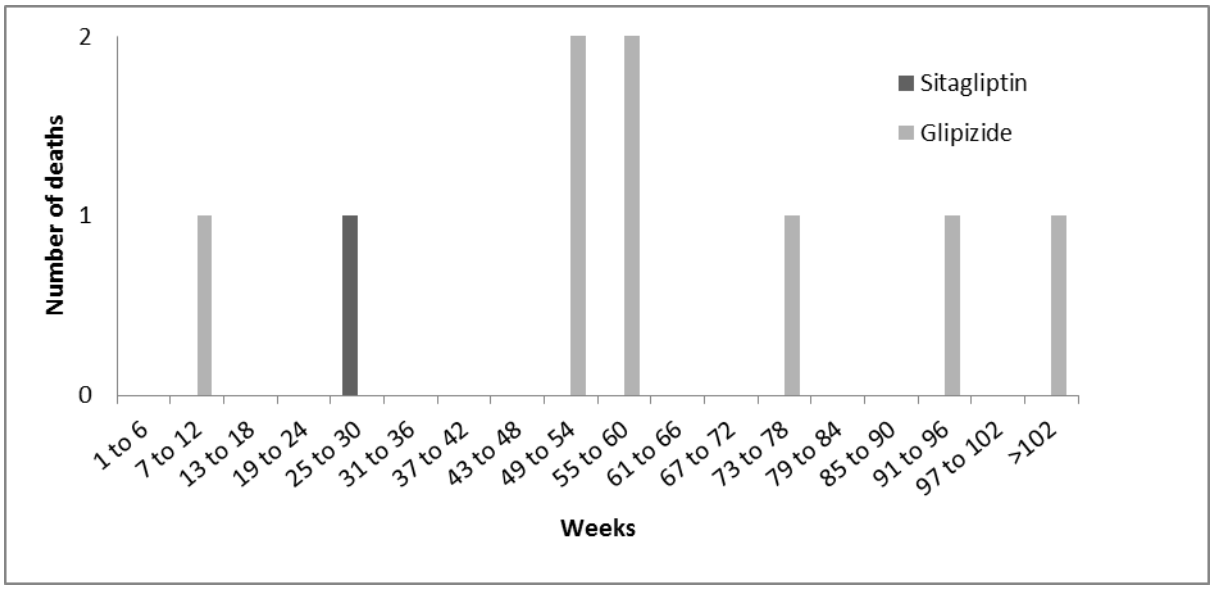
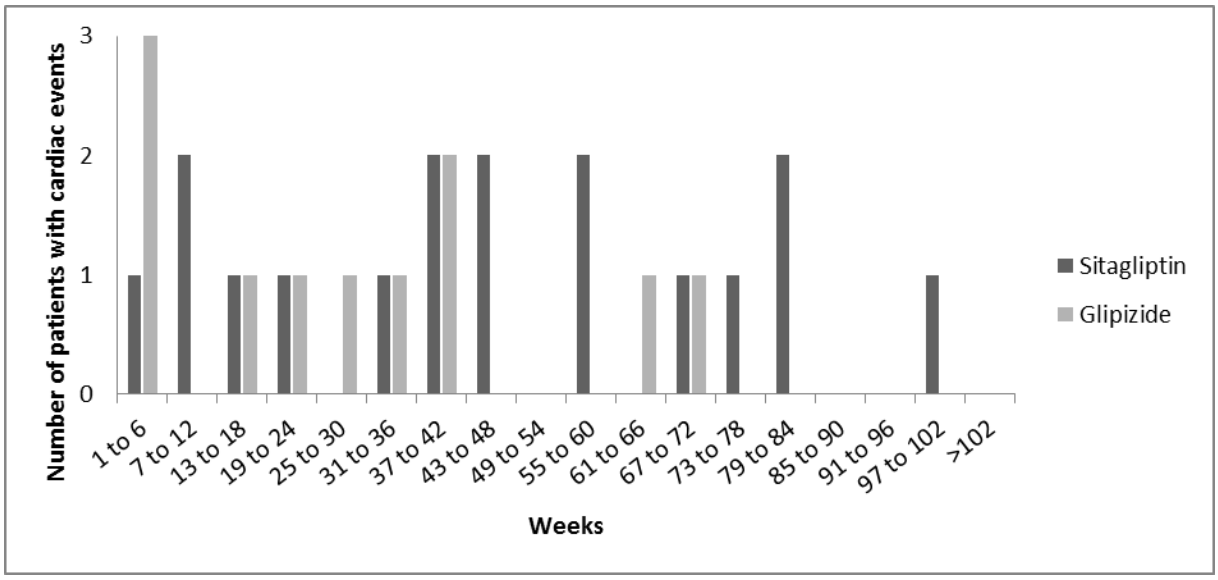
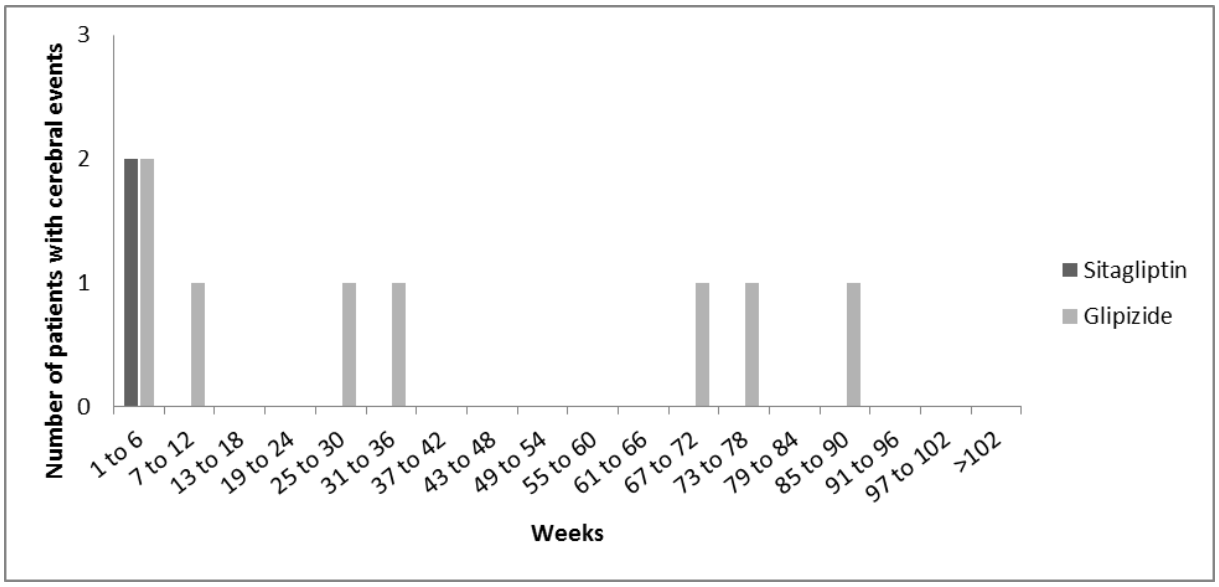


Figure 11: Time course of deaths (sitagliptin plus metformin vs. glipizide plus metformin)



Presentation of cardiac events operationalized as SAEs from the SOC "cardiac disorders" (according to MedDRA)

Figure 12: Time course of cardiac events (sitagliptin plus metformin vs. glipizide plus metformin)



Presentation of cerebral events operationalized as SAEs from the SOC "nervous system disorders" (according to MedDRA)

Figure 13: Time course of cerebral events (sitagliptin plus metformin vs. glimepiride plus metformin)

Consequences for study inclusion and assessment

There were no indications that the different therapeutic strategies in the study P024 had major impact. It was unclear whether this resulted solely from the specifications for glipizide titration, which were less strict compared with the studies with linagliptin or saxagliptin mentioned, or also from a greater blood-glucose lowering efficacy of sitagliptin versus linagliptin or saxagliptin. Eventually, however, this led to the results of the study P024 being interpretable and usable for the benefit assessment of sitagliptin.

Uncertainties regarding the overview of the evidence resulted from:

- missing data on the time course of the hypoglycaemias,
- the uncertainty about how many patients received a maximum tolerated dose of metformin without achieving adequate glycaemic control.

The uncertainties described resulted in a downgrading of the certainty of results of the study P024.

Characteristics of the study population

Table 32 shows the characteristics of the patients in the study P024.

Table 32: Characteristics of the study populations (general information) – RCT, direct comparison: sitagliptin plus metformin vs. glipizide plus metformin

Study Characteristic Category	Sitagliptin plus metformin	Glipizide plus metformin
P024		
N	588	584
Age [years]: mean (SD)	56.8 (9.3)	56.6 (9.8)
Sex f/m [%]	42.9/57.1	38.7/61.3
Body weight (kg): mean (SD)	89.5 (17.4)	89.7 (17.5)
BMI (kg/m²): mean (SD)	31.2 (5.0)	31.3 (5.2)
Duration of diabetes [years]: mean (SD)	6.5 (6.1)[a]	6.2 (5.4)
HbA1c value at start of study [%]: mean (SD)	7.7 (0.9)[b]	7.6 (0.9)[c]
HbA1c value at start of study [%]: [n (%)]		
< 8.0	375 (64.0)[b]	381 (65.5)[c]
≥ 8.0 to < 9.0	151 (25.8)[b]	141 (24.2)[c]
≥ 9.0	60 (10.2)[b]	60 (10.3)[c]
Daily metformin dose [mg]: mean (SD)	no data	no data
Ethnicity [n (%)]		
Caucasian	432 (73.5)	434 (74.3)
Asian	50 (8.5)	49 (8.4)
Black/Afro-American	41 (7.0)	35 (6.0)
Other	65 (11.1)[d]	66 (11.3)[d]

a: Patients analysed: 587.
b: Patients analysed: 586.
c: Patients analysed: 582.
d: Institute's calculation.
BMI: Body Mass Index; f: female; HbA1c: haemoglobin A1c; m: male; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

There were no important differences regarding patients' characteristics between the treatment arms. The mean value of HbA1c at the start of the study was 7.7% and 7.6% in the 2 arms. About 65% of the patients had an HbA1c value of below 8% at the start of the study. It was unclear in how many patients the HbA1c value was below 7.5% or even below 7%. Based on current findings, however, it cannot be assumed for a large part of the patients that they had inadequate glycaemic control that would have needed intensified treatment.

Risk of bias at study level

Table 33 shows the risk of bias at study level.

Table 33: Risk of bias at study level – RCT, direct comparison: combination of sitagliptin plus metformin vs. glipizide + 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			
P024	yes	yes	yes	yes	yes	yes	low
RCT: randomized controlled trial; vs.: versus							

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

Further information about the study design, study populations and risk of bias at the study level can be found in Module 4B, Sections 4.3.1.2.1 and 4.3.1.2.2, and Appendix 4-G of the dossier, and in Sections 2.9.3.5.1 and 2.9.3.5.2 of the full dossier assessment.

2.4.3.3 Results on added benefit (research question B2)

The patient-relevant outcomes already considered in research question B1 were included in the assessment of the added benefit of the combination of sitagliptin plus metformin. These are shown in Section 2.4.2.3. The deviations from the company's approach regarding the consideration of outcomes are also described in this Section. These were identical for the present research question. The reasons for inclusion and information on the operationalization of these outcomes can be found in Section 2.9.2.5.3 of the full dossier assessment.

Table 34 shows for which outcomes of the study P024 data were available.

Table 34: Matrix of outcomes – RCT, direct comparison: combination of sitagliptin plus metformin vs. glipizide plus metformin

Study	Outcomes									
	All-cause mortality	Cardiac morbidity	Cerebral morbidity	Health-related quality of life	Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)	Severe hypoglycaemias	Pancreatitis	Renal impairment	SAEs	Treatment discontinuation due to AEs
P024	yes	yes[a]	yes[a]	–[b]	yes	yes	yes[c]	yes[d]	yes	yes

a: Used by the company by means of a combined outcome of cardiac and cerebral events. Operationalized in this assessment using non-fatal SAEs of the MedDRA SOC "cardiac disorders" and "nervous system disorders".
b: No evaluable data.
c: Operationalized using the Preferred Term "pancreatitis" according to MedDRA. No predefined outcome of the company.
d: Operationalized using non-fatal SAEs of the MedDRA SOC "renal and urinary disorders". No predefined outcome of the company.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class according to MedDRA; vs.: versus

Although there were data on most outcomes, the results, particularly on micro- and macrovascular late complications, were insufficient due to the size and duration of the study.

Table 35 shows the risk of bias for these outcomes.

Table 35: Risk of bias at study and outcome level – RCT, direct comparison: combination of sitagliptin plus metformin vs. glipizide plus metformin

Study		Outcomes									
	Study level	All-cause mortality	Cardiac morbidity	Cerebral morbidity	Health-related quality of life	Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)	Severe hypoglycaemias	Pancreatitis	Renal impairment	SAEs	Treatment discontinuation due to AEs
P024	l	l	h[a]	h[a]	–[b]	h[c]	h[c]	h[d]	h[a]	l	l

a: By approximation post-hoc operationalized using the MedDRA SOC.
b: Outcome was not recorded.
c: Time course of the hypoglycaemias not presented.
d: By approximation post-hoc operationalized using the MedDRA PT.
AE: adverse event; h: high; MedDRA: Medical Dictionary for Regulatory Activities; PT: MedDRA Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class according to MedDRA; vs.: versus

The assessment of the risk of bias at outcome level deviated from the company's assessment as follows:

- Since the company did not cite them as separate or predefined outcomes, it did not assess the risk of bias for cardiac morbidity, cerebral morbidity, renal impairment and pancreatitis.
- The company rated the risk of bias as low for symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl) and for severe hypoglycaemias. The risk of bias was rated as high for this assessment, however, because there was no information on the time course.

Further information about the choice of outcome and risk of bias at the outcome level can be found in Module 4B, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier, and in Sections 2.9.3.5.2 and 2.9.3.5.3 of the full dossier assessment.

Table 36 summarizes the results on the comparison of the combination "sitagliptin plus metformin" with "glipizide plus metformin". The data from the company's dossier were supplemented, where necessary, by the Institute's own calculations. The tables contain results on the overall rate of AEs and on the change in body weight as additional information.

The OR offers a good approximation of the RR in low numbers of events. Hence in event rates of ≤ 1% (in at least one cell), the Peto OR instead of the RR was calculated as effect measure and used for the assessment.

Due to lacking or unsuitable data in Module 4B, the outcomes "cardiac morbidity", "cerebral morbidity" and "renal impairment" could only be considered by approximation using non-fatal SAEs of the corresponding MedDRA SOCs. The outcome "pancreatitis" was assessed using the MedDRA Preferred Term "pancreatitis".

Table 36: Results – RCT, direct comparison: combination of sitagliptin plus metformin vs. glipizide plus metformin

Study Outcome category Outcome	Sitagliptin plus metformin		Glipizide plus metformin		Sitagliptin plus metformin vs. glipizide plus metformin
	N[a]	Patients with events n (%)	N[a]	Patients with events n (%)	RR/Peto-OR[b] [95% CI]; p-value[c]
P024[d]					
Mortality					
All-cause mortality	588	1 (0.2)	584	8 (1.4)	0.21 [0.06; 0.77]; 0.021
Morbidity					
Cardiac morbidity[e]	588	15 (2.6)	584	11 (1.9)	1.35 [0.63; 2.92]; 0.553[f]
Cerebral morbidity[g]	588	2 (0.3)	584	8 (1.4)	0.30 [0.09; 1.03]; 0.064[f]
Health-related quality of life	Not recorded				
AEs					
Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)					
After week 52	588	4 (0.7)	584	44 (7.5)	0.17 [0.10; 0.31]; < 0.001
After week 104	588	5 (0.9)	584	48 (8.2)	0.18 [0.10; 0.32]; < 0.001
Severe hypoglycaemias					
After week 52	588	1 (0.2)	584	7 (1.2)	0.22 [0.05; 0.88]; 0.038[f]
After week 104	588	1 (0.2)	584	9 (1.5)	0.20 [0.06; 0.69]; 0.011[f]
HbA1c change	See Figure 10 for information on the change in HbA1c value during the study				
Pancreatitis	588	2[i] (0.3[f])	584	0 (0)	7.35 [0.46; 117.67]; 0.500[f]
Renal impairment[h]	588	4 (0.7)	584	4 (0.7)	0.99 [0.25; 3.99]; > 0.999[f]
Overall rate AEs[j]	588	452 (76.9)	584	480 (82.2)	-
Overall rate SAEs[j,k]	588	64 (10.9)	584	73 (12.5)	0.87 [0.64; 1.19]; 0.414[f]
Treatment discontinuation due to AEs[k]	588	23 (3.9)	584	29 (5.0)	0.79 [0.46; 1.35]; 0.398[f]

(continued)

Table 36: Results – RCT, direct comparison: combination of sitagliptin plus metformin vs. glipizide plus metformin (continuation)

Study Outcome category Outcome	Sitagliptin plus metformin			Glipizide plus metformin			Sitagliptin plus metformin vs. glipizide plus metformin
	N[l]	Values at start of study mean (SD)	Change at end of study mean (SD)	N[l]	Values at start of study mean (SD)	Change at end of study mean (SD)	ΔLSM[m] [95% CI]; p-value
Supplementary outcome							
Body weight after week 52	547[n]	89.4 (16.9)	-1.3 (0.3)	534	89.5 (17.1)	1.2 (0.3)	-2.5 [-3.1; -2.0]; no data
Body weight after week 104	Not presented in the present report[o]						

a: All patients as treated.
b: Peto OR provided in event numbers ≤ 1% in at least one cell.
c: Fisher's exact test.
d: Unless stated otherwise, the results after 104 weeks are presented.
e: Serious cardiac events. MedDRA SOC "cardiac disorders", without deaths.
f: Institute's calculation.
g: Serious cerebral events. MedDRA SOC "nervous system disorders", without deaths.
h: Serious renal events. MedDRA SOC "renal and urinary disorders", without deaths.
i: 2 events are mentioned in the dossier. 1 patient with pancreatitis and 1 patient with chronic pancreatitis are cited in the clinical study report. Based on the information provided it is unclear whether these were 2 different patients.
j: Hypoglycaemic events were also recorded here. There were no hypoglycaemias as SAEs in the study P024. 4 patients in the glipizide arm discontinued treatment due to hypoglycaemias. Without these 4 patients, the values of the 2 groups continue to approach each other.
k: Non-fatal SAEs.
l: Unless stated otherwise, LOCF analysis of the ITT population. Includes all patients according to their randomization who received at least one dose of the study medication and for whom a baseline and at least one further measurement were available.
m: Adjusted for prior treatment and baseline values.
n: Change at end of study and difference of the change at end of study were estimated using an ANCOVA. Missing values were supplemented with LOCF.
o: Only analysis without replacement of missing values available. The data are not presented because the proportion of the patients who were not considered in the analysis was > 30% or the difference of the proportions of patients who were not considered was more than 15 percentage points between the treatment arms.

ΔLSM: difference calculated with the least squares method; AE: adverse event; ANCOVA: analysis of covariance; CI: confidence interval; HbA1c: haemoglobin A1c; ITT: intention to treat; LOCF: last observation carried forward; MedDRA: Medical Dictionary for Regulatory Activities; N: number of analysed patients; n: number of patients with event; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SD: standard deviation; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Mortality

All-cause mortality

There was a statistically significant difference for all-cause mortality in favour of treatment with sitagliptin plus metformin in comparison with glipizide plus metformin. This assessment

was based on few events overall observed in the study. This led to a hint of an added benefit of the combination of sitagliptin plus metformin in comparison with glipizide plus metformin for all-cause mortality.

This assessment deviated from that of the company. From the joint consideration of the studies P803 (comparison with glimepiride plus metformin) and P024 (comparison with glipizide plus metformin), the company derived proof of an added benefit versus sulfonylureas as a group.

Morbidity

Cardiac morbidity

15 cardiac events occurred under sitagliptin plus metformin, and 11 under glipizide plus metformin; the difference was not statistically significant. An added benefit of the combination of sitagliptin plus metformin in comparison with glipizide plus metformin is not proven for cardiac morbidity.

This assessment deviated from that of the company. The company used a combined outcome of cardiac and cerebral events and, from the joint consideration of the studies P803 (comparison with glimepiride plus metformin) and P024 (comparison with glipizide plus metformin), derived proof of an added benefit versus sulfonylureas as a group for this outcome.

Cerebral morbidity

2 cerebral events occurred under sitagliptin, and 8 under glipizide. The difference was not statistically significant. An added benefit of the combination of sitagliptin plus metformin in comparison with glipizide plus metformin is not proven for cardiac morbidity.

This deviated from the company, which did not include this outcome separately in its benefit assessment.

Health-related quality of life

No data on health-related quality of life were recorded in the study P024.

Adverse events

Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)

There were fewer symptomatic hypoglycaemias (confirmed by a measured blood glucose level of ≤ 50 mg/dl) under sitagliptin plus metformin than under glipizide. The result was statistically significant. This led to a hint of lesser harm from the combination of sitagliptin plus metformin in comparison with glipizide plus metformin for symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl).

This assessment deviated from that of the company. From the joint consideration of the studies P803 (comparison with glimepiride plus metformin) and P024 (comparison with

glipizide plus metformin), the company derived proof of an added benefit versus sulfonylureas as a group.

Severe hypoglycaemias

1 severe hypoglycaemia occurred under sitagliptin plus metformin, and 9 under glipizide. The difference was statistically significant. This led to a hint of lesser harm from the combination of sitagliptin plus metformin in comparison with glipizide plus metformin for severe hypoglycaemias.

From the joint consideration of the studies P803 (comparison with glimepiride plus metformin) and P024 (comparison with glipizide plus metformin), the company derived proof of an added benefit versus sulfonylureas as a group.

Overall rate of serious adverse events

There was no statistically significant difference between treatment with sitagliptin plus metformin and glipizide plus metformin regarding the overall rate of SAEs. Greater or lesser harm from the combination of sitagliptin plus metformin in comparison with glipizide plus metformin is not proven for the overall rate of SAEs.

This assessment concurred with that of the company, which also derived no added benefit for the overall rate of SAEs.

Treatment discontinuations due to adverse events

There was no statistically significant difference between treatment with sitagliptin plus metformin and glipizide plus metformin regarding the overall rate of AEs that led to treatment discontinuation. Greater or lesser harm from the combination of sitagliptin plus metformin in comparison with glipizide plus metformin is not proven for the overall rate of AEs that led to treatment discontinuation.

This assessment deviated from that of the company, which "did not conduct a rating of the overview of the evidence" in the 2 studies "because of the different directions of the effects".

Pancreatitis and renal impairment

2 cases of pancreatitis occurred under sitagliptin, and none under glipizide. Renal impairment occurred in 4 patients under both treatments. Greater or lesser harm from the combination of sitagliptin plus metformin in comparison with glipizide plus metformin is not proven for pancreatitis and renal impairment.

This assessment deviated from that of the company, which did not include these outcomes.

Subgroups

Subgroup analyses according to the potential effect modifiers "age" (< 65 years versus ≥ 65 years[7]) and "sex" (male versus female) were included in the benefit assessment. The subgroup analysis of the hypoglycaemias after prior treatment presented by the company was not considered because it was only based on the adjusted event-based (c-log-log regression), and not on the patient-based analysis (see Section 2.9.2.5.3 of the full dossier assessment).

Table 37 presents the subgroup analyses for which there was proof or indication of an interaction. The subgroup analysis of mortality is presented because all deaths occurred in the subgroup of men.

Table 37: Subgroups: outcomes according to sex and age, RCT, direct comparison: combination of sitagliptin plus metformin vs. glipizide plus metformin

Study Outcome	Sitagliptin plus metformin		Glipizide plus metformin		Sitagliptin plus metformin vs. glipizide plus metformin	
Characteristic Subgroup	N[a]	Patients with events n (%)	N[a]	Patients with events n (%)	RR/Peto OR[b] [95% CI]	p-value[c]
P024						
All-cause mortality						
Sex						
Men	336	1 (0.3)	358	8 (2.2)	0.22 [0.06; 0.82]	0.024
Women	252	0 (0)	226	0 (0)	n.c.	n.c.
					Interaction:	n.c.
Cardiac events[d]						
Sex						
Men	336	14 (4.2)	358	7 (2.0)	2.13 [0.87; 5.22]	0.095
Women	252	1 (0.4)	226	4 (1.8)	0.27 [0.05; 1.55]	0.154
					Interaction:	0.061[e] 0.038[f]

a: All patients as treated (APaT population).
b: Peto OR provided instead of RR in event numbers ≤ 1% in at least one cell.
c: Institute's calculation, unconditional exact test (CSZ method according to [11]).
d: Data from the patient listings according to Preferred Term.
e: Calculation based on RR.
f: Calculation based on Peto OR.

CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; n.c.: not calculated; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; vs.: versus

For the outcome "all-cause mortality", the test for interaction could not be conducted for the effect modifier "sex" because all events only occurred in men. There was an advantage for

[7] There was no information on whether the categories were predefined. They concurred with the ones of the studies P063 and P803, however.

men of 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, the conclusion on added benefit regarding all-cause mortality is limited to the subgroup of men.

There was a hint of an interaction (on the basis of the Peto OR) for the effect modifier "sex" in the study P024 for the outcome "cardiac events". There were no statistically significant differences between the treatment groups neither for women nor for men. Hence no different conclusions were derived on the added benefit for men and women.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier, and in Sections 2.9.3.5.2 and 2.9.3.5.3 of the full dossier assessment.

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

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 Appendix A of Benefit Assessment A11-02 [2].

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 added benefit.

2.4.3.4.1 Assessment of added benefit at outcome level

The available data presented in Section 2.4.3.3 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 and a hint of lesser harm both for the outcomes "symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)" and "severe hypoglycaemias" for the total population. The extent of the respective added benefit at outcome level was estimated from these results (see Table 38). Since there were no indications of a systematic bias of the results after 104 weeks of treatment duration, these assessments were solely conducted on the basis of the 104-week data.

Table 38: Extent of added benefit at outcome level: combination of sitagliptin plus metformin vs. glipizide plus metformin

Outcome category **Outcome**	**Sitagliptin plus metformin vs. glimepiride plus metformin** **Patients (%) with event** **Effect estimates [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	1 (0.2) vs. 8 (1.4) Peto OR: 0.21 [0.06; 0.77] p = 0.021 probability: "hint"	
Men	1 (0.3) vs. 8 (2.2) Peto OR: 0.22 [0.06; 0.82] p = 0.024 probability: "hint"	Outcome category: survival time $CI_o < 0.85$ added benefit, extent: "major"
Women	0 (0) vs. 0 (0) not calculated	Added benefit not proven
Morbidity		
Cardiac morbidity	15 (2.6) vs. 11 (1.9) RR: 1.35 [0.63; 2.92] p = 0.553	Added benefit not proven
Cerebral morbidity	2 (0.3) vs. 8 (1.4) Peto OR: 0.30 [0.09; 1.03] p = 0.064	Added benefit not proven
Health-related quality of life		
	No data available	Added benefit not proven

(continued)

Table 38: Extent of added benefit at outcome level: combination of sitagliptin plus metformin vs. glipizide plus metformin (continuation)

Outcome category **Outcome**	**Sitagliptin plus metformin vs. glimepiride plus metformin** **Patients (%) with event** **Effect estimates [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
AEs		
Overall rate of SAEs	64 (10.9) vs. 73 (12.5) RR: 0.87 [0.64; 1.19] p = 0.414	Greater/lesser harm not proven
Overall rate of AEs that led to treatment discontinuation	23 (3.9) vs. 29 (5.0) RR: 0.78 [0.45; 1.36] p = 0.398	Greater/lesser harm not proven
Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl) after week 104	5 (0.9) vs. 48 (8.2) Peto OR: 0.18 [0.10; 0.32] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs CI_o < 0.80 lesser harm, extent: "considerable"
Severe hypoglycaemias after week 104	1 (0.2) vs. 9 (1.5) Peto OR: 0.20 [0.06; 0.69] p = 0.011 probability: "hint"	Outcome category: serious/severe AEs CI_o < 0.75 and risk < 5% lesser harm, extent: "considerable"
Renal impairment	4 (0.7) vs. 4 (0.7) Peto OR: 0.99 [0.25; 3.99] p > 0.999	Greater/lesser harm not proven
Pancreatitis	2 (0.3) vs. 0 (0) Peto OR: 7.35 [0.46; 117.67] p = 0.500	Greater/lesser harm not proven

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_o.
AE: adverse event; CI: confidence interval; CI_o: upper limit of the CI; OR: odds ratio; RR: relative risk; SAE: serious adverse event; vs.: versus

2.4.3.4.2 Overall conclusion on added benefit

Table 39 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 39: Positive and negative effects from the assessment of the combination of sitagliptin plus metformin compared with glipizide plus metformin

Positive effects	Negative effects
Hint of an added benefit for men – extent: "major" (all-cause mortality)	—
Hint of lesser harm – extent: "considerable" (non-serious/non-severe AEs: symptomatic hypoglycaemias)	
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 major added benefit in all-cause mortality (only for men) and a hint of lesser harm with considerable extent both for symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl) and severe hypoglycaemias.

There was neither an advantage nor a disadvantage of the combination of sitagliptin plus metformin versus glipizide plus metformin regarding micro- and macrovascular late complications. No sufficient data were available on these outcomes, however. This led to an additional uncertainty. It did not seem appropriate, however, to question the advantage in all-cause mortality observed in men because of this. Overall, in men, there is therefore a hint of a major added benefit of sitagliptin versus glipizide. 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 because of the additional uncertainty.

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.

Overall, there is a hint of a major added benefit in men and a hint of a non-quantifiable added benefit (not more than "considerable") 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 sugar levels are aimed at. For patients without such a treatment goal, there is no proof of added benefit of sitagliptin.

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

2.4.3.5 List of included studies

P024

1. 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.

2. Merck. An investigational drug study in patients with type 2 diabetes mellitus: full text view [online]. In: ClinicalTrials.gov. 07 April 2010 [accessed: 13 June 2013]. URL: http://www.clinicaltrials.gov/ct2/show/NCT00094770.

3. 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.

4. 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 mellitus with inadequate glycemic control on metformin monotherapy: study P024; supplemental statistical data analysis plan [unpublished]. 2006.

5. 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 P024V1; clinical study report [unpublished]. 2006.

6. 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 therapy: study P024; clinical study report [unpublished]. 2007.

7. 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.

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 plus sulfonylurea (studies completed up to 1 February 2013)
- Bibliographical literature search on sitagliptin plus sulfonylurea (last search on 25 February 2013 – cut-off date 1 February 2013)
- Search in trial registries for studies on sitagliptin plus sulfonylurea (last search on 1 February 2013)
- Bibliographical literature search on human insulin plus sulfonylurea (last search on 26 September 2012)
- Search in trial registries for studies on human insulin plus sulfonylurea (last search on 26 September 2012)

The Institute's own search:

- Bibliographical literature search on gliptins to check the search results of the company (last search on 19 March 2013)
- Search in trial registries for studies on gliptins to check the search results of the company (last search on 21 March 2013)

The company did not identify any direct comparative studies or studies for an indirect comparison on sitagliptin plus sulfonylurea versus the ACT specified by the G-BA. The company did not claim an added benefit for this subindication.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4C, Sections 4.2.2 and 4.2.3 of the dossier, and in Section 2.9.4 of the full dossier assessment.

2.5.2 Results on added benefit (research question C)

No relevant data were available for the research question "sitagliptin plus sulfonylurea". Hence the added benefit versus the ACT specified by the G-BA is not proven.

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

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of sitagliptin plus sulfonylurea in comparison with the ACT specified by the G-BA (human insulin plus sulfonylurea [glibenclamide, glimepiride], if applicable treatment only with human insulin). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This result concurs with that of the company.

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 plus metformin plus sulfonylurea (studies completed up to 1 February 2013)
- Bibliographical literature search on sitagliptin plus metformin plus sulfonylurea (last search on 25 February 2013 – cut-off date 1 February 2013)
- Search in trial registries for studies on sitagliptin plus metformin plus sulfonylurea (last search on 1 February 2013)
- Bibliographical literature search on human insulin with or without metformin (last search on 26 September 2012)
- Search in trial registries for studies on human insulin with or without metformin (last search on 26 September 2012)

The Institute's own search:

- Bibliographical literature search on gliptins to check the search results of the company (last search on 19 March 2013)
- Search in trial registries for studies on gliptins to check the search results of the company (last search on 21 March 2013)

The company did not identify any direct comparative studies or studies for an indirect comparison on sitagliptin plus metformin plus sulfonylurea versus the ACT specified by the G-BA. The company did not claim an added benefit for this subindication.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4D, Sections 4.2.2 and 4.2.3 of the dossier, and in Section 2.9.5 of the full dossier assessment.

2.6.2 Results on added benefit (research question D)

No relevant data were available for the research question on the combination of sitagliptin with metformin and sulfonylurea. Hence the added benefit versus the ACT specified by the G-BA is not proven.

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

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of sitagliptin in combination with metformin and sulfonylurea in comparison with the ACT specified by the G-BA (human insulin plus metformin, treatment only with human insulin if metformin is not sufficiently effective). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This result concurs with that of the company.

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 plus insulin (studies completed up to 1 February 2013)
- Bibliographical literature search on sitagliptin plus insulin (last search on 25 February 2013 – cut-off date 1 February 2013)
- Search in trial registries for studies on sitagliptin plus insulin (last search on 1 February 2013)

The Institute's own search:

- Bibliographical literature search on gliptins to check the search results of the company (last search on 19 March 2013)
- Search in trial registries for studies on gliptins to check the search results of the company (last search on 21 March 2013)

No additional studies were identified in the Institute's search.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4E, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.9.6.2 and 2.9.6.4.1 of the full dossier assessment.

The data presented by the company were unsuitable to draw conclusions on the added benefit of sitagliptin in combination with insulin. This is justified below.

The company included a direct comparative study in the assessment. Its characteristics are presented in Table 40 and Table 41.

Table 40: Characteristics of the studies included by the company – RCT, direct comparison: sitagliptin plus insulin (plus metformin) vs. human insulin (plus metformin)

Study	Study design	Study duration	Population	
			Type of prior treatment	Criteria for inadequate glycaemic control
Hong 2012	RCT parallel active-controlled single-centre open-label	▪ Screening phase: 4 weeks ▪ Treatment: 24 weeks	Insulin treatment for at least 3 months, with a dosage of ≥ 10 units/day for ≥ 4 weeks before enrolment	HbA1c 7.5-11%

HbA1c: haemoglobin A1c; RCT: randomized controlled trial; vs.: versus

Table 41: Characteristics of the interventions – RCT, direct comparison: sitagliptin plus insulin (plus metformin) vs. human insulin (plus metformin)

Study	Sitagliptin plus insulin (plus metformin) Number of patients	Human insulin (plus metformin) Number of patients
Hong 2012	Insulin plus sitagliptin (100 mg/day)[a] N = 70 The insulin dose remained unchanged.	Intensification of insulin treatment (insulin dose increase)[a] N = 70 The patients were instructed to increase their insulin dose in steps of ≥ 10% over the course of the study (at any time and again at the 12-week follow-up) if their HbA1c was not within the target level (≤ 7.0%). The patients could additionally adjust their insulin dose by 2 units/week based on their blood glucose levels measured. The patients were instructed to use the same formulation of insulin and, if possible, the same treatment regimen throughout the entire study.

Concomitant treatment[b]	Sitagliptin plus insulin plus OAD; (n = 61) Number of patients (%)	Insulin intensification plus OAD; (n = 63) Number of patients (%)
Sulfonylureas	15 (24.6)	15 (23.8)
Glinides	8 (13.1)	10 (15.9)
Metformin	28 (45.9)	26 (41.3)
Glitazones	4 (6.6)	2 (3.2)
α-glucosidase inhibitors	19 (31.1)	27 (42.9)

a: The dose of oral antihyperglycaemic drugs was not changed during the study. The investigators could decrease a patient's insulin dose according to their clinical judgements only in the event of severe or repeated hypoglycaemic episodes.
b: A patient could receive several concomitant treatments.
HbA1c: haemoglobin A1c; N: number of randomized patients; n: number of patients analysed; OAD: oral antidiabetic drug; RCT: randomized controlled trial; vs.: versus

Hong 2012 was an exploratory, randomized, open-label study with a 24-week treatment period. Patients aged 30 to 70 years who had received insulin treatment for at least 3 months were enrolled. Insulin treatment had to have been administered at a dose of at least 10 units/day and for a minimum of 4 weeks. The patients were additionally treated with different OADs. The study aimed to investigate the efficacy and safety of an additional administration of sitagliptin in comparison with an insulin dose increase on the basis of an ongoing insulin treatment (and additional OAD treatment).

The study Hong 2012 was unsuitable for assessing the added benefit because the patients enrolled did not correspond to the target population. Sitagliptin is approved for administration in combination with insulin with or without metformin. There is no approval for combination with other OADs under insulin treatment. However, to a major extent, the patients received other OADs besides metformin in both treatment arms (see Table 41). The other OADs used in the study were α-glucosidase inhibitors, sulfonylureas, glinides and glitazones. It could not be derived from the available information how large the proportion of patients was who were treated in compliance with the approval (no oral concomitant medication or monotherapy with metformin), and there were also no results for an approval-compliant subpopulation.

Regardless of this, it cannot be derived from the available information that the patients in the comparator group had all possibilities of treatment optimization. According to the information, only the dose was to be adjusted and the patients were to use the same formulation of insulin and, if possible, the same treatment regimen throughout the entire study. Correspondingly, only conclusions specifically versus an insulin dose increase and not versus another possibility of insulin optimization could be drawn from this study.

Further information about the study design and the study populations can be found in Module 4E, Section 4.3.1.2. and Appendix 4-F of the dossier, and in Section 2.9.6.4.2 of the full dossier assessment.

2.7.2 Results on added benefit (research question E)

No relevant data were available for the research question "sitagliptin plus insulin (with or without metformin)". Hence the added benefit versus the ACT specified by the G-BA is not proven.

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

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of sitagliptin plus insulin (with or without metformin) in comparison with the ACT specified by the G-BA (human insulin plus metformin, or only human insulin if metformin is not tolerated according to the SPC or not sufficiently effective). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This result deviates from that of the company, which derived an indication of a considerable added benefit of sitagliptin plus insulin (with or without metformin) versus the intensification of insulin treatment (insulin dose increase).

Overall, there is no proof of an added benefit of sitagliptin plus insulin (with or without metformin). Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

2.8 Extent and probability of added benefit - summary

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

Table 42: 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	*Treatment goal near-normal blood glucose levels*: hint of a minor added benefit *Other treatment goal:* added benefit not proven
B2	Sitagliptin plus metformin	Glipizide plus metformin[a]	*Treatment goal near-normal blood glucose levels:* men: hint of a major added benefit women: hint of an added benefit (extent "non-quantifiable", not more than "considerable") *Other treatment goal:* added benefit not proven
C	Sitagliptin plus sulfonylurea	Human insulin plus sulfonylurea (glibenclamide, glimepiride, if applicable only treatment 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 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, direct comparative studies of sitagliptin versus glipizide (research question A2) and sitagliptin plus metformin versus glipizide plus metformin (research question B2) were additionally assessed.			

It should also be noted that the data on late complications (particularly on the prevention of micro- and macrovascular events) presented by the company were insufficient. The prevention of micro- and macrovascular late complications is an important goal in the treatment of patients with type 2 diabetes mellitus. It is not comprehensible that such data for sitagliptin are still lacking. At the time of this assessment, sitagliptin has already been approved throughout Europe for more than 6 years (since March 2007). The gliptin saxagliptin, which was approved considerably later (in October 2009), these data are apparently already available and will be presented shortly [18]. Long-term data on sitagliptin are to be available in 2015 at the earliest [19].

The G-BA decides on added benefit.

Further information about the extent and probability of the added benefit can be found in Modules 4A-E, Section 4.4 of the dossier, and in Sections 2.9.2.9 and 2.9.3.9 of the full dossier assessment.

References for English extract

Please see full dossier assessment for full reference list.

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