

IQWiG Reports – Commission No. A16-43

Saxagliptin/metformin (type 2 diabetes mellitus) –

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

Extract

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycosylated haemoglobin A1c
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of saxagliptin/metformin. The pharmaceutical company (hereinafter referred to as “the company” submitted a first dossier of the drug to be evaluated on 15 November 2012 for the early benefit assessment. This dossier was assessed in dossier assessment A12-16 and in the corresponding addendum A13-14. In this procedure, by decision of 1 October 2013, the G-BA limited its decision until 1 October 2015. By decision of 19 February 2015, this limitation period was prolonged until 1 July 2016. The assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 4 July 2016.

Research question

The aim of the present report was to assess the added benefit of the fixed combination of saxagliptin and metformin (saxagliptin/metformin) in adult patients aged 18 years and older with type 2 diabetes mellitus in the following approved subindications:

- **Saxagliptin/metformin:** as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets
- **Saxagliptin/metformin in combination with insulin:** (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus when insulin and metformin alone do not provide adequate glycaemic control

The assessment was conducted for 2 research questions versus the appropriate comparator therapy (ACT) specified by the G-BA. These are shown in Table 2.

Table 2: Research questions of the benefit assessment of saxagliptin/metformin

Research question	Subindication	Appropriate comparator therapy ^a
A	Saxagliptin/metformin	Metformin plus sulfonylurea (glibenclamide, glimepiride)
B	Saxagliptin/metformin plus insulin	Human insulin plus metformin <i>(note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)</i>

a: Presentation of the respective ACT specified by the G-BA.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product characteristics

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

For research question A, however, the company did not limit the sulfonylureas to glibenclamide and glimepiride and additionally cited glipizide as comparator therapy for this research question.

The present benefit assessment was conducted for both research questions in comparison with the ACTs specified by the G-BA. For research question A, studies with glipizide were also considered and assessed separately.

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

Study SAVOR-TIMI 53

The company presented analyses of the SAVOR-TIMI 53 study for both research questions. The SAVOR-TIMI 53 study was an RCT, which lasted several years, which was conducted in patients at high cardiovascular risk, and which compared saxagliptin with placebo (each in addition to "standard treatment"). The aim of this study was both to exclude that cardiovascular events occurred more frequently under saxagliptin than under placebo (condition of the regulatory authorities) and to prove that saxagliptin reduces cardiovascular events (treatment goal in the use of saxagliptin).

Different subpopulations of the SAVOR-TIMI 53 study were considered in the analyses relating to the research questions presented by the company. The company used these subpopulations to compare saxagliptin/metformin with the respective ACT. These were unsuitable for the research questions because either the structural equality between the comparator groups formed by the company was eliminated (research question A) and/or there was no comparison with the ACT (research questions A and B).

Irrespective of this, the SAVOR-TIMI 53 study is of particular importance for the therapeutic indication of type 2 diabetes mellitus because of its size and the outcomes investigated (especially cardiovascular events and all-cause mortality). The majority of the patients included in the study did not concur with the target population of the present benefit assessment, however. The proportion of patients in the total population who either received no metformin or who received metformin at a dosage below 1700 mg/day was between 47% and 65% (the exact number could not be inferred from the information provided in the study documents).

The SAVOR-TIMI 53 study and its limitations are assessed and described in detail in benefit assessment A16-42 on saxagliptin (single agent), which is published at the same time as the present benefit assessment of the fixed combination.

Results

Research question A: saxagliptin/metformin

The company included 3 RCTs with saxagliptin for research question A: study D1680C00001, study D1680L00002, and study SAVOR-TIMI 53.

The studies D1680C00001 and D1680L00002 had already been assessed in the first assessment of saxagliptin/metformin (A12-16) and in the corresponding addendum to the first assessment (A13-14). In the current dossier, the company presented no new data on the 2 studies. The results concurred with those of the first assessment.

The analysis of the SAVOR-TIMI 53 study presented by the company for research question A was unsuitable for the present benefit assessment. From both treatment arms of the study, the company chose patients who had received approval-compliant pretreatment for research question A. From this subpopulation, the company chose only those patients from the saxagliptin group who had been treated with concomitant antidiabetic treatment except sulfonylureas (part of the ACT) after randomization to saxagliptin. In the placebo group, the company chose those patients who had received additional sulfonylureas as part of their concomitant antidiabetic medication within 3 months after randomization to placebo. Due to this approach, there was no structural equality between the comparator groups formed by the company. This was already apparent from the drastically different patient numbers: 563 (6.8%) patients in the saxagliptin group and 24 (0.3%) patients in the comparator group were included in the analysis.

The analysis of the SAVOR-TIMI 53 study presented by the company on research question A was unsuitable for the present benefit assessment. In summary, there was no hint of an added benefit of saxagliptin/metformin for adults with type 2 diabetes mellitus with inadequate glycaemic control under metformin monotherapy alone in comparison with the ACT. An added benefit is therefore not proven.

Research question B: saxagliptin/metformin plus insulin

The company identified the studies CV181057 and SAVOR-TIMI 53, which it used for the assessment of research question B. The company had already presented the CV181057 study for the first assessment of saxagliptin/metformin (A12-16). The company presented no new data on this study in the dossier. The results concurred with those of the first assessment.

The analysis of the SAVOR-TIMI 53 study presented by the company for research question B was unsuitable for the present benefit assessment. From both treatment arms, the company chose those patients who had received pretreatment with metformin ≥ 1700 mg and insulin in compliance with the approval for research question B and who, according to the approval, had no moderate to severe renal impairment (creatinine clearance of < 60 mL/min). In this case, there is a high probability that structural equality is maintained between the comparator groups of the subpopulation formed in this way. The design of the SAVOR-TIMI 53 study did not ensure adequate implementation of the ACT, however. Patients with inadequate

glycaemic control under treatment with insulin plus metformin alone are the target population of research question B. The antidiabetic therapy therefore needs to be optimized for the patients. In the saxagliptin arm, there was treatment escalation with saxagliptin. In the comparator arm, in contrast, optimization of the concomitant insulin therapy was not ensured. It could be inferred from the clinical study report (CSR) of the SAVOR-TIMI 53 study that fewer than one third of the patients received an increase of their insulin dose by $\geq 25\%$ for at least 3 months in the total population of the study. It remained unclear whether these treatments were used in accordance with the approval specifications of the Summary of Product Characteristics (SPC) and concurred with the G-BA's specification (human insulin).

Even if it was assumed that a large proportion of the subpopulation formed by the company required no treatment escalation, the analysis presented by the company was unsuitable: The subpopulation did not concur with the approval of saxagliptin/metformin (and hence not with the target population of research question B) because the requirement of treatment escalation is a prerequisite for the use of saxagliptin/metformin.

In summary, there was no hint of an added benefit of saxagliptin/metformin plus insulin for adults with type 2 diabetes mellitus with inadequate glycaemic control under insulin and metformin in comparison with the ACT. An added benefit is therefore not proven.

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

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

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

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

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

Research question	Subindication	Appropriate comparator therapy ^a	Extent and probability of added benefit
A	Saxagliptin/metformin	Sulfonylurea (glibenclamide, glimepiride) + metformin	Added benefit not proven
B	Saxagliptin/metformin plus insulin	Metformin + human insulin <i>(treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)</i>	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product characteristics			

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of the fixed combination of saxagliptin and metformin (saxagliptin/metformin) in adult patients aged 18 years and older with type 2 diabetes mellitus in the following approved subindications:

- **Saxagliptin/metformin:** as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets
- **Saxagliptin/metformin in combination with insulin:** (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus when insulin and metformin alone do not provide adequate glycaemic control

Moreover, saxagliptin/metformin is also approved in combination with a sulfonylurea. Following the G-BA decision from 1 October 2013, the added benefit of this triple combination therapy is not proven [3]. This decision was not limited and is not subject of this assessment.

The assessment was conducted for 2 research questions versus the ACT specified by the G-BA. These are shown in Table 4.

Table 4: Research questions of the benefit assessment of saxagliptin/metformin

Research question	Subindication	Appropriate comparator therapy ^a
A	Saxagliptin/metformin	Metformin plus sulfonylurea (glibenclamide, glimepiride)
B	Saxagliptin/metformin plus insulin	Human insulin plus metformin <i>(note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)</i>
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product characteristics		

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

For research question A, however, the company did not limit the sulfonylureas to glibenclamide and glimepiride and additionally cited glipizide as comparator therapy for this research question.

The present benefit assessment was conducted for both research questions in comparison with the ACTs specified by the G-BA. For research question A, studies with glipizide were also considered and assessed separately.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

SAVOR-TIMI 53

The company presented analyses of the SAVOR-TIMI 53 study for both research questions. The SAVOR-TIMI 53 study was an RCT, which lasted several years, which was conducted in patients at high cardiovascular risk, and which compared saxagliptin with placebo (each in addition to "standard treatment"). The aim of this study was both to exclude that cardiovascular events occurred more frequently under saxagliptin than under placebo (condition of the regulatory authorities) and to prove that saxagliptin reduces cardiovascular events (treatment goal in the use of saxagliptin) [4].

Different subpopulations of the SAVOR-TIMI 53 study were considered in the analyses relating to the research questions. The company used these subpopulations to compare saxagliptin with the respective ACT. The following Sections 2.3 and 2.4 on the research questions A and B assess, among other things, whether these analyses of the SAVOR-TIMI 53 study relating to the research questions were suitable for the benefit assessment.

Irrespective of this, the SAVOR-TIMI 53 study is of particular importance for the therapeutic indication of type 2 diabetes mellitus because of its size and the outcomes investigated. However, the majority of the total population did not concur with the target population of the fixed combination saxagliptin/metformin. The SAVOR-TIMI 53 study included patients who were not treated with metformin (approximately 30% of the total population) and patients who received metformin below the dosage of 1700 mg/day mandated for the fixed combination (approximately 17% to 35% of the total population; the exact number could not be inferred from the information provided in the study documents). Overall, about 47% to 65% of the total population did not concur with the target population of the fixed combination saxagliptin/metformin.

The information on the study design and on the results of the SAVOR-TIMI 53 study as well as the limitations of this study are presented and assessed in benefit assessment A16-42 on saxagliptin (see Appendix A of dossier assessment A16-42 [5]).

2.3 Research question A: saxagliptin/metformin

2.3.1 Information retrieval and study pool (research question A)

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

Sources of the company in the dossier:

- study list on saxagliptin (status: 4 April 2016)
- bibliographical literature search on saxagliptin (last search on 1 April 2016)
- search in trial registries for studies on saxagliptin (last search on 5 April 2016)

To check the completeness of the study pool:

- search in trial registries for studies on saxagliptin (last search on 11 July 2016)

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

From the steps of information retrieval mentioned, the company identified 3 RCTs with saxagliptin, which it used for research question A: study D1680C00001 [6,7], study D1680L00002 [8], and study SAVOR-TIMI 53 (D1680C00003) [4]. The company had already presented studies D1680C00001 and D1680L00002 for the first assessment of saxagliptin/metformin (A12-16 [9]) and in the corresponding addendum to the first assessment (A13-14 [10]). The company newly submitted the SAVOR-TIMI 53 study with the current dossier.

Studies D1680C00001 and D1680L00002

Both studies D1680C00001 and D1680L00002 had already been assessed in dossier assessment A12-16 and addendum A13-14. In the current dossier, the company presented no new data on the 2 studies. All relevant information can therefore be found in dossier assessment A12-16 [9], addendum A13-14 [10], and in the G-BA decision on the first assessment of saxagliptin/metformin [11].

Study SAVOR-TIMI 53

The SAVOR-TIMI 53 study included treatment-naïve or pretreated patients aged 40 years and older with type 2 diabetes mellitus and a glycosylated haemoglobin A1c (HbA1c) value of 6.5% to < 12% at the start of the study. Another criterion for study inclusion was the presence of cardiovascular disease and/or multiple cardiovascular risk factors. The patients were randomly assigned to a saxagliptin arm or to the placebo arm, with stratification according to the cardiovascular risk and the severity of renal insufficiency at the start of the study.

A detailed description of the design and the patient characteristics of the SAVOR-TIMI 53 study can be found in Appendix A of dossier assessment A16-42.

Patients with different pretreatments were included in the SAVOR-TIMI 53 study. The total population of the SAVOR-TIMI 53 study therefore mostly did not concur with the target population of research question A (saxagliptin/metformin). For research question A, the company therefore selected those patients from the study population of the SAVOR-TIMI 53 study who had received only pretreatment with a metformin dose of ≥ 1700 mg and who, in compliance with the approval, had no moderate to severe renal impairment (creatinine clearance of < 60 mL/min). In addition, the company stated that it had excluded patients with further contraindications to metformin. It was not clear from the company's documents, however, which contraindications it referred to and how many patients were affected by this.

This subpopulation with approval-compliant metformin pretreatment concurs with the target population of research question A. However, the study design of the SAVOR-TIMI 53 study (comparison of saxagliptin versus placebo, each in addition to "standard treatment") did not allow a direct comparison of the combination of saxagliptin/metformin with the ACT (metformin plus sulfonylurea) because the patients in both treatment groups were allowed to receive concomitant antidiabetic medication consisting of numerous treatment options in the further course of the study.

The company therefore considered only those patients in the saxagliptin group who had been treated with concomitant antidiabetic treatment except sulfonylureas (part of the ACT) after randomization to saxagliptin. According to the company, it chose this approach to exclude that the treatment effect was biased by the administration of the comparator therapy (sulfonylurea) in the intervention arm. In the placebo group, the company chose those patients who had received additional sulfonylureas as part of their concomitant antidiabetic medication within 3 months after randomization to placebo. The company considered this to "imitate a direct randomization" to sulfonylurea.

The company noted that randomization was not maintained because of the different selection in both treatment groups, which resulted in a high risk of bias. Nonetheless, the company considered this analysis to be the best possible approximation to the specifications of this research question.

The company's approach was unsuitable for the present benefit assessment for several reasons.

- 1) The patient numbers of the groups selected by the company already showed clearly that no structural equality of the comparator groups formed by the company could be assumed. In the SAVOR-TIMI 53 study, the patients were allocated to the 2 treatment groups in a ratio of 1:1 (8280 patients to the saxagliptin arm and 8212 patients to the placebo arm). The subpopulation created by the company for research question A included 563 patients from the saxagliptin group (6.8%) and 24 patients from the placebo group (0.3%).
- 2) The HbA1c and fasting plasma glucose levels at the start of the study proved that there was no structural equality between the comparator groups of the company: The mean HbA1c value at the start of the study was 7.4% for the subpopulation of the saxagliptin group and 8.5% in the subpopulation of the placebo group. The mean fasting plasma glucose levels at the start of the study also differed between the subpopulation of the saxagliptin group with 143.3 mg/dL and the subpopulation of the placebo group with 174.1 mg/dL.
- 3) For its comparison, the company chose patients who received different concomitant medications in addition to saxagliptin or placebo within the randomized study. From the saxagliptin group, only patients were chosen for whom the treating physician apparently considered sulfonylureas to be unsuitable or not necessary. From the placebo group, however, only patients were chosen who received sulfonylureas for the first 3 months after randomization. These different selection criteria chosen by the company for both treatment arms were another reason why structural equality of the comparator groups formed by the company was not ensured.
- 4) The company selected post hoc patients in the placebo arm who received sulfonylureas within 3 months after randomization. Hence the characteristic for the creation of the subpopulations for the placebo group only arose in the course of the study (within 3 months after randomization) and in dependence on the therapy conducted up to then. It was not clear from the study documents how many of the patients in the placebo group chosen by the company for research question A received sulfonylureas directly after randomization.

In summary, the analysis of the SAVOR-TIMI 53 study presented by the company for research question A was unsuitable for the present benefit assessment.

2.3.2 Results on added benefit (research question A)

For research question A, the company presented the studies D1680C00001 and D1680L00002 known from the first assessment. The results on these 2 studies concurred with those of the first assessment.

The analysis of the SAVOR-TIMI 53 study presented by the company on research question A was unsuitable for the present benefit assessment. In summary, there was no hint of an added benefit of saxagliptin/metformin for adults with type 2 diabetes mellitus with inadequate glycaemic control under metformin monotherapy alone or those already being treated with the

combination of saxagliptin and metformin as separate tablets in comparison with the ACT. An added benefit of saxagliptin/metformin is therefore not proven.

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

The data presented by the company showed that the added benefit of saxagliptin/metformin is not proven for patients with inadequate glycaemic control under metformin monotherapy or those already being treated with the combination of saxagliptin and metformin as separate tablets.

This deviates from the company's assessment, which derived proof of a considerable added benefit for saxagliptin/metformin.

2.4 Research question B: saxagliptin/metformin plus insulin

2.4.1 Information retrieval and study pool (research question B)

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

Sources of the company in the dossier:

- study list on saxagliptin (status: 4 April 2016)
- bibliographical literature search on saxagliptin (last search on 1 April 2016)
- search in trial registries for studies on saxagliptin (last search on 5 April 2016)

To check the completeness of the study pool:

- search in trial registries for studies on saxagliptin (last search on 11 July 2016)

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

From the steps of information retrieval mentioned, the company identified 2 RCTs, which it used for the assessment of research question B: study CV181057 [12,13] and the study SAVOR-TIMI 53 (D1680C00003) [4]. The company had already presented the CV181057 study for the first assessment of saxagliptin/metformin (A12-16 [9]). The company newly submitted the SAVOR-TIMI 53 study with the current dossier.

Study CV181057

The CV181057 study was already assessed in dossier assessment A12-16. It was not relevant for the present benefit assessment (research question B). The company presented no new data in the dossier that would change this assessment.

A detailed description of the CV181057 study can be found in dossier assessment A12-16.

Study SAVOR-TIMI 53

A detailed description of the design and the study characteristics of the SAVOR-TIMI 53 study can be found in Section 2.3.1 and in Appendix A of dossier assessment A16-42.

Patients with different pretreatments were included in the SAVOR-TIMI 53 study. The total population of the SAVOR-TIMI 53 study therefore mostly did not concur with the target population of research question B (saxagliptin/metformin plus insulin). For research question B, the company therefore selected those patients from the study population of the SAVOR-TIMI 53 study who had received only pretreatment with a metformin dose of ≥ 1700 mg and insulin and who, in compliance with the approval, had no moderate to severe renal impairment (creatinine clearance of < 60 mL/min).

This subpopulation with approval-compliant insulin and metformin pretreatment concurs with the target population of research question B.

Hence the company considered patients who had received insulin plus metformin before the start of the study and who were allocated either to the saxagliptin group or to the comparator group at the start of the study. The company considered this to be a direct comparison between insulin plus metformin plus saxagliptin and insulin plus metformin plus placebo in which structural equality of the patients was maintained.

It is correct that there is a high probability that structural equality between the comparator groups created by the company was maintained in this case. The design of the SAVOR-TIMI 53 study did not ensure adequate implementation of the ACT, however. Patients with inadequate glycaemic control under treatment with insulin plus metformin alone are the target population of research question B. The antidiabetic therapy therefore needs to be optimized for the patients. For the patients of the subpopulation created by the company, treatment escalation in the saxagliptin arm consisted in additional administration of saxagliptin (and the additional further antidiabetic treatment). For patients in the comparator arm, in contrast, optimization of the ongoing insulin therapy was not ensured.

The CSR of the SAVOR-TIMI 53 study shows that only 2028 patients (24.5%) in the total population in the saxagliptin group and 2572 patients (31.3%) in the placebo group received additional antidiabetic treatment in the course of the study. Only 363 patients (4.6%) in the saxagliptin arm and 508 patients (6.2%) in the placebo arm received increase of their insulin dose by $\geq 25\%$ for at least 3 months (see Appendix A.1 in A16-42). It remained unclear whether these treatments were used in accordance with the approval specifications of the SPC and concurred with the G-BA's specification (human insulin).

It was unclear how many patients in the subpopulation created by the company received an escalation of their ongoing inadequate insulin therapy because the company presented no data on this. The fact that the ongoing insulin treatment was inadequate in at least a large proportion of the relevant subpopulation resulted, on the one hand, from the inclusion criteria of the SAVOR-TIMI 53 study (see Appendix A of dossier assessment A16-42). On the other, this could also be seen in the HbA1c values at the start of the study: The mean value was 8.3% in the subpopulation of the saxagliptin group and 8.4% in the subpopulation of the placebo group. The HbA1c value was $\geq 8\%$ in more than half of the patients (about 53% in the saxagliptin group and about 57% in the placebo group). Even if it was assumed that a large proportion of the subpopulation formed by the company required no treatment escalation, the analysis presented by the company was unsuitable: The subpopulation did not concur with the approval of saxagliptin/metformin (and hence not with the target population of research question B) because the requirement of treatment escalation is a prerequisite for the use of saxagliptin/metformin [14].

In summary, the results of the subpopulation of the SAVOR-TIMI 53 study considered by the company were unsuitable for the benefit assessment of saxagliptin/metformin (research question B).

2.4.2 Results on added benefit (research question B)

The company presented no data suitable for the benefit assessment for research question B. The CV181057 study from the first assessment A12-16 presented again provided no new findings for the benefit assessment. The analysis of the SAVOR-TIMI 53 study presented by the company on research question B was unsuitable for the present benefit assessment. This also applied to the analysis of the total population of the SAVOR-TIMI 53 study.

In summary, there was no hint of an added benefit of saxagliptin/metformin plus insulin for adults with type 2 diabetes mellitus with inadequate glycaemic control under insulin and metformin alone in comparison with the ACT. An added benefit of saxagliptin/metformin plus insulin is therefore not proven.

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

Based on the data presented by the company, the added benefit of saxagliptin/metformin plus insulin is not proven for patients with inadequate glycaemic control under insulin and metformin.

This deviates from the company's assessment, which derived an indication of a considerable added benefit for saxagliptin/metformin plus insulin.

2.5 Extent and probability of added benefit

An overview of the extent and probability of added benefit for the different subindications of saxagliptin/metformin in comparison with the respective relevant ACTs is given Table 5.

Table 5: Saxagliptin/metformin – extent and probability of added benefit

Research question	Subindication	Appropriate comparator therapy ^a	Extent and probability of added benefit
A	Saxagliptin/metformin	Sulfonylurea (glibenclamide, glimepiride) + metformin	Added benefit not proven
B	Saxagliptin/metformin plus insulin	Metformin + human insulin <i>(treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)</i>	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product characteristics			

For both research questions, this assessment deviates from that of the company, which claimed proof of considerable added benefit for research question A (saxagliptin/metformin) and an indication of considerable added benefit for research question B (saxagliptin/metformin plus insulin).

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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