IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – No. 161

Addendum to Commission A12-16 (saxagliptin/metformin)[1]

Addendum

Commission: A13-14
Version: 1.0
Status: 12 April 2013

[1]Translation of the document "Addendum zum Auftrag A12-16 (Saxagliptin/metformin)", (Version 1.0; Status: 12 April 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:
Addendum to Commission A12-16 (saxagliptin/metformin)

Contracting agency:
Federal Joint Committee

Date of commission:
27 March 2013

Internal Commission No.:
A13-14

Address of publisher:
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Keywords: saxagliptin, metformin, diabetes mellitus – type 2, benefit assessment

[1] Due to data protection regulations, employess have the right not to be named

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
FAS	full analysis set
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
RCT	randomized controlled trial
SAE	serious adverse event
SGB	*Sozialgesetzbuch* (Social Code Book)
SPC	Summary of Product Characteristics
vs.	versus

1 Background

On 27 March 2013, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A12-16 (benefit assessment of saxagliptin/metformin [1]).

In the commenting procedure on the assessment of saxagliptin/metformin, on 07 March 2013 the pharmaceutical company (hereinafter abbreviated to "the company") submitted further data to the G-BA that went beyond the information in the dossier. On the one hand these referred to data on Study D1680L00002 (comparison of saxagliptin/metformin vs. glipizide/ metformin). This study was already included in the company's dossier, but was not used by IQWiG to assess added benefit, as the comparator therapy (glipizide) did not correspond to the appropriate comparator therapy (ACT) specified a priori by the G-BA (glimepiride or glibenclamide). On the other hand, the data refer to Study D1680C00001 (comparison of saxagliptin/metformin vs. glimepiride/metformin). This study was not included in the company's dossier, as according to the company, the corresponding clinical study report had not yet been completed. This report was submitted by the company together with the comment on Benefit Assessment A12-16.

The commission of the G-BA for the assessment of these 2 studies reads as follows:

"In this context the data should be assessed with regard to the question as to whether the studies and analyses submitted by the company for saxagliptin/metformin versus glimepiride/ metformin (Study D1680L00002) prove an added benefit of saxagliptin/metformin. In addition, under consideration of the data submitted in the dossier (Study D1680C00001) it is to be assessed whether an added benefit is proven for saxagliptin/metformin versus glipizide/ metformin."

In the following Chapter 2, in compliance with the commission, the two studies D1680C00001 (comparison of saxagliptin/metformin vs. glipizide/metformin, Section 2.1) and D1680L00002 (comparison of saxagliptin/metformin vs. glimepiride/metformin, Section 2.2) are presented separately and assessed.

The responsibility for the present assessment and the result of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The decision on added benefit is made by the G-BA.

2 Assessment

The aim of the present addendum is the assessment of the added benefit of the fixed drug combination of saxagliptin and metformin versus the following comparator therapies:

- a dual therapy of glipizide and metformin (on the basis of Study D1680C00001), and
- a dual therapy of glimepiride and metformin (on the basis of Study D1680L00002).

The assessment was conducted in compliance with the approval status of saxagliptin/ metformin [2] for the following therapeutic indication:

- As an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets (named in the following text as the combination of saxagliptin and metformin).

In both studies saxagliptin and metformin were administered as individual drugs and not as a fixed combination. Nevertheless both studies were used for the assessment of the fixed combination.

The currently effective Summary of Product Characteristics (SPC) [3] was used to answer the question as to whether glimepiride was administered in compliance with the approval status in Study D1680L00002. As glipizide is no longer approved in Germany, the last SPC effective for Germany was requested from the Federal Institute for Drugs and Medical Devices and used [4].

The assessment was conducted based on patient-relevant outcomes:

2.1 Comparison of saxagliptin/metformin versus glipizide/metformin: Study D1680C00001

2.1.1 Study characteristics

Table 1 displays an overview of the design of Study D1680C00001. Table 2 describes the interventions used in Study D1680C00001. Table 3 and Table 4 show the characteristics of the target population (metformin dose ≥ 1700 mg daily) and, as supplementary information, of the total population of Study D1680C00001.

Table 1: Characteristics of the studies included – RCT, direct comparison – treatment regimen saxagliptin vs. treatment regimen glipizide (Study D1680C00001, dual combination with metformin)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
D1680C00001	RCT, double-blind, parallel, multi-centre	Adults with type 2 diabetes mellitus, Pretreatment with metformin as monotherapy. Metformin daily dose ≥ 1500 mg	Treatment regimen with saxagliptin (N = 428) Treatment regimen with glipizide (N = 430) Thereof target population:[b] Treatment regimen with saxagliptin (n = 234) Treatment regimen with glipizide (n = 222)	Enrolment: 3 weeks Lead-in: 2 weeks Main treatment: 52 weeks Extension phase: 52 weeks	130 study centres in 11 countries in Europe, Asia 12/2007 – 08/2010	Primary: HbA1c-change from start of study to Week 52 Secondary: Hypoglycaemia, adverse events

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

b: Relevant population for the assessment: patients with a metformin dose of ≥ 1700 mg daily.

N: number of randomized patients, n: relevant subpopulation, RCT: randomized controlled trial

Table 2: Characteristics of the interventions – RCT, direct comparison – treatment regimen saxagliptin vs. treatment regimen glipizide (Study D1680C00001, dual combination with metformin)

Study	Intervention	Control	Concomitant therapy
D1680C00001	Saxagliptin once daily 5 mg Placebo for glipizide Blood-glucose target level: there was an up-titration of the non-blood-glucose lowering substance placebo in the first 18 weeks of treatment in 3-week intervals, as long as the fasting blood-glucose levels were > 110 mg/dL[a] or if the highest tolerated dose had been reached (pseudotitration)	Placebo for saxagliptin Glipizide 5, 10, 15 or 20 mg Blood-glucose target level: there was an up-titration of the glipizide dose in the first 18 weeks of treatment in 3-week intervals, as long as the fasting blood-glucose levels were > 110 mg/dL[a] or if the highest tolerated dose had been reached	Metformin[b] 1500, 2000, 2500 or 3000 mg daily

a: Under consideration of self-measurement of patients and measurement in the study centre.
b: In the lead-in phase the current dose of metformin was adapted as follows: patients who received 1500-1999 mg metformin were switched to 1500 mg daily; accordingly 2000-2499 mg to 2000 mg daily; 2500-2550 mg to 2500 mg daily and 3000 mg daily. The dose was not allowed to be changed during the course of the study.
RCT: randomized controlled trial

Table 3: Characteristics of the study populations– RCT, direct comparison – treatment regimen saxagliptin vs. treatment regimen glipizide (Study D1680C00001, dual combination with metformin, target population)

Group	Treatment regimen saxagliptin+metformin	Treatment regimen glipizide+metformin
N[a]	234	221
Age [years]: mean (SD)	56.7 (9.9)	57.2 (10.0)
Sex f/m [%]	46.6/53.4	38.9/61.1
Disease duration [years]: mean (SD)	5.8 (4.6)	5.5 (5.0)
HbA1c at start of study [%]: mean (SD)	7.7 (0.9)	7.7 (0.9)
HbA1c value at start of study [%]: categories [n (%)]	n.d.	n.d.
Daily metformin dose [mg]: mean (SD)	n.d.	n.d.
Ethnicity [n (%)]	n.d.	n.d.

a: Based on the randomized analysis set population (defined as all randomized patients with administration of at least one dose of study medication)
f: female; m: male; N: number of randomized and treated patients; n.d.: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 4: Characteristics of the study populations– RCT, direct comparison – treatment regimen saxagliptin vs. treatment regimen glipizide (Study D1680C00001, dual combination with metformin, total population)

Group	Treatment regimen saxagliptin+metformin	Treatment regimen glipizide+metformin
N[a]	428	430
Age [years]: mean (SD)	57.5 (10.3)	57.6 (10.4)
Sex f/m [%]	50.5/49.5	46.0/54.0
Disease duration [years]: mean (SD)	5.5 (4.5)	5.4 (4.7)
HbA1c value at start of study [%]: mean (SD)	7.7 (0.9)	7.7 (0.9)
HbA1c at start of study [%]: categories [n (%)]		
▫ < 7.0%	99 (23.1)	105 (24.4)
▫ ≥ 7.0% to < 8.0%	190 (44.4)	186 (43.3)
▫ ≥ 8.0% to < 9.0%	93 (21.7)	105 (24.4)
▫ ≥ 9.0%	46 (10.7)	34 (7.9)
Daily metformin dose [mg]: mean (SD)	1937.9 (484.8)	1882.6 (453.7)
Ethnicity [n (%)]		
▫ White	352 (82.2)	362 (84.2)
▫ Asian	73 (17.1)	65 (15.5)
▫ Black/African American	1 (0.2)	0 (0.0)
▫ Other	2 (0.5)	3 (0.7)

a: Based on the randomized analysis set population (defined as all randomized patients who took at least one dose of study medication)
f: female; m: male; N: number of randomized and treated patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Study design

Study D1680C00001 was a company-sponsored randomized active-controlled double-blind approval study. Participants in the study were adult patients with type 2 diabetes mellitus who did not achieve adequate glycaemic control, despite metformin monotherapy in a daily dose of ≥ 1500 mg. Inadequate glycaemic control was defined as an HbA1c above 6.5%; patients were included with an HbA1c between 6.5% to ≤ 10%.

The study comprised a 3-week enrolment phase, a 2-week lead-in phase with administration of placebo and metformin, as well as a treatment phase including a main treatment phase (the first 52 weeks) and an extension phase (a further 52 weeks). The overall treatment duration was 104 weeks.

After randomization patients received the following study medications: saxagliptin 5 mg once daily or glipizide 5, 10, 15 or 20 mg once or twice daily (depending on the daily dose), in each case with administration of placebo of the other medication. In addition patients received

metformin in both groups. Depending on the dose before the start of study, the metformin dose in each case was specified as a standardized dose of 1500 mg, 2000 mg, 2500 mg or 3000 mg daily. As following approval-compliant use, the fixed combination of saxagliptin/ metformin has to be administered with a dose of at least 1700 mg metformin, only a subpopulation of Study D1680C00001 is relevant for the present assessment [2]. The target population only amounted to some 50% of the total study population.

The initial dose of glipizide/placebo was 5 mg daily and was up-titrated in the first 18 weeks of the main treatment phase in 3-week intervals, as long as the fasting blood-glucose levels were above 110 mg/dL (under consideration of self-measurement of patients and measurement in the study centre) or the individual maximum tolerated dose had been reached. Due to the fact that titration with a blood-glucose lowering drug was only conducted in the glipizide group, but not in the saxagliptin group, Study D1680C00001 does not represent a comparison of the two drugs, but a comparison of two combined interventions (treatment regimen plus drug). In addition, the specified criterion for the adaptation of the glipizide dose (fasting blood glucose ≤ 110 mg/dL) was close to the normal level. Because of the study results on blood-glucose lowering to the near-normal level [5], current guidelines recommend blood-glucose lowering to the near-normal level only after an individual balancing of benefits and risks, and in principle target levels should be agreed upon under consideration of individual circumstances [6,7]. It should also be noted that according to the most recently effective SPC on glipizide [4], treatment should be adapted individually. Titration to a near-normal target level independent of individual considerations, as conducted in Study D1680C00001, is not envisaged in the SPC.

Study population

No relevant differences between treatment groups regarding age, sex, disease duration or HbA1c at the start of the study were evident for the total population or for the target population. The patients in the target population had a mean age of about 57 years. The proportion of women was about 47% in the saxagliptin group and about 39% in the glipizide group. The disease duration was 5.5 years. Mainly patients classified as “white” participated in the study.

The mean daily metformin dose in the total population was about 1900 mg before the start of the study. No such information was available for the target population. Because of the algorithm used in the study for the dose-finding of metformin, the metformin dose in the target population before the start of the study was at least 2000 mg daily (corresponding to 67% of the maximum approved dose). For the target population it can thus be assumed that the approval criterion “pretreatment with metformin with the maximally tolerated dose” was mostly fulfilled.

HbA1c (long-term marker for the mean blood glucose level) had a mean value of 7.7% at the start of the study. However, in about a quarter of patients, HbA1c was < 7.0% (23.1% in the saxagliptin group and 24.4% in the glipizide group; only data on the total population).

According to current knowledge, for a relevant proportion of patients one cannot assume inadequate glycaemic control that would have required intensified therapy. Particularly in these patients, intensified blood-glucose lowering therapy was associated with an increased risk of hypoglycaemia.

Summary

For fundamental reasons, no added benefit of saxagliptin/metformin versus glipizide/ metformin can be derived from Study D1680C00001. This is particularly due to the following reasons:

- Treatment regimens, not just drugs, were compared in the study. It is therefore uncertain that the effects observed in the study are in each case attributable to the drugs used. They could have been caused by the different treatment regimens alone.
- The target level used in the study was close to the normal level and was specified independent of individual considerations. Titration directed towards a target level, in particular to a near-normal level, is not envisaged in the SPC for glipizide.
- For a relevant proportion of patients included in the study one cannot assume inadequate glycaemic control that would have required intensified therapy.

The results of Study D1680C00001 itself support this assumption, as presented in the following Section 2.1.2.

2.1.2 Results

Blood-glucose lowering: HbA1c

The following Figure 1 shows the change in HbA1c (according to adjusted mean value for HbA1c at the start of the study) during the 104-week treatment phase of Study D1680C00001. Figure 2 shows the course of the absolute HbA1c mean values. In both analyses, missing values were replaced with the last observation carried forward (LOCF) approach (in each case data for the total population; corresponding data were not available for the target population). Figure 3 shows the change in HbA1c in the target population, but without replacement of missing values.[2] Data on the course of HbA1c mean values in the target population were not available.

[2]Differences in the course of the curve after Week 60 are due to the type of analysis (repeated measures analysis without replacement of missing values). With this type of analysis, the curves also cross in the total population after Week 60. In the present case, this type of analysis is of low informative value due to the high number of missing values (already nearly 30% after 52 weeks).

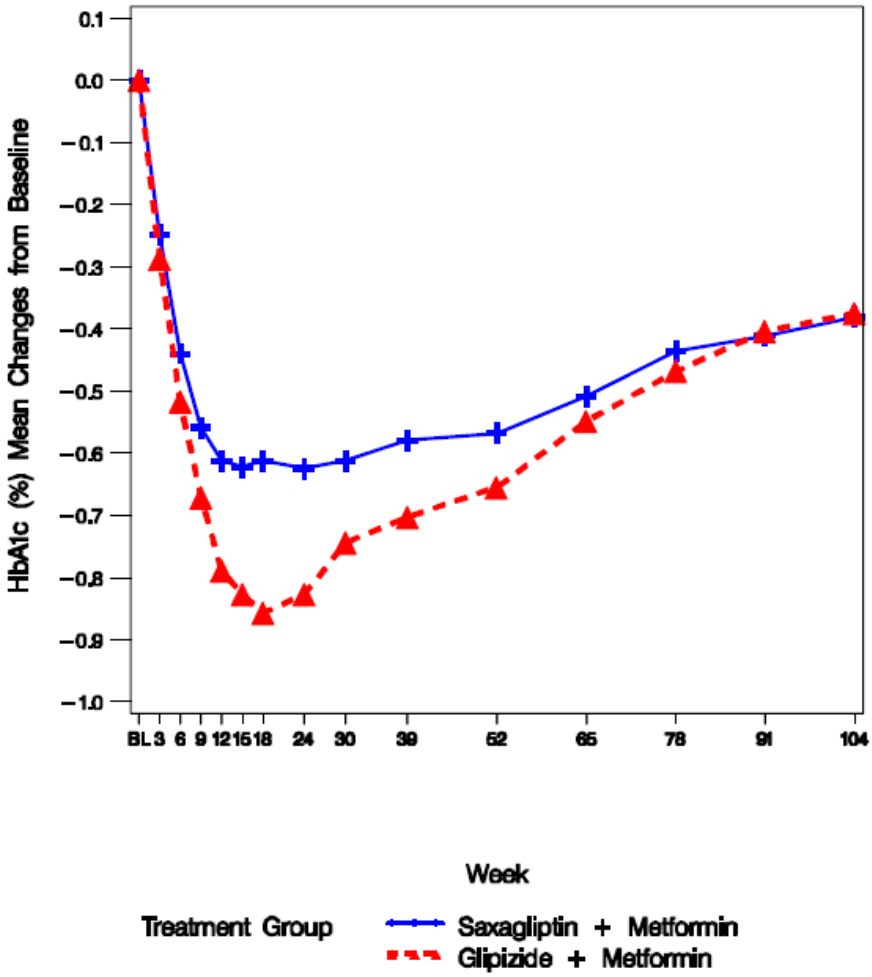


Figure 1: Change in HBA1c over the course of Study D1680C00001 (full analysis set, LOCF, total population).

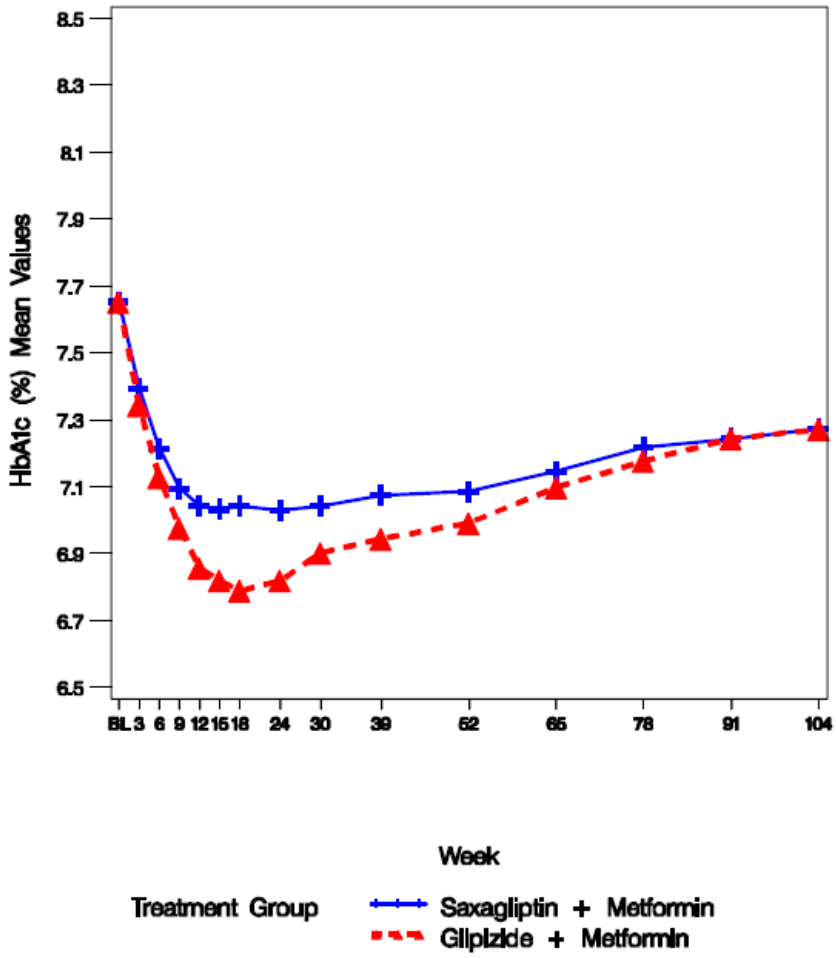


Figure 2: Change in HBA1c (mean values) over the course of Study D1680C00001 (full analysis set, LOCF, total population).

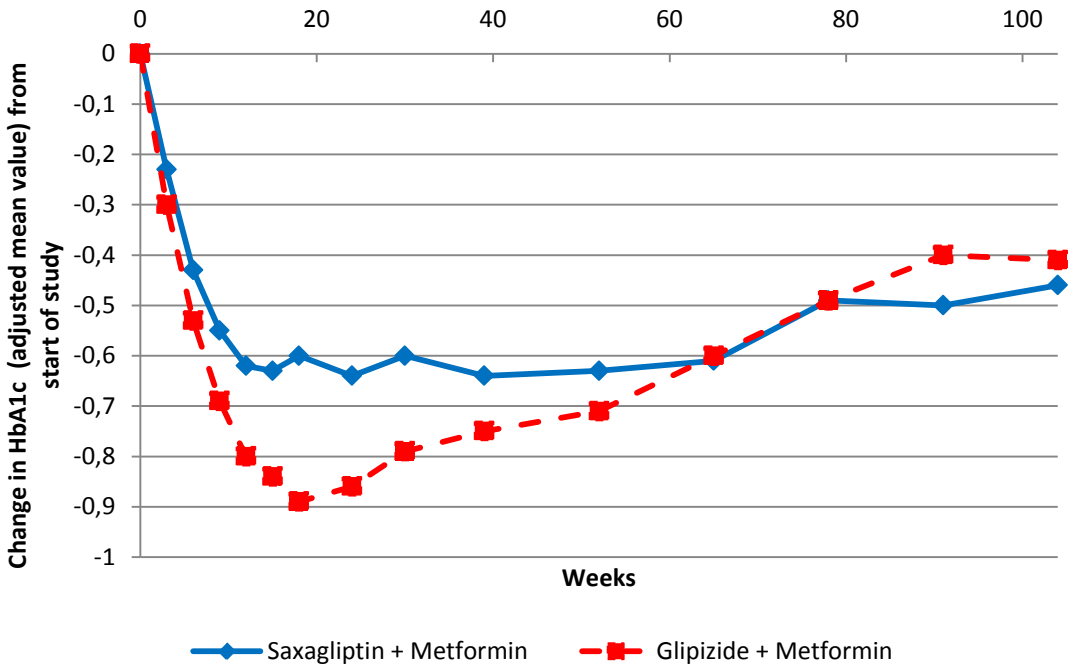


Figure 3: Change in HBA1c value over the course of Study D1680C00001 (full analysis set, LOCF, repeated measures analysis, target population).

If one considers the time course of the change in the HbA1c, a rapid decrease of HbA1c to the aspired near-normal level is evident under target-level directed treatment with glipizide during the titration phase (first 18 weeks of the study). The minimum HbA1c was reached at the end of the titration phase (at Week 18). A decrease in HbA1c was also observed in the saxagliptin group. However, in relation to the glipizide group it was markedly less pronounced.

In the first 3 to 6 weeks of the study the difference in the decrease in HbA1c was not yet markedly pronounced. This can be explained by the fact that HbA1c is a long-term marker that shows the average blood-glucose level during a 6-12 week period. It cannot therefore be expected that the effectiveness of intensified treatment can be evaluated in the first weeks by means of HbA1c.

The difference between treatment groups was greatest after 18 weeks. The effect of the titration phase influenced the subsequent treatment phase and was particularly visible within the first half of the study (up to Week 52). At the end of study the HbA1c values of both treatment groups approximated to each other, and showed a mean value of just over 7% in each group.

Hypoglycaemia

The time course of the occurrence of hypoglycaemia corresponds as expected to the described course of blood-glucose lowering. Figure 4 shows the time to occurrence of the first hypoglycaemic event (Kaplan-Meier curve) in the total population of D1680C00001. Due to

the lack of better data, all events described as hypoglycaemia are presented, independent of severity and independent of whether they were confirmed by blood-glucose measurement or not. It is therefore probable that events not relevant to the assessment are also included. Figure 5 shows the time course of all confirmed hypoglycaemic events (not only first events) in the target population (operationalized as symptomatic hypoglycaemic events with a blood-glucose level ≤ 50 mg/dL).

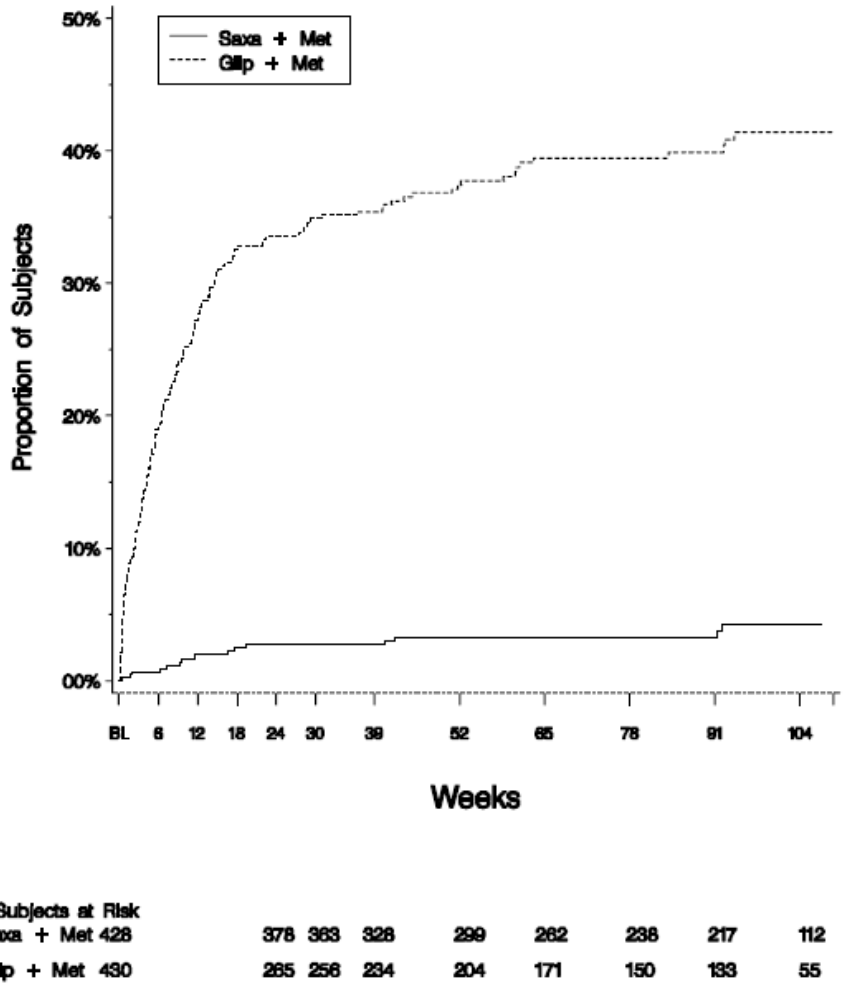
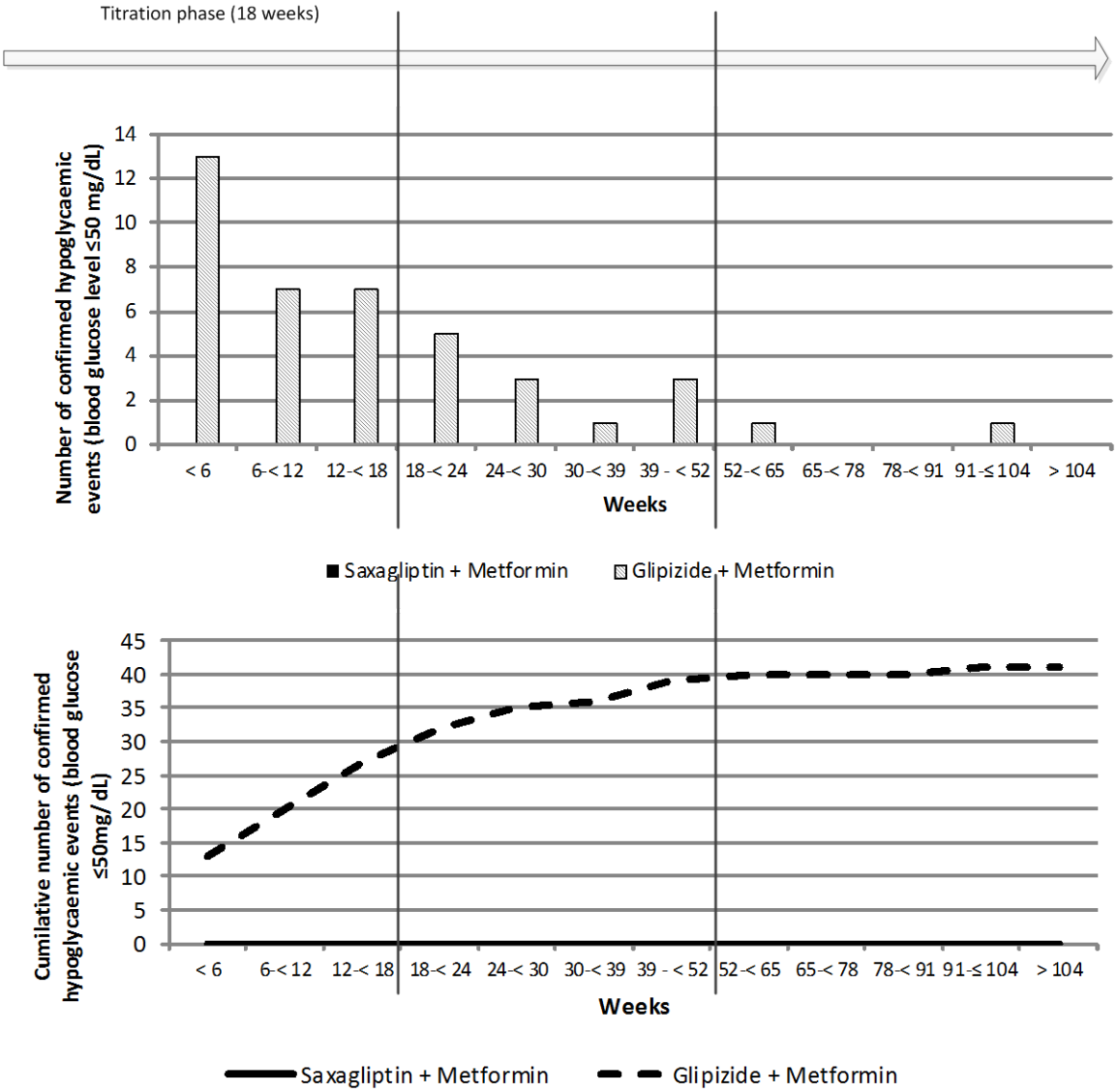


Figure 4: Time to first hypoglycaemic event over the course of Study D1680C00001 (safety analysis set, total population).



The first vertical line shows the end of the titration phase (18 weeks). The second vertical line shows the end of the first treatment phase (Week 52).

Figure 5: Time course of the confirmed hypoglycaemic events over the course of Study D1680C00001 (full analysis set, target population).

It emerged that especially during the target-level directed treatment in the first 18 weeks (this corresponds to the duration of the titration phase), there was a risk of a first hypoglycaemic event under glipizide. In the further course of the study the risk decreased drastically. Such a clear difference between study phases was not shown for saxagliptin.

The confirmed hypoglycaemic events showed a similar result. Such events under glipizide also particularly occurred in the first titration phase of the study (18 weeks) and hardly occurred at all after Week 52 (only 2 events in Week 53 to Week 104).

10 of the 13 observed confirmed hypoglycaemic events up to Week 6 occurred until Week 3, that is, under a minimum glipizide dose. These events cannot therefore be explained by titration, but rather by the fact that patients were included in the study for whom treatment escalation was evidently not necessary and in whom minimum-dose glipizide had already led to marked blood-glucose lowering.

The course of severe hypoglycaemic events could not be inferred from the available documents. So-called "major" hypoglycaemic events were recorded in the study. However, the operationalization used is unsuitable to actually only record severe hypoglycaemic events. It also covers those hypoglycaemic events that are not associated with serious neurological symptoms/conditions such as coma and those that require third-party assistance (e.g. from relatives or friends) but do not require medical interventions.

In summary, it can be determined that the time course of occurrence of hypoglycaemic events corresponded to blood-glucose lowering. The substantial difference in blood-glucose lowering between treatment groups was apparently induced by the one-sided specification of the target level for glipizide. The HbA1c values achieved indicate that for most patients no treatment escalation would have been necessary. On the basis of Study D1680C00001, no added benefit can therefore be inferred due to a lower rate of hypoglycaemic events of saxagliptin/ metformin versus glipizide/metformin.

Further outcomes

Results on mortality, as well as on cardiac or cerebral events, could only be inferred from data on adverse events. Study D1680C00001 was not designed to infer an advantage or non-inferiority of saxagliptin/metformin versus glipizide/metformin for the outcomes particularly relevant to the area of treatment. Due to the above-described deficiencies in study design, such data would however not be interpretable in the sense of an advantage specific to one of the drugs.

Data on health-related quality of life were not recorded in Study D1680C00001.

Data on adverse events (including serious AEs and treatment discontinuations due to AEs) were also not interpretable, especially as hypoglycaemic events were also recorded under these outcomes.

Results of Study D1680C00001 are shown in the following Table 5 for reasons of completeness. If available, data on the target population are preferentially presented, and effect estimates are only presented for this population.

Table 5: Results for the comparison of the treatment regimen saxagliptin versus treatment regimen glipizide (Study D1680C00001, dual combination with metformin)

Outcome category Outcome	Treatment regimen saxagliptin+metformin		Treatment regimen glipizide+metformin		Saxagliptin vs. glipizide
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	Effect estimates [95% CI] p-value
Mortality					
All-cause mortality	No data were available for the target population. Data for the total population:				
	428	4 (0.9)	430	2 (0.5)	-
Cardiac events[b]	No data were available for the target population. Data for the total population:				
	428	13 (3.0)	430	10 (2.3)	-
Cerebral events	No data were available for the target population. Data for the total population:				
Nervous system disorders[c]	428	5 (1.2)	430	5 (1.2)	-
Health-related quality of life					
	Not recorded				
Adverse events					
Hypoglycaemia					
Severe hypoglycaemia[d]	234	n.d.	222	n.d.	n.d.
Confirmed severe hypoglycaemia (blood glucose ≤50 mg/dL)	234	0 (0.0)	222	23 (10.4)	Peto OR[e]: 0.12 [0.05; 0.27] p < 0.001[f]
HbA1c change	See previous figures for data on HbA1c during the course of the study				
Pancreatitis	No data were available for the target population. Data for the total population:				
	428	1 (0.2)	430	1 (0.2)	-
Overall rate AE[g]	234	159 (67.9)	222	166 (74.8)	-
Overall rate SAE[g]	234	29 (12.4)	222	30 (13.5)	RR[e]: 0.92 [0.57; 1.48] p = 0.775[f]
Treatment discontinuation due to AE[g]	234	16 (6.8)	222	12 (5.4)	RR[e]: 1.26 [0.61; 2.61] p = 0.557[f]

(continued on next page)

Table 5: Results for the comparison of the treatment regimen saxagliptin versus treatment regimen glipizide (Study D1680C00001, dual combination with metformin) (continued)

Outcome category **Outcome**	**Treatment regimen saxagliptin+metformin**			**Treatment regimen glipizide+metformin**			**Saxagliptin vs. glipizide**
	N[a]	**Patients with event n (%)**		**N[a]**	**Patients with event n (%)**		**Effect estimates [95% CI] p-value**
Supplementary outcome "body weight"							
Weight increase of at least 7%[h]	234	2 (0.9)		220	17 (7.7)		Peto OR[e]: 0.18 [0.07; 0.45] p < 0.001[f]
Change in body weight in kg[i]	N	Values at start of study mean (SE)	Change at end of study mean (SE)	N	Values at start of study mean (SE)	Change at end of study mean (SE)	Mean difference:
	232	91.6 (1.2)	-1.7 (0.3)	220	90.4 (1.3)	1.3 (0.3)	-2.9 [-3.7; -2.1] p < 0.001

a: Corresponds to the safety analysis set population (defined as all randomized patients who took at least one dose of study medication, classified to the first study medication actually received) unless otherwise stated.

b: Serious cardiac events. MedDRA SOC "Cardiac disorders". The company presented an analysis of cardiac events for the target population; however, this also contains non-serious events.

c: Serious cerebral events. MedDRA SOC "Nervous system disorders". An analysis of only ischaemic events, e.g. TIA or stroke, was not available.

d: Results for severe hypoglycaemic events could not be inferred from the available data, see also previous text.

e: Institute's calculation; asymptotic.

f: Institute's calculation, unconditional exact test (CSZ method according to [8]).

g: Hypoglycaemic events were also recorded here.

h: LOCF analysis of the FAS population.

i: Mean values adjusted to weight at start of study (LOCF analysis of the FAS population).

AE: adverse event; CI: confidence interval; CSZ; convexity, symmetry, z score; FAS: full analysis set; ITT: intention-to-treat; N: number of analysed patients; n: number of patients with event; n.d.: no data; OR: odds ratio, RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SE: standard error; TIA: transient ischaemic attack; vs.: versus

2.1.3 Summarizing conclusion on added benefit

Study D1680C00001 does not provide proof of an added benefit of the fixed combination of saxagliptin/metformin versus treatment with glipizide plus metformin.

2.2 Comparison of saxagliptin/metformin versus glimepiride/metformin: Study D1680L00002

2.2.1 Study characteristics

Table 6 shows an overview of the design of Study D1680L00002. Table 7 describes the interventions used in Study D1680L00002. Table 8 and Table 9 show the characteristics of the target population (metformin dose ≥ 1700 mg daily) and, as supplementary information, the total population of Study D1680L00002.

Table 6: Characteristics of the studies included – RCT, direct comparison – treatment regimen saxagliptin versus treatment regimen glimepiride (Study D1680L00002, dual combination with metformin)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome, secondary outcomes[a]
D1680L00002	RCT, double-blind, parallel, multi-centre	Elderly patients (≥ 65 years) with type 2 diabetes mellitus. Pre-treatment with stable metformin dose as mono-therapy	Treatment regimen with saxagliptin (N = 360) Treatment regimen with glimepiride (N =360) Thereof target population:[b] Treatment regimen with saxagliptin (n = 190) Treatment regimen with glimepiride (n = 171)	Enrolment: 2 weeks Lead-in: 2 weeks Treatment phase 52 weeks	152 study centres in 13 countries in Europe 10/2009 – 06/2012	Primary: proportion of patients reaching HbA1c value < 7% without confirmed or severe hypoglycaemia Secondary: quality of life, hypoglycaemic events, adverse events

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

b: Relevant population for the assessment: patients with a metformin dose of ≥ 1700 mg daily

N: number of randomized patients, n: relevant subpopulation, RCT: randomized controlled trial

Table 7: Characteristics of the interventions – RCT, direct comparison – treatment regimen saxagliptin versus treatment regimen glimepiride (Study D1680L00002, dual combination with metformin)

Study	Intervention	Control	Concomitant therapy
D1680L00002	Saxagliptin once daily 5 mg Placebo for glimepiride Blood-glucose target level: there was an up-titration of the non-blood-glucose lowering substance placebo in the first 12 weeks of treatment in 3-week intervals, as long as the fasting blood-glucose levels were > 110 mg/dL[a] or if the highest tolerable dose had been reached (pseudotitration)	Placebo for saxagliptin Glimepiride 1, 2, 3, 4 or 6 mg Blood-glucose target level: there was an up-titration of the glimepiride dose in the first 12 weeks of treatment in 3-week intervals, as long as the fasting blood-glucose levels were > 110 mg/dL[a] or if the highest tolerable dose had been reached	Metformin: continuation of the daily dose administered at start of study
a: Under consideration of self-measurement of patients and measurement in the study centre RCT: randomized controlled trial			

Table 8: Characteristics of the study populations – RCT, direct comparison – treatment regimen saxagliptin versus treatment regimen glimepiride (Study D1680L00002, dual combination with metformin, target population)

Group	Treatment regimen saxagliptin+metformin	Treatment regimen glimepiride+metformin
N[a]	190	171
Age [years]: mean (SD)	71.8 (5.3)	72.1 (5.1)
Sex f/m [%]	40.5/59.5	36.3/63.7
Disease duration [years]: mean (SD)	9.1 (7.0)	8.7 (6.9)
HbA1c at start of study [%]: mean (SD)	7.6 (0.7)	7.7 (0.6)
HbA1c at start of study [%]: categories [n (%)]	n.d.	n.d.
Daily metformin dose [mg]: mean (SD)	n.d.	n.d.
Ethnicity [n (%)]	n.d.	n.d.
a: Based on the randomized analysis set population (defined as all randomized patients with administration of at least one dose of study medication) f: female; m: male; N: number of randomized and treated patients; n.d.: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus		

Table 9: Characteristics of the study populations – RCT, direct comparison – treatment regimen saxagliptin versus treatment regimen glimepiride (Study D1680L00002, dual combination with metformin, total population)

Group	Treatment regimen saxagliptin+metformin	Treatment regimen glimepiride+metformin
N[a]	360	360
Age [years]: mean (SD)	72.5 (5.7)	72.7 (5.4)
Sex f/m [%]	39.7/60.3	36.7/63.3
Disease duration [years]: MW (SD)	7.6 (6.4)	7.6 (6.0)
HbA1c at start of study [%]: mean (SD)	7.6 (0.7)	7.6 (0.7)
HbA1c at start of study [%]: categories [n (%)]		
< 7.0	41 (11.4)	43 (11.9)
≥ 7.0 to < 8.0	237 (65.8)	229 (63.6)
≥ 8.0 to < 9.0	64 (17.8)	74 (20.6)
≥ 9.0	17 (4.7)	13 (3.6)
Not reported	1 (0.3)	1 (0.3)
Daily metformin dose [mg]: mean (SD)	1646.8 (705.3)	1571.7 (670.6)
Ethnicity [n (%)]		
Caucasian	352 (97.8)	355 (98.6)
Asian	1 (0.3)	1 (0.3)
Black	1 (0.3)	0 (0.0)
Other	6 (1.7)	4 (1.1)

a: Based on the randomized analysis set population (defined as all randomized patients)
f: female; m: male; N: number of randomized and treated patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Study design

Study D1680L00002 was a company-sponsored randomized active-controlled double-blind clinical study. Participants in the study were exclusively elderly patients (≥ 65 years of age) with type 2 diabetes mellitus who did not achieve adequate glycaemic control, despite metformin monotherapy in any daily dose. Inadequate glycaemic control was defined as an HbA1c above 7.0%; patients were included with an HbA1c between 7.0% to ≤ 9%.

The study comprised a 2-week enrolment phase, a 2-week lead-in phase with administration of placebo and metformin, as well as a treatment phase of 52 weeks.

After randomization patients received the following study medications: saxagliptin 5 mg once daily or glimepiride 1, 2, 3, 4 or 6 mg once daily, in each case with administration of placebo for the other study medication. In addition to administration of saxagliptin or glimepiride in both groups, metformin was to be continued as basic therapy as at the start of the study and in

an unchanged dose. As following approval-compliant use, the fixed combination of saxagliptin/metformin has to be administered with a dose of at least 1700 mg metformin, only a subpopulation of Study D1680L00002 is relevant for the present assessment [2]. The target population amounted to about 50% of the total study population.

The initial dose of glimepiride/placebo was 1 mg daily and was up-titrated in the first 12 weeks of the main treatment phase in 3-week intervals, as long as the fasting blood-glucose levels were above 110 mg/dL (under consideration of self-measurement of patients and measurement in the study centre) or the individual maximum tolerated dose had been reached.

Due to the fact that titration with a blood-glucose lowering drug was only conducted in the glimepiride group, but not in the saxagliptin group, Study D1680L00002 does not represent a comparison of the two drugs, but a comparison of two combined interventions (treatment regimen plus drug). In addition, the specified criterion for the adaptation of glimepiride dose (fasting blood glucose ≤ 110 mg/dL) was close to the normal level and very low, particularly considering the age of the patients. Because of the study results on blood-glucose lowering to the near-normal level [5], current guidelines recommend blood-glucose lowering to the near-normal level only after an individual balancing of benefits and risks, and in principle target levels should be agreed upon under consideration of individual circumstances. Due to several factors, among others, comorbidity, shorter life expectation and increased risk of hypoglycaemia, in elderly patients (as also included in Study D1680L00002) one can assume that higher HbA1c values are more likely to be a treatment goal [6,7]. Particularly blood-glucose lowering to near-normal levels, as aspired to in the glimepiride group, will probably not come into question regularly. The already existing higher risk for hypoglycaemia in the older patient population was increased by the study requirements to reach a target level at the near-normal level. In addition, according to the SPC on glimepiride [3], treatment should be adapted individually. Titration independent of individual considerations with a near-normal target level, as conducted in Study D1680L00002, is not envisaged in the SPC.

Study population

No relevant differences between treatment groups regarding age, sex, disease duration or HbA1c value at the start of the study were evident for the total population or for the target population. The patients in the target population had a mean age of about 70 years. About 40% of the population included were female. The disease duration was some 7.6 years. Almost exclusively patients of Caucasian origin participated in the study.

The mean daily metformin dose in the total population was about 1600 mg before the start of the study. No corresponding information on the target population was available. According to the inclusion criteria, patients with any daily metformin dose were eligible to participate in the study. The metformin dose was in the range between 250 mg and 4000 mg daily. On the one hand this led to the inclusion of patients whose daily metformin dose was very low, for example only 250 mg (corresponding to 8% of the maximum approved dose). No information can be found in the study documents that the investigator had to check or confirm that the

metformin dose taken at the start of the study was the maximum tolerated dose. It can thus be assumed that some of the patients included did not fulfil the approval criterion "pre-treatment with the maximum tolerated dose of metformin". Due to the requirements for the fixed combination (metformin dose ≥ 1700 mg daily, corresponding to ≥ 57% of the maximum dose), it can however be assumed that in the present assessment this is fulfilled within the target population to a lesser extent than in the total population; however, a conclusive assessment is not possible. On the other hand, patients were also treated with a non-approved metformin dose (> 3000 mg daily [9]). How many patients this applied to cannot be estimated either.

HbA1c (long-term marker for the average blood glucose level) had a mean value of 7.6% at the start of the study. However, in about 12% of patients (only data on the total population) HbA1c was < 7.0% (despite the inclusion criterion of HbA1c > 7.0%); in about two thirds of patients the value was in the range of ≥ 7.0% to < 8.0%. According to current knowledge, for a relevant proportion of patients one cannot assume inadequate glycaemic control that would have required intensified treatment (particularly considering the age of patients). Such treatment goals do not represent a realistic treatment decision for the elderly population investigated. Particularly in these patients, intensified blood-glucose lowering therapy was associated with an increased risk of hypoglycaemia.

Summary

For fundamental reasons, no added benefit of saxagliptin/metformin versus glimepiride/ metformin can be derived from Study D1680L00002. This is in particular due to the following reasons:

- Treatment regimens, not just drugs, were compared in the study. It is therefore uncertain that the effects observed in the study are in each case attributable to the drugs used. They can also be caused by the different treatment regimens alone.
- The target level used in the study was close to the normal level, even though exclusively elderly patients were included in the study. In addition, the target level was specified independent of individual considerations.
- For a relevant proportion of patients included in the study one cannot assume inadequate glycaemic control that would have required intensified treatment (particularly considering the age of patients).

The results of Study D1680L00002 itself support this assumption as presented in the following Section 2.2.2.

2.2.2 Results

Blood-glucose lowering: HbA1c

The following Figure 6 shows the change in HbA1c (mean values) in the total population. Figure 7 shows the course of the absolute HbA1c mean values. In both analyses missing values were replaced with LOCF (in each case data for the total population; corresponding data were not available for the target population). Figure 8 shows the change in HbA1c in the target population, but without replacement of missing values. Data on the course of absolute HbA1c mean values in the target population were not available.

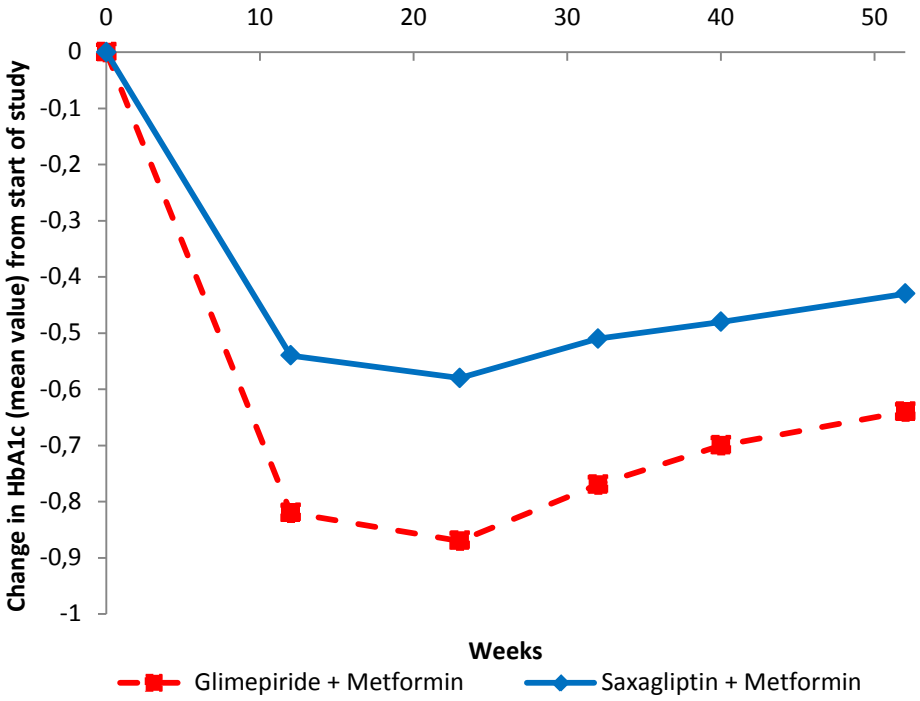


Figure 6: Change in HBA1c over the course of Study D1680L00002 (full analysis set, LOCF, total population).

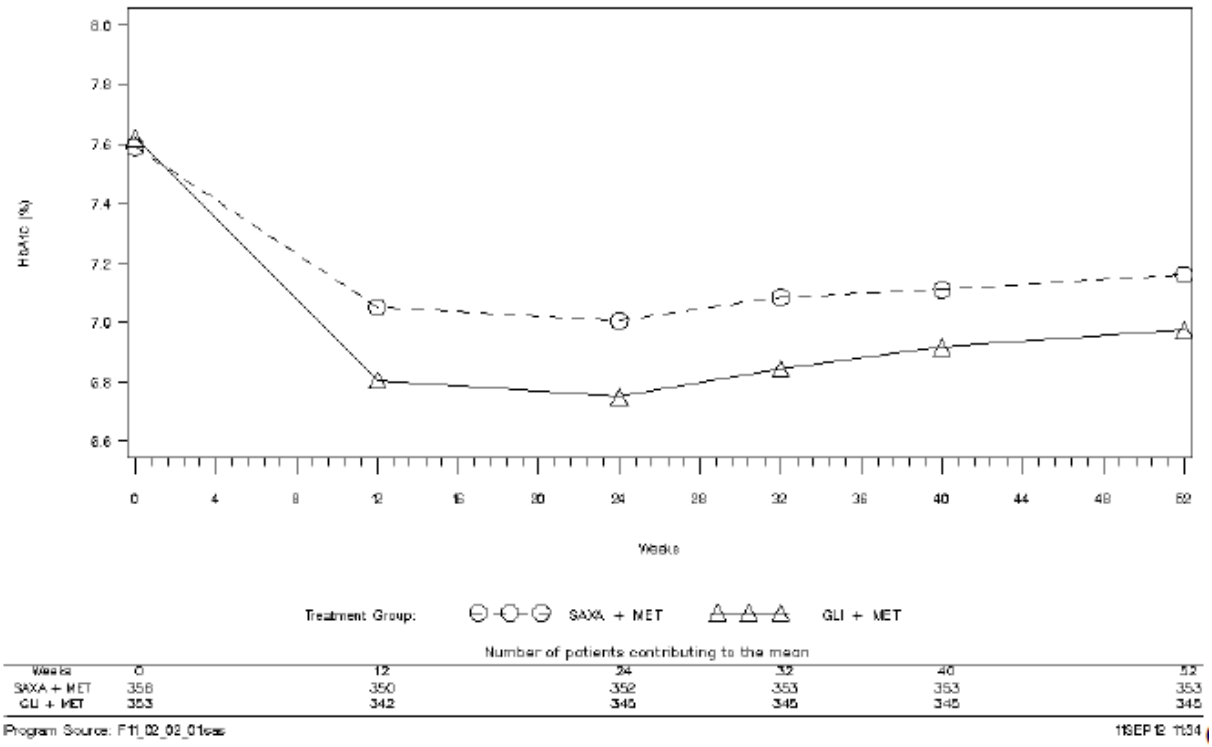


Figure 7: Change in HBA1c (mean values) over the course of Study D1680L00002 (full analysis set, LOCF, total population).

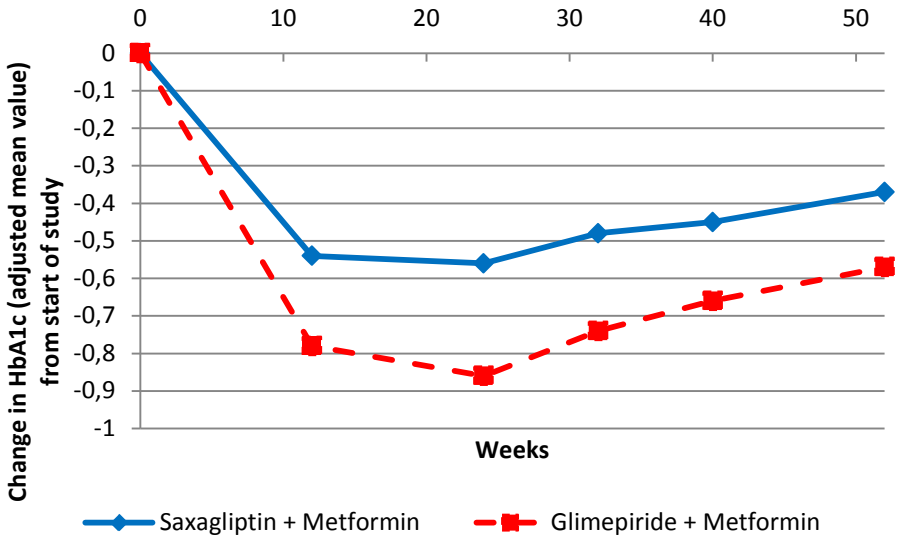


Figure 8: Change in HBA1c over the course of Study D1680L00002 (full analysis set, LOCF, repeated measures analysis, target population).

If one considers the time course of the change in HbA1c, a rapid decrease in HbA1c to the aspired near-normal level is evident under target-level directed treatment with glimepiride during the titration phase (first 12 weeks of the study). The minimum HbA1c value was

reached at Week 24. A decrease in HbA1c was also observed in the saxagliptin group. In relation to the glimepiride group it was markedly less pronounced. The difference between treatment groups was greatest after Week 24.

The effect of the titration phase influenced the subsequent treatment phase and was visible during the whole course of the study. The difference in HbA1c between treatment groups reached in Week 24 largely remained until the end of study. At the end of study the mean values were about 7 % (7.2% under saxagliptin and 7.0% under glimepiride).

In the comments on Assessment A12-16 [10], the company pointed out that a statistically significant interaction existed for the characteristic "age" with regard to the difference in the mean change in HbA1c ($p = 0.0389$ for the interaction in the total population). According to the company, there was no relevant difference for patients < 75 years (difference in mean values 0.08 [-0.10; 0.26]), whereas the difference was clearly notable in patients older than 75 years (difference in mean values: 0.36 [0.11; 0.61]). The analysis presented by the company is insufficient for evaluation of decrease in HbA1c, as it does not capture the time course. The two following figures show the time course separated according to age groups. This showed that the titration-related difference in HbA1c existed in both age groups and the HbA1c courses only approximated to each other close to the end of study for patients aged under 75 years.

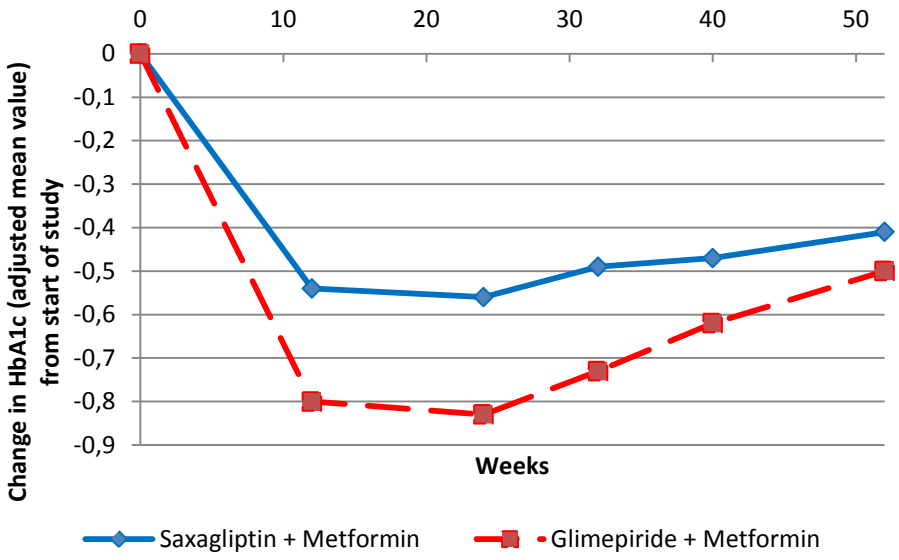


Figure 9: Change in HBA1c over the course of Study D1680L00002 (full analysis set population, repeated measures analysis, target population, age group < 75 years)

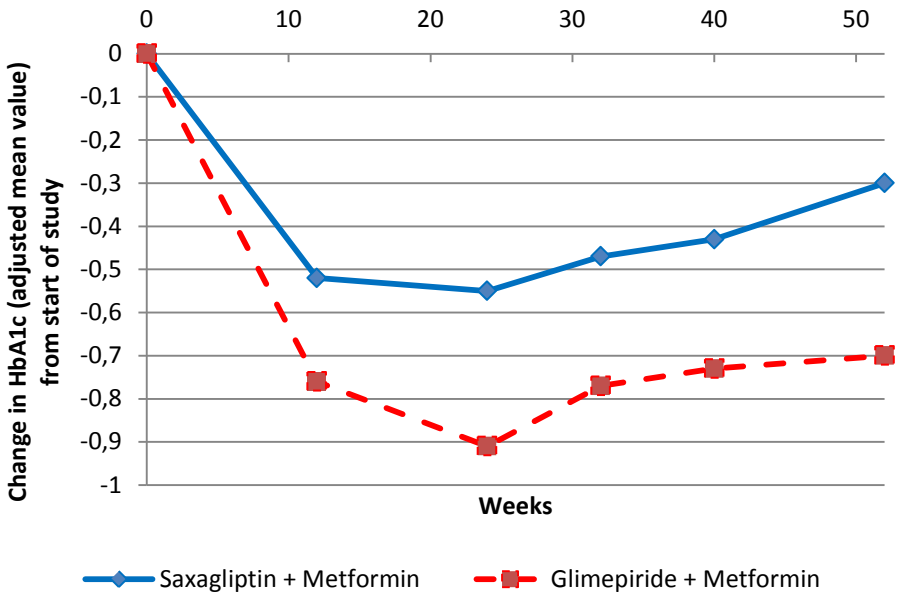


Figure 10: Change in HBA1c value over the course of the Study D1680L00002 (full analysis set, LOCF, repeated measures analysis, target population, age group ≥ 75 years)**Hypoglycaemia**

The time course of the occurrence of hypoglycaemia corresponds as expected with the described course of blood-glucose lowering. Figure 11 shows the time to occurrence of the first hypoglycaemic event (Kaplan-Meier curve) in the total population of D1680L00002. Severe hypoglycaemia[3] relevant to the assessment as well as (due to a lack of better data) symptomatic or asymptomatic hypoglycaemia with a blood-glucose level ≤ 54 mg/dL are presented.[4] The latter presumably also contain results not relevant to the assessment. Figure 12 and Figure 13 show the time course of all patient-relevant hypoglycaemic events (not only first events) in the total population (operationalized as major[3] hypoglycaemic events [Figure 12] and as confirmed symptomatic hypoglycaemic events with a blood-glucose level ≤ 50 mg/dL [Figure 13]).

[3] Major hypoglycaemic events were defined as follows "symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour, with or without blood glucose level < 3 mmol/L (< 54 mg/dL), but with prompt recovery after glucose or glucagon administration."

[4] These events were defined as follows: "any event defined as either a symptomatic event with blood glocuse level < 3 mmol/L (< 54mg/dL) and no need for external assistance, or an asymptomatic blood glucose measurement < 3 mmol/L (< 54mg/dL)."

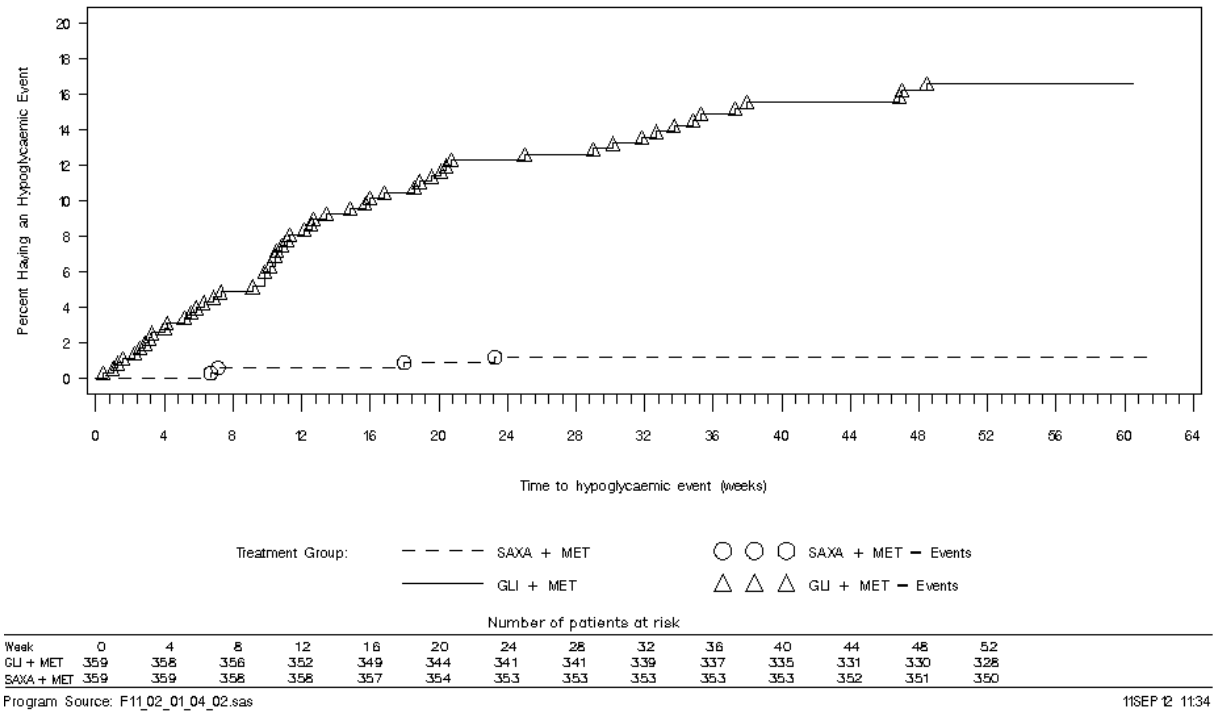


Figure 11: Time to first hypoglycaemic event over the course of Study D1680L00002 (safety analysis set, total population).

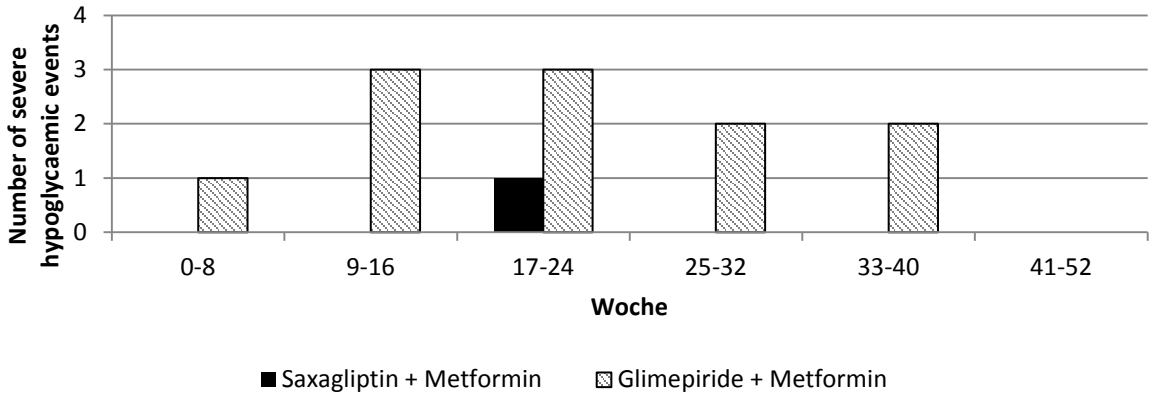


Figure 12: Time course of severe hypoglycaemic events over the course of Study D1680L00002 (safety analysis set, total population).

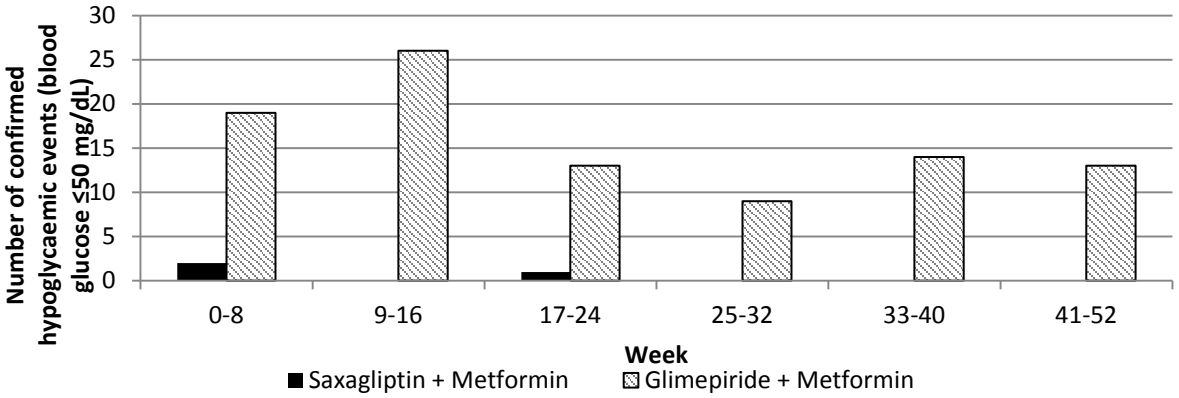


Figure 13: Time course of confirmed hypoglycaemic events over the course of Study D1680L00002 (safety analysis set, total population).

It was shown that in patients who experience hypoglycaemic events under glimepiride, these events had already occurred in the first 24 weeks during the rapid decrease of HbA1c values. Hypoglycaemic events only occurred sporadically under saxagliptin. It was shown for severe and confirmed hypoglycaemic events that such events were slightly more common under glimepiride in the first 24 weeks, but also occurred in the second study phase, in line with the continuing difference in HbA1c values up to the end of study. As the time course of hypoglycaemic events was available only for the total population, but not for the target population, it is unclear whether a similar picture is shown in the target population (in whom a higher metformin dose was a precondition for treatment).

Hypoglycaemic events under glimepiride also occurred in the first 3 weeks of the study, that is, also under the lowest glimepiride dose. Such events cannot therefore be explained by the titration, but rather by the fact that the study included patients for whom treatment escalation was evidently not necessary and in whom the lowest glimepiride dose had led to a marked blood-glucose lowering.

In summary it can be determined that the time course of occurrence of hypoglycaemic events corresponded to blood-glucose lowering. The substantial differences in blood-glucose lowering between treatment groups were apparently induced by the one-sided specification of the target level for glimepiride. This applies equally to patients below and over 75 years of age. The HbA1c values achieved indicate that for most patients, no treatment escalation would have been necessary. On the basis of Study D1680L00002, no added benefit can be inferred due to a lower rate of hypoglycaemic events of saxagliptin/metformin versus glimepiride/metformin.

Further outcomes

Results on mortality as well as on cardiac or cerebral events could only be inferred from data on adverse events. Study D1680L00002 was not designed to infer an advantage or non-inferiority of saxagliptin/metformin versus glimepiride/metformin for the outcomes

particularly relevant to the area of treatment. Due to the above-described deficiencies in study design and in the included population, such data would however not be interpretable in the sense of an advantage specific to one of the drugs.

Quality of life was recorded with the EQ-5D questionnaire. These data were only available for the total population in whom no statistically significant difference was shown (difference in mean values: -1.0 [-3.4, 1.4]; p = 0.404). However, due to the described deficiencies in the study, these data are not interpretable.

The data on adverse events (including serious AEs and treatment discontinuations due to AEs) were also not interpretable, especially as hypoglycaemic events were also recorded under these outcomes.

Results of Study D1680L00002 are shown in the following Table 10 for reasons of completeness. If available, data on the target population are preferentially presented, and effect estimates are only presented for this population.

Table 10: Results for the comparison of treatment regimen saxagliptin versus treatment regimen glimepiride (Study D1680L00002, dual combination with metformin)

Outcome category **Outcome**	**Treatment regimen saxagliptin+metformin**		**Treatment regimen glimepiride +metformin**		**Saxagliptin vs. glimepiride**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**Effect estimates [95% CI] p-value**
Mortality					
All-cause mortality[a]	190	1 (0.5)	171	0 (0.0)	p = 0.421[b]
Cardiac events[c,d]	No data were available for the target population. Data for the total population:				
	359	10 (2.8)	359	9 (2.5)	-
Cerebral events[c]	No data were available for the target population. Data for the total population:				
Nervous system disorders[e]	359	1 (0.3)	359	4 (1.1)	-
Health-related quality of life					
	No data were available for the target population. Data for the total population:				
EQ-5D VAS[f]	N	Values at start of study mean (SE) / Change at end of study mean (SE)	N	Values at start of study mean (SE) / Change at end of study mean (SE)	-
	334	73.7 (1.1) / 0.6 (0.9)	327	73.3 (1.1) / 1.6 (0.9)	-
Adverse events					
Hypoglycaemia					
Severe[c]	No data were available for the target population. Data for the total population:				
	359	1 (0.3)	359	6 (1.7)	-
Confirmed symptomatic hypoglycaemia (blood glucose ≤50 mg/dL)[c]	190	1 (0.5)	171	19 (11.1)	Peto OR[g]: 0.13 [0.05; 0.33] p < 0.001[b]
HbA1c change	See previous figures for data on HbA1c during the course of the study				
Pancreatitis[c]	No data were available for the target population. As no pancreatitis events occurred in the total population, the data also apply to the target population				
	359	0 (0.0)	359	0 (0.0)	-
Overall rate AE[c,h]	190	117 (61.6)	171	99 (57.9)	-
Overall rate SAE[c,h]	190	25 (13.2)	171	16 (9.4)	RR[g]: 1.41 [0.78; 2.54] p = 0.266[b]
Treatment discontinuations due to AE[c,h]	190	11 (5.8)	171	3 (1.8)	RR[g,i]: 3.30 [0.94; 11.63] p = 0.049[b]

(continued on next page)

Table 10: Results for the comparison of treatment regimen saxagliptin versus treatment regimen glimepiride (Study D1680L00002, dual combination with metformin) (continued)

Outcome category **Outcome**	**Treatment regimen saxagliptin+metformin**			**Treatment regimen glimepiride +metformin**			**Saxagliptin vs. glimepiride**
	N	**Patients with event n (%)**		**N**	**Patients with event n (%)**		**Effect estimates [95% CI] p-value**
Supplementary outcome body weight							
Weight increase of at least 7%[j]	187	5 (2.7)		166	3 (1.8)		RRg: 1.48 [0.36; 6.10] p = 0.619b
Change in body weight in kg[k]	N	Values at start of study mean (SE)	Change at end of study mean (SE)	N	Values at start of study mean (SE)	Change at end of study mean (SE	Difference in means
	189	84.1 (1.2)	-0.58 (0.2)	167	83.1 (1.2)	0.96 (0.2)	-1.5 [-2.2. -0.9] p = n.d.

a: Randomized analysis set population (defined as all randomized patients).

b: Institute's calculation, unconditional exact test (CSZ method according to [8]).

c: Safety analysis set population (defined as all randomized subjects who took at least one dose of study medication.

d: Serious cardiac events. MedDRA SOC "Cardiac disorders". The company presented an analysis of cardiac events for the target population; however, this also contains non-serious events.

e: Serious cerebral events. MedDRA SOC "Nervous system disorders". An analysis of only ischaemic events, e.g. TIA or stroke, was not available.

f: Mean values adjusted according to baseline value – Analysis of the full analysis set population (defined as all randomized patientswho took at least one dose of study medication, have a non-missing efficacy value at the start of the study and at least one value in the treatment phase).

g: Institute's calculation; asymptotic.

h: Hypoglycaemic events were also recorded here.

i: Discrepancy between p-value (exact) and confidence interval (asymptotic) due to different calculation methods.

j: LOCF analysis of the FAS population.

k: Mean values adjusted to weight at start of study (LOCF analysis of the FAS population).

AE: adverse event; CI: confidence interval; CSZ; convexity, symmetry, z score; FAS: full analysis set; ITT: intention-to-treat; N: number of analysed patients; n: number of patients with event; n.d.: no data; OR: odds ratio, RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SE: standard error; TIA: transient ischaemic attack; vs.: versus

2.2.3 Summarizing conclusion on added benefit

Study D1680L00002 does not provide proof of an added benefit of the fixed combination of saxagliptin/metformin versus treatment with glimepiride plus metformin.

2.3 Data sources for the studies assessed

Study D1680C00001

Astra Zeneca, Bristol-Myers Squibb. Additional analyses of endpoints and subgroups for study: a 52-week international, multi-centre, 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.

AstraZeneca, Bristol-Myers Squibb. Additional analyses of hypoglycemic events 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]. 2013.

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.

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.

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.

Study D1680L00002

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.

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.

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