IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Albiglutid – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 23 December 2014). 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.

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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. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
DPP-4	dipeptidyl peptidase 4
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLP-1	glucagon-like-peptide 1
HbA1c	glycosylated haemoglobin A1c
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug albiglutide. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 1 October 2014.

Research question

The aim of this report was to assess the added benefit of albiglutide for the treatment of adults with type 2 diabetes mellitus in the following approved subindications:

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to contraindications or intolerance.

Combination therapy

In combination with other glucose-lowering medicinal products including basal insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

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

Table 2: Subindications, research questions and ACTs on albiglutide considered in the benefit assessment

Research question	Subindication[a]	Research question of the company[b]	ACT specified by the G-BA
A	Monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to contraindications or intolerance	Module A monotherapy with albiglutide	Sulfonylurea (glibenclamide or glimepiride)
B	Combination with another blood-glucose lowering drug (except insulin) when this, together with diet and exercise, does not provide adequate glycaemic control	Module B albiglutide + metformin	Metformin + sulfonylurea (glibenclamide or glimepiride) *(note: If metformin is inappropriate according to the SPC, human insulin is to be used as treatment option.)*
C	Combination with at least 2 other blood-glucose lowering drugs when these, together with diet and exercise, do not provide adequate glycaemic control	Module C albiglutide + metformin + sulfonylurea	Metformin + human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)*
D	Combination with insulin[c] (with or without oral antidiabetics)	Module D albiglutide + insulin glargine with or without oral antidiabetics	Metformin + human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)*

a: Subdivisions of the therapeutic indication according to the G-BA.
b: Designation corresponds to the coding in the company's dossier.
c: According to the SPC, only the combination with basal insulin is approved, but not with other types of insulin therapy.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

Deviating from the company, the total therapeutic indication, and not only specific combinations of albiglutide within the respective indication, was considered for research questions B to D.

The assessment was conducted based on patient-relevant outcomes and on direct comparative randomized controlled trials (RCTs) with a minimum duration of 24 weeks.

Results

Research question A: albiglutide monotherapy

The company presented no relevant data for research question A. Hence the added benefit of albiglutide in monotherapy versus the ACT specified by the G-BA (sulfonylurea [glibenclamide or glimepiride]) is not proven.

Research question B: albiglutide in combination with another blood-glucose lowering drug (except insulin)

Study GLP 112753 (HARMONY 3, hereinafter referred to as "HARMONY 3") was included in the assessment. In the study, albiglutide + metformin was compared with glimepiride + metformin.

The HARMONY 3 study was a randomized, active- and placebo-controlled, double-blind approval study sponsored by the company with a treatment phase of 156 weeks in total. Adult patients with type 2 diabetes mellitus were enrolled in whom no sufficient glycaemic control was achieved despite treatment with metformin at a stable dosage of ≥ 1500 mg (or maximum tolerated dosage < 1500 mg/day) (glycosylated haemoglobin A1c [HbA1c] at the last visit in the run-in/stabilization phase between 7% and 10%).

The study comprised a 2-week screening phase, a 4-week run-in/stabilization phase, a double-blind randomized treatment phase of 156 weeks, and follow-up of 8 weeks. One interim analysis was planned per protocol after all patients had reached week 104.

Treatment regimen and glimepiride dosage

After randomization, the patients in the arms relevant for the assessment received one of the following study treatments:

- daily metformin (≥ 1500 mg) at their current dosage + once weekly albiglutide 30 mg subcutaneously

or

- daily metformin (≥ 1500 mg) at their current dosage + daily glimepiride 2 mg

The patients additionally received placebo of the other drug to maintain blinding. Starting from week 4 after randomization, blinded dose adjustment of albiglutide from 30 to 50 mg or of glimepiride from 2 to 4 mg could be conducted if needed. The criteria for dose increase were identical in both treatment arms.

Risk of bias

The risk of bias of the HARMONY 3 study at study level and for most outcomes was rated as low. Deviating from the company, the outcomes "severe hypoglycaemias" and "symptomatic hypoglycaemias" (blood glucose ≤ 70 mg/dL and ≤ 54 mg/dL) were rated as potentially highly biased because of the use of glimepiride in the HARMONY 3 study. According to the approval of glimepiride, a low starting dose and stepwise increase, based on the metabolic control aimed at, up to a maximum daily dose of 6 mg are recommended. In the HARMONY 3 study, the use of glimepiride described above was within the specifications of the approval. However, with the dosages used in the study, the dosages of 1 mg, 3 mg, 5 mg and 6 mg were not available to the investigators. As a result, neither the lowest starting dose of 1 mg nor titration steps of 1 mg could be administered. This may have consequences on the

treatment effects, particularly regarding hypoglycaemias. Considering the time courses of hypoglycaemias and of the HbA1c value, there was a notable increase in hypoglycaemias in the glimepiride arm at the start of the study and in the further course of the study in comparison with albiglutide while the HbA1c value decreased in a nearly identical way (up to approximately 24 weeks). In the further course, the HbA1c decrease from albiglutide was even more pronounced. Hence it cannot be assumed that the differences between hypoglycaemic events of the 2 study arms can be explained solely by the use of glimepiride described. An influence on the results cannot be excluded, however. The risk of bias was therefore assumed to be high for the outcomes on hypoglycaemias in the HARMONY 3 study.

General note on the presentation of results and types of analysis

For some of the outcomes included in the assessment, analyses on several time periods were available (all patients had reached at least week 104, total observation period of 164 weeks). For the present assessment, the analysis of the longest available time period was used for each outcome. Hence deviating from the results presented in the company's dossier, analyses at the time point 164 weeks were included in the assessment for most outcomes.

Mortality

There was no statistically significant difference between the treatment groups regarding deaths. An added benefit of albiglutide + metformin compared with glimepiride + metformin for overall survival is therefore not proven.

Morbidity

- stroke (all, adjudicated) and stroke (nonfatal, adjudicated)

There was no statistically significant difference between the treatment groups regarding stroke for both outcomes. An added benefit of albiglutide + metformin compared with glimepiride + metformin for the 2 outcomes on stroke is therefore not proven.

- cardiac morbidity

The difference between the treatment groups for the outcome "cardiac morbidity" was not statistically significant. An added benefit of albiglutide + metformin compared with glimepiride + metformin for cardiac morbidity is therefore not proven.

Health-related quality of life

The outcome "health-related quality of life" was not recorded in the HARMONY 3 study.

Adverse events

- serious adverse events (SAEs) and discontinuation due to adverse events (AEs)

There were no statistically significant differences between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". Greater or lesser harm from albiglutide + metformin in comparison with glimepiride + metformin is therefore not proven.

- severe hypoglycaemias

There was no statistically significant difference between the treatment groups regarding severe hypoglycaemias. Greater or lesser harm from albiglutide + metformin in comparison with glimepiride + metformin is therefore not proven.

- confirmed symptomatic hypoglycaemias (blood glucose ≤ 70 mg/dL and blood glucose ≤ 54 mg/dL)

Statistically significantly fewer symptomatic hypoglycaemias occurred under albiglutide + metformin (both confirmed by blood glucose ≤ 70 mg/dL and by blood glucose ≤ 54 mg/dL) than under glimepiride + metformin.

Due to the high risk of bias, there is overall a hint of lesser harm from albiglutide + metformin than from glimepiride + metformin for the outcome of symptomatic hypoglycaemias (blood glucose ≤ 70 mg/dL and ≤ 54 mg/dL).

- injection site reactions

Regarding the proportion of patients with at least one injection site reaction up to week 164, there was a statistically significant difference to the disadvantage of albiglutide + metformin.

Since patients in the comparator arm received placebo injections, the available results represent the substance-specific difference – injection with albiglutide versus injection with placebo. The fact that the ACT glimepiride is administered orally has to be taken into account. Due to the form of administration it has to be assumed that results for this outcome cannot occur at all under the use of glimepiride. Hence the observed effect (substance-specific difference) regarding injection site reactions is underestimated with regard to the present research question (assessment of the substance-specific effects plus harm from the injection itself). This has no consequence for the present benefit assessment, however, because the effect size already resulted in the greatest extent ("considerable") for this outcome category of non-serious/non-severe AEs.

Research question C: albiglutide in combination with at least 2 other blood-glucose lowering drugs

The company presented no relevant data for research question C. Hence the added benefit of albiglutide in combination with at least 2 other blood-glucose lowering drugs versus the ACT specified by the G-BA (metformin + human insulin) is not proven.

Research question D: albiglutide in combination with insulin (with or without oral antidiabetics)

The company presented no relevant data for research question D. Hence the added benefit of albiglutide + insulin (with or without oral antidiabetics) versus the ACT specified by the G-BA (metformin + human insulin) is not proven.

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 albiglutide compared with the ACT is assessed as follows:

Research question A: albiglutide monotherapy

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of albiglutide in monotherapy in comparison with the ACT specified by the G-BA (sulfonylurea [glibenclamide or glimepiride]). Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

Research questions B: albiglutide in combination with another blood-glucose lowering drug (except insulin)

Overall, one positive effect and one negative effect remain in the same outcome category (non-serious/non-severe AEs). There was a positive effect in the outcome category "non-serious/non-severe AEs" for confirmed symptomatic hypoglycaemias with a hint of lesser harm (extent: "considerable"). There was a negative effect in the outcome category "non-serious/non-severe AEs" for injection site reactions with an indication of greater harm (extent: "considerable"). Hence there are opposing conclusions on AEs. Although there are opposing effects of the same extent, the disadvantage regarding injection site reactions cannot completely outweigh the advantage regarding confirmed symptomatic hypoglycaemias. However, it resulted in weakening the extent so that there is overall a hint of a minor added benefit of albiglutide + metformin versus glimepiride + metformin.

No sufficient data were available on micro- and macrovascular late complications. This led to an additional uncertainty.

In summary, there is a hint of a minor added benefit of albiglutide + metformin in comparison with glimepiride + metformin.

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

This deviates from the company's approach, which derived an indication of a considerable added benefit of albiglutide + metformin versus the ACT.

Furthermore, the added benefit is not proven for the dual combination with blood-glucose lowering drugs other than metformin and insulin. The company presented no data for other combinations.

Research question C: albiglutide in combination with at least 2 other blood-glucose lowering drugs

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of albiglutide in combination with at least 2 other blood-glucose lowering drugs in comparison with the ACT specified by the G-BA (metformin + human insulin). Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived. The company claimed no added benefit for this research question.

Research question D: albiglutide in combination with insulin (with or without oral antidiabetics)

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of albiglutide in combination with insulin (with or without oral antidiabetics) in comparison with the ACT specified by the G-BA (metformin + human insulin). Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived. The company claimed no added benefit for this research question.

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

Table 3: Albiglutide – extent and probability of added benefit

Research question	**Subindication**	**ACT**	**Extent and probability of added benefit**
A	Monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to contraindications or intolerance	Sulfonylurea (glibenclamide or glimepiride)	Added benefit not proven
B	Albiglutide + metformin combination with another blood-glucose lowering drug (except metformin and insulin) when this, together with diet and exercise, does not provide adequate glycaemic control	Metformin + sulfonylurea (glibenclamide or **glimepiride**[a]) (note: If metformin is inappropriate according to the SPC, human insulin is to be used as treatment option.)	Hint of an added benefit, extent: "minor" added benefit not proven
C	Combination with at least 2 other blood-glucose lowering drugs when these, together with diet and exercise, do not provide adequate glycaemic control	Metformin + human insulin (note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)	Added benefit not proven
D	Combination with insulin (with or without oral antidiabetics)	Metformin + human insulin (note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)	Added benefit not proven

a: The company chose no option, but presented a study versus glimepiride. Hence glimepiride is the ACT and is printed in **bold**.

ACT: appropriate comparator therapy; SPC: Summary of Product Characteristics

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

2.2 Research question

The aim of this report was to assess the added benefit of albiglutide for the treatment of adults with type 2 diabetes mellitus in the following approved subindications:

Monotherapy
When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to contraindications or intolerance.

Combination therapy
In combination with other glucose-lowering medicinal products including basal insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

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

Table 4: Subindications, research questions and ACTs on albiglutide considered in the benefit assessment

Research question	**Subindication**[a]	**Research question of the company**[b]	**ACT specified by the G-BA**
A	Monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to contraindications or intolerance	Module A monotherapy with albiglutide	Sulfonylurea (glibenclamide or glimepiride)
B	Combination with another blood-glucose lowering drug (except insulin) when this, together with diet and exercise, does not provide adequate glycaemic control	Module B albiglutide + metformin	Metformin + sulfonylurea (glibenclamide or glimepiride) *(note: If metformin is inappropriate according to the SPC, human insulin is to be used as treatment option.)*
C	Combination with at least 2 other blood-glucose lowering drugs when these, together with diet and exercise, do not provide adequate glycaemic control	Module C albiglutide + metformin + sulfonylurea	Metformin + human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)*
D	Combination with insulin[c] (with or without oral antidiabetics)	Module D albiglutide + insulin glargine with or without oral antidiabetics	Metformin + human insulin *(note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)*

a: Subdivisions of the therapeutic indication according to the G-BA.
b: Designation corresponds to the coding in the company's dossier.
c: According to the SPC, only the combination with basal insulin is approved, but not with other types of insulin therapy.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The research questions considered by the company in Modules B to D only covered parts of the approved therapeutic indication of albiglutide:

- In research question B, combinations with other blood-glucose lowering drugs (e.g. sulfonylureas or dipeptidyl peptidase 4 [DPP-4] inhibitors) are an option besides the combination with metformin.
- In research question C, combinations with other blood-glucose lowering drugs (e.g. DPP-4 inhibitors) are an option besides the combination with metformin and sulfonylurea.
- In research question D, combinations with other types of insulin (basal insulin) are an option besides the combination with insulin glargine.

The company oriented its research questions towards the interventions used in its approval studies and did not address the deviations from the research question (see Section 2.8.1 of the full dossier assessment).

The present dossier assessment comprises the complete research questions, which include all possible combinations.

Research question A: albiglutide monotherapy

The benefit assessment for albiglutide monotherapy was conducted in comparison with the ACT sulfonylurea (glibenclamide or glimepiride) specified by the G-BA. The company claimed to follow the G-BA's specification, but chose no specific sulfonylurea as ACT.

Research questions B: albiglutide in combination with another blood-glucose lowering drug (except insulin)

For the dual combination of albiglutide with another blood-glucose lowering drug (except insulin), the G-BA specified metformin + sulfonylurea (glibenclamide or glimepiride) as ACT with the note that human insulin is to be used as treatment option if metformin is inappropriate according to the Summary of Product Characteristics (SPC). The company claimed to follow the G-BA's specification for the combination of albiglutide and metformin, but chose no specific sulfonylurea as ACT. The company named no ACT for combinations of albiglutide with another blood-glucose lowering drug (except insulin or metformin).

Research question C: albiglutide in combination with at least 2 other blood-glucose lowering drugs

For research question C, the G-BA specified metformin + human insulin as ACT with the note that treatment was to be conducted with human insulin alone when metformin is not sufficiently effective or not tolerated according to the SPC. The company named human insulin + metformin as ACT, thus following the G-BA's specification. It argued in Module 3 C, Section 3.1, that insulin analogues would also be an option as ACT. However, this had no consequence because it adhered to its choice of using human insulin as ACT, and in Module 4 C (Sections 4.2.1 and 4.2.2) also only searched for studies in which human insulin + metformin was used as comparator therapy. The company named no ACT for further combinations of albiglutide with at least 2 other blood-glucose lowering drugs (except metformin and sulfonylurea). The present assessment was conducted versus the ACT specified by the G-BA.

Research question D: albiglutide in combination with insulin (with or without oral antidiabetics)

For research question D, the G-BA specified metformin + human insulin as ACT with the note that treatment was to be conducted with human insulin alone when metformin is not sufficiently effective or not tolerated according to the SPC. The company named human insulin + metformin as ACT, thus following the G-BA's specification. It argued in

Module 3 D, Section 3.1 that insulin analogues would also be an option as ACT. However, this had no consequence because it adhered to its choice of using human insulin as ACT, and in Module 4 D (Sections 4.2.1 and 4.2.2) also only searched for studies in which human insulin + metformin was used as comparator therapy. The company named no ACT for the combination of albiglutide with other insulins (except insulin glargine). The present assessment was conducted versus the ACT specified by the G-BA.

Summary

In summary, the assessment of albiglutide in the different research questions presented was conducted versus the ACTs specified by the G-BA.

The assessment was conducted based on patient-relevant outcomes and on direct comparative RCTs with a minimum duration of 24 weeks.

2.3 Research question A: albiglutide monotherapy

2.3.1 Information retrieval and study pool (research question A)

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

- study list on albiglutide (studies completed up to 18 July 2014)
- bibliographical literature search on albiglutide (last search on 21 July 2014)
- search in trial registries for studies on albiglutide (last search on 31 July 2014)

The company identified no relevant study for a comparison of albiglutide in monotherapy versus the ACT specified by the G-BA.

2.3.2 Results on added benefit (research question A)

The company presented no relevant data for research question A. Hence the added benefit of albiglutide in monotherapy versus the ACT specified by the G-BA (sulfonylurea [glibenclamide or glimepiride]) is not proven.

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

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of albiglutide in monotherapy in comparison with the ACT specified by the G-BA (sulfonylurea [glibenclamide or glimepiride]). Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived. The company claimed no added benefit for this research question.

2.3.4 List of included studies (research question A)

Not applicable as the company did not present any relevant studies in its dossier from which an added benefit of albiglutide in monotherapy versus the ACT specified by the G-BA (sulfonylurea [glibenclamide or glimepiride]) can be derived.

2.4 Research question B: albiglutide in combination with another blood-glucose lowering drug (except insulin)

2.4.1 Information retrieval and study pool (research question B)

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

- study list on albiglutide (studies completed up to 18 July 2014)
- bibliographical literature search on albiglutide (last search on 21 July 2014)
- search in trial registries for studies on albiglutide (last search on 31 July 2014)

To check the completeness of the study pool:

- search in trial registries for studies on albiglutide (last search on 17 October 2014)

No additional relevant study was identified from the check.

2.4.1.1 Studies included (research question B)

Study HARMONY 3 listed in the following table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: albiglutide + metformin vs. glimepiride + metformin

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
HARMONY 3	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of albiglutide + metformin corresponded to that of the company. It included study GLP 112753 (HARMONY 3, hereinafter referred to as "HARMONY 3"). In the study, albiglutide + metformin was compared with glimepiride + metformin.

Section 2.4.4 contains a reference list for the study included.

2.4.1.2 Study characteristics (research question B)

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: albiglutide + metformin vs. glimepiride + metformin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
HARMONY 3	RCT, double-blind, parallel	Adult patients with type 2 diabetes mellitus with inadequate glycaemic control under metformin treatment	Albiglutide + metformin (N = 315) glimepiride + metformin (N = 317) sitagliptin + metformin (N = 313)[b] placebo + metformin (N = 104)[b]	▪ Screening: approximately 2 weeks ▪ Run-in/stabilization: 4 weeks ▪ Treatment phase: 156 weeks in total ▪ Follow-up: 8 weeks	289 centres in 10 countries: Germany, Hong Kong, Mexico, Peru, Philippines, Russia, South Africa, Spain, United Kingdom, United States 2/2009-3/2013	Primary outcome: change in HbA1c after 104 weeks of treatment Secondary outcomes: hypoglycaemias, cardiovascular morbidity, 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 this benefit assessment.
b: The arm is not relevant for the assessment and is not shown in the next tables.
HbA1c: glycosylated haemoglobin A1c; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: albiglutide + metformin vs. glimepiride + metformin

Study	Albiglutide + metformin	Glimepiride + metformin
HARMONY 3	Metformin (≥ 1500 mg) at current dosage, daily + albiglutide, 30 mg subcutaneously once weekly (if needed, blinded dose adjustment to 50 mg starting from week 4 after randomization) + sitagliptin placebo, daily + glimepiride placebo, daily	Metformin (≥ 1500 mg) at current dosage, daily + glimepiride 2 mg, daily (if needed, blinded dose adjustment to 4 mg starting from week 4 after randomization) + sitagliptin placebo, daily + albiglutide placebo, subcutaneously once weekly
	▪ Pretreatment: pretreatment at least 12 weeks before screening with metformin ≥ 1500 mg/day (or maximum tolerated dose < 1500 mg/day for at least 8 weeks before randomization) at a stable dose for at least 8 weeks ▪ As-needed medications: Hyperglycaemic rescue medication (dose increase of the study medication or administration of so-called rescue medication of physician's choice [other antidiabetics except other GLP-1 receptor agonists like exenatide or liraglutide as well as the DPP-4 inhibitor sitagliptin] in addition to the randomized study medication and background therapy) was allowed within defined glucose thresholds. ▪ Concomitant medication prohibited: ▫ antidiabetic medication except metformin and the study medication ▫ oral corticosteroids or systemic corticosteroids given as injection (individual doses of oral corticosteroids or repeated doses of up to 2 days were allowed) ▫ antiretroviral drugs ▫ prescription or over-the-counter drugs for weight reduction	
DPP-4: dipeptidyl peptidase 4;GLP-1: glucagon-like-peptide 1; RCT: randomized controlled trial; vs.: versus		

Study design

The HARMONY 3 study was a randomized, active- and placebo-controlled, double-blind approval study sponsored by the company with a treatment phase of 156 weeks in total. Adult patients with type 2 diabetes mellitus were enrolled in whom no sufficient glycaemic control was achieved despite treatment with metformin at a stable dosage of ≥ 1500 mg (or maximum tolerated dosage < 1500 mg/day) (HbA1c at the last visit in the run-in/stabilization phase between 7% and 10%). Before screening, all patients had to have received metformin for at least 12 weeks and at a stable dosage for at least 8 weeks. The study comprised a 2-week screening phase, a 4-week run-in/stabilization phase, a double-blind randomized treatment phase of 156 weeks, and follow-up of 8 weeks. One interim analysis was planned per protocol after all patients had reached at least week 104.

A total of 1049 patients were randomly assigned in a ratio of 3:3:3:1 to one of the 4 treatment arms albiglutide + metformin, glimepiride + metformin, sitagliptin + metformin, and placebo + metformin. Patients were stratified by HbA1c value (< 8.0% versus ≥ 8.0%), history of

myocardial infarction (yes versus no) and age (< 65 versus ≥ 65 years). In the 2 study arms relevant for the present assessment, 315 patients were randomly allocated to the albiglutide arm, and 317 patients to the glimepiride arm. Of the randomized patients, 302 patients in the albiglutide arm, and 307 patients in the glimepiride arm actually received the planned treatment (safety population).

The primary outcome of the study was the change in HbA1c after 104 weeks of treatment.

Dates of analysis

In Section 4.3.1.3 in Module 4 B of the dossier, the company exclusively presented analyses in which events were included until the time point at which all patients had reached at least week 104. As described above, the total study comprised a treatment period of 156 weeks and a follow-up period of 56 days so that the observation period lasted 164 weeks in total. For the present assessment, the analysis of the longest available time period was used for each outcome. Hence deviating from the results presented in the company's dossier, analyses at the time point 164 weeks were included in the assessment for most outcomes.

Treatment regimen

After randomization, the patients in the arms relevant for the assessment received one of the following study treatments:

- daily metformin (≥ 1500 mg) at their current dosage + once weekly albiglutide 30 mg subcutaneously + daily sitagliptin placebo + daily glimepiride placebo

or

- daily metformin (≥ 1500 mg) at their current dosage + daily glimepiride 2 mg + daily sitagliptin placebo + once weekly albiglutide placebo subcutaneously

Starting from week 4 after randomization, blinded dose adjustment of albiglutide from 30 to 50 mg or of glimepiride from 2 to 4 mg could be conducted if needed. The criteria for dose increase were identical in both treatment arms. Hyperglycaemic rescue medication of physician's choice (other antidiabetics except other glucagon-like-peptide 1 (GLP-1) receptor agonists like exenatide or liraglutide as well as the DPP-4 inhibitor sitagliptin) in addition to the randomized study medication and background therapy was allowed in the study arms within defined glucose thresholds. Patients who had received dose increase of the study medication had to have received this higher dose for at least 4 weeks before they could be administered hyperglycaemic rescue medication. The criteria for dose increase of the study medication and for administration of hyperglycaemic rescue medication in the HARMONY 3 study can be found in Table 8.

Table 8: Study HARMONY 3 - conditions for dose increase or hyperglycaemic rescue medication

Time since start of treatment	**Dose increase of study medication**	**Hyperglycaemic rescue medication**
≥ day 1 and < week 2	No dose increase	No rescue medication
≥ week 2 and < week 4	No dose increase	One single fasting blood glucose value ≥ 280 mg/dL
Week 4	One single fasting blood glucose value ≥ 250 mg/dL, and HbA1c value unchanged or increased since start of study	One single fasting blood glucose value ≥ 280 mg/dL
> week 4 and < week 12	One single fasting blood glucose value ≥ 250 mg/dL, and HbA1c value unchanged or increased since start of study	One single fasting blood glucose value ≥ 250 mg/dL and previous dose increase for ≥ 4 weeks
≥ week 12 and < week 24	HbA1c value ≥ 7.5% and decrease by ≤ 0.5% since start of study	HbA1c value ≥ 8.5% and decrease by ≤ 0.5% since start of study and previous dose increase for ≥ 4 weeks
≥ week 24 and < week 104	HbA1c value ≥ 7.5%	HbA1c value ≥ 8.5% and previous dose titration for ≥ 4 weeks
≥ week 104 and < week 143	HbA1c value ≥ 7.5%	HbA1c value ≥ 8.5% and previous dose increase for ≥ 4 weeks
≥ week 143 and < week 156	No dose increase	HbA1c value ≥ 8.5% and previous dose increase for ≥ 4 weeks

Glimepiride dosage

As described above, the starting dose of glimepiride was 2 mg daily, and could be increased once to a blinded dose of 4 mg starting from week 4 after randomization. According to the SPC of glimepiride, in patients in whom no adequate metabolic control is achieved on their maximum daily dose of metformin alone, treatment is initiated with a low dosage, which is then gradually increased up to a maximum daily dose of 6 mg depending on the metabolic control aimed at [3]. In fact, 1 mg, 3 mg, 5 mg, and 6 mg dosages were not available to the investigators. Hence the patients included could not start with the lowest starting dose of 1 mg, and it was not possible to administer titration steps of 1 mg. Likewise, the dosage could not be increased to the approved maximum dosage of up to 6 mg daily. Instead of stepwise titration at 1- to 2-week intervals, only one single dose increase by 2 mg could be performed. The study design made it therefore impossible to conduct a treatment optimized for the individual patient by using the options of an approval-compliant use of glimepiride. Overall, however, the use of glimepiride in the HARMONY 3 study, with dosages of 2 mg and 4 mg, was in compliance with the approval. The uncertainties resulting from the starting dose that was presumably too high for at least some of the patients, and from the limitations regarding the possibilities of titration in the study, are described below.

It was clear from the treatment regimen of the HARMONY 3 study that the recommended dose increase of the drug reflected all dosages of the approval in the albiglutide arm, in

contrast to the glimepiride arm [3,4]. It was uncertain whether the effects observed in the study are only attributable to the respective drugs used or whether the restrictions regarding the use of glimepiride influenced the results. The time courses of the hypoglycaemias and of the HbA1c values have to be considered to assess this.

The company presented the time course of hypoglycaemias in the dossier only for the operationalization of non-severe symptomatic hypoglycaemias and only up to the time point week 104. This operationalization was not used in the present assessment. The company only presented the results on the proportion of patients with events, but no time courses, for the relevant operationalizations of the present assessment (e.g. symptomatic hypoglycaemias [blood glucose ≤ 70 mg/dL and ≤ 54 mg/dL]) in the dossier.

Figure 1 shows the time course of non-severe symptomatic hypoglycaemias (on the basis of the events) in the HARMONY 3 study up to week 104.

Figure 2 shows the change in HbA1c value in comparison with the baseline value up to week 104 in the HARMONY 3 study. Missing values were replaced with the last observation carried forward (LOCF).

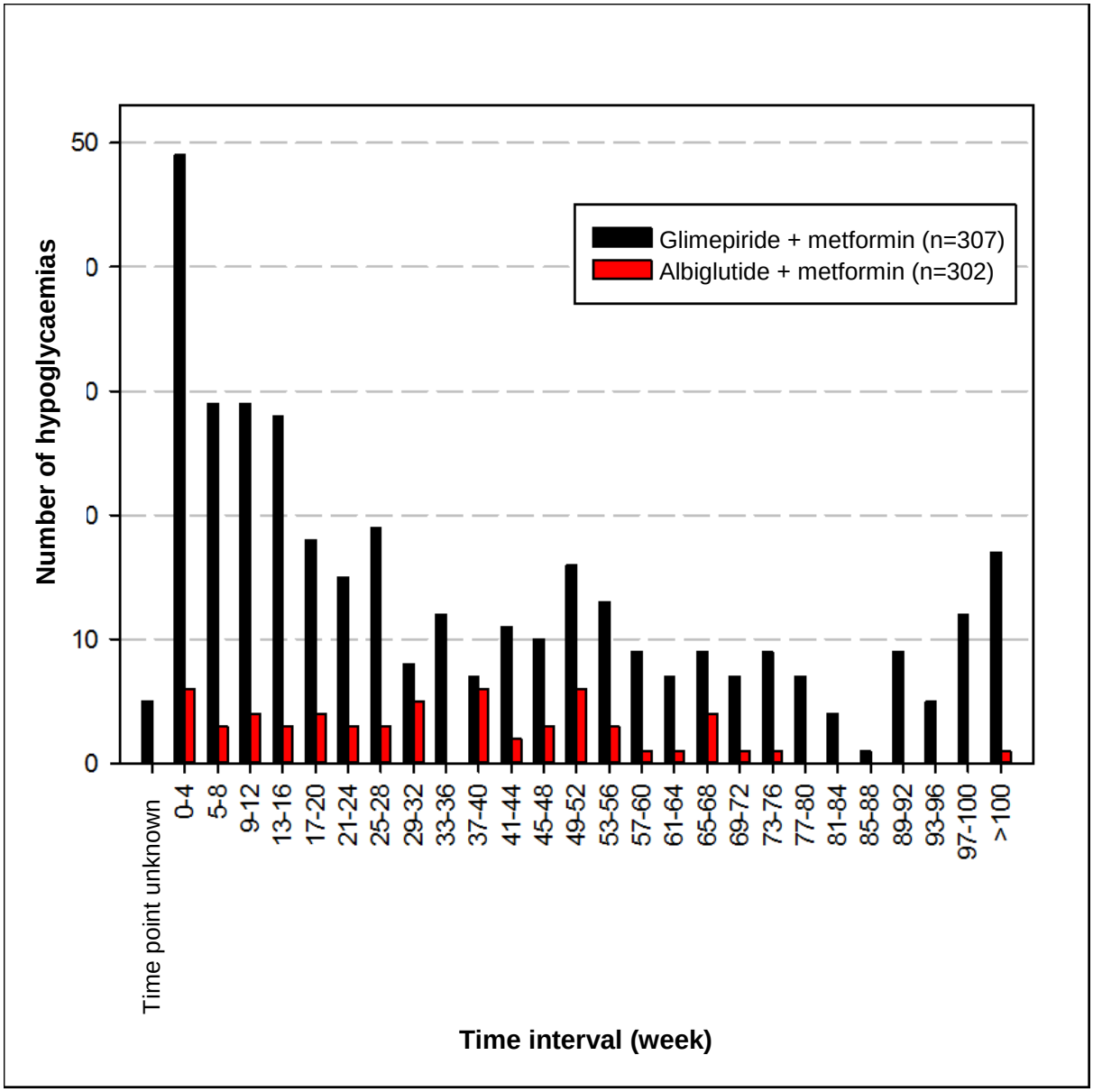
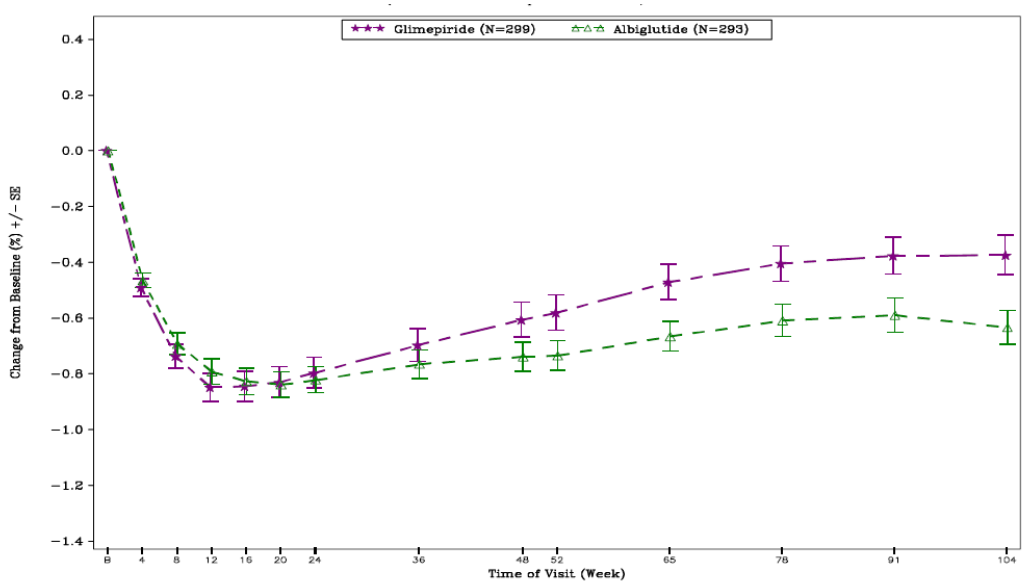


Figure 1: Time course of non-severe symptomatic hypoglycaemias in the HARMONY 3 study up to week 104



HbA1c: glycosylated haemoglobin A1c; LOCF: last observation carried forward

Figure 2: Change in HbA1c value in comparison with the baseline value up to week 104 in the HARMONY 3 study

There was a notable increase in hypoglycaemias in the glimepiride arm at the start of the study, also in comparison with albiglutide, for the operationalization shown. At a lower level, there was a higher number of hypoglycaemias in the glimepiride than in the albiglutide arm also over the total further course of the study.

At the same time, the HbA1c values up to approximately week 24 decreased in a nearly identical way from the baseline value in both relevant study arms (albiglutide + metformin versus glimepiride + metformin). Starting from week 24, the HbA1c decrease from albiglutide was even more pronounced. However, considerably fewer hypoglycaemias occurred in the albiglutide arm also after week 24.

It is unclear whether a comparable course of the hypoglycaemias would have occurred also under an administration of glimepiride that makes use of the possibilities of the approval (starting dose of 1 mg instead of 2 mg, stepwise dose adjustment). It appears questionable whether a dose increase by 2 mg instead of a possible stepwise titration in 1 mg steps was suitable for all patients. The lack of the 1 mg dosage, the 3 mg dosage and (with limitation) the dosage of more than 4 mg may result both in over- and in underdosing at an individual level. It cannot be excluded that a dose of 1 mg, 3 mg or 5 mg would have been the required dose for adequate glycaemic control for some of the patients.

It can therefore not be excluded with certainty that the notable increase of hypoglycaemias in the glimepiride arm at the start may at least partly be associated with the fixed starting dose of 2 mg glimepiride, which was presumably too high for at least some of the patients. It can also not be excluded that there was an association between intensifying therapy in the form of a

single dose increase by 2 dose steps at the same time (from 2 mg to 4 mg) and the hypoglycaemias in the glimepiride arm that occurred in the time course. In total, 56% of the patients in the albiglutide arm, and 57% of the patients in the glimepiride arm received a dose increase in the course of the study (see Table 9).

Table 9: Study HARMONY 3 – overview dose increase

	Albiglutide + metformin N = 302	**Glimepiride + metformin N = 307**
Number of patients without dose increase (%)	133 (44.0)	132 (43.0)
Number of patients with dose increase (%)	169 (56.0)	175 (57.0)
Time to dose increase (weeks) mean (min, max)	41.9 (13, 134)	41.6 (6, 142)
Number of patients with dose increase per time interval (%)		
≥ week 4 and < week 12	0	0
≥ week 12 and < week 24	58 (19.2)	58 (18.9)
≥ week 24 and < week 104	101 (33.4)	103 (33.6)
≥ week 104 and < week 143	10 (3.3)	10 (3.3)
a: For patients with dose increase, time from first dose to dose increase. max: maximum; min: minimum; N: number of analysed patients		

On the other hand, it cannot be assumed either that the differences between the hypoglycaemic events of the 2 study arms and simultaneous improved blood glucose control under albiglutide (starting from week 24) can be explained solely by the use of glimepiride described.

Overall, the assessment of hypoglycaemias in the HARMONY 3 study is subject to uncertainty due to the aspects presented above. It is not assumed that the further outcomes such as cardiac events and stroke were largely influenced by the strict use of glimepiride. In the glimepiride arm, these events did not occur before week 17, and they did not occur at the time of a dose increase. Furthermore, certain specific AE outcomes such as injection site reactions were obviously not influenced by the therapeutic regimen with glimepiride. Hence only for the outcomes on hypoglycaemias was the additional uncertainty weighted so heavily that these outcomes were considered to be potentially highly biased (see Section 2.8.3.2.4.2 of the full dossier assessment).

Consequences for study inclusion and assessment

Overall, the use of glimepiride – with the limitations presented – in the HARMONY 3 study was within the framework of the approval. The HARMONY 3 study was considered to be relevant for the assessment of the added benefit of albiglutide in combination with another blood-glucose lowering drug (except insulin).

Uncertainties mainly resulted from the fixed starting dose that was presumably too high for at least some of the patients, and from the intensified therapy in form of a single dose increase by 2 dose steps (from 2 mg to 4 mg) in the glimepiride arm.

The uncertainties described resulted in a downgrading of the certainty of results for the assessment of hypoglycaemias in the HARMONY 3 study.

Characteristics of the study population

Table 10 shows the characteristics of the patients in the study included.

Table 10: Characteristics of the study populations – study populations – RCT, direct comparison: albiglutide + metformin vs. glimepiride + metformin

Study characteristics category	Albiglutide + metformin N = 315[a]	Glimepiride + metformin N = 317[a]
HARMONY 3		
Age [years] mean (SD)	54 (10)	54 (10)
Sex: [F/M], %	55/45	49[b]/51[b]
Body weight (kg): mean (SD)	89.6 (18.4)	91.7 (20.4)
BMI (kg/m²): mean (SD)	32.7 (5.6)	32.5 (5.5)
Duration of diabetes [years]: mean (SD)[c]	6.0 (4.3)	6.0 (4.7)
HbA1c value [%]: mean (SD)	8.1 (0.8)	8.1 (0.8)
HbA1c value, n (%)		
< 8.0%	158 (52.3)	146 (47.6)
≥ 8.0%	144 (47.7)	161 (52.4)
Background metformin dose, n (%)		
< 1500 mg/day	22 (7.4)	16 (5.2)
≥ 1500 mg/day	276 (92.6)	289 (94.8)
Ethnicity, n (%)		
white[d]	213 (70.5)	227 (73.9)
non-white[e]	89 (29.5)	80 (26.1)
Treatment discontinuations[f], n (%)	110 (34.9)	116 (36.6)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b: Institute's calculation.
c: When parts of the dates of the diagnosis were missing, January was included for missing month, and the first of the month for missing day.
d: This group included white-Caucasian/European heritage, white-Arab/North African heritage.
e: This group included black (African American/African heritage) and other non-white (Indian or native Alaskans, Asian – central/South Asian heritage, Asia – East Asian heritage, Asia – Japanese heritage, Asia – South East Asian heritage, native Hawaiians or other pacific islanders).
f: Up to week 156.
BMI: body mass index; F: female; HbA1c: glycosylated haemoglobin A1c; M: male; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

There was no important difference between the treatment arms regarding age, sex, body weight, body mass index (BMI), diabetes duration, background metformin dose, and number of treatment discontinuations. The mean age of patients was 54 years and mean disease duration with type 2 diabetes mellitus was 6 years. Approximately the same proportion of men and women were included in the 2 study arms. The majority of the patients in the 2 study arms received a metformin dose of ≥ 1500 mg/day. The mean HbA1c value in the 2 study arms was 8.1% at the start of the study, and under 8% in approximately 50% of the patients at the start of the study. It remains unclear whether inadequate glycaemic control can be assumed for all patients included against the background of current knowledge. Regarding ethnicity, the proportion of whites (70%) was notably larger than the proportion of non-whites. 34.9% of the patients in the albiglutide arm, and 36.6% of the patients in the glimepiride arm, and thus approximately one third of the patients in both arms, discontinued treatment.

Risk of bias at study level

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: albiglutide + metformin vs. glimepiride + metformin

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
HARMONY 3	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

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

2.4.2 Results on added benefit (research question B)

2.4.2.1 Outcomes included (research question B)

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.8.3.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - stroke (all, adjudicated)

- stroke (nonfatal, adjudicated)
- cardiac morbidity (Medical Dictionary for Regulatory Activities [MedDRA] System Organ Class [SOC])

- Adverse events
  - SAEs
  - discontinuation due to AEs
  - hypoglycaemias (interpretation in connection with change in HbA1c value over time)
    - severe hypoglycaemias
    - symptomatic hypoglycaemias (blood glucose ≤ 70 mg/dL and ≤ 54 mg/dL)
  - injection site reactions

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 B). Reasons for the choice of outcomes are given in Section 2.8.3.2.4.3 of the full dossier assessment.

Table 12 shows for which outcomes data were available in the studies included.

Table 12: Matrix of outcomes – RCT, direct comparison: albiglutide + metformin vs. glimepiride + metformin

Study[a]	Outcomes									
	All-cause mortality	Stroke (all, adjudicated)	Stroke (nonfatal, adjudicated)	Cardiac morbidity	Severe hypoglycaemias	Symptomatic hypoglycaemias blood glucose ≤ 70 mg/dL/≤ 54 mg/dL	Health-related quality of life	SAEs	Discontinuation due to AEs	Injection site reactions
HARMONY 3	Yes	Yes[b]	Yes[b]	Yes	Yes	Yes[c]	No	Yes	Yes	Yes

a: Unless stated otherwise, all events since the start and within 56 days after the end of the treatment up to week 164 are considered.
b: Events up to the time point at which all patients reached week 104.
c: For the operationalization ≤ 54 mg/dL, these were results up to the time point at which all patients reached week 104.
AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.4.2.2 Risk of bias (research question B)

Table 13 shows the risk of bias for these outcomes.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: albiglutide + metformin vs. glimepiride + metformin

Study	Study level	Outcomes									
		All-cause mortality	Stroke (all, adjudicated)	Stroke (nonfatal, adjudicated)	Cardiac morbidity	Severe hypoglycaemias	Symptomatic hypoglycaemias blood glucose ≤ 70 mg/dL/≤ 54 mg/dL	Health-related quality of life	SAEs	Discontinuation due to AEs	Injection site reactions
HARMONY 3	L	L	L	L	L	H	H	-[a]	L	L	L

a: The outcome was not recorded in the HARMONY 3 study.
AE: adverse event; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The assessment of the risk of bias at outcome level deviates from that of the company.

Deviating from the company, the outcomes "severe hypoglycaemias" and "symptomatic hypoglycaemias" (blood glucose ≤ 70 mg/dL and ≤ 54 mg/dL) were rated as potentially highly biased because of the use of glimepiride in the HARMONY 3 study (see Section 2.4.1.2). Detailed reasons for the assessment of the risk of bias can be found in Section 2.8.3.2.4.2 of the full dossier assessment.

2.4.2.3 Results (research question B)

Table 14 and Table 15 summarize the results on the comparison of albiglutide + metformin with glimepiride + metformin in patients with type 2 diabetes mellitus. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

As described in Section 2.4.1, analyses on several time periods were partly available (all patients had reached at least week 104, total observation period of 164 weeks). For the present assessment, the analysis of the longest available time period was used for each outcome. Hence deviating from the results presented in the company's dossier, analyses at the time point 164 weeks were included in the assessment for most outcomes.

As the HARMONY 3 study had a low risk of bias, the derivation of an indication is principally possible. This concurs with the company's assessment. Any possible weakening of the results by outcome-specific aspects will be noted separately for individual outcomes in the following presentation of the results.

The following descriptions only include results from the subgroup analyses in cases where the derivation of the conclusion on the added benefit is important for the respective outcome. See Section 2.4.2.4 for the detailed presentation of the results from subgroup analyses.

Table 14: Results (dichotomous outcomes) – RCT, direct comparison: albiglutide + metformin vs. glimepiride + metformin

Study outcome category outcome[a]	Albiglutide + metformin		Glimepiride + metformin		Albiglutide + metformin vs. glimepiride + metformin
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value[b]
HARMONY 3					
Mortality					
All-cause mortality	302	4 (1.3)[c]	307	6 (2.0)[c]	0.68 [0.19; 2.38][d]; 0.568
Morbidity					
Stroke (all, adjudicated)[e]	302	3 (1.0)	307	1 (0.3)	3.05 [0.32; 29.15]; 0.330
Stroke (nonfatal, adjudicated)[e]	302	3 (1.0)	307	1 (0.3)	3.05 [0.32; 29.15]; 0.330
Cardiac morbidity	302	12 (4.0)	307	5 (1.6)	2.44 [0.87; 6.84][d]; 0.081
Health-related quality of life	Outcome not recorded				
Adverse events					
AEs	302	263 (87.1)	307	261 (85.0)	
SAEs	302	44 (14.6)	307	36 (11.7)	1.24 [0.82; 1.87][d]; 0.309
Discontinuation due to AEs	302	24 (7.9)	307	17 (5.5)	1.44 [0.79; 2.62][d]; 0.246
Severe hypoglycaemias	302	0 (0)	307	1 (0.3)	ND; 0.343
Symptomatic hypoglycaemias					
blood glucose ≤ 70 mg/dL	302	12 (4.0)	307	66 (21.5)	0.18 [0.10; 0.33][d]; < 0.001
blood glucose ≤ 54 mg/dL[f]	302	3 (1.0)	307	24 (7.8)	0.13 [0.04; 0.42]; < 0.001
Injection site reactions	302	55 (18.2)	307	26 (8.5)	2.15 [1.39; 3.33][d]; < 0.001

a: Unless stated otherwise, all events since the start and within 56 days after the end of the treatment up to week 164 are considered.
b: Institute's calculation, unconditional exact test (CSZ method according to [5]).
c: Institute's calculation.
d: Institute's calculation of effect estimate and CI (asymptotic).
e: Events up to the time point at which all patients reached week 104.
f: Events up to at least week 104 without consideration of the observations under and after rescue medication.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: severe adverse event; vs.: versus

Table 15: Results (continuous outcomes) – albiglutide + metformin vs. glimepiride + metformin

Study outcome category outcome	Albiglutide + metformin			Glimepiride + metformin			Albiglutide + metformin vs. glimepiride + metformin
	N	Baseline values mean (SD)	Values week 104 mean[a] (SD)	N	Baseline values mean (SD)	Change/ values week 104 mean[a] (SD)	Effect [95% CI]; p-value[b]
HARMONY 3							
Supplementary outcome "body weight"							
Change from baseline	296	89.61 (18.38)	88.43 (18.47)	302	91.88 (20.51)	93.03 (20.77)	−2.37 [−3.03; −1.71]; < 0.0001

a: LOCF for missing post-baseline values and body weight values after rescue medication.
b: Effect estimation, CI and p-value result from an ANCOVA adjusted for body weight, HBA1c category (< 8.0%/≥ 8.0%), previous myocardial infarctions (yes/no), age category (< 65/≥ 65 years), and region (ex-USA, USA-North, USA-South Atlantic, USA-South Central, USA-West), each at baseline.
ANCOVA: analysis of covariance; CI: confidence interval; LOCF: last observation carried forward; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Mortality

A total of 4 deaths occurred under albiglutide + metformin, and 6 deaths under glimepiride + metformin, in the HARMONY 3 study for the period up to week 164. There was no statistically significant difference between the treatment groups. An added benefit of albiglutide + metformin compared with glimepiride + metformin for overall survival is therefore not proven.

This concurs with the company's assessment, which used the results at the data cut-off at which all patients had reached at least week 104 as the basis for its assessment, however.

Morbidity

Stroke (all, adjudicated) and stroke (nonfatal, adjudicated)

3 strokes occurred under albiglutide + metformin, and one stroke occurred under glimepiride + metformin up to at least week 104. None of these events was fatal, and the results for both outcomes are therefore identical. The difference between the treatment groups was not statistically significant. An added benefit of the combination of albiglutide + metformin compared with glimepiride + metformin for the 2 outcomes on stroke is therefore not proven.

This concurs with the company's assessment for these 2 outcomes.

Cardiac morbidity

12 cardiac events occurred under albiglutide + metformin, and 5 cardiac events occurred under glimepiride + metformin for the period up to week 164. The difference between the treatment groups was not statistically significant. An added benefit of albiglutide + metformin compared with glimepiride + metformin for cardiac morbidity is therefore not proven.

This concurs with the company's assessment, which used the results at the data cut-off at which all patients had reached at least week 104 as the basis for its assessment, however.

Health-related quality of life

The outcome "health-related quality of life" was not recorded in the HARMONY 3 study.

Adverse events

The AEs, SAEs and discontinuations due to AEs that most commonly occurred in the HARMONY 3 study are presented in Appendix A of the full dossier assessment.

Serious adverse events and discontinuation due to adverse events

There were no statistically significant differences in the HARMONY 3 study between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs" for the period up to week 164. Greater or lesser harm from albiglutide + metformin in comparison with glimepiride + metformin is therefore not proven.

This concurs with the company's assessment, which used the results at the data cut-off at which all patients had reached at least week 104 as the basis for its assessment, however.

Severe hypoglycaemias

A total of 1 severe hypoglycaemia (under glimepiride + metformin) occurred in the HARMONY 3 study for the period up to week 164. The difference was not statistically significant. Greater or lesser harm from albiglutide + metformin in comparison with glimepiride + metformin is therefore not proven.

This deviates from the company's assessment, which used the results at the data cut-off at which all patients had reached at least week 104 as the basis for its assessment. No severe hypoglycaemias occurred in the study up to this time point. Hence the company derived no conclusion on the extent of added benefit for this outcome in the dossier.

Confirmed symptomatic hypoglycaemias (blood glucose ≤ 70 mg/dL and ≤ 54 mg/dL)

Even though a blood-glucose threshold of ≤ 54 mg/dL has a higher validity, non-severe symptomatic events with a blood-glucose threshold of ≤ 70 mg/dL were additionally considered in the present assessment. The reason for this is that, for the benefit assessment, only the analyses on the blood glucose threshold of ≤ 70 mg/dL were planned a priori in the study, and that analyses for the period up to week 164 were also available (see Section 2.8.3.2.4.3 of the full dossier assessment).

There were fewer symptomatic hypoglycaemias (confirmed by a measured blood glucose level of ≤ 70 mg/dL) under albiglutide + metformin than under glimepiride + metformin over the period of up to week 164. The result was statistically significant. There were fewer symptomatic hypoglycaemias under albiglutide + metformin than under glimepiride + metformin also for the second operationalization of symptomatic hypoglycaemias (confirmed by a measured blood glucose level of ≤ 54mg/dL) up to the time point at which all patients had reached at least week 104. The result was also statistically significant.

Both operationalizations of the outcome "symptomatic hypoglycaemias" were rated as potentially highly biased because of the uncertainties on the use of glimepiride in the HARMONY 3 study described in Section 2.4.1.2.

Hence there is a hint of lesser harm from albiglutide + metformin than from glimepiride + metformin for the outcome of symptomatic hypoglycaemias (blood glucose ≤ 70 mg/dL and ≤ 54 mg/dL).

This contradicts the company's assessment. The company derived an indication of an added benefit of albiglutide + metformin versus glimepiride + metformin for both operationalizations of the outcome "symptomatic hypoglycaemias" (blood glucose ≤ 70 mg/dL and ≤ 54 mg/dL) on the basis of the analyses at 104 weeks.

Injection site reactions

Regarding the proportion of patients with at least one injection site reaction up to week 164, there was a statistically significant difference to the disadvantage of albiglutide + metformin.

Since patients in the comparator arm received placebo injections, the available results represent the substance-specific difference – injection with albiglutide versus injection with placebo. The fact that the ACT glimepiride is administered orally has to be taken into account. Due to the form of administration it has to be assumed that results for this outcome cannot occur at all under the use of glimepiride. Hence the observed effect (substance-specific difference) regarding injection site reactions is underestimated with regard to the present research question (assessment of the substance-specific effects plus harm from the injection itself). This has no consequence for the present benefit assessment, however, because the effect size already resulted in the greatest extent ("considerable") for this outcome category of non-serious/non-severe AEs.

This largely concurs with the assessment of the company, which also derived greater harm from albiglutide + metformin, but rated it as non-quantifiable.

Outcomes "adverse events" and "body weight" additionally presented

The outcomes "AEs" and "body weight" were only presented as additional information and are not further commented on.

2.4.2.4 Subgroups and other effect modifiers (research question B)

For selected characteristics, the respective subgroups were investigated for the presence of heterogeneous treatment effects in order to identify possible effect modifications. The company presented in its dossier corresponding analyses for the outcomes it rated as relevant at the data cut-off at which all patients had reached at least week 104. There were therefore no subgroup analyses on the total period of 164 weeks. If effect modifications were identified on the basis of the subgroup analyses up to at least 104 weeks, it was examined whether these were applicable to the situation up to week 164, e.g. because the proportion of patients with event had not increased to a relevant degree at the level of the total population.

Subgroup analyses for the following characteristics were considered:

- baseline HbA1c value: < 8.0%, ≥ 8.0%
- sex: male, female
- ethnicity: white versus non-white
- age at randomization: < 65 years, ≥ 65 years

The subgroup characteristics presented by the company and their dimensions and cut-off values for the primary outcome "change in HbA1c" had been planned a priori in the studies. There were no subgroup analyses for the following outcomes: all-cause mortality, stroke, cardiac morbidity, and severe hypoglycaemias. The company justified this with the fact that the number of patients with events was too small for these outcomes (see Section 2.8.3.2.2 of the full dossier assessment).

For the outcome "injection site reactions", the subgroup analyses presented by the company were not considered further because the available results only recorded the substance-specific difference between the albiglutide injection versus a placebo injection. Moreover, as described above, the subgroup analyses were only available for the data cut-off at which all patients had reached at least week 104.

Only the results on subgroups and outcomes with at least indications of an interaction between treatment effect and subgroup characteristic and with statistically significant results in at least one subgroup are presented. The prerequisite for proof of different subgroup effects is a statistically significant interaction ($p < 0.05$). A p-value of ≥ 0.05 and < 0.2 provides an indication of an effect modification.

No effect modifications were identified for the following outcomes: SAEs, discontinuation due to AEs and symptomatic confirmed hypoglycaemias. This concurs with the company's assessment.

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

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of added benefit at outcome level (research question B)

The data availability presented in Section 2.4.2 resulted both in a hint of lesser harm from the combination albiglutide + metformin in comparison with glimepiride + metformin for symptomatic hypoglycaemias (blood glucose ≤ 54 mg/dL and ≤ 70 mg/dL) and in an indication of greater harm for injection site reactions.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 16).

Table 16: Extent of added benefit at outcome level: albiglutide + metformin vs. glimepiride + metformin

Outcome category **outcome**	**Albiglutide + metformin** **vs. glimepiride + metformin** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	1.3% vs. 2.0% RR: 0.68 [0.19; 2.38] p = 0.568	Added benefit not proven
Morbidity		
Stroke (all)	1.0% vs. 0.3% RR: 3.05 [0.32; 29.15] p = 0.330	Added benefit not proven
Stroke (nonfatal)	1.0% vs. 0.3% RR: 3.05 [0.32; 29.15] p = 0.330	Added benefit not proven
Cardiac morbidity	4.0% vs. 1.6% RR: 2.44 [0.87; 6.84] p = 0.081	Added benefit not proven
Health-related quality of life		
	No data available	
Adverse events		
SAEs	14.6% vs. 11.7% RR: 1.24 [0.82; 1.87] p = 0.309	Greater/lesser harm not proven
Discontinuation due to AEs	7.9% vs. 5.5% RR: 1.44 [0.79; 2.62] p = 0.246	Greater/lesser harm not proven
Severe hypoglycaemias	0% vs. 0.3% ND p = 0.343	Greater/lesser harm not proven
Symptomatic hypoglycaemias		
blood glucose ≤ 70 mg/dL	4.0% vs. 21.5% RR: 0.18 [0.10; 0.33] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 lesser harm, extent: "considerable"
blood glucose ≤ 54 mg/dL	1.0% vs. 7.8% RR: 0.13 [0.04; 0.42] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 lesser harm, extent: "considerable"
Injection site reactions	18.2% vs. 8.5% RR: 2.15 [1.39; 3.33] RR[c]: 0.47 [0.30; 0.72] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 greater harm, extent: "considerable"

(continued)

Table 16: Extract of added benefit at outcome level: albiglutide + metformin vs. glimepiride + metformin (continued)

a: Probability provided if statistically significant differences were present. b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u. c: Proportion of events albiglutide + metformin vs. glimepiride + metformin (reversed direction of effect to enable direct use of limits to derive the extent of added benefit). AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; ND: no data; RR: relative risk; SAE: serious adverse event; vs.: versus

2.4.3.2 Overall conclusion on added benefit (research question B)

Table 17 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of albiglutide in comparison with metformin + sulfonylurea (glibenclamide or glimepiride)

Positive effects	**Negative effects**
Non-serious/non-severe adverse events ▪ confirmed symptomatic hypoglycaemias hint of lesser harm, extent: “considerable”	Non-serious/non-severe adverse events ▪ Injection site reactions indication of greater harm, extent: “considerable”
No sufficient data were available on micro- and macrovascular late complications.	

Overall, one positive effect and one negative effect remain in the same outcome category (non-serious/non-severe AEs). There was a positive effect in the outcome category “non-serious/non-severe AEs” for confirmed symptomatic hypoglycaemias with a hint of lesser harm (extent: “considerable”). There was a negative effect in the outcome category “non-serious/non-severe AEs” for injection site reactions with an indication of greater harm (extent: “considerable”). Hence there are opposing conclusions on AEs. Although there are opposing effects of the same extent, the disadvantage regarding injection site reactions cannot completely outweigh the advantage regarding confirmed symptomatic hypoglycaemias. However, it resulted in weakening the extent so that there is overall a hint of a minor added benefit of albiglutide + metformin versus glimepiride + metformin.

No sufficient data were available on micro- and macrovascular late complications. This led to an additional uncertainty.

In summary, there is a hint of a minor added benefit of albiglutide + metformin in comparison with glimepiride + metformin.

This deviates from the company’s approach, which derived an indication of a considerable added benefit of albiglutide + metformin versus the ACT.

Furthermore, the added benefit is not proven for the dual combination with blood-glucose lowering drugs other than metformin and insulin. The company presented no data for other combinations.

The result of the assessment of the added benefit of albiglutide + metformin in comparison with the ACT is summarized in Table 18.

Table 18: Albiglutide + metformin – extent and probability of added benefit

Research question	**Subindication**	**ACT**[a]	**Extent and probability of added benefit**
B	Albiglutide + metformin[b]	Metformin + sulfonylurea (glibenclamide or **glimepiride**[c]) *(note: If metformin is inappropriate according to the SPC, human insulin is to be used as treatment option.)*	Hint of an added benefit, extent: "minor"
	combination with another blood-glucose lowering drug (except metformin and insulin) when this, together with diet and exercise, does not provide adequate glycaemic control		added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b: Research question of the company.
c: The company chose no option, but presented a study versus glimepiride. Hence glimepiride is the ACT and is printed in **bold**.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

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

2.4.4 List of included studies (research question B)

HARMONY 3

Ahren B, Johnson SL, Stewart M, Cirkel DT, Yang F, Perry C et al. HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. Diabetes Care 2014; 37(8): 2141-2148.

GlaxoSmithKline. Efficacy and safety of albiglutide in treatment of type 2 diabetes: study results [online]. In: Clinicaltrials.gov. 11 August 2014 [accessed: 22 October 2014]. URL: http://clinicaltrials.gov/ct2/show/results/NCT00838903.

GlaxoSmithKline. A randomized, double-blind, placebo- and active-controlled, parallel-group, multicenter study to determine the efficacy and safety of albiglutide when used in combination with metformin compared with metformin plus sitagliptin, metformin plus glimepiride, and metformin plus placebo in subjects with type 2 diabetes mellitus [online]. In: EU Clinical Trials Register. [Accessed: 22 July 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number%3A2008-007660-41+.

GlaxoSmithKline. A randomized, double-blind, placebo- and active-controlled, parallel-group, multicenter study to determine the efficacy and safety of albiglutide when used in combination with metformin compared with metformin plus sitagliptin, metformin plus glimepiride, and metformin plus placebo in subjects with type 2 diabetes mellitus: study GLP112753; clinical study report [unpublished]. 2012.

GlaxoSmithKline. Pancreatitis Adjudication Committee (PAC) report [unpublished]. 2012.

GlaxoSmithKline. A randomized, double-blind, placebo- and active-controlled, parallel-group, multicenter study to determine the efficacy and safety of albiglutide when used in combination with metformin compared with metformin plus sitagliptin, metformin plus glimepiride, and metformin plus placebo in subjects with type 2 diabetes mellitus: year 3 report; study GLP112753; clinical study report [unpublished]. 2013.

GlaxoSmithKline. Efficacy and safety of albiglutide in treatment of type 2 diabetes: full text view [online]. In: Clinicaltrials.gov. 29 May 2014 [accessed: 22 July 2014]. URL: http://ClinicalTrials.gov/show/NCT00838903.

GlaxoSmithKline. SAS output GLP112753 (HARMONY 3), Germany final data through week 104 [unpublished]. 2014.

GlaxoSmithKline. SAS output GLP112753 (HARMONY 3), pancreatitis adjudicated [unpublished]. 2014.

GlaxoSmithKline. SAS output GLP112753 (HARMONY 3), sensitivity analysis hypoglycemic events [unpublished]. 2014.

GlaxoSmithKline. A randomized, double-blind, placebo and active-controlled, parallel-group, multicenter study to determine the efficacy and safety of albiglutide when used in combination with metformin compared with metformin plus sitagliptin, metformin plus glimepiride, and metformin plus placebo in subjects with type 2 diabetes mellitus: protocoll summary [online]. In: GSK Clinical Study Register. 10 July 2014 [accessed: 22 July 2014]. URL: http://www.gsk-clinicalstudyregister.com/study/112753#ps.

GlaxoSmithKline. HARMONY 3: Hypoglykämien über Zeit; Graphiken; Quellendokument [unpublished]. 2014.

Nauck M, Acusta A, Hennig M, Seidel D, Monz B. Hypoglykämien bei Metformin-behandelten Patienten mit Typ 2 Diabetes, die entweder Albiglutid oder Glimepirid erhielten: eine Sekundäranalyse von HARMONY 3 [poster]. Diabetes Kongress 2014: 49. Jahrestagung Deutsche Diabetes Gesellschaft; 28-31 May 2014; Berlin, Germany.

Nauck M, Hennig M, Seidel D. Wirksamkeit und Sicherheit von Albiglutid bei Metformin-behandelten Patienten mit Typ 2 Diabetes: Ergebnisse der HARMONY 3 Studie [poster]. Diabetes Kongress 2014: 49. Jahrestagung Deutsche Diabetes Gesellschaft; 28-31 May 2014; Berlin, Germany.

2.5 Research question C: albiglutide in combination with at least 2 other blood-glucose lowering drugs

2.5.1 Information retrieval and study pool (research question C)

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

- study list on albiglutide (studies completed up to 18 July 2014)
- bibliographical literature search on albiglutide (last search on 21 July 2014)
- search in trial registries for studies on albiglutide (last search on 31 July 2014)

The company identified no relevant study for a comparison of albiglutide with at least 2 other blood-glucose lowering drugs versus the ACT specified by the G-BA.

2.5.2 Results on added benefit (research question C)

The company presented no relevant data for the research question on albiglutide in combination with at least 2 other blood glucose lowering drugs. Hence the added benefit of albiglutide in combination with at least 2 other blood-glucose lowering drugs versus the ACT specified by the G-BA (metformin + human insulin) is not proven.

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

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of albiglutide in combination with at least 2 other blood-glucose lowering drugs in comparison with the ACT specified by the G-BA (metformin + human insulin). Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived. The company claimed no added benefit for this research question.

2.5.4 List of included studies (research question C)

Not applicable as the company did not present any relevant studies in its dossier from which an added benefit of albiglutide in combination with at least 2 other blood-glucose lowering drugs versus the ACT specified by the G-BA (metformin + human insulin) can be derived.

2.6 Research question D: albiglutide in combination with insulin (with or without oral antidiabetics)

2.6.1 Information retrieval and study pool (research question D)

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

- study list on albiglutide (studies completed up to 18 July 2014)
- bibliographical literature search on albiglutide (last search on 21 July 2014)
- search in trial registries for studies on albiglutide (last search on 31 July 2014)

The company identified no relevant study for a comparison of albiglutide in combination with insulin versus the ACT specified by the G-BA.

2.6.2 Results on added benefit (research question D)

The company presented no relevant data for the research question on albiglutide in combination with insulin (with or without oral antidiabetics). Hence the added benefit of albiglutide + insulin (with or without oral antidiabetics) versus the ACT specified by the G-BA (metformin + human insulin) is not proven.

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

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of albiglutide in combination with insulin (with or without oral antidiabetics) in comparison with the ACT specified by the G-BA (metformin + human insulin). Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived. The company claimed no added benefit for this research question.

2.6.4 List of included studies (research question D)

Not applicable as the company did not present any relevant studies in its dossier from which an added benefit of albiglutide in combination with insulin (with or without oral antidiabetics) versus the ACT specified by the G-BA (metformin + human insulin) can be derived.

2.7 Extent and probability of added benefit – summary

An overview of the extent and probability of added benefit for the different subindications of albiglutide in comparison with the relevant ACTs is given Table 19.

Table 19: Albiglutide – extent and probability of added benefit

Research question	Subindication	ACT	Extent and probability of added benefit
A	Monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to contraindications or intolerance	Sulfonylurea (glibenclamide or glimepiride)	Added benefit not proven
B	Albiglutide + metformin combination with another blood-glucose lowering drug (except metformin and insulin) when this, together with diet and exercise, does not provide adequate glycaemic control	Metformin + sulfonylurea (glibenclamide or **glimepiride**[a]) (note: If metformin is inappropriate according to the SPC, human insulin is to be used as treatment option.)	Hint of an added benefit, extent: "minor" added benefit not proven
C	Combination with at least 2 other blood-glucose lowering drugs when these, together with diet and exercise, do not provide adequate glycaemic control	Metformin + human insulin (note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)	Added benefit not proven
D	Combination with insulin (with or without oral antidiabetics)	Metformin + human insulin (note: treatment only with human insulin if metformin is not sufficiently effective or not tolerated according to the SPC)	Added benefit not proven

a: The company chose no option, but presented a study versus glimepiride. Hence glimepiride is the ACT and is printed in **bold**.
ACT: appropriate comparator therapy; SPC: Summary of Product Characteristics

In summary, there is a hint of a minor added benefit of albiglutide + metformin in comparison with glimepiride + metformin. An added benefit of albiglutide in comparison with the ACT is not proven for albiglutide in combination with other blood-glucose lowering drugs (except metformin and insulin) and for research questions A, C, and D.

For research question B, this deviates from the company's assessment, which derived an indication of a considerable added benefit of albiglutide + metformin versus the ACT.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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