

IQWiG Reports – Commission No. A16-42

Saxagliptin
(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)
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 the drug saxagliptin. The company submitted a first dossier of the drug to be evaluated on 28 March 2013 for the early benefit assessment. This dossier was assessed in dossier assessment A13-01. 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 pharmaceutical company (hereinafter referred to as “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 saxagliptin in adult patients aged 18 years and older with type 2 diabetes mellitus in the following approved subindications:

- **Combination of saxagliptin and metformin:** when metformin monotherapy, with diet and exercise, does not provide adequate glycaemic control;
- **Combination of saxagliptin and sulfonylurea:** in patients for whom use of metformin is considered inappropriate, when sulfonylurea monotherapy, with diet and exercise, does not provide adequate glycaemic control;
- **Combination of saxagliptin and insulin with or without metformin:** when treatment with insulin with or without metformin, alone, with diet and exercise, does not provide adequate glycaemic control;
- **Combination of saxagliptin and metformin and sulfonylurea:** when treatment with metformin plus sulfonylurea alone, with diet and exercise, does not provide adequate glycaemic control.

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

Table 2: Research questions of the benefit assessment of saxagliptin

Research question	Subindication	Appropriate comparator therapy ^a
A	Saxagliptin plus metformin	Metformin plus sulfonylurea (glibenclamide, glimepiride)
B	Saxagliptin plus sulfonylurea	Human insulin in combination with a sulfonylurea (glibenclamide, glimepiride), if applicable only treatment with human insulin
C	Saxagliptin plus insulin with or without metformin	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>
D	Saxagliptin plus metformin plus sulfonylurea	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 all research questions.

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

The present benefit assessment was conducted for all 4 research questions in comparison with the ACTs specified by the G-BA. For research questions A and B, 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 all 4 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).

Patients with different pretreatments were included in the SAVOR-TIMI 53 study. The majority of the total population of the SAVOR-TIMI 53 study therefore did not concur with the respective target populations of research questions A to D.

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 with the respective ACT. These analyses were unsuitable for the research questions because either the structural equality between the comparator groups formed by the company was eliminated (research questions A, B, and D) and/or there was no comparison with the ACT (research questions A, B, C, and D).

Irrespective of the suitability of these analyses for the research questions A to D, the SAVOR-TIMI 53 study was assessed due to its importance for the therapeutic indication of type 2 diabetes mellitus overall.

Results

Research question A: saxagliptin plus metformin

The company included 3 RCTs with saxagliptin for research question A: study D1680C00001, study D1680L00002, and study SAVOR-TIMI 53. The company had already presented the studies D1680C00001 and D1680L00002 for the first assessment of saxagliptin (A13-01).

The studies D1680C00001 and D1680L00002 had already been assessed in dossier assessment A13-01 and addendum A13-14 (addendum to the assessment of saxagliptin/metformin). 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. Of 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: 1299 patients (15.7%) in the saxagliptin group and 39 patients (0.5%) 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 the combination of saxagliptin and 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 plus sulfonyleurea

On the one hand, the company identified the SAVOR-TIMI 53 study and, on the other, 2 studies for an indirect comparison: study CV181040 (saxagliptin versus placebo) and study Tovi 1998 (sulfonyleurea versus placebo).

Together with 4 other studies on the ACT, the company had already presented the 2 studies CV181040 and Tovi 1998 for the first assessment of saxagliptin. Based on this, the company had conducted an indirect comparison, which was irrelevant for the benefit assessment. The indirect comparison now presented on the basis of the studies CV181040 and Tovi 1998 was also unsuitable because the CV181040 study did not investigate the target population.

The analysis of the SAVOR-TIMI 53 study presented by the company for research question B was unsuitable for the present benefit assessment. The company's approach corresponded to the approach described under research question A; for research question B, however, the company chose patients treated with saxagliptin plus sulfonyleurea for the saxagliptin group and patients treated with insulin (with or without sulfonyleurea) for the comparator group. The missing structural equality was also shown in research question B. This was already apparent from the drastically different patient numbers: 396 patients (4.8%) in the saxagliptin group and 9 patients (0.1%) in the comparator group were included in the analysis.

In summary, there was no hint of an added benefit of the combination of saxagliptin and sulfonyleurea for adults with type 2 diabetes mellitus with inadequate glycaemic control under sulfonyleurea monotherapy for whom use of metformin seems inadequate in comparison with the ACT. An added benefit is therefore not proven.

Research question C: saxagliptin plus insulin with or without metformin

The company identified the studies CV181057 and SAVOR-TIMI 53, which it used for the assessment of research question C. The company had already presented the CV181057 study for benefit assessment A13-01. 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 C was unsuitable for the present benefit assessment. From both treatment arms of the study, the company chose those patients who had received approval-compliant pretreatment (only with insulin and metformin) for research question C. 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 with or without metformin alone are the target population of research question C. 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 (and hence not with the target population of research question C) because the requirement of treatment escalation is a prerequisite for the use of saxagliptin.

In summary, there was no hint of an added benefit of the combination of saxagliptin plus insulin (with or without metformin) for adults with type 2 diabetes mellitus with inadequate glycaemic control under insulin (with or without metformin) in comparison with the ACT. An added benefit is therefore not proven.

Research question D: saxagliptin plus metformin plus sulfonyleurea

The company identified the SAVOR-TIMI 53 study and, for an indirect comparison, study D1680L00006 (saxagliptin plus metformin plus sulfonyleurea versus placebo plus metformin plus sulfonyleurea). The company had already presented the D1680L00006 study and an indirect comparison based on it for the first assessment of saxagliptin. This was irrelevant for the benefit assessment because the studies on the ACT were unsuitable.

The analysis of the SAVOR-TIMI 53 study presented by the company for research question D was unsuitable for the present benefit assessment. From the total population, the company chose patients from both treatment arms of the study who had received approval-compliant pretreatment for research question D. Of this subpopulation, the company selected only those patients from the saxagliptin group of the study who had been treated with concomitant antidiabetic treatment except insulin (part of the ACT) after randomization to saxagliptin. In the placebo group, the company aimed to only consider those patients who had switched treatment from sulfonyleurea to insulin as part of their concomitant antidiabetic treatment within 3 months after randomization. According to the company, these patients were not included in the placebo group, which is why there were no results for the planned comparison. Irrespective of the company's arguments, there would have been no structural equality between the comparator groups because of this approach in patient selection for both treatment arms of the SAVOR-TIMI 53 study.

For the indirect comparison, the company included the placebo-controlled D1680L00006 study and the SAVOR-TIMI 53 study for saxagliptin. The company chose metformin plus

sulfonylurea as common comparator. However, the company identified no study comparing the ACT with the common comparator.

In summary, there were no relevant data for the assessment of the added benefit of saxagliptin plus metformin plus sulfonylurea.

There was no hint of an added benefit of the combination of saxagliptin plus metformin plus sulfonylurea for adults with type 2 diabetes mellitus with inadequate glycaemic control under a combination of metformin and sulfonylurea 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 the drug saxagliptin compared with the ACT is assessed as follows:

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

Table 3: Saxagliptin – extent and probability of added benefit

Research question	Subindication	ACT^a	Extent and probability of added benefit
A	Saxagliptin plus metformin	Metformin plus sulfonylurea (glibenclamide or glimepiride)	Added benefit not proven
B	Saxagliptin plus sulfonylurea	human insulin in combination with a sulfonylurea (glibenclamide, glimepiride), if applicable only treatment with human insulin	Added benefit not proven
C	Saxagliptin 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
D	Saxagliptin plus metformin plus sulfonylurea	Human insulin plus metformin (note: treatment only with human insulin if metformin is not sufficiently effective)	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			

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].

The G-BA decides on the added benefit.

Study SAVOR-TIMI 53

Besides the analyses referring to the research questions, the company also presented results on the total population of the SAVOR-TIMI 53 study in its dossier. However, overall no conclusions on positive or negative effects of saxagliptin in comparison with the ACT can be derived from the SAVOR-TIMI 53 study. The following reasons in particular were decisive for this:

- Patients with different pretreatments were included. The majority of the total population of the SAVOR-TIMI 53 study therefore did not concur with the respective target populations of research questions A to D.
- Saxagliptin (plus concomitant antidiabetic medication) was compared with placebo (plus concomitant antidiabetic medication). Hence there was no comparison with the ACT.
- The blood-glucose lowering treatment was inadequate for a large proportion of the patients (either not sufficiently optimized or no approval-compliant use):
 - Adequate treatment escalation particularly in the placebo arm was not observed despite existing need of escalation of the patients.
 - The treatment escalations that were only conducted to a minor degree could also indicate that there was no need of escalation in a relevant proportion of the patients, neither at the start of the study nor in the course of the study. Treatment with saxagliptin is not approved for these patients, however.
- About 40% of the patients had a systolic blood pressure of ≥ 140 mmHg both at the start of the study and at the end of the treatment. It was unclear whether and when patients with an increased systolic measurement received an escalation by dose increase of blood-pressure lowering medication or administration of a further drug.
- The data on blood pressure and of the antidiabetic therapy indicate that regional standards of care may have played an important role in the SAVOR-TIMI 53 study and that the data of the total population are not simply transferable to the German health-care context.

Results from the SAVOR-TIMI 53 study

Overall, the results of the SAVOR-TIMI 53 study for the use of saxagliptin versus placebo, each in addition to antidiabetic “standard treatment”, showed:

- no disadvantage of saxagliptin regarding all-cause mortality or cardiovascular mortality
- no advantage of saxagliptin regarding all-cause mortality or cardiovascular mortality
- a disadvantage of saxagliptin for the outcome “hospitalization due to cardiac failure”
- no disadvantage of saxagliptin regarding further outcomes of cardiovascular morbidity
- no advantage of saxagliptin regarding cardiovascular morbidity

- a disadvantage of saxagliptin for the outcome “symptomatic hypoglycaemia”; no conclusion was possible for the outcome “severe hypoglycaemia” because there was no analysis in a valid operationalization

2.2 Research question

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

- **Combination of saxagliptin and metformin:** when metformin monotherapy, with diet and exercise, does not provide adequate glycaemic control;
- **Combination of saxagliptin and sulfonylurea:** in patients for whom use of metformin is considered inappropriate, when sulfonylurea monotherapy, with diet and exercise, does not provide adequate glycaemic control;
- **Combination of saxagliptin and insulin with or without metformin:** when treatment with insulin with or without metformin, alone, with diet and exercise, does not provide adequate glycaemic control;
- **Combination of saxagliptin and metformin and sulfonylurea:** when treatment with metformin plus sulfonylurea alone, with diet and exercise, does not provide adequate glycaemic control.

Moreover, saxagliptin is also approved in combination with glitazones. This subindication is not subject of this assessment because glitazones for the treatment of type 2 diabetes mellitus are excluded from prescription [3].

Saxagliptin is also approved as monotherapy. Since the benefit assessment on saxagliptin as monotherapy was discontinued by the G-BA by decision of 17 April 2014, this subindication is also not subject of this assessment [4].

The assessment was conducted for 4 research questions versus the appropriate comparator therapy (ACT) specified by the G-BA. These research questions are shown in Table 4.

Table 4: Research questions of the benefit assessment of saxagliptin

Research question	Subindication	Appropriate comparator therapy ^a
A	Saxagliptin plus metformin	Metformin plus sulfonylurea (glibenclamide, glimepiride)
B	Saxagliptin plus sulfonylurea	human insulin in combination with a sulfonylurea (glibenclamide, glimepiride), if applicable only treatment with human insulin
C	Saxagliptin plus insulin with or without metformin	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>
D	Saxagliptin plus metformin plus sulfonylurea	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 all research questions.

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

The present benefit assessment was conducted for all 4 research questions in comparison with the ACTs specified by the G-BA. For research questions A and B, 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. This concurs with the company's inclusion criteria.

Study SAVOR-TIMI 53

The company presented analyses of the SAVOR-TIMI 53 study for all 4 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) [5].

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 to 2.6 on the research questions A to D 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 was assessed due to its importance for the therapeutic indication of type 2 diabetes mellitus overall (see Appendix A of the full dossier assessment).

2.3 Research question A: saxagliptin plus metformin

2.3.1 Information retrieval and study pool

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) [5]. The company had already presented the studies D1680C00001 and D1680L00002 for the first assessment of saxagliptin (A13-01) [9]. 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 A13-01 and addendum A13-14 (addendum to the assessment of saxagliptin/metformin). In the current dossier, the company presented no new data on the 2 studies. All relevant information can therefore be found in dossier assessment A13-01 [9], addendum A13-14 [10], and in the G-BA decision on the first assessment of saxagliptin [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 an 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 the full dossier assessment.

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 in the dual combination with metformin). For research question A, the company therefore selected patients who had only been pretreated with metformin from the study population of the SAVOR-TIMI 53 study. From these patients, the company excluded the following patient groups for both treatment groups due to their creatinine clearance value:

- patients with a creatinine clearance of < 45 mL/min because metformin is contraindicated in patients with severe renal impairment [12]
- patients with a creatinine clearance of ≥ 50 mL/min and < 60 mL/min because these patients were treated with a saxagliptin dose of 5 mg daily in the study, which is not in compliance with the approval
- patients with a creatinine clearance of ≥ 45 mL/min and < 50 mL/min who received a metformin dose of more than 1000 mg daily (according to the approval requirement of metformin [12])

As a result, almost all patients with a creatinine clearance of < 60 mL/min were actually excluded. 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 plus metformin with the ACT (metformin plus sulfonyleurea) 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 sulfonyleureas (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 (sulfonyleurea) in the intervention arm. In the placebo group, the company chose those patients who had received additional sulfonyleureas as part of their concomitant antidiabetic medication within 3 months after randomization to placebo. The company considered this to "imitate a direct randomization" to sulfonyleurea.

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 1299 patients from the saxagliptin group (15.7%) and 39 patients from the placebo group (0.5%).
- 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 8.4% in the subpopulation of the placebo group. The mean fasting plasma glucose levels at the start of the study also differed between the saxagliptin group with 142.3 mg/dL and the subpopulation of the placebo group with 171.5 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

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 the combination of saxagliptin and metformin for adults with type 2 diabetes mellitus with inadequate glycaemic control under metformin monotherapy alone in comparison with the ACT. An added benefit of saxagliptin is therefore not proven.

2.3.3 Extent and probability of added benefit

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

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

Additional information: results from the SAVOR-TIMI 53 study

The company presented an analysis of the SAVOR-TIMI 53 study, referring both to research question A and to the total population of the study. The analysis of the study relating to the research questions was unsuitable for the benefit assessment because structural equality of the comparator groups chosen by the company was not ensured. The results of the total population of the SAVOR-TIMI 53 study were also unsuitable for conclusions on research question A because it did not consider the target population relevant for research question A and the ACT.

The results of the SAVOR-TIMI 53 study for the use of saxagliptin versus placebo, each in addition to antidiabetic "standard treatment", showed:

- no disadvantage of saxagliptin regarding all-cause mortality or cardiovascular mortality
- no advantage of saxagliptin regarding all-cause mortality or cardiovascular mortality
- a disadvantage of saxagliptin for the outcome "hospitalization due to cardiac failure"
- no disadvantage of saxagliptin regarding further outcomes of cardiovascular morbidity
- no advantage of saxagliptin regarding cardiovascular morbidity
- a disadvantage of saxagliptin for the outcome "symptomatic hypoglycaemia"; no conclusion was possible for the outcome "severe hypoglycaemia" because there was no analysis in a valid operationalization

2.4 Research question B: saxagliptin plus sulfonylurea

2.4.1 Information retrieval and study pool

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)
- bibliographical literature search on the ACT (last search on 11 April 2016)
- search in trial registries for studies on the ACT (last search on 13 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, on the one hand, identified the SAVOR-TIMI 53 study (D1680C00003 [5]).

On the other, the company identified 2 studies for an indirect comparison: study CV181040 [13] (saxagliptin versus placebo) and study Tovi 1998 [14] (sulfonylurea versus placebo). Together with 4 other studies on the ACT, the company had already presented these 2 studies for the first assessment of saxagliptin. Based on this, the company had conducted an indirect comparison, which was irrelevant for the benefit assessment. The indirect comparison now presented on the basis of the studies CV181040 and Tovi 1998 was also unsuitable because the CV181040 study did not investigate the target population (see dossier assessment A13-01 [9]).

Study SAVOR-TIMI 53

The company included the SAVOR-TIMI 53 study for the direct comparison of saxagliptin plus sulfonylurea with human insulin plus sulfonylurea. The study is described in detail in Section 2.3.1 and in Appendix A of the full dossier assessment.

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 in the dual combination with sulfonylurea). For research question B, the company therefore selected patients who had only been pretreated with sulfonylurea from the study population of the SAVOR-TIMI 53 study. Of these patients, the company excluded all patients with a creatinine clearance of ≥ 50 mL/min and

< 60 mL/min for both treatment groups because in the study these patients received saxagliptin in a dose (5 mg/day) that is not approved for patients with this grade of renal insufficiency. In addition, the company stated that it had excluded patients with contraindications to sulfonylurea. It was not clear from the company's documents how many and which patients were affected. 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 sulfonylurea pretreatment concurs with the target population of research question B. 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 plus sulfonylurea with the ACT (human insulin plus sulfonylurea [glibenclamide, glimepiride]; if applicable only human insulin) 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 insulin (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 (human insulin plus sulfonylurea, if applicable only human insulin) in the intervention arm. In the placebo group, the company considered those patients who had received additional insulin with or without sulfonylurea as part of their concomitant antidiabetic medication within 3 months after randomization to placebo. From the company's point of view, this imitated a direct randomization to insulin with or without 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 B included 396 patients from the saxagliptin group (4.8%) and 9 patients from the placebo group (0.01%).
- 2) The HbA1c and fasting glucose levels at the start of the study proved that there was in fact no structural equality between the comparator groups of the company: The mean HbA1c value at the start of the study was 7.7% for the subpopulation of the saxagliptin group and 8.3% in the subpopulation of the placebo group. The mean fasting plasma glucose levels at the start of the study also differed between the saxagliptin group with 154.4 mg/dL and the placebo group with 184.3 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 insulin to be unsuitable or not necessary. From the placebo group, however, only patients were chosen who received insulin 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 patients in the placebo arm who received additional insulin with or without sulfonylurea 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 B received insulin directly after randomization.

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

Indirect comparison

The company conducted an adjusted indirect comparison of saxagliptin plus sulfonylurea versus insulin plus sulfonylurea or insulin monotherapy. As in the first assessment of saxagliptin, the company used the studies CV181040 and Tovi 1998 for this indirect comparison. The indirect comparison was already assessed in dossier assessment A13-01; it was unsuitable for the benefit assessment of saxagliptin (research question B). A detailed explanation can be found in dossier assessment A13-01.

Summary

Overall, no relevant data were available for assessing the added benefit of saxagliptin plus sulfonylurea versus the ACT, neither for a direct comparison nor for an indirect comparison.

2.4.2 Results on added benefit

The company presented no data suitable for the benefit assessment for research question B, neither for a direct comparison nor for an indirect comparison. The indirect comparison of studies from the first assessment A13-01 presented again provided no new findings for the present 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 the combination of saxagliptin and sulfonylurea for adults with type 2 diabetes mellitus with inadequate glycaemic control under sulfonylurea monotherapy for whom use of metformin seems inadequate in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

Based on the data presented by the company, the added benefit of saxagliptin plus sulfonylurea is not proven in patients with inadequate glycaemic control under sulfonylurea monotherapy for whom use of metformin seems inadequate.

This deviates from the company's assessment, which derived a hint of a considerable added benefit of the combination of saxagliptin and sulfonylurea.

2.5 Research question C: saxagliptin plus insulin with or without metformin

2.5.1 Information retrieval and study pool

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 C: study CV181057 [15,16] and the study SAVOR-TIMI 53 (D1680C00003) [5]. The company had already presented the CV181057 study for benefit assessment A13-01 [15]. The company newly submitted the SAVOR-TIMI 53 study with the current dossier.

Study CV181057

The CV181057 study was already assessed in dossier assessment A13-01. It was not relevant for the present benefit assessment (research question C). 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 A13-01.

Study of direct comparison 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 the full dossier assessment.

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 C (saxagliptin in combination with insulin with or without metformin). For research question C, the company therefore initially selected patients who had only been pretreated with insulin and metformin from the study population of the SAVOR-TIMI 53 study. From these patients, the company excluded the following patient groups for both treatment groups due to their creatinine clearance value:

- patients without moderate or severe impairment of renal function (creatinine clearance of < 45 mL/min)
- patients with a creatinine clearance of ≥ 50 mL/min and < 60 mL/min because in the study these patients received saxagliptin in a dose (5 mg/day) that is not approved for patients with this grade of renal insufficiency
- patients with a creatinine clearance of ≥ 45 mL/min and < 50 mL/min receiving a metformin dose of more than 1000 mg/day (according to the approval requirement of metformin [12])

As a result, almost all patients with a creatinine clearance of < 60 mL/min were actually excluded.

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

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 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 with or without metformin alone are the target population of research question C. 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 concomitant 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 383 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. 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 the full dossier assessment). 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 54% in the saxagliptin group and about 56% 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 (and hence not with the target population of research question C) because the requirement of treatment escalation is a prerequisite for the use of saxagliptin [17].

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 (research question C).

2.5.2 Results on added benefit

The company presented no data suitable for the benefit assessment for research question C. The CV181057 study from the first assessment A13-01 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 C 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 the combination of saxagliptin plus insulin (with or without metformin) for adults with type 2 diabetes mellitus with inadequate glycaemic control under insulin (with or without metformin) in comparison with the ACT. An added benefit is therefore not proven.

2.5.3 Extent and probability of added benefit

Based on the data presented by the company, the added benefit of saxagliptin plus insulin (with or without metformin) is not proven for patients with inadequate glycaemic control with insulin (with or without metformin).

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

2.6 Research question D: saxagliptin plus metformin plus sulfonyleurea

2.6.1 Information retrieval and study pool

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)
- bibliographical literature search on the ACT (last search on 4 April 2016)
- search in trial registries for studies on the ACT (last search on 12 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, on the one hand, identified the SAVOR-TIMI 53 study (D1680C00003 [5]).

On the other, the company identified a study for an indirect comparison, study D1680L00006 [18] (saxagliptin plus metformin plus sulfonyleurea versus placebo plus metformin plus sulfonyleurea). The company had already presented this study and an indirect comparison based on it for the first assessment of saxagliptin. This was irrelevant for the benefit assessment because the studies on the ACT were unsuitable.

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 the full dossier assessment.

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 D (saxagliptin in the triple combination with metformin and sulfonyleurea). For research question D, the company therefore selected patients who had only been pretreated with metformin and a sulfonyleurea from the study population of the SAVOR-TIMI 53 study. From these patients, the company excluded the following patient groups for both treatment groups due to their creatinine clearance value:

- patients with a creatinine clearance of ≥ 50 mL/min and < 60 mL/min because in the study these patients received saxagliptin in a dose (5 mg/day) that is not approved for patients with this grade of renal insufficiency [17]
- patients with a creatinine clearance of ≥ 45 mL/min and < 50 mL/min receiving a metformin dose of more than 1000 mg/day (according to the approval requirement of metformin [12])

As a result, almost all patients with a creatinine clearance of < 60 mL/min were actually excluded. In addition, the company stated that it had also excluded patients with contraindications to sulfonylurea or 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 and sulfonylurea pretreatment concurs with the target population of research question D. 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 plus metformin plus sulfonylurea with the ACT (human insulin plus metformin; if applicable only human insulin) 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 insulin (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 (human insulin plus metformin, if applicable only human insulin) in the intervention arm. In the placebo group, the company aimed to only consider those patients who had switched treatment from sulfonylurea to insulin as part of their concomitant antidiabetic treatment within 3 months after randomization. The company considered this to "imitate a direct randomization" to insulin plus metformin. According to the company, these patients were not included in the placebo group, which is why there were no results for the planned comparison. The company therefore concluded that no comparison with the ACT specified by the G-BA was possible for the present research question.

Irrespective of the company's arguments, structural equality between the comparator groups would not have been maintained because of the approach of the patient selection chosen by the company.

In summary, there were no relevant data for the assessment of the added benefit of saxagliptin plus metformin plus sulfonylurea.

Indirect comparison

Since no data from randomized studies of direct comparisons were available, the company aimed at an adjusted indirect comparison. The company included the placebo-controlled D1680L00006 study and the SAVOR-TIMI 53 study for saxagliptin [5,18]. The company chose metformin plus sulfonylurea as common comparator. However, the company identified no study comparing the ACT with the common comparator. Hence no indirect comparison could be conducted. The D1680L00006 study is therefore not described.

Summary

Overall, no relevant data were available for assessing the added benefit of saxagliptin plus metformin plus sulfonylurea versus the ACT human insulin plus metformin (if applicable only human insulin), neither for a direct comparison nor for an indirect comparison.

2.6.2 Results on added benefit

The company presented no data suitable for the benefit assessment for research question D.

There was no hint of an added benefit of the combination of saxagliptin plus metformin plus sulfonylurea for adults with type 2 diabetes mellitus with inadequate glycaemic control under a combination of metformin and sulfonylurea in comparison with the ACT. An added benefit is therefore not proven.

2.6.3 Extent and probability of added benefit

The company presented no suitable data for the assessment of the added benefit of saxagliptin plus metformin plus sulfonylurea in patients with inadequate glycaemic control under a combination therapy of metformin and sulfonylurea. Hence an added benefit of saxagliptin plus metformin is not proven for these patients.

This is in accordance with the assessment of the company.

2.7 Extent and probability of the added benefit – summary

An overview of the extent and probability of added benefit for the different subindications of saxagliptin in comparison with the respective relevant ACT is given below.

Table 5: Saxagliptin – extent and probability of added benefit

Research question	Subindication	ACT ^a	Extent and probability of added benefit
A	Saxagliptin plus metformin	Metformin plus sulfonylurea (glibenclamide or glimepiride)	Added benefit not proven
B	Saxagliptin plus sulfonylurea	human insulin in combination with a sulfonylurea (glibenclamide, glimepiride), if applicable only treatment with human insulin	Added benefit not proven
C	Saxagliptin 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
D	Saxagliptin plus metformin plus sulfonylurea	Human insulin plus metformin (note: treatment only with human insulin if metformin is not sufficiently effective)	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			

This assessment deviates from that of the company for research questions A, B and C. The company claimed proof of considerable added benefit for research question A (saxagliptin plus metformin), a hint of considerable added benefit for research question B (saxagliptin plus sulfonylurea), and an indication of a minor added benefit for research question C (saxagliptin plus insulin with or without metformin).

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22.04.2015 [Accessed: 01.06.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.
2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. *Biom J* 2015; 58(1): 43-58
3. Bundesministerium für Gesundheit. Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL); Anlage III: Übersicht der Verordnungseinschränkungen und -ausschlüsse Glitazone zur Behandlung des Diabetes mellitus Typ 2. *Bundesanzeiger* 2010; 62(175): 3855.
4. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über die Einstellung der Nutzenbewertung von Arzneimitteln im Bestandsmarkt [online]. 17.04.2014 [Accessed: 01.12.2015]. URL: https://www.g-ba.de/downloads/39-261-1976/2014-03-17_35a_EinstellungBestandsmarkt_BAnz.pdf.
5. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013; 369(14): 1317-1326.
6. Göke B, Gallwitz B, Eriksson J, Hellqvist A, Gause-Nilsson I. Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. *Int J Clin Pract* 2010; 64(12): 1619-1631.
7. Göke B, Gallwitz B, Eriksson JG, Hellqvist A, Gause-Nilsson I. Saxagliptin vs. glipizide as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: long-term (52-week) extension of a 52-week randomised controlled trial. *Int J Clin Pract* 2013; 67(4): 307-316.
8. Schernthaner G, Duran-Garcia S, Hanefeld M, Langslet G, Niskanen L, Östgren CJ et al. Efficacy and tolerability of saxagliptin compared with glimepiride in elderly patients with type 2 diabetes: a randomized, controlled study (GENERATION). *Diabetes Obes Metab* 2015; 17(7): 630-638.
9. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Saxagliptin: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A13-01 [online]. 27.06.2013 [Accessed: 05.07.2013]. (IQWiG-Berichte; Volume 174). URL: https://www.iqwig.de/download/A13-01_Saxagliptin_Nutzenbewertung-35a-SGB-V.pdf.

10. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Addendum zum Auftrag A12-16 (Saxagliptin/Metformin): Auftrag A13-14 [online]. 12.04.2013 [Accessed: 03.05.2013]. (IQWiG-Berichte; Volume 161). URL: https://www.iqwig.de/download/A13-14_Addendum-zum-Auftrag-A12-16_Saxagliptin-Metformin.pdf.
11. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL); Anlage XII: Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Saxagliptin [online]. 01.10.2013 [Accessed: 07.12.2015]. URL: https://www.g-ba.de/downloads/40-268-2521/2013-10-01_AM-RL-XII_Saxagliptin_TrG.pdf.
12. Merck. Glucophage 500 mg/- 850 mg/- 1000 mg Filmtabletten: Fachinformation [online]. 02.2015. URL: <http://www.fachinfo.de>.
13. Chacra AR, Tan GH, Apanovitch A, Ravichandran S, List J, Chen R. Saxagliptin added to a submaximal dose of sulphonylurea improves glycaemic control compared with uptitration of sulphonylurea in patients with type 2 diabetes: a randomised controlled trial. *Int J Clin Pract* 2009; 63(9): 1395-1406.
14. Tovi J, Engfeldt P. Well-being and symptoms in elderly type 2 diabetes patients with poor metabolic control: effect of insulin treatment. *Pract Diabetes Int* 1998; 15(3): 73-77.
15. Barnett AH, Charbonnel B, Donovan M, Fleming D, Chen R. Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. *Curr Med Res Opin* 2012; 28(4): 513-523.
16. Barnett AH, Charbonnel B, Li J, Donovan M, Fleming D, Iqbal N. Saxagliptin add-on therapy to insulin with or without metformin for type 2 diabetes mellitus: 52-week safety and efficacy. *Clin Drug Investig* 2013; 33(10): 707-717.
17. AstraZeneca. Onglyza 2,5 mg/5 mg Filmtabletten: Fachinformation [online]. 10.2015. URL: <http://www.fachinfo.de>.
18. Moses RG, Kalra S, Brook D, Sockler J, Monyak J, Visvanathan J et al. A randomized controlled trial of the efficacy and safety of saxagliptin as add-on therapy in patients with type 2 diabetes and inadequate glycaemic control on metformin plus a sulphonylurea. *Diabetes Obes Metab* 2014; 16(5): 443-450.

The full report (German version) is published under <https://www.iqwig.de/en/projects-results/projects/drug-assessment/a16-42-saxagliptin-benefit-assessment-according-to-35a-social-code-book-v.7520.html>.