IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A13-01

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

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment "Saxagliptin – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 27 June 2013). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

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

Contracting agency:
Federal Joint Committee

Commission awarded on:
28 March 2013

Internal Commission No.:
A13-01

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

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

Medical and scientific advice:

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

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

IQWiG employees involved in the dossier assessment:[2]

- Natalia Wolfram
- Katharina Biester
- Ulrich Grouven
- Elke Hausner
- Thomas Kaiser
- Stefan K. Lhachimi
- Kerstin Staeck
- Min Zhou

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

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

Table of contents

List of tables[3]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BfArM	*Bundesinstitut für Arzneimittel und Medizinprodukte* (Federal Institute for Drugs and Medical Devices)
DPP-4	dipeptidyl peptidase 4
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
IR	immediate release
OAD	oral antidiabetic drug
RCT	randomized controlled trial
SGB	*Sozialgesetzbuch* (Social Code Book)
SPC	Summary of Product Characteristics
XR	extended release

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 benefit assessment formed part of the assessment of the established drug market of gliptins, which was commissioned by the G-BA on 7 June 2012. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 28 March 2013.

Research question

The benefit assessment of saxagliptin was conducted according to the approval for the following therapeutic indication: treatment of adult patients with type 2 diabetes mellitus.

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

According to the company's consultation request to the G-BA, an appropriate comparator therapy (ACT) was specified for each of the subindications. This benefit assessment concurs with the G-BA's specifications.

Table 2: Overview of the ACT for saxagliptin

Research question[a]	Subindication	ACT specified by the G-BA
A	Saxagliptin plus metformin	Metformin plus sulfonylurea (glibenclamide, glimepiride)[b]
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 (note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)
D	Saxagliptin plus metformin plus sulfonylurea	Human insulin plus metformin (note: treatment only with human insulin if metformin is not sufficiently effective)

a: Designation corresponds to the coding in the company's dossier.
b: According to the commission by the G-BA, direct comparative studies versus glipizide were to be additionally assessed.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The company specified additionally an alternative ACT for each of the 4 subindications. The corresponding assessments were not considered any further in this dossier assessment because the company's rationales were not accepted.

Results

The company did not provide any relevant studies versus the ACTs for any of the research questions considered.

Combination of saxagliptin plus metformin

One direct comparative study (D1680L00002) was identified for the comparison of saxagliptin plus metformin versus the ACT specified by the G-BA (research question A1). One direct comparative study (D1680C00001) was available for the comparison of saxagliptin plus metformin versus glipizide plus metformin (research question A2). These 2 studies were already presented by the company for the fixed combination saxagliptin/metformin and assessed (assessment A13-14). No new aspects resulted from the data presented by the company for the present assessment, so the Institute in principle refers to the assessment A13-14.

Combination of saxagliptin plus sulfonylurea

The company presented an adjusted indirect comparison of saxagliptin plus sulfonylurea versus the ACT. On the saxagliptin side, the company included a placebo-controlled study (CV181040). On the comparator side, the company included 5 studies, which were relevant from the company's point of view (Shank 1995, Birkeland 1994, Tovi 1998, Nathan 1999 and Turner 1998). In 4 out of the 6 studies (CV181040, Birkeland 1994, Nathan 1999 and Turner 1998), an unsuitable patient population was studied (no patients with inadequate glycaemic control under a maximum tolerated dose of sulfonylurea). Moreover, the following reasons in particular were against the usability of the studies:

- In 2 studies (CV181040 and Turner 1998), patients had neither a contraindication nor an intolerance of metformin.
- The relevant study phase in the study Shank 1995 was only 3 months, and was therefore too short.
- With regards to content, the intermediate comparator of the studies Shank 1995 and Birkeland 1994 was not comparable with the one of the study CV181040.

Combination of saxagliptin plus insulin with or without metformin

The company presented 2 direct comparative studies (CV181057 [also presented already for the fixed combination saxagliptin/metformin, see dossier assessment A12-16] and D1680C00007). Both studies were unsuitable for assessing the added benefit, as in the studies it was prohibited to adjust the insulin therapy to individual necessities in the first treatment phase, particularly in the comparator groups. The therapy from the first treatment phase was continued in the second study phase. But in contrast to the first treatment phase, the insulin dosage in the studies could be changed individually in both treatment arms. It remained unclear for both studies according to which criteria a change to a different type of insulin was performed, and whether changing the type of insulin and, if necessary, the insulin regimen,

was accompanied by an adequate patient education course. Moreover, because at this point the patients in the intervention arm in both studies had already been treated with saxagliptin, while the patients in the comparator arm had received no optimization of their prior treatment, the intervention and control groups of both studies no longer had the same conditions when the second phase started. Overall, the results of the second treatment phases and thus the entire studies could also not be used for assessing the added benefit.

Regardless of this, the data on study D1680C00007 presented by the company would not have been relevant because the company did not consider the approval status of saxagliptin and the research question adequately. On the one hand, saxagliptin is not approved for patients with end-stage renal impairment (approximately 23% of the patients in the study had end-stage renal impairment). On the other hand, some the patients were partially treated with oral antidiabetics (OADs) (other than metformin) in addition to saxagliptin and insulin (approximately 27% of the patients), which was not in compliance with the approval of saxagliptin and therefore did not concur with the present research question.

Combination of saxagliptin plus sulfonylurea plus metformin

The company presented an adjusted indirect comparison of saxagliptin plus sulfonylurea plus metformin versus the ACT. On the saxagliptin side, the company included a placebo-controlled study (D1680L00006). On the comparator side, the company included 3 studies, which were relevant from the company's point of view. In all 3 studies, the suitable patient population was not studied (no patients with inadequate glycaemic control under a maximum tolerated dose of both metformin and sulfonylurea). They were also too short (study duration of < 24 weeks). Optimization of the insulin therapy in the comparator group was not possible or only possible to a limited extent. Moreover, the following reasons in particular were against the usability of the 3 studies:

- Calle-Pascuale 1995 was a non-RCT, in which metformin was only used in a sub-maximum dose (850 mg a day).
- In Kavapil 2006 and Malone 2003, the sulfonylurea was neither used according to its approval nor in the same way as in the saxagliptin study.

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

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

Table 3: Saxagliptin – extent and probability of added benefit

Research question	Subindication	Comparator therapy	Extent and probability of added benefit
A1	Saxagliptin plus metformin	Metformin plus sulfonylurea (glibenclamide or glimepiride)	Added benefit not proven
A2	Saxagliptin plus metformin	Metformin plus glipizide[a]	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: According to the commission by the G-BA, the added benefit of saxagliptin plus metformin vs. glipizide plus metformin was also assessed.
G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics; vs.: versus

As the added benefit is not proven for any subindication, there are also no patient groups for whom a therapeutically important added benefit could be derived.

The G-BA decides on added benefit.

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

2.2 Research questions

Saxagliptin is indicated in adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control. The benefit assessment of saxagliptin was conducted according to the approval status [3] for the following subindications:

- **Combination of saxagliptin plus metformin:** when metformin alone, with diet and exercise, does not provide adequate glycaemic control;
- **Combination of saxagliptin plus sulfonylurea:** in patients for whom use of metformin is considered inappropriate, when the sulfonylurea alone, with diet and exercise, does not provide adequate glycaemic control;
- **Combination of saxagliptin plus 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 plus metformin plus 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 [3]. This subindication is not subject of this assessment because glitazones for the treatment of type 2 diabetes mellitus are excluded from prescription [4].

According to the company's consultation request to the G-BA, an ACT was specified for each of the 4 subindications cited above. These are shown in Table 4 presented below.

Table 4: Overview of the ACT for saxagliptin

Research question[a]	Subindication	ACT specified by the G-BA
A	Saxagliptin plus metformin	Metformin plus sulfonylurea (glibenclamide, glimepiride)[b]
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 (note: treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)
D	Saxagliptin plus metformin plus sulfonylurea	Human insulin plus metformin (note: treatment only with human insulin if metformin is not sufficiently effective)

a: Designation corresponds to the coding in the company's dossier.

b: According to the commission by the G-BA, direct comparative studies versus glipizide were to be additionally assessed.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

Combination of saxagliptin plus metformin (research question A)

The ACT specified by the G-BA "metformin plus sulfonylureas (glibenclamide, glimepiride)" was used for this subindication. According to the commission by the G-BA, the added benefit of saxagliptin versus glipizide was also assessed. In this benefit assessment, the added benefit of saxagliptin was therefore assessed versus the following comparator therapies:

- **Research question A1:** ACT specified by the G-BA (metformin plus sulfonylurea [glimepiride or glibenclamide])
- **Research question A2:** glipizide plus metformin

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

This approach deviated from that of the company. On the one hand, it defined an additional patient group for whom sulfonylureas are unsuitable. This patient population cited by the company was seen as a not clearly definable subpopulation in the therapeutic indication and was not considered in this benefit assessment. Further information can be found in the benefit assessment of the fixed combination saxagliptin/metformin (coding A) [8]. The same company did not present any additional relevant arguments in the dossier presented (see Section 2.8.2.1 of the full dossier assessment).

On the other hand, the company cited the combination of metformin plus sulfonylurea as ACT, but without limitation to the drugs glibenclamide and glimepiride specified by the G-BA. The company pointed out that the added benefit should be derived on the basis of an approval study, in which the sulfonylurea glipizide had been used. According to the commission by the G-BA, however, it is additionally investigated in this assessment whether there is proof of an added benefit of saxagliptin plus metformin versus a comparator therapy "metformin plus glipizide" (assessment of direct comparative studies only).

Combination of saxagliptin plus sulfonylurea (research question B)

The ACT specified by the G-BA "human insulin in combination with a sulfonylurea (glibenclamide, glimepiride), if applicable only treatment with human insulin" was used for this subindication.

This approach deviated from that of the company. On the one hand, the company defined an additional patient group for whom insulin is not yet indicated. The company did not provide further characteristics of this population, however. This patient population was seen as a not clearly definable subpopulation in the therapeutic indication and was not considered in this benefit assessment. Further information can be found in the benefit assessment of

dapagliflozin (coding C) [10]. The same company did not provide any additional relevant arguments in the dossier presented (see also Section 2.8.3.1 of the full dossier assessment).

On the other hand, the company cited a combination of metformin plus sulfonylureas as ACT, but without limitation to the drugs glibenclamide and glimepiride.

Combination of saxagliptin plus insulin with or without metformin (research question C)

The ACT specified by the G-BA "human insulin plus metformin (if applicable, treatment only with human insulin if metformin is not tolerated according to the SPC or not sufficiently effective)" was used for this subindication.

This approach deviated from that of the company. The company defined an additional patient group, for whom insulin dose escalation had to be avoided, but did not provide further characteristics of this population. This patient population was seen as a not clearly definable subpopulation in the therapeutic indication and was not considered in this benefit assessment. Further information can be found in the benefit assessment of dapagliflozin (coding D) [10]. The same company did not provide any additional arguments in the dossier presented (see Section 2.8.4.1 of the full dossier assessment).

Combination of saxagliptin plus metformin plus sulfonylurea (research question D)

The ACT specified by the G-BA "human insulin plus metformin (if applicable, treatment only with human insulin if metformin is not sufficiently effective)" was used for this subindication.

The company additionally cited a combination therapy consisting of metformin and sulfonylurea plus another dipeptidyl peptidase 4 (DPP-4) inhibitor as alternative comparator therapy. This patient population cited by the company was seen as a not clearly definable subpopulation in the therapeutic indication and was not considered in this benefit assessment. Further information can be found in Section 2.8.5.1 of the full dossier assessment.

Summary

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

Further information about the research question can be found in Module 3A – 3D, Section 3.1 and Module 4A – 4D, Section 4.2.1 of the dossier, and in Sections 2.8.1, 2.8.2.2, 2.8.3.2, 2.8.4.2 and 2.8.5.2 of the full dossier assessment.

2.3 Research question A: combination of 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 plus metformin (studies completed up to 21 January 2013)
- Bibliographical literature search on saxagliptin plus metformin (last search 4 February 2013)
- Search in trial registries for studies on saxagliptin plus metformin (last search 21 January 2013)
- Bibliographical literature search to identify systematic reviews with cerebral and cardiac outcomes. However, the studies identified were unsuitable for proving an added benefit versus the ACT specified by the G-BA. This search could therefore not be used (see comment in Sections 2.8.2.4.1 and 2.8.2.8 of the full dossier assessment).

The Institute's own search:

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

The company targeted its information retrieval towards its definition of the ACT (metformin plus sulfonylurea without limitation to glibenclamide and glimepiride). Corresponding to its research question, its study pool included 2 studies that tested the combination of saxagliptin plus metformin with a treatment consisting of metformin plus glibenclamide (study D1680L00002) or metformin plus glipizide (study D1680C00001). These studies were presented and assessed separately, according to the research questions of this benefit assessment.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4A, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.8.2.2 and 2.8.2.4.1 of the full dossier assessment.

2.3.2 Research question A1: comparison of saxagliptin plus metformin versus metformin plus sulfonylurea (glimepiride or glibenclamide)

2.3.2.1 Study pool

One direct comparative study (comparison of saxagliptin plus metformin versus glimepiride plus metformin, study D1680L00002 [11,12]) was identified from the steps of information retrieval mentioned in Section 2.3.1. This study was already presented by the company for the

fixed combination saxagliptin/metformin and assessed in the addendum A13-14 [13]. No new aspects resulted from the data presented by the company for this assessment, so the Institute in principle refers to the assessment A13-14. The tables on study design (Table 16), on the interventions used in the study (Table 17), on the study population (Table 18) and on the results (Table 19) are presented in Appendix A of the full dossier assessment, however, because only a subpopulation of the study was to be considered for the fixed combination saxagliptin/metformin. No fundamental changes result from considering the total population however.

Further information about the result of information retrieval, the resulting study pool, the study design, populations and results can be found in Module 4A, Sections 4.3.1.1, 4.3.1.2.1 and Appendix 4-F of the dossier and in Section 2.8.2.4.2 of the full dossier assessment.

2.3.2.2 Results on added benefit

No relevant data were available for saxagliptin plus metformin, research question A1. Hence the added benefit versus the ACT specified by the G-BA (metformin plus sulfonylurea [glibenclamide, glimepiride]) is not proven.

2.3.2.3 Extent and probability of added benefit

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of saxagliptin plus metformin in comparison with the ACT specified by the G-BA (metformin plus sulfonylurea [glibenclamide, glimepiride]). Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This result deviates from that of the company, which derived an added benefit in comparison with glipizide by taking into consideration results of an additional study.

Further information about the extent and probability of the added benefit can be found in Module 4A, Section 4.4 of the dossier and in Section 2.8.2.9.2 of the full dossier assessment.

2.3.3 Research question A2: comparison of saxagliptin plus metformin versus metformin plus glipizide

2.3.3.1 Study pool

One direct comparative study (comparison of saxagliptin plus metformin versus glipizide plus metformin, study D1680C00001 [14-17]) was identified from the steps of information retrieval mentioned in Section 2.3.1. This study was already presented by the company for the fixed combination saxagliptin/metformin and assessed in the addendum A13-14 [13]. No new aspects resulted from the data presented by the company for this assessment, so the Institute in principle refers to the assessment A13-14. It is to be noted, however, that the algorithm used in the study for finding the dose of metformin (reduction of the metformin dose at the start of the study, see Table 21 of the full dossier assessment) resulted in patients being treated with a reduced metformin dose in the study although a higher dose had obviously been tolerated before. According to this scheme, the dose was generally reduced in patients with a metformin dose of up to 2499 mg. The proportion of patients in whom such a dose reduction

was conducted, was therefore potentially higher in the total population than in the subpopulation relevant for the fixed combination because the dose range 1500 to 1999 was not relevant for the assessment of the fixed combination.

The tables on study design (Table 20), on the interventions used in the study (Table 21), on the study population (Table 22) and on the results (Table 23) are presented in Appendix B of the full dossier assessment because only a subpopulation of the study was to be considered for the fixed combination saxagliptin/metformin.

Further information about the result of information retrieval, the resulting study pool, the study design, populations and results can be found in Module 4A, Sections 4.3.1.1, 4.3.1.2.1 and Appendix 4-F of the dossier and in Section 2.8.2.4.2 of the full dossier assessment.

2.3.3.2 Results on added benefit

No relevant data were available for saxagliptin plus metformin, research question A2. Hence the added benefit versus metformin plus glipizide is not proven.

2.3.3.3 Extent and probability of added benefit

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of saxagliptin plus metformin in comparison with metformin plus glipizide. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This result deviates from that of the company, which derived an added benefit in comparison with glimepiride by taking into consideration results of an additional study.

Further information about the extent and probability of the added benefit can be found in Module 4A, Section 4.4 of the dossier and in Section 2.8.2.9.2 of the full dossier assessment.

2.4 Research question B: combination of 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 plus sulfonylurea (studies completed up to 21 January 2013)
- Bibliographical literature search on saxagliptin plus sulfonylurea (last search 4 February 2013)
- Search in trial registries for studies on saxagliptin plus sulfonylurea (last search 21 January 2013)
- Bibliographical literature search on insulin plus sulfonylurea or insulin monotherapy (last search 7 February 2013)
- Search in trial registries for studies on human insulin plus sulfonylurea or human insulin monotherapy (last search 25 February 2013)

The Institute's own search:

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

No relevant direct comparative study suitable for assessing the added benefit of saxagliptin plus sulfonylurea versus the ACT was identified from the steps of information retrieval mentioned.

The company therefore conducted an adjusted indirect comparison of saxagliptin plus sulfonylurea versus insulin plus sulfonylurea or insulin monotherapy. The company presented 6 studies for this comparison. On the saxagliptin side, the company included the placebo-controlled study CV181040, which was relevant from the company's point of view [18-21]. The company chose sulfonylurea (+ placebo) as intermediate comparator. On the comparator side, the company identified 5 studies, which were relevant from the company's point of view [22-26].

The studies presented by the company were unsuitable for answering the present research question. Table 5 shows the characteristics of the studies.Table 6 displays a description of the interventions or potential intermediate comparators. Table 7 summarizes the reasons for exclusion.

Table 5: Characteristics of the studies included by the company – indirect comparison: saxagliptin plus sulfonylurea vs. human insulin with or without sulfonylurea

Study	Study design	Study duration	Population	
			Type of prior treatment	Criteria for inadequate glycaemic control
CV181040	RCT, double-blind, parallel, multicentre	▪ Screening phase: 2 weeks ▪ Lead-in phase[a]: 4 weeks ▪ Main treatment: 24 weeks ▪ Extension phase: 52 weeks	Adult patients with type 2 diabetes mellitus Prior treatment with a sub-maximal dose[b] of a sulfonylurea for at least 2 months before screening	▪ At screening: HbA1c value ≥ 7.5% and ≤ 10% ▪ At randomization: HbA1c ≥ 7.0% and FPG ≥ 140 mg/dl
Shank 1995	RCT, mono-centre, parallel with open-label observation phase, blinding: no data[c]	▪ Phase I: 2 months, switch to glipizide ▪ Phase II[d]: 3 months	Adult patients with type 2 diabetes mellitus Prior treatment with maximal dose of a sulfonylurea[e]	▪ FPG > 140 mg/dl at least twice during prior treatment ▪ FPG ≤ 280 mg/dl during 2 weeks without treatment with a sulfonylurea
Birkeland 1994	RCT, open-label, parallel, monocentre	▪ Run-in: 3 months ▪ Treatment: 12 months	Adult patients with type 2 diabetes mellitus Prior treatment with diet alone or in combination with glibenclamide (dose 1.75 – 10.5 mg a day, micronized form)	▪ HbA1c 7 – 10%
Tovi 1998	RCT, open-label, parallel, monocentre	12 months	Elderly patients (> 70 years) with type 2 diabetes mellitus Suspected secondary treatment failure during the treatment with high doses of sulfonylureas (7 – 10.5 mg of glibenclamide or 10 – 15 mg of glipizide)	▪ HbA1c > 7.5%
Nathan 1999	RCT, parallel, double-blind, monocentre	9 months	Adult patients with type 2 diabetes mellitus Prior treatment with diet alone for 1 month	▪ HbA1c ≥ 6.5% ▪ FPG ≥ 140 mg/dl
Turner 1998 (UKPDS)	RCT, open-label, multicentre, parallel for the group "primary diet failure"[f]	6 years	Adult patients with newly diagnosed type 2 diabetes mellitus, prior treatment with diet alone for at least 3 months	▪ FPG > 170 mg/dl or persisting hypoglycaemic symptoms

(continued on next page)

Table 5: Characteristics of the studies included by the company – indirect comparison: saxagliptin plus sulfonylurea vs. human insulin with or without sulfonylurea (continuation)

a: The current treatment with a sulfonylurea was discontinued in the lead-in phase. All patients switched to glibenclamide 7.5 mg.

b: The suitable dosage of a sulfonylurea had to be within a range predefined in the study protocol. The allowed daily doses of a selection of sulfonylureas a relevant proportion of patients were pretreated with were as follows: (1) glibenclamide (61.0% of the relevant study population): 3– 9 mg (micronized form) and 5 – 15 mg (nonmicronized form, not approved in Germany); (2) glimepiride (16.3% of the patients): 2 – 6 mg, all of them Institute's calculation. Discrepant data on the proportion of the patients treated with sulfonylureas between CSR on main treatment phase (24 weeks) and extension phase (up to 52 weeks). The patients were also allowed to be treated with other sulfonylureas, data are not shown.

c: Blinding was not described in the publication.

d: Further phases of the study (III and IV) were not relevant because no comparison of the interventions with the comparator glipizide was conducted in these phases.

e: Prior treatment with glipizide was not allowed. No information about which sulfonylureas were used.

f: 3 patient populations were described in the publication: primary diet failure group population, main randomization group population and diet-controlled group population. The company only used one population (primary diet failure group). Only data on the primary diet failure group are therefore presented in this table and the following tables.

CSR: clinical study report; FPG: fasting plasma glucose; RCT: randomized controlled trial; UKPDS: United Kingdom Prospective Diabetes Study; vs.: versus

Table 6: Characteristics of the interventions – indirect comparison: saxagliptin plus sulfonylurea vs. human insulin with or without sulfonylurea

Study	Intervention Number of patients	Intermediate comparator Number of patients
CV181040[a]	▪ Saxagliptin 5 mg a day ▪ Glibenclamide (open-label administration) 7.5 mg ▪ Placebo for glibenclamide (blinded administration) ▪ N = 253	▪ Placebo for saxagliptin ▪ Glibenclamide (open-label administration) 7.5 mg ▪ Glibenclamide 2.5 mg (blinded administration) ▪ N = 267
	Main treatment Target blood glucose level: There was an up-titration of placebo or glibenclamide (blinded administration) in week 2 or 4 of the study, as long as MFPG was ≥ 100mg/dl (or MFWBG ≥ 95mg/dl), and no reduction of glibenclamide (open-label administration) had taken place.	
	Extension phase There was an up-titration of placebo or glibenclamide (blinded administration) of the non-blood-glucose lowering substance placebo if the HbA1c at week 30 was ≥ 7%, glibenclamide (open-label administration) was not down-titrated in the first 24 weeks (main treatment), and the patients had not received rescue medication.	
	Rescue medication From week 4 onwards, additional metformin up to 2500 mg a day could be administered under certain conditions. Then patients had to discontinue the study and entered the extension phase; metformin treatment was continued.	
Shank 1995	▪ Intervention 1: ▫ NPH insulin: 5 units/1.73 m^2. Up-titration to 20 units/1.73 m^2. The insulin had to remain stable after the maximum dose was reached. ▫ N = 10 ▪ Intervention 2: ▫ NPH insulin: 5 units/1.73m^2 + glipizide 20 mg twice a day. Up-titration of NPH insulin: see intervention 1. Glipizide: stable ▫ N = 10	▪ Glipizide: 20 mg twice a day[b] ▪ N = 10
Birkeland 1994	Intermediate acting insulin: initial dose 8 units twice a day ▪ Up-titration of insulin as long as HbA1c ≥ 7.5%, FBG above 126 mg/dl and postprandial blood glucose level above 180 mg/dl ▪ N = 18	Glibenclamide ▪ Up-titration of glibenclamide as long as HbA1c ≥ 7.5%, FBG above 7.0 mmol/l and postprandial blood glucose level above 180 mg/dl avoiding hypoglycaemic events ▪ Maximum daily dose: 10.5 mg ▪ N = 18

(continued on next page)

Table 6: Characteristics of the interventions – indirect comparison: saxagliptin plus sulfonylurea vs. human insulin with or without sulfonylurea (continuation)

Study	Intervention Number of patients	Intermediate comparator Number of patients
Tovi 1998	Insulin[c] ▪ Initial dose: no data ▪ Dose adjustment depending on target blood glucose level 108 – 216 mg/dl during the course of the day ▪ N = 22	Glibenclamide or glipizide: continuation of prior treatment (glibenclamide 7 – 10.5 mg or glipizide 10 – 15 mg) ▪ N = 18, of which: ▫ glibenclamide (n = no data) ▫ glipizide (n = no data)
Nathan 1999	▪ NPH insulin: initial dose 15 units a day. Weekly dose adjustment depending on target blood glucose level (FPG < 6.4 mmol/l) without hypoglycaemia (twice the prior dose was maximally permitted) ▪ Placebo for glimepiride ▪ N = 15	▪ Glibenclamide: initial dose 2.5 mg ▪ Gradual weekly dose adjustment of 5 mg/day maximum, depending on target blood glucose level (FPG < 115 mg/dl) without hypoglycaemia. Maximal dose 10 mg twice a day ▪ Placebo for NPH insulin ▪ N = 16
Turner 1998 (UKPDS)	▪ Chlorpropamide or glibenclamide ▪ Initial dose: no data ▪ Up-titration as long as FPG above 6.0 mmol/l without hypoglycaemia ▪ Maximum daily dose: chlorpropamide 500 mg, glibenclamide 20 mg ▪ Metformin was administered additionally if FPG was ≥ 270 mg/dl on ≥ 2 subsequent visits and under maximum dose of the sulfonylurea ▪ Patients who received both a maximum dose of metformin (2550 mg a day) and a maximum dose of the sulfonylurea, and had FPG ≥ 270 mg/dl on ≥ 2 subsequent visits discontinued treatment and started insulin therapy. ▪ N = 231, of which: ▫ chlorpropamide (n = 107) ▫ glibenclamide (n = 124)	▪ Ultralente insulin ▪ Initial dose and adjustment: no data ▪ Optional additional administration of a soluble insulin 2 or 3 times a day and a mixtures of medium-acting and short-acting insulin twice a day at a blood glucose level of > 126 mg/dl ▪ N = 178

a: The company did not use a third comparator group.

b: It was unclear from the publication whether the dose was 20 mg or 40 mg a day.

c: No information about the type of insulin

FPG: fasting plasma glucose; MFPG: mean fasting plasma glucose; MFWBG: mean fasting whole blood glucose; N: number of randomized patients; n: relevant subpopulation of the company: NPH: neutral protamine Hagedorn; UKPDS: United Kingdom Prospective Diabetes Study; vs.: versus

Table 7: Overview of the reasons for exclusion of the studies – indirect comparison: saxagliptin plus sulfonylurea vs. human insulin with or without sulfonylurea

Study	Reasons for exclusion				
	Population (type of prior treatment)	Study duration	Interventions/ACT	Intermediate comparators	Metformin intolerance or contraindications
Saxagliptin plus sulfonylurea vs. sulfonylurea plus placebo					
CV181040	●		○		●
(Human) insulin (plus sulfonylurea) vs. sulfonylurea					
Shank 1995		●	○	○	○
Birkeland 1994	●			○	○
Tovi 1998			○		
Nathan 1999	●			○	
Turner 1998 (UKPDS)	●				●

●: reason for exclusion; ○: uncertainty
ACT: appropriate comparator therapy; UKPDS: United Kingdom Prospective Diabetes Study; vs.: versus

In 4 out of the 6 studies used by the company (CV181040, Birkeland 1994, Nathan 1999 and Turner 1998), an inappropriate patient population was studied, i.e. no patients with inadequate glycaemic control under a maximum dose of sulfonylurea:

- Patients under a suboptimal dose of a sulfonylurea were generally eligible for participating in the studies CV181040 and Birkeland 1994. After randomization, the glibenclamide dose was up-titrated in both studies. These studies therefore answer the question whether it is better to initiate dual therapy or increase the dose of a sulfonylurea for patients who are in the middle of treatment with a sulfonylurea.
- Patients who were exclusively under prior treatment with diet alone were eligible for participating in the studies Nathan 1988 and Turner 1988.

Furthermore, there were no contraindications or intolerance of metformin in the patients in 2 studies (CV181040 and Turner 1998). Because of the study specification to administer metformin as (rescue) medication, the second approval requirement for saxagliptin ("for whom use of metformin is considered inappropriate") was apparently not met. The publications on 2 other studies (Shank 1995 and Birkeland 1994 [23]) did not provide information on this.

Moreover, the following reasons were against the usability of the studies:

- The relevant study phase in the study Shank 1995 (phase II) was only 3 months, and was therefore too short. This study was therefore unsuitable for the comparison with the study CV181040 with a total duration of 6 months. In addition, the intermediate comparator glipizide was continuously used at maximum dose. It was unclear from the publication whether the glipizide dose was 20 mg or 40 mg a day. Hence the manner of sulfonylurea treatment did not concur with the one used in the study CV181040. In addition, a dosage of 40 mg a day would not be compliant with the approval [7].
- In the study Birkeland 1994, glibenclamide was up-titrated during the course of the study with the maximum dose of glibenclamide being 10.5 mg. By comparison, over 90% of the patients in the intermediate comparator arm of the study CV181040 received 15 mg of glibenclamide. As it is unclear whether the micronized form of glibenclamide was used in the study CV181040, no final conclusions can be drawn on the comparability of the intermediate comparator.

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.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4B, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.8.3.2 and 2.8.3.4.1 of the full dossier assessment. Further information about the result of information retrieval and the resulting study pool can be found in Module 4B, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Section 2.8.3.4 of the full dossier assessment.

2.4.2 Results on added benefit

No relevant studies were available for saxagliptin plus sulfonylurea, neither for a direct comparison, nor for an indirect comparison. Hence for this subindication, there is no proof of an added benefit versus the ACT specified by the G-BA.

2.4.3 Extent and probability of added benefit

On the basis of the available data, there is no proof of an added benefit of the combination of saxagliptin plus sulfonylurea versus the ACT specified by the G-BA. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This deviates from the company’s assessment, which derived an overall added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4A, Section 4.4 of the dossier and in Section 2.8.2.9.2 of the full dossier assessment.

2.5 Research question C: combination of 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 plus insulin with or without metformin (studies completed up to 21 January 2013)
- Bibliographical literature search on saxagliptin plus insulin with or without metformin (last search 4 February 2013)
- Search in trial registries for studies on saxagliptin plus insulin with or without metformin (last search 21 January 2013)

The Institute's own search:

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

No relevant study suitable for assessing the added benefit of saxagliptin in the relevant subindication was identified from the steps of information retrieval mentioned. In contrast, the company presented 2 randomized placebo-controlled studies (CV181057 and D1680C00007), which were relevant from the company's point of view.

The study CV181057 was already presented by the company for the fixed combination saxagliptin/metformin and assessed in the dossier assessment A12-16 [9]. No new findings resulted from the information now presented by the company.

The study D1680C00007 was a placebo-controlled study with patients with renal impairment (severity grades "moderate" to "end-stage") who did not achieve adequate glycaemic control under prior antidiabetic treatment (OADs excluding metformin and/or insulin).

In the beginning of the study, the patients went through a run-in phase with diet and exercise. The basic therapy started before was to be continued unchanged during this phase. The run-in phase was followed by the treatment phase with a total duration of 52 weeks. The treatment phase consisted of 2 phases: the stable treatment phase (the first 12 weeks) and the flexible treatment phase (the last 40 weeks).

In the stable treatment phase, patients in both treatment arms were required to continue their prior treatment unchanged, i.e. it was neither allowed to change the type of insulin nor the

type of insulin therapy. Changing the insulin dose was only possible for safety reasons. Antidiabetic therapy would usually already be optimized in less pronounced fluctuations of blood glucose levels so that hypoglycaemia and hyperglycaemia do not occur in the first place, and not only as a reaction to these events.

The patients' therapy from the first treatment phase was continued in the flexible treatment phase (no new randomization). But in contrast to the first treatment phase, the insulin dosage in the study could be changed individually in both treatment arms. Other medications including insulin could also be added. It was not finally clear, however, whether it was possible to change the type of insulin and, if applicable, of the insulin regimen in this phase. It was also unclear (if such a change was possible), according to which criteria a change to a different type of insulin was performed, and whether changing the type of insulin and, if applicable, the insulin regimen, was accompanied by an adequate patient education course.

Moreover, because at this point the patients in the intervention arm in both studies had already been treated with saxagliptin, whereas the patients in the comparator arm had received no optimization of their prior treatment, the intervention and control groups no longer had the same conditions when the second phase started. Overall, as with the first treatment phases, the results of the second treatment phase and thus the entire study D1680C00007 could not be used for assessing the added benefit.

Regardless of this, the data presented by the company would not have been relevant because it did not consider the approval status of saxagliptin and the research question adequately. On the one hand, saxagliptin is not approved for patients with end-stage renal impairment (approximately 23% of the patients in the study had end-stage renal impairment). On the other hand, some the patients were partially treated with OADs (other than metformin) in addition to saxagliptin and insulin (approximately 27% of the patients), which was not in compliance with the approval of saxagliptin and therefore did not concur with the present research question.

2.5.2 Results on added benefit

There were no relevant studies for the subindication of the combination of saxagliptin plus insulin with or without metformin. Hence for this subindication, there is no proof of an added benefit versus the ACT specified by the G-BA. This deviates from the company's result, which derived an added benefit from the data it submitted based on the study CV181057 (but not based on the study D1680C00007).

2.5.3 Extent and probability of added benefit

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of saxagliptin plus insulin with or without metformin in comparison with the ACT specified by the G-BA. Hence there are also no patient groups for whom a

therapeutically important added benefit could be derived. This assessment deviates from that of the company, which derived an overall added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4C, Section 4.4 of the dossier, and in Section 2.8.4.9.2 of the full dossier assessment.

2.6 Research question D: combination of saxagliptin plus metformin plus sulfonylurea

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 plus metformin plus sulfonylurea (studies completed up to 21 January 2013)
- Bibliographical literature search on saxagliptin plus metformin plus sulfonylurea (last search 4 February 2013)
- Search in trial registries for studies on saxagliptin plus metformin plus sulfonylurea (last search 21 January 2013)
- Bibliographical literature search on insulin (with or without metformin) (last search 24 January 2013)
- Search in trial registries for studies on insulin (with or without metformin) (last search 12 February 2013)

The Institute's own search:

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

No relevant study suitable for assessing the added benefit of saxagliptin plus metformin plus sulfonylurea versus the ACT was identified from the steps of information retrieval mentioned. The company therefore conducted an indirect comparison. The studies used by the company are described below and reasons are given why they were unsuitable for answering the present research question.

The company conducted an adjusted indirect comparison of saxagliptin plus metformin plus sulfonylurea versus metformin plus insulin or versus insulin monotherapy. The company presented 4 studies for this adjusted indirect comparison. On the saxagliptin side, the company included the placebo-controlled study D1680L00006. The company chose metformin plus sulfonylurea (+ placebo) as intermediate comparator. On the comparator side, the company identified 3 studies, which were relevant for an indirect comparison from the company's point of view (Calle-Pascuale 1995 [27], Kavapil 2006 [28] and Malone 2003 [29]). However, all 3 studies were unsuitable for answering the present research question. Table 8 shows the characteristics of the studies and Table 9 a description of the interventions. Table 10 summarizes the reasons for exclusion.

Table 8: Characteristics of the studies included by the company – indirect comparison: saxagliptin plus metformin plus sulfonylurea vs. human insulin plus metformin

Study	Study design	Study duration	Population	
			Type of prior treatment	Criteria for inadequate glycaemic control
D1680L00006	RCT, double-blind[a], parallel, multicentre	▪ Screening phase: 2 weeks ▪ Treatment: 24 weeks	Prior treatment with a combination of metformin (XR or IR) (≥ 1500 mg) and sulfonylurea (≥ 50% of the maximum recommended dosage), both in maximum tolerated dose for at least 8 weeks before the first study visit	HbA1c ≥ 7% and ≤ 10% on first visit
Calle-Pascuale 1995	Non-RCT, open-label, parallel	4 months	Prior treatment with sulfonylurea for at least 1 year, and at maximum dose (glipizide 20 mg or equivalent) for the last 6 months at least, without further interventions	HbA1c: more than 2 values > 7% in the last 6 months
Kavapil 2006	RCT, open-label, parallel, multicentre	16 weeks	Prior treatment with metformin monotherapy ≥ 850 mg/day, at least 1 month	"Not adequately controlled" (no information on HbA1c value)
Malone 2003	RCT, open-label, parallel, multicentre	▪ Run-in: 2 weeks ▪ Treatment: 16 weeks	Prior treatment with metformin or a second-generation sulfonylurea for at least 3 months and in maximum clinically effective dose within the last 30 days	HbA1c > 125% of the normal value

a: Applies to saxagliptin and placebo (open-label for sulfonylurea and metformin)
IR: immediate release; RCT: randomized controlled trial; XR: extended release; vs.: versus

Table 9: Characteristics of the interventions in the studies included by the company – indirect comparison: saxagliptin plus metformin plus sulfonylurea vs. human insulin plus metformin

Study	Intervention Number of patients	Comparator Number of patients
D1680L00006	▪ Saxagliptin: 5 mg a day ▪ Metformin: continuation of the stable dose given at the start of the study (≥ 1500 mg) ▪ Sulfonylurea[a]: continuation of the stable dose given at the start of the study (≥ 50% of the maximum recommended dosage) ▪ N = 129	▪ Placebo for saxagliptin ▪ Metformin: continuation of the stable dose given at the start of the study (≥ 1500 mg) ▪ Sulfonylurea[a]: continuation of the stable dose given at the start of the study (≥ 50% of the maximum recommended dosage) ▪ N = 128
Calle-Pascuale 1995[b]	▪ Zn insulin: 0.3 IU/kg once a day ▪ N = 12	▪ Sulfonylurea: no information about the sulfonylurea used ▪ Metformin: 850 mg once a day ▪ N = 12
Kavapil 2006[b]	▪ BIAsp 30: initial dose 0.2 IU/kg a day (distributed to twice a day), individual up-titration every 1 – 7 days in steps of 2 – 4 units/injection ▪ Metformin: mean dose (range) approximately 1660 mg (500 – 3000 mg) a day ▪ N = 116	▪ Glibenclamide: initial dose 1.75 mg once a day up to 10.5 mg maximum[c] ▪ Metformin: mean dose (range) approximately 1660 mg (500 – 3000 mg) a day ▪ N = 114
Malone 2003	▪ Insulin lispro mix (25% insulin lispro and 75% NPL): dosage depending on target blood glucose level: < 7 mmol/l, 2 hours after a meal < 10 mmol/l without increasing the frequency of hypoglycaemia ▪ Metformin: 1500 – 2550 mg (distributed to 2 – 3 times a day), stable dose after third visit[e] ▪ N = 296	▪ Glibenclamide: dosage depending on target blood glucose level: < 7 mmol/l[d] ▪ Metformin: 1500 – 2550 mg (distributed to 2 – 3 times a day), stable dose after third visit[e] ▪ N = 301

a: Sulfonylureas used (Institute's calculations): glibenclamide (7.8%), gliclazide (42.4%), glimepiride (46.3%), glipizide (3.5%)
b: Third comparator group not relevant/not used by the company
c: Maximum dose could be exceeded; administration was then distributed to twice a day; no information on the doses and on the proportion of patients taking > 10.5 mg
d: Average dosage 14.2 mg (not approval-compliant; approval: 10.5 mg/day maximum); no information on the proportion of patients who received a dose of > 10.5 mg
e: mean dose (no information on variance): intervention: 1813 mg, intermediate comparator: 1968 mg
BIAsp: biphasic insulin aspart 30; IU: international units; N: number of randomized patients; NPL: neutral protamine lispro; RCT: randomized controlled trial; vs.: versus; Zn: zinc

Table 10: Overview of the reasons for exclusion of the studies – indirect comparison: saxagliptin plus metformin plus sulfonylurea vs. human insulin plus metformin

	Reasons for exclusion				
Comparison Study	**Study design**	**Population (type of prior treatment)**	**Study duration**	**Interventions/ACT**	**Intermediate comparators**
Saxagliptin + metformin + sulfonylurea vs. placebo + metformin + sulfonylurea					
D1680L00006				○	○
Insulin vs. sulfonylurea plus metformin					
Calle-Pascuale 1995	●	●	●	●	●
Insulin plus metformin vs. sulfonylurea plus metformin					
Kavapil 2006		●	●	●	●
Malone 2003		●	●	●	●

●: reason for exclusion; ○: uncertainty
ACT: appropriate comparator therapy; vs.: versus

In principle, the placebo-controlled study D1680L00006 concurred with the inclusion and exclusion criteria of the present research question. Hence the study, in principle, was suitable for an indirect comparison versus the ACT using the intermediate comparator "metformin plus sulfonylurea plus placebo". There was an uncertainty with regards to the sulfonylureas used, however. A large proportion (42.4%) of the patients enrolled in the study were treated with gliclazide instead of glibenclamide (as in 2 of the other studies with the ACT). So it remained unclear whether the comparator intervention would be suitable as intermediate comparator for the indirect comparison with the other studies. The company did not address this issue. It should also be noted that the patients enrolled in the study were treated both with metformin extended release (XR) and with metformin immediate release (IR). The metformin XR formulation is not approved in Europe [30]. It remained unclear how many patients of the total population were treated with metformin XR formulation.

All 3 studies the company used for the comparator side (Calle-Pascuale 1995 [27], Kavapil 2006 [28] and Malone 2003 [29]) were not relevant for the present research question. In all 3 studies, an inappropriate patient population was studied (no patients with inadequate glycaemic control under a maximum tolerated dose of both metformin and sulfonylurea). They were also too short (study duration of < 24 weeks). Optimization of the insulin therapy was not possible or only possible to a limited extent. Moreover, the following reasons were against the usability of the 3 studies:

- Calle-Pascuale 1995 was a non-RCT. Metformin was only used in a sub-maximum dose (850 mg a day). Moreover, there was no information about which sulfonylurea was used.
- In Kavapil 2006, the sulfonylurea was not used continuously in the maximum tolerated dose, but up-titrated in the course of the study. Hence the type of sulfonylurea treatment concurred neither with the approval requirement nor with the treatment in study D1680L00006. In addition, the maximum dose of glibenclamide of 10.5 mg a day [5] could be exceeded. It remained unclear how large the proportion of patients with approval-compliant dosage was.
- The comparator arm in Malone 2003 was also unsuitable as intermediate comparator because the sulfonylurea was not administered continuously in the maximum tolerated dose, but up-titrated. The maximum approved dose of glibenclamide could also be exceeded in Malone 2003.

Summary

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

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4D, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.8.5.2 and 2.8.5.4.1 of the full dossier assessment. Further information about the result of information retrieval and the resulting study pool can be found in Module 4D, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Section 2.8.5.4 of the full dossier assessment.

2.6.2 Results on added benefit

No relevant data were available for saxagliptin plus metformin plus sulfonylurea, neither for a direct comparison, nor for an indirect comparison. Hence the added benefit of saxagliptin in this subindication versus the ACT is not proven.

2.6.3 Extent and probability of added benefit

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of saxagliptin plus metformin plus sulfonylurea in comparison with the ACT specified by the G-BA. Hence there are also no patient groups for whom a therapeutically important added benefit could be derived. This assessment deviates from that of the company, which derived an overall added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4D, Section 4.4 of the dossier, and in Section 2.8.5.9.2 of the full dossier assessment.

2.7 Extent and probability of added benefit - summary

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

Table 11: Saxagliptin – extent and probability of added benefit

Research question	Subindication	Comparator therapy	Extent and probability of added benefit
A1	Saxagliptin plus metformin	Metformin plus sulfonylurea (glibenclamide or glimepiride)	Added benefit not proven
A2	Saxagliptin plus metformin	Metformin plus glipizide[a]	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: According to the commission by the G-BA, the added benefit of saxagliptin plus metformin vs. glipizide plus metformin was also assessed.
G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The G-BA decides on added benefit.

Further information on the extent and probability of added benefit can be found in Module 4A to 4D, Sections 4.4 of the dossier, and in Sections 2.8.2.9.2, 2.8.3.9.2, 2.8.4.9.2, 2.8.5.9.2 and 2.8.5.9 of the full dossier assessment.

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 4.0 [online]. 23.09.2011 [accessed: 05.05.2012]. URL: https://www.iqwig.de/download/General_Methods_4-0.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to § 35a Social Code Book V; extract; commission no. A11-02 [online]. 29.09.2011 [accessed: 05.05.2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. AstraZeneca, Bristol-Myers Squibb. Onglyza 2,5 mg/5 mg Filmtabletten: Fachinformation [online]. 02.2013 [accessed: 15.04.2013]. URL: http://www.fachinfo.de.

4. 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.

5. Sanofi. Euglucon N: Fachinformation [online]. 10.2012 [accessed: 10.05.2013]. URL: http://www.fachinfo.de.

6. Sanofi-Aventis. Amaryl: Fachinformation [online]. 06.2011 [accessed: 08.04.2013]. URL: http://www.fachinfo.de.

7. Pfizer. Fachinformation Glibenese [unpublished]. 2000.

8. Pfizer Corporation Austria. Minidiab 5 mg Tabletten: Fachinformation [online]. 01.2013 [accessed: 18.06.2013]. URL: https://pharmaweb.ages.at/downloadDoc.jsf?docId=FIP1296708641.

9. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Saxagliptin/Metformin: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A12-16 [online]. 13.02.2013 [accessed: 09.04.2013]. (IQWiG-Berichte; volume 152). URL: https://www.iqwig.de/download/A12-16_Saxagliptin_Metformin_Nutzenbewertung_35a_SGB_V.pdf.

10. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dapagliflozin: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A12-18 [online]. 12.03.2013 [accessed: 18.03.2013]. (IQWiG-Berichte; volume 155). URL: https://www.iqwig.de/download/A12-18_Dapagliflozin_Nutzenbewertung_35a-SGB-V.pdf.

11. Astra Zeneca, Bristol-Myers Squibb. Additional analyses of endpoints and subgroups for study: a 52-week, randomised, double blind, active-controlled, multi-centre phase 3b/4 study to evaluate the efficacy and tolerability of saxagliptin compared to glimepiride in elderly patients with type 2 diabetes mellitus who have inadequate glycaemic control on metformin monotherapy [unpublished]. 2012.

12. AstraZeneca. A 52-week, randomised, double blind, active-controlled, multi-centre phase 3b/4 study to evaluate the efficacy and tolerability of saxagliptin compared to glimepiride in elderly patients with type 2 diabetes mellitus who have inadequate glycaemic control on metformin monotherapy: study D1680L00002; clinical study report [unpublished]. 2012.

13. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Addendum zum Auftrag A12-16 (Saxagliptin/Metformin): Addendum; 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.

14. Astra Zeneca, Bristol-Myers Squibb. Additional analyses of endpoints and subgroups for study: a 52-week international, multi-center, randomized, parallel-group, double-blind, active-controlled, phase III study with a 52-week extension period to evaluate the safety and efficacy of saxagliptin in combination with metformin compared with sulphonylurea in combination with metformin in adult patients with type 2 diabetes who have inadequate glycemic control on metformin therapy alone (short-term + long-term clinical study report) [unpublished]. 2012.

15. AstraZeneca, Bristol-Myers Squibb. A 52-week international, multi-center, randomized, parallel-group, double-blind, active-controlled, phase III study with a 52-week extension period to evaluate the safety and efficacy of saxagliptin in combination with metformin compared with sulphonylurea in combination with metformin in adult patients with type 2 diabetes who have inadequate glycemic control on metformin therapy alone: study D1680C00001; clinical study report [unpublished]. 2010.

16. AstraZeneca, Bristol-Myers Squibb. A 52-week international, multi-center, randomized, parallel-group, double-blind, active-controlled, phase III study with a 52-week extension period to evaluate the safety and efficacy of saxagliptin in combination with metformin compared with sulphonylurea in combination with metformin in adult patients with type 2 diabetes who have inadequate glycemic control on metformin therapy alone (short-term + long-term clinical study report): study D1680C00001; clinical study report [unpublished]. 2011.

17. 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.

18. Chacra AR, Tan GH, Ravichandran S, List J, Chen R. Safety and efficacy of saxagliptin in combination with submaximal sulphonylurea versus up-titrated sulphonylurea over 76 weeks. Diab Vasc Dis Res 2011; 8(2): 150-159.

19. 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.

20. Bristol-Myers Squibb. A multicenter, randomized, double-blind, placebo-controlled phase 3 trial to evaluate the efficacy and safety of saxagliptin in combination with glyburide in subjects with type 2 diabetes who have inadequate glycemic control on glyburide alone: study CV181040; clinical study report [unpublished]. 2008.

21. Bristol-Myers Squibb. A multicenter, randomized, double-blind, placebo-controlled phase 3 trial to evaluate the efficacy and safety of saxagliptin in combination with glyburide in subjects with type 2 diabetes who have inadequate glycemic control on glyburide alone: study CV181040; clinical study report for short-term + long-term double-blind treatment [unpublished]. 2009.

22. Shank ML, Del Prato S, DeFronzo RA. Bedtime insulin/daytime glipizide: effective therapy for sulfonylurea failures in NIDDM. Diabetes 1995; 44(2): 165-172.

23. Birkeland KI, Hanssen KF, Urdal P, Berg K, Vaaler S. A long-term, randomized, comparative study of insulin versus sulfonylurea therapy in type 2 diabetes. J Intern Med 1994; 236(3): 305-313.

24. 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.

25. Nathan DM, Roussell A, Godine JE. Glyburide or insulin for metabolic control in non-insulin-dependent diabetes mellitus: a randomized, double-blind study. Ann Intern Med 1988; 108(3): 334-340.

26. Turner R, Murchison L, Wright AD, Oakley N, Kohner E, Hayes R et al. United Kingdom prospective diabetes study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. Ann Intern Med 1998; 128(3): 165-175.

27. Calle-Pascual AL, Garcia-Honduvilla J, Martin-Alvarez PJ, Vara E, Calle JR, Munguira ME et al. Comparison between acarbose, metformin, and insulin treatment in type 2 diabetic patients with secondary failure to sulfonylurea treatment. Diabete Metab 1995; 21(4): 256-260.

28. Kvapil M, Swatko A, Hilberg C, Shestakova M, Kvapil M, Swatko A et al. Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes. Diabetes Obes Metab 2006; 8(1): 39-48.

29. Malone JK, Beattie SD, Campaigne BN, Johnson PA, Howard AS, Milicevic Z et al. Therapy after single oral agent failure: adding a second oral agent or an insulin mixture? Diabetes Res Clin Pract 2003; 62(3): 187-195.

30. European Medicines Agency. Komboglyze: European public assessment report [online]. 16.12.2011 [accessed: 01.02.2013]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002059/WC500119390.pdf.

The full report (German version) is published under https://www.iqwig.de/de/projekte_ergebnisse/projekte/arzneimittelbewertung/a13_01_saxagliptin_nutzenbewertung_gemaess_35a_sgb_v_dossierbewertung.3644.html.