IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Dulaglutid – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 April 2015). 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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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
APPADL	Ability to Perform Physical Activities of Daily Living
BMI	body mass index
CUI	clinical utility index
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycosylated haemoglobin A1c
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IW-SP	Impact of Weight on Self-Perception
LBSS	Low Blood Sugar Survey
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model repeated measures
NVL	Nationale VersorgungsLeitlinie (National Care Guideline)
OAD	oral antidiabetic
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

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 dulaglutide. 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 2 February 2015.

Research question

The aim of the present report was to assess the added benefit of dulaglutide for the treatment of adults with type 2 diabetes mellitus in comparison with the appropriate comparator therapy (ACT) specified by the G-BA.

Four different research questions result from the different combinations with other blood-glucose lowering drugs. These are shown in Table 2.

Table 2: Subindications, research questions and ACTs for dulaglutide

Research question	Subindication[a]	Research question of the company	ACT specified by the G-BA
A	Monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications	Module 4 A dulaglutide as monotherapy	Sulfonylurea (glibenclamide or glimepiride)
B	Dual combination therapy with an OAD when this, together with diet and exercise, does not provide adequate glycaemic control	Module 4 B dulaglutide + metformin	Metformin plus sulfonylurea (glibenclamide or glimepiride) *(note: if metformin is considered inappropriate according to the SPC, human insulin is to be used as treatment option)*
C	Triple combination therapy with 2 OADs when these, together with diet and exercise, do not provide adequate glycaemic control	Module 4 C dulaglutide + metformin + glimepiride	Metformin plus human insulin *(note: if applicable, treatment only with human insulin if metformin is not tolerated or not sufficiently effective according to the SPC)*
D	Combination with insulin, with or without OAD, when this, together with diet and exercise, does not provide adequate glycaemic control	Module 4 D dulaglutide + insulin lispro with or without metformin	Metformin plus human insulin *(note: if applicable, treatment only with human insulin if metformin is not tolerated or not sufficiently effective according to the SPC)*
a: Subdivisions of the therapeutic indication according to the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetic; SPC: Summary of Product Characteristics			

Deviating from the company, which only considered part of the possible combinations for research questions B to D, the assessment was conducted for the entire subindication in each case.

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

Results

Research question A: dulaglutide monotherapy

The company presented no relevant data for research question A. Hence there is no proof of added benefit of dulaglutide in monotherapy versus the ACT specified by the G-BA.

Research question B: dulaglutide in dual combination with an oral antidiabetic

Dulaglutide in dual combination with metformin

No studies of direct comparison were identified for this research question.

The indirect comparison between the studies AWARD-5 and HARMONY 3 was included in the assessment of the added benefit of dulaglutide in combination with metformin. Three further indirect comparisons presented by the company are unsuitable for the assessment, particularly because of incomplete data and lack of similarity between the study populations.

Study design and treatment regimen (AWARD-5)

The AWARD-5 study was a randomized, active-controlled, double-blind approval study (phase 2/3) sponsored by the company to compare dulaglutide with sitagliptin (each with metformin), which consisted of 2 stages. Stage 1 served as a dose-ranging study to choose the 2 dosages out of 7 dulaglutide dosages, the efficacy of which was to be further investigated in Stage 2. These 2 dosages were 0.75 and 1.5 mg dulaglutide/week. Only the 1.5 mg dulaglutide and the sitagliptin arm of the study are relevant for the present benefit assessment (304 and 315 patients respectively).

The study consisted of a lead-in phase of up to 11 weeks, a 104-week treatment phase (Stage 1 and 2) and a 4-week follow-up phase.

Patients who had received metformin or another oral antidiabetic (OAD) as monotherapy or a combination therapy of metformin with other OADs, and patients without pretreatment were enrolled. The majority of the patients received metformin as monotherapy or in dual combination (88.2% and 86.3% respectively of the patients in the dulaglutide and the sitagliptin arm).

The patients received fixed dulaglutide or sitagliptin dosages (in addition to ≥ 1500 mg metformin/day). Escalation of the study medication depending on the patients' needs was not envisaged.

Study design and treatment regimen (HARMONY 3)

The HARMONY 3 study was a randomized, active-controlled, double-blind phase 3 study. 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/day (or maximum tolerated dosage < 1500 mg/day) (glycosylated haemoglobin A1c [HbA1c] at the last visit in the stabilization phase between 7% and 10%). Four treatment arms were investigated in the study: albiglutide, glimepiride, sitagliptin and placebo (each with metformin). The glimepiride and the sitagliptin arm are relevant for the present benefit assessment (317 and 313 patients respectively). All patients additionally received ≥ 1500 mg/day metformin.

The study consisted of a 4-week stabilization phase, a treatment phase of 156 weeks and a follow-up phase of 8 weeks. An interim analysis was planned per protocol after all patients had reached at least week 104.

Whereas the sitagliptin dosage in the study was fixed, the glimepiride dosage could be increased from 2 mg/day to 4 mg/day. Doses of 1 mg, 3 mg, 5 mg, and 6 mg were not available. An uncertainty therefore remains regarding the influence of the glimepiride treatment regimen. Nonetheless, the results of the HARMONY 3 study were considered to be interpretable and were used for the indirect comparison, also because of comparable HbA1c courses in the glimepiride and sitagliptin arm.

Similarity of the AWARD-5 and HARMONY 3 studies

The study populations were comparable both between the 2 studies and between the individual arms of the respective studies.

The common comparator (sitagliptin + metformin) was also sufficiently similar for the studies available. On the one hand, the specifications on dosing were identical in both studies, on the other, the decrease in HbA1c value in the sitagliptin arms of both studies was comparable.

Overall, the 2 studies AWARD-5 and HARMONY 3 were considered to be sufficiently similar so that the assumption of similarity for an adjusted indirect comparison was not rejected.

Risk of bias

The risk of bias at study level was rated as low for both studies. For the AWARD-5 study, the risk of bias of all outcomes was also rated as low. For the HARMONY 3 study, the risk of bias was rated as low for all outcomes except for severe and symptomatic confirmed

hypoglycaemias, which were rated as having a high risk of bias due to the uncertainties regarding the use of glimepiride in the study.

General note on the presentation of results and types of analysis

In contrast to the HARMONY 3 study, rescue medication was not allowed in the AWARD-5 study. Hence for the HARMONY 3 study, the analyses up to the rescue medication, if available, were used for the indirect comparison. This concerns the outcomes on hypoglycaemia and the outcomes "diarrhoea" and "nausea".

Since an adjusted indirect comparison according to Bucher with only one study each was used for research question B, and no direct comparison was available, it was not possible to check homogeneity and consistency. Hence at most hints of added benefit or harm were derived from the available data.

Mortality

- All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome "all-cause mortality". Hence there is no hint of an added benefit of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride). An added benefit for this outcome is therefore not proven.

Morbidity

No sufficient data were available on the outcome "cardiovascular morbidity" and on further micro- and macrovascular late complications.

Health-related quality of life

No relevant data were available for the indirect comparison for the outcome "health-related quality of life".

Adverse events

- Serious adverse events and discontinuation due to adverse events

The indirect comparison showed no statistically significant differences between the treatment groups for the outcomes "serious adverse events (SAEs)" and "discontinuation due to adverse events (AEs)". Hence there is no hint of greater or lesser harm of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride); an added benefit for these outcomes is therefore not proven.

- Severe hypoglycaemia

No severe hypoglycaemia occurred in the relevant treatment arms of both studies. Hence there is no hint of greater or lesser harm of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride). An added benefit for this outcome is therefore not proven.

- Symptomatic hypoglycaemia (blood glucose ≤ 54 mg/dL; blood glucose ≤ 70 mg/dL)

There were only analyses on hypoglycaemias with the blood-glucose threshold of ≤ 70 mg/dL, but no analyses on the threshold of ≤ 54 mg/dL.

There was a statistically significant difference in favour of dulaglutide + metformin versus glimepiride + metformin for symptomatic hypoglycaemia with a blood glucose threshold of ≤ 70 mg/dL. This results in a hint of lesser harm of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride).

- Gastrointestinal disorders

There was no statistically significant difference between the treatment groups for the outcome "gastrointestinal disorders". Hence there is no hint of greater or lesser harm of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride). An added benefit for this outcome is therefore not proven.

- Nausea, diarrhoea and vomiting

There was a statistically significant difference to the disadvantage of dulaglutide + metformin in comparison with glimepiride + metformin for the outcomes "nausea", "diarrhoea" and "vomiting". This results in hints of greater harm of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride).

- Pancreatitis

No confirmed pancreatitis occurred in any of the patients in both relevant treatment arms. Hence there is no hint of greater or lesser harm of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride). An added benefit for this outcome is therefore not proven.

- Injection site reactions

There was no statistically significant difference between the treatment groups for the outcome "injection site reactions". Hence there is no hint of greater or lesser harm of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride). An added benefit for this outcome is therefore not proven.

The fact that the patients in the glimepiride arm received placebo injections because the ACT glimepiride is administered orally has to be taken into account. Due to the form of administration it can be assumed that results for this outcome cannot occur at all under the use of glimepiride. The actual difference between the interventions is underestimated as a result. Since the proportion of events in the dulaglutide was low (1.3%) and also below the proportion of events in the glimepiride study (7.8%), this has no consequences for the present benefit assessment.

Dulaglutide in dual combination with an OAD other than metformin

The company presented no relevant studies on dual combinations of dulaglutide with an OAD other than metformin. Hence there is no proof of an added benefit of dulaglutide with an OAD other than metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride).

Research question C: dulaglutide in triple combination therapy with 2 oral antidiabetics

The company presented no relevant studies of direct comparisons for research question C.

The indirect comparison presented by the company is unsuitable for the present benefit assessment because both studies included by the company, AWARD-2 and LAPTOP, are not comparable regarding the common comparator (insulin glargine + metformin + glimepiride) and the study population. The sensitivity analyses conducted by the company are unsuitable to remove the lack of comparability of the common comparator or of the study populations of the studies AWARD-2 and LAPTOP. In addition, the suitability of the LAPTOP study for the indirect comparison is doubtful because it is not guaranteed that the majority of the patients included in the LAPTOP study correspond to the target population (inadequate glycaemic control under maximum tolerated dose of metformin).

Hence there is no proof of an added benefit of dulaglutide in the triple combination with 2 OADs in comparison with the ACT metformin + human insulin (or treatment only with human insulin if metformin is not tolerated or not sufficiently effective according to the Summary of Product Characteristics [SPC]).

Research question D: dulaglutide in combination with insulin with or without oral antidiabetic

Dulaglutide in combination with a short-acting insulin with or without metformin

The H9X-MC-GBDD study (hereinafter referred to as “AWARD-4”) was included in the assessment of dulaglutide in combination with a short-acting insulin with or without metformin.

The AWARD-4 study was a randomized, active-controlled study sponsored by the company with a treatment phase of 52 weeks. Adult patients (≥ 18 years) with type 2 diabetes mellitus with inadequate glycaemic control under optimized and stable insulin dosage in conventional insulin treatment alone or in combination with OAD treatment together with diet and exercise were enrolled.

A total of 884 patients were randomly assigned in a ratio of 1:1:1 to 3 treatment arms: dulaglutide 0.75 mg daily (293 patients), dulaglutide 1.5 mg daily (295 patients) und insulin glargine (296 patients), each + insulin lispro with or without metformin. Of the 2 dulaglutide arms, only the arm with a dosage of 1.5 mg/week was relevant for the present benefit assessment.

After the screening phase, the study consisted of 3 study phases: a 9-week lead-in phase, a 52-week treatment phase and a 4-week follow-up phase.

Treatment regimen and dose adjustments

The AWARD-4 study was a study with intensive insulin therapy targeted at near-normal blood-glucose levels in both treatment groups.

Insulin treatment with insulin glargine and insulin lispro was optimized with defined algorithms in the course of the study. The insulin glargine dose was adapted on the basis of 3 previous fasting plasma glucose levels, aiming at a target value between 71 and 99 mg/dL. The insulin lispro doses for administration before breakfast, before lunch and before the evening meal was also adapted (for all treatment groups equally) according to a prespecified algorithm based on the 3 last fasting plasma glucose levels before lunch, before the evening meal and before bedtime. The target values were between 71 and 100 mg/dL (before lunch, before the evening meal) and between 71 and 130 mg/dL (before bedtime).

Risk of bias

The risk of bias at study level for the AWARD-4 study was rated as low. Except for the outcomes "all-cause mortality" and "SAEs", the risk of bias of the outcomes was rated as high because of the subjective component in the open-label study design.

General note on the presentation of results and types of analysis

Analyses on several time periods were partly available for the outcomes included in the assessment. For the present assessment, the analysis of the longest available time period was used for each outcome (also after administration of rescue medication). Hence analyses at the time point 52 weeks were included in the assessment for most outcomes.

Mortality

- All-cause mortality

There was no statistically significant difference between the treatment groups regarding deaths. Hence there is no hint of an added benefit of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). An added benefit for this outcome is therefore not proven.

Morbidity

- Health status (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS])

There was no statistically significant difference between the treatment groups for the outcome "health status". Hence there is no hint of an added benefit of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). An added benefit for this outcome is therefore not proven.

- Micro- and macrovascular late complications

No evaluable data were available on the outcome "cardiovascular morbidity" and on further micro- and macrovascular late complications.

Health-related quality of life

No relevant data were available in the AWARD-4 study for the outcome "health-related quality of life".

Adverse events

- Serious adverse events

For the outcome "SAEs", there was a statistically significant difference in favour of dulaglutide + insulin lispro with or without metformin in comparison with insulin glargine + insulin lispro with or without metformin for the time period of up to week 52. Events occurred across all organ classes without increase in any area. Overall, there is therefore an indication of lesser harm of the combination of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin) for this outcome.

- Discontinuation due to AEs

Treatment with dulaglutide + insulin lispro with or without metformin in comparison with the combination therapy with insulin glargine + insulin lispro with or without metformin resulted in a statistically significantly greater proportion of patients with discontinuation due to AEs for the time period up to week 52. Overall, there is therefore a hint of greater harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin) for the outcome "discontinuation due to AEs". It can be inferred from the recordings of the most common AEs in the AWARD-4 study that the majority of events that led to discontinuation can be classified as non-serious.

- Severe hypoglycaemia

There were no evaluable data for the outcome "severe hypoglycaemia".

- Symptomatic hypoglycaemia (blood glucose < 54 mg/dL and blood glucose ≤ 70 mg/dL)

There was no statistically significant difference between the treatment groups for the outcomes of symptomatic hypoglycaemia (blood glucose < 54 mg/dL and blood glucose ≤ 70 mg/dL). Hence there is no hint of greater or lesser harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). An added benefit for these outcomes is therefore not proven.

- Gastrointestinal disorders, nausea, diarrhoea and dyspepsia

There was a statistically significant difference to the disadvantage of treatment with dulaglutide + insulin lispro with or without metformin in comparison with insulin glargine + insulin lispro with or without metformin for the outcomes "gastrointestinal disorders",

"nausea", "diarrhoea" and "dyspepsia". In each case this resulted in a hint of greater harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin).

- Vomiting

There was a statistically significant difference to the disadvantage of treatment with dulaglutide + insulin lispro with or without metformin in comparison with insulin glargine + insulin lispro with or without metformin for the outcome "vomiting". In addition, there was proof of an effect modification by the characteristic "age" for this outcome. For patients < 65 years, this resulted in a hint of greater harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). For patients ≥ 65 years, there is no hint of greater harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin).

- Appetite loss

There was a statistically significant difference to the disadvantage of treatment with dulaglutide + insulin lispro with or without metformin in comparison with insulin glargine + insulin lispro with or without metformin for the outcome "appetite loss". This resulted in a hint of greater harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin).

- Pancreatitis

Regarding the proportion of patients with pancreatitis, no events occurred under treatment with dulaglutide + insulin lispro with or without metformin or under treatment with insulin glargine + insulin lispro with or without metformin. Hence there is no hint of greater or lesser harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). An added benefit for this outcome is therefore not proven.

- Injection site reactions

There was no statistically significant difference between the treatment groups for the outcome "injection site reactions". Hence there is no hint of greater or lesser harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). An added benefit for this outcome is therefore not proven.

Dulaglutide in combination with a long-acting insulin with or without oral antidiabetic

The company presented no relevant data on the combination of dulaglutide with a long-acting insulin with or without OAD. Hence there is no proof of an added benefit of dulaglutide in these combinations in comparison with the ACT metformin + human insulin (or treatment only with human insulin if metformin is not tolerated or not sufficiently effective according to the SPC).

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 dulaglutide compared with the ACT is assessed as follows:

Research question A: dulaglutide monotherapy

Since no relevant study was presented for research question A, there is no proof of an added benefit of dulaglutide 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 question B: dulaglutide in dual combination with an oral antidiabetic

Dulaglutide in dual combination with metformin

Overall, one positive effect and several negative effects with the same certainty of results and the same extent remain.

The positive effect was shown in the outcome category "non-serious/non-severe AEs" for confirmed symptomatic hypoglycaemia (blood glucose ≤ 70mg/dL) with a hint of lesser harm (extent: "considerable").

Negative effects were shown in the outcome category "non-serious/non-severe AEs" for the 3 outcomes "nausea", "vomiting" and "diarrhoea" with hints of greater harm (extent: in each case "considerable").

Furthermore, no sufficient data were available on micro- and macrovascular late complications.

In summary, there is therefore no proof of added benefit of dulaglutide in the dual combination with metformin versus the ACT metformin + sulfonylurea (glibenclamide or glimepiride) for patients with type 2 diabetes mellitus.

Dulaglutide in dual combination with an OAD other than metformin

There is no proof of added benefit of the dual combination of dulaglutide with oral blood-glucose lowering drugs other than metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride).

[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].

Research question C: dulaglutide in triple combination therapy with 2 oral antidiabetics

Since no relevant study was presented for the benefit assessment, there is no proof of an added benefit of dulaglutide in the triple combination with 2 OADs in comparison with the ACT metformin + human insulin (or treatment only with human insulin if metformin is not tolerated or not sufficiently effective according to the SPC). Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

Research question D: dulaglutide in combination with insulin with or without oral antidiabetic

Dulaglutide in combination with a short-acting insulin with or without metformin

Overall, one positive effect and several negative effects with different certainty of results, but the same extent, remain.

The positive effect was shown in the outcome category "serious/severe AEs" for the outcome "SAEs" with an indication of lesser harm under dulaglutide + short-acting insulin with or without metformin (extent: "considerable").

There were negative effects in the outcome category "non-serious/non-severe AEs" for the following outcomes: discontinuation due to AEs, gastrointestinal disorders, nausea, diarrhoea, vomiting, dyspepsia and decreased appetite, in each case with a hint of greater harm under dulaglutide + short-acting insulin with or without metformin (extent: "considerable"). For the outcome "vomiting", the negative effect only applies to patients < 65 years.

No sufficient data were available on micro- and macrovascular late complications.

In the balancing of the results, the negative effects for the outcomes "discontinuation due to AEs", "gastrointestinal disorders", "nausea", "diarrhoea", "vomiting", "dyspepsia" and "appetite loss" do not fully outweigh the advantage of dulaglutide regarding SAEs. However, they resulted in a weakening of the advantage so that, overall, there is a hint of a minor added benefit of dulaglutide + short-acting insulin with or without metformin in comparison with the ACT metformin + human insulin.

Dulaglutide in combination with a long-acting insulin with or without oral antidiabetic

The company presented no data on other combinations of dulaglutide with a long-acting insulin with or without OAD. Overall, this resulted in no proof of added benefit of dulaglutide + long-acting insulin with or without OAD versus the ACT metformin + human insulin.

Summary

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

Table 3: Dulaglutide – extent and probability of added benefit

Research question	**Subindication**	**ACT**	**Extent and probability of added benefit**
A	Dulaglutide monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications	Sulfonylurea (glibenclamide or glimepiride)	Added benefit not proven
B	Dulaglutide + metformin	Metformin + sulfonylurea (glibenclamide or **glimepiride**[a]) *(note: if metformin is considered inappropriate according to the SPC, human insulin is to be used as treatment option)*	Added benefit not proven
	Dulaglutide + OAD other than metformin when this, together with diet and exercise, does not provide adequate glycaemic control		Added benefit not proven
C	Dulaglutide + 2 OADs when these, together with diet and exercise, do not provide adequate glycaemic control	Metformin + human insulin *(note: if applicable, treatment only with human insulin if metformin is not tolerated or not sufficiently effective according to the SPC)*	Added benefit not proven
D	Dulaglutide + short-acting insulin with or without metformin	Metformin + human insulin *(note: if applicable, treatment only with human insulin if metformin is not tolerated or not sufficiently effective according to the SPC)*	Hint of a minor added benefit
	Dulaglutide + long-acting insulin with or without OAD when this, together with diet and exercise, does not provide adequate glycaemic control		Added benefit not proven

a: The company chose no option, but presented studies versus glimepiride. Hence glimepiride is the ACT and is printed in **bold**.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetic; 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 questions

The aim of the present report was to assess the added benefit of dulaglutide for the treatment of adults with type 2 diabetes mellitus in comparison with the ACT.

Four different research questions within the therapeutic indication result from the different combinations with other blood-glucose lowering drugs. These are presented in Table 4 together with the respective ACTs specified by the G-BA.

Table 4: Subindications, research questions and ACTs for dulaglutide

Research question	**Subindication**[a]	**Research question of the company**	**ACT specified by the G-BA**
A	Monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications	Module 4 A dulaglutide as monotherapy	Sulfonylurea (glibenclamide or glimepiride)
B	Dual combination therapy with an OAD when this, together with diet and exercise, does not provide adequate glycaemic control	Module 4 B dulaglutide + metformin	Metformin plus sulfonylurea (glibenclamide or glimepiride) *(note: if metformin is considered inappropriate according to the SPC, human insulin is to be used as treatment option)*
C	Triple combination therapy with 2 OADs when these, together with diet and exercise, do not provide adequate glycaemic control	Module 4 C dulaglutide + metformin + glimepiride	Metformin plus human insulin *(note: if applicable, treatment only with human insulin if metformin is not tolerated or not sufficiently effective according to the SPC)*
D	Combination with insulin, with or without OAD when this, together with diet and exercise, does not provide adequate glycaemic control	Module 4 D dulaglutide + insulin lispro with or without metformin	Metformin plus human insulin *(note: if applicable, treatment only with human insulin if metformin is not tolerated or not sufficiently effective according to the SPC)*
a: Subdivisions of the therapeutic indication according to the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetic; SPC: Summary of Product Characteristics			

The company did not completely investigate the research questions B to D because it only considered part of the possible combinations in each case. It based its research questions on the studies with dulaglutide it had conducted and did not address the missing combinations.

Regarding the ACT, the company followed the G-BA's specifications for all research questions. The company additionally considered studies with glipizide for research question B. This had no consequences for the present assessment, however, because the corresponding indirect comparison is unsuitable for the benefit assessment.

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

2.3 Research question A: dulaglutide monotherapy

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on dulaglutide (studies completed up to 1 December 2014)
- bibliographical literature search on dulaglutide (last search on 1 December 2014)
- search in trial registries for studies on dulaglutide (last search on 1 December 2014)

To check the completeness of the study pool:

- search in trial registries for studies on dulaglutide (last search on 21 January 2015)

No relevant study on the comparison of dulaglutide with the ACT specified by the G-BA (sulfonylurea [glibenclamide or glimepiride]) was identified for the present research question. This concurs with the company's assessment.

Alternatively, the company used a study on the comparison of dulaglutide with metformin for its assessment (Study AWARD-3; other study name: H9X-MC-GBDC). This study is unsuitable for the derivation of conclusions on the added benefit of dulaglutide versus the ACT specified by the G-BA (sulfonylurea [glibenclamide or glimepiride]).

2.3.2 Results on added benefit

The company presented no relevant data for research question A. Hence there is no proof of added benefit of dulaglutide in monotherapy versus the ACT specified by the G-BA.

2.3.3 Extent and probability of added benefit

Since no relevant study was presented for research question A, there is no proof of an added benefit of dulaglutide 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 also claimed no added benefit for the comparison versus the ACT specified by the G-BA, but derived an indication of minor added benefit in comparison with the alternative comparator therapy (metformin as monotherapy) it had chosen.

2.3.4 List of included studies

Not applicable as the company in its assessment did not present any relevant studies on the comparison with the ACT specified by the G-BA.

2.4 Research question B: dulaglutide in dual combination with an oral antidiabetic

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on dulaglutide (studies completed up to 1 December 2014)
- bibliographical literature search on dulaglutide (last search on 1 December 2014)
- search in trial registries for studies on dulaglutide (last search on 1 December 2014)
- bibliographical literature search on the ACT (last search on 21 November 2014)
- search in trial registries for studies on the ACT (last search on 1 December 2014)

To check the completeness of the study pool:

- search in trial registries for studies on dulaglutide (last search on 21 January 2015)
- search in trial registries for studies on sitagliptin (last search on 4 March 2015)

No relevant study of direct comparison was identified from the check.

2.4.1.1 Studies included

Dulaglutide in dual combination with metformin

In Module 4 B of the dossier, the company presented a total of 4 indirect comparison, 3 with the common comparator sitagliptin, and one with the common comparator liraglutide:

- Common comparator: sitagliptin + metformin
  - studies AWARD-5 (dulaglutide + metformin) and Arechavaleta 2011 (glimepiride + metformin)
  - studies AWARD-5 (dulaglutide + metformin) and Nauck 2007/Seck 2010 (glipizide + metformin)
  - studies AWARD-5 (dulaglutide + metformin) and HARMONY 3 (glimepiride + metformin)
- Common comparator: liraglutide + metformin
  - studies AWARD-6 (dulaglutide + metformin) and LEAD-2 (glimepiride + metformin)

Except for the comparison between the studies AWARD-5 and HARMONY 3, the indirect comparisons considered by the company are unsuitable for the assessment of the added benefit of dulaglutide. This is due to the following reasons:

The comparisons between the AWARD-5 study and the Arechavaleta 2011 (30 weeks) and Nauck 2007/Seck 2010 (104 weeks) studies are unsuitable for the benefit assessment because in both cases the data presented on AEs were incomplete and did not allow to draw an appropriate overall conclusion on added benefit. Moreover, the study populations in the AWARD-5 and the Arechavaleta 2011 studies were not sufficiently similar (see Section 2.8.3.2.3.2 of the full dossier assessment).

The indirect comparison between the studies AWARD-6 and LEAD-2 (26 weeks) is unsuitable for the benefit assessment because, on the one hand, the populations were not sufficiently similar with regard to baseline HbA1c, and, on the other, the HbA1c decrease in the respective liraglutide arms of the 2 studies was also not comparable. In addition, it was not guaranteed in the LEAD-2 study that the patients had received their maximum tolerated dose of metformin. A detailed explanation of this can be found in Section 2.8.3.2.3.2 of the full dossier assessment.

Hence only the indirect comparison between the studies AWARD-5 and HARMONY 3 was included in the assessment of the added benefit of dulaglutide in combination with metformin (see Table 5). Data from studies with a duration of 104 weeks were therefore available for research question B.

Table 5: Study pool – RCT, indirect comparison: dulaglutide + metformin vs. glimepiride + metformin (research question B)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Study with dulaglutide			
H9X-MC-GBCF (AWARD-5)[b]	Yes	Yes	No
Study with glimepiride			
HARMONY 3	No	No	Yes
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. b: Hereinafter referred to as AWARD-5. RCT: randomized controlled trial; vs.: versus			

Section 2.4.4 contains a reference list for the studies included.

Dulaglutide in dual combination with an OAD other than metformin

No relevant studies on dual combinations of dulaglutide with an OAD other than metformin were identified. This concurs with the company's assessment.

2.4.1.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, indirect comparison: dulaglutide + metformin vs. glimepiride + metformin (research question B)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study with dulaglutide						
AWARD-5	RCT, double-blind, parallel, combined phase 2/3 study (2 stages), placebo- and active-controlled	Adult (18 to 75 years) patients with type 2 diabetes mellitus with HBA1c > 8% and ≤ 9.5% despite adapted diet and physical exercise alone, or with HbA1c ≥ 7% and ≤ 9.5% on monotherapy with metformin or another OAD or on combination therapy of metformin with another OAD	Each in combination with metformin (Stage 1 + 2): ▪ dulaglutide (0.75 mg) (N = 302)[b] ▪ dulaglutide (1.5 mg) (N = 304) ▪ sitagliptin (N = 315) ▪ placebo/sitagliptin (N = 177)[b]	▪ Lead-in phase: up to 11 weeks ▪ Treatment phase: 104 weeks ▪ Follow-up phase: 4 weeks	111 study centres in 12 countries: Canada, France, Germany, India, Mexico, Poland, Romania, Russia, South Korea, Spain, Taiwan, United States of America 10/2008 – 7/2012	Primary: change in HbA1c after 52 weeks of treatment Secondary: health-related quality of life, AEs, hypoglycaemia
Study with glimepiride						
HARMONY 3	RCT, double-blind, parallel, placebo- and active-controlled	Adult patients with type 2 diabetes mellitus with HbA1c of 7.0% to 10.0% with prior metformin treatment ≥ 1500 mg/day for ≥ 3 months	Each in combination with metformin: ▪ glimepiride (N = 317) ▪ sitagliptin (N = 313) ▪ albiglutide (N = 315)[b] ▪ placebo (N = 104)[b]	▪ Lead-in phase: 4 weeks ▪ Treatment phase: 156 weeks ▪ Follow-up phase: 8 weeks	289 study centres in 10 countries 2/2009 – 3/2013	Primary: Change in HbA1c after 104 weeks of treatment Secondary: AEs, hypoglycaemia

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: The arm is not relevant for the assessment and is no longer shown below.
AE: adverse event; HbA1c: glycosylated haemoglobin A1c; N: number of randomized patients; OAD: oral antidiabetic; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the interventions – RCT, indirect comparison: dulaglutide + metformin vs. glimepiride + metformin (research question B)

Study	Intervention/comparator intervention	Common comparator	Concomitant medication
Study with dulaglutide			
AWARD-5	Dulaglutide (1.5 mg), once weekly, subcutaneous injection + metformin (≥ 1500 mg/day), orally + placebo for sitagliptin once daily (OAD treatment as described in the column "concomitant medication") *Change of metformin dose/discontinuation of randomized study medication* ▪ According to the prescribing information, the use of metformin could be temporarily discontinued for a short period of time (e.g. in case of severe dehydration, planned surgery, or radiological examinations involving iodinated contrast materials). If discontinuation of the drug lasted longer than 14 days, the patient could be excluded from the study. ▪ In case of clinically significant hypoglycaemia the metformin dose could be reduced no more than twice. If persistent hypoglycaemia occurred, discontinuation of metformin was to be considered. ▪ In case of persistent or increased hyperglycaemia, increase of the metformin dose was allowed.	Placebo for dulaglutide, once weekly, subcutaneous injection + metformin (≥ 1500 mg/day), orally + sitagliptin (100 mg), once daily, orally (OAD treatment as described in the column "concomitant medication")	*OAD treatment* ▪ *Lead-in phase, 11 weeks* ▫ The patients were instructed to discontinue all OADs except metformin. ▫ Metformin (≥ 1500 mg/day) had to be used from the beginning of the lead-in phase. ▫ All patients received a minimum metformin dosage of 1500 mg/day. This dosage had to be stable for at least 6 weeks before randomization. It was not allowed to exceed the maximum locally approved dose. ▪ *Treatment phase, 104 weeks* ▫ Continuation of the OAD treatment with metformin established in the lead-in phase ▪ *Permitted medication:* ▫ insulins for short-term treatment of acute conditions ▪ *Prohibited medication:* ▫ drugs that permanently affect gastrointestinal motility ▫ drugs to promote weight loss ▫ use of systemic glucocorticoids for more than 14 consecutive days ▫ central nervous system stimulants

(continued)

Table 7: Characteristics of the interventions – RCT, indirect comparison: dulaglutide + metformin vs. glimepiride + metformin (research question B) (continued)

Study	Intervention/comparator intervention	Common comparator	Concomitant medication
Study with glimepiride			
HARMONY 3	Glimepiride, once daily, orally + metformin (≥ 1500 mg/day), orally, at current dosage + placebo for sitagliptin, once daily, orally *Titration, dose increase of glimepiride* ▪ starting dose: 2 mg/day ▪ dose increase (week 4 to 143) to 4 mg/day possible *Discontinuation of randomized study medication:* ▪ discontinuation in case of severe or repeated hypoglycaemia	Placebo for glimepiride, once daily, orally + metformin (≥ 1500 mg/day), orally, at current dosage + sitagliptin (100 mg), once daily, orally	▪ *OAD treatment* ▫ pretreatment at least 12 weeks before screening with metformin ≥ 1500 mg/day (or maximum tolerated dosage < 1500 mg/day for at least 8 weeks before randomization) at a stable dosage for at least 8 weeks ▪ *As-needed medication:* ▫ glycaemic rescue medication was allowed within a defined range of glucose levels

HbA1c: glycosylated haemoglobin A1c; OAD: oral antidiabetic; RCT: randomized controlled trial; vs.: versus

Dulaglutide study (AWARD-5)

Study design

The AWARD-5 study was a randomized, active-controlled, double-blind approval study (phase 2/3) sponsored by the company to compare dulaglutide with sitagliptin (each with metformin), which consisted of 2 stages.

Stage 1 was conducted for dose-finding of dulaglutide (in the sense of a phase 2 study) and included 9 parallel treatment arms: 7 arms with different dosages of dulaglutide (0.25 to 3.0 mg/week), one arm with sitagliptin and one arm with placebo (followed by sitagliptin after 26 weeks). Patients in all arms additionally received metformin. In Stage 1 of the study, 230 patients were randomly assigned in a ratio of 3:1:1 to the interventions dulaglutide, sitagliptin and placebo (followed by sitagliptin after 26 weeks). The probabilities of randomization into both control arms were constant. Randomization to the 7 dulaglutide arms was adaptive based on interim analyses of the benefit-risk profile of the individual dosages. After randomization of more than 200 patients, 2 dulaglutide dosages were selected for further investigation in Stage 2. These 2 dosages were 0.75 mg/week and 1.5 mg/week. The selection was based on a predefined clinical utility index (CUI), which included changes from baseline HbA1c, weight, pulse rate, and diastolic blood pressure.

In Stage 2 of the study (in the sense of a phase 3 study), further 972 patients were randomly assigned in a ratio of 2:2:2:1 to the selected treatment arms dulaglutide (0.75 mg/week), dulaglutide (1.5 mg/week), sitagliptin and placebo (followed by sitagliptin) (each with metformin). Randomization was stratified by countries and baseline HbA1c (≤ 8.5%; > 8.5%). Only 2 of the 4 treatment arms are relevant for the present benefit assessment (1.5 mg/week dulaglutide and sitagliptin).

Patients who had received metformin or another OAD as monotherapy or a combination therapy of metformin with another OAD were enrolled. Patients without pretreatment were also enrolled. 88.2% and 86.3% (dulaglutide and sitagliptin arm) of the patients in this study received metformin (as monotherapy or in dual combination) at enrolment. It can therefore be assumed that the majority of the patients in the AWARD-5 study fulfilled the criterion “inadequate glycaemic control under metformin”. The proportion of patients without prior therapy was notably below 10%.

After screening, the study consisted of a lead-in phase of up to 11 weeks, a 104-week treatment phase (Stage 1 and 2) and a 4-week follow-up phase. Since the patients had received a stable metformin dosage of ≥ 1500 mg/day for at least 6 weeks before randomization, the lead-in phase served to adapt the metformin dose to this requirement if necessary and to discontinue any additional OADs.

The design of the AWARD-5 study was aimed at including a patient population with inadequate glycaemic control despite monotherapy with metformin at a dose of ≥ 1500 mg

daily. It was therefore assumed that the patients mostly complied with the target population of research question B.

The primary outcome of the study was the change in HbA1c after 52 weeks of treatment.

Treatment regimen

Depending on the treatment arm, the patients received 1.5 mg/week dulaglutide or 100 mg/day sitagliptin (and in each case additionally ≥ 1500 mg/day metformin). Escalation of the study medication depending on the patients' needs was not envisaged.

Rescue medication was not allowed in this study. In case of persistent hyperglycaemia with blood glucose levels above the predefined threshold values, the patients had to discontinue the study.

Glimepiride study (HARMONY 3)

Study design

The HARMONY 3 study was a randomized, active-controlled, double-blind phase 3 study. 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) and who had an HbA1c value between 7% and 10% at the last visit in the stabilization phase. Before screening, all patients had to have received metformin for at least 12 weeks and at a stable dosage for at least 8 weeks of this period.

The study consisted of a 4-week stabilization phase, a treatment phase of 156 weeks and a follow-up phase of 8 weeks. An 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 the 4 treatment arms albiglutide, glimepiride, sitagliptin and placebo (each with metformin). Randomization was 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, 317 patients were randomly allocated to the glimepiride arm, and 313 patients to the sitagliptin arm.

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

Treatment regimen

After randomization, the patients either received a fixed dose of 100 mg/day sitagliptin or a dose of 2 mg/day glimepiride, which could be continued with a masked increase to 4 mg/day starting from week 4. All patients additionally received ≥ 1500 mg/day metformin. Hyperglycaemic rescue medication of investigator's choice was allowed in addition to the randomized study medication and background therapy within defined glucose thresholds.

Patients who had received a 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.

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 dose, which is then gradually increased up to the maximum daily dose of 6 mg depending on the metabolic control aimed at [3]. In the HARMONY 3 study, doses of 1 mg, 3 mg, 5 mg, and 6 mg were not available. Hence the patients could not start with the lowest starting dose of 1 mg, and it was not possible to administer titration steps of 1 mg. The dosage could also not be increased to the approved maximum dosage of up to 6 mg. Instead of stepwise dose increase, only one single dose increase by 2 mg could be performed. It was 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.

Figure 1 shows the change in HbA1c value in comparison with the baseline value up to week 104 in the HARMONY 3 study. Missing values were imputed with the last observation carried forward (LOCF) value.

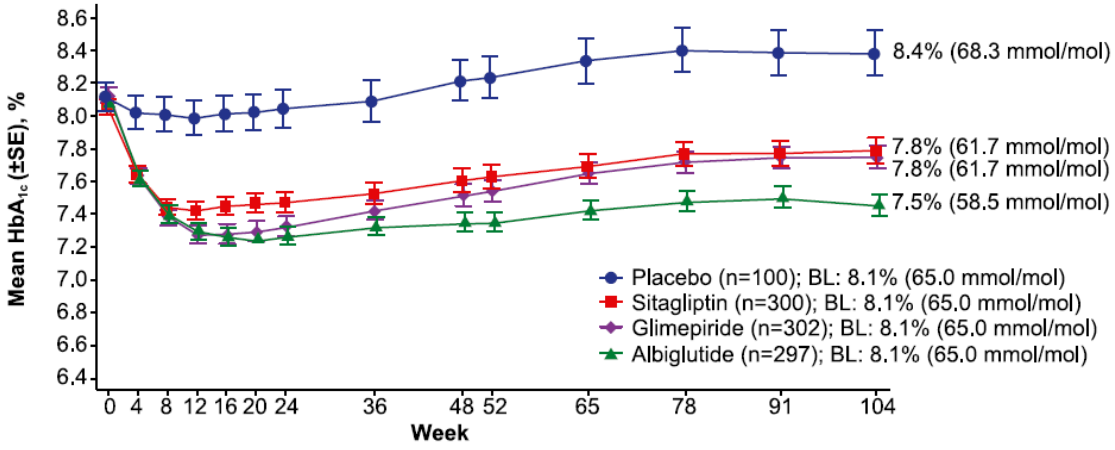

Figure 1: Change in HbA1c value in comparison with the baseline value up to week 104 in the HARMONY 3 study [4].

Overall, the picture of the HbA1c courses was largely consistent in the 2 treatment arms sitagliptin + metformin and glimepiride + metformin. The maximum difference in HbA1c between the 2 treatment arms was approximately 0.2 percentage points (read from the graph). Since the available documents on HARMONY 3 provide no information on the time courses of the hypoglycaemia or other patient-relevant outcomes (cerebral or cardiac events) for the sitagliptin + metformin and the glimepiride + metformin arms, an uncertainty remains regarding the influence of the glimepiride treatment regimen. The results of the

HARMONY 3 study were considered to be interpretable, however, and were used for the indirect comparison.

Similarity of the AWARD-5 and HARMONY 3 studies

Study populations

Table 8 shows the characteristics of the patients in the studies included.

Table 8: Characteristics of the study populations – RCT, indirect comparison: dulaglutide + metformin vs. glimepiride + metformin (research question B)

Study Group	N[a]	Age [years] mean (SD)	Sex [F/M] %	Body weight [kg] mean (SD)	BMI [kg/m^2] mean (SD)	Duration of diabetes [years] mean (SD)	HbA1c value [%] mean (SD)	Ethnicity [white/non-white] %	Treatment discontin-uations n (%)
Dulaglutide study									
AWARD-5									
dulaglutide 1.5 mg[b]	304	54 (10)	52/48	86.7 (17.5)	31.4 (4.6)	7.0 (5.5)	8.1 (1.1)	52/48[c, d]	112 (36.8)[e]
sitagliptin[b]	315	54 (10)	52/48	86.0 (16.9)	31.0 (4.2)	7.2 (4.9)	8.1 (1.1)	50/50[c, d]	129 (41.0)[e]
Glimepiride study									
HARMONY 3									
sitagliptin[b]	313	54 (10)	54/46	90.3 (19.1)	32.5 (5.4)	5.8 (4.8)	8.1 (0.8)	75[f]/18[d, g, h]	90 (28.8[d])
glimepiride[b]	317	54 (10)	49/51	91.8 (20.4)	32.5 (5.5)	6.0 (4.8)	8.1 (0.8)	72[f]/18[d, g, h]	89 (28.1[d])

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: Plus metformin.
c: This group includes patients of African origin, Native Australians and/or Torres Strait Islanders, Asia – East Asian origin, Asia – West Asian origin (Indian subcontinent), Native Americans and of Latin American origin.
d: Institute's calculation.
e: Patients who discontinued the study.
f: According to the publication [4], this group includes patients of white, Caucasian and European origin.
g: This group includes patients of Afro-American/African origin and Asian origin [4].
h: According to the publication [4], relative to the number of analysed patients, 302 (sitagliptin) vs. 307 (glimepiride). No information available on 22 vs. 32 patients.

BMI: body mass index; F: female; HbA1c: glycosylated haemoglobin A1c; M: male; N: number of randomized patients; n: number of patients with event; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Both studies (AWARD-5 and HARMONY 3) aimed at including a patient population with inadequate glycaemic control despite monotherapy with metformin (≥ 1500 mg/day). It was therefore assumed that the patients in both studies mostly complied with the target population.

There was no relevant difference between the studies or between the individual arms of the respective studies regarding the characteristics age, sex and duration of disease. The mean age of the patients was 54 years, and the mean duration of diabetes was 7 and 6 years (AWARD-5 and HARMONY 3). Approximately the same proportion of men and women were included in all study arms considered.

There was also no important difference regarding the mean HbA1c value at baseline, which was approximately 8.1% in all treatment arms of both studies. The mean weight of the patients was somewhat lower in the AWARD-5 study (87 and 86 kg in the dulaglutide and sitagliptin arm) than in the HARMONY 3 study (90.3 and 91.8 kg in the sitagliptin and glimepiride arm). The body mass index (BMI) was comparable in all 4 study arms and was approximately 31.2 kg/m^2 in the AWARD-5 study and 31.5 kg/m^2 in the HARMONY 3 study.

36.8% and 41.0% (dulaglutide and sitagliptin arm) of the patients discontinued the study in the AWARD-5 study. For the HARMONY 3 study, only data on treatment discontinuations were available. The proportion of patients who discontinued treatment was somewhat lower in the HARMONY 3 study (28.8% and 28.1% in the sitagliptin and glimepiride arm) than the proportion of patients who discontinued the study in the AWARD-5 study.

No decisive differences between the AWARD-5 and the HARMONY 3 studies regarding the study populations can be derived from the available data so that both studies were considered to be sufficiently similar for an adjusted indirect comparison in this respect.

Treatment regimen

As described for the HARMONY 3 study, there was an uncertainty for the glimepiride arm because of the starting dose of 2 mg, which was too high, and the defined dose increase to 4 mg because presumably this did not constitute the optimum treatment for at least part of the patients.

A comparison of the HbA1c courses under dulaglutide + metformin (in the AWARD-5 study, Figure 2) and glimepiride + metformin (in the HARMONY 3 study, Figure 1), with comparable baseline HbA1c values, showed a reduction of the HbA1c value from dulaglutide (1.5 mg) already in the first 3 months of treatment (-1.26%), which was notably higher than the maximum reduction observed under glimepiride (approximately -0.82% at week 12, estimated from Figure 1). The glimepiride treatment regimen used in the HARMONY 3 study therefore probably did not lead to a relevant increase in the probability of hypoglycaemia in patients in the glimepiride arm of the HARMONY 3 study in comparison with the patients in the dulaglutide of the AWARD-5 study.

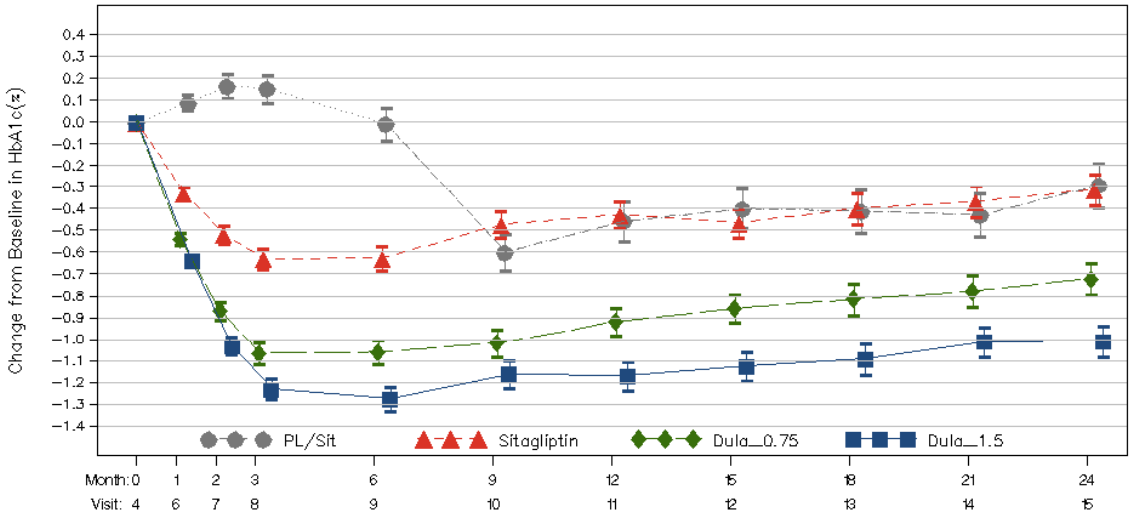

Figure 2: Change in HbA1c value in comparison with the baseline value up to week 104 in the AWARD-5 study (missing values imputed with MMRM)

Common comparator

The comparability of the common comparator (sitagliptin + metformin) is also relevant for an adjusted indirect comparison. This was considered to be sufficient for the available studies.

On the one hand, the dose specifications of the common comparator were identical in both studies: 100 mg/day sitagliptin in combination with ≥ 1500 mg/day metformin.

On the other, the similarity was also apparent in a comparable lowering of HbA1c in the sitagliptin arms of both studies. From nearly identical HbA1c values at baseline (8.09% in AWARD-5 and 8.1% in HARMONY 3), the maximum lowering of the HbA1c value (after approximately 12 weeks) from sitagliptin + metformin was 0.63% in the AWARD-5 study and approximately 0.64% in the HARMONY 3 study (estimated from Figure 1). At week 104, sitagliptin + metformin lowered the mean HbA1c value by 0.31% (AWARD-5) and 0.28% (HARMONY 3).

Consequences for study inclusion and assessment

No important differences between the studies considered could be inferred from the available data. Overall, the 2 studies AWARD-5 and HARMONY 3 were considered to be sufficiently similar so that the assumption of similarity for an adjusted indirect comparison was not rejected.

Risk of bias at study level

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, indirect comparison: dulaglutide + metformin vs. glimepiride + metformin (research question B)

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			
Study with dulaglutide							
AWARD-5	Yes	Yes	Yes	Yes	Yes	Yes	Low
Study with glimepiride							
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 for both studies. The information contained in the benefit assessment of albiglutide (A14-36) [5] was included in the assessment of the risk of bias for the HARMONY 3 study.

The assessment for the HARMONY 3 study deviates from the rating of the company, which considered the criterion “reporting independent of the results” as unclear and rated the risk of bias at study level as high for this study.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.8.3.2.5.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - micro- and macrovascular late complications
- Health-related quality of life
- Adverse events
  - SAES
  - AEs
  - severe hypoglycaemia
  - symptomatic hypoglycaemia (blood glucose ≤ 54 mg/dL; blood glucose ≤ 70 mg/dL)
  - gastrointestinal disorders
    - nausea
    - diarrhoea
    - vomiting
  - pancreatitis
  - 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 2.8.3.2.5.3 of the full dossier assessment.

Table 10 shows for which outcomes data were available in the studies included.

Table 10: Matrix of outcomes – RCT, indirect comparison: dulaglutide + metformin vs. glimepiride + metformin (research question B)

Study	Outcomes													
	All-cause mortality	Morbidity (micro- and macrovascular late complications)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe hypoglycaemia	Symptomatic hypoglycaemia (blood glucose ≤ 54 mg/dL)	Symptomatic hypoglycaemia (blood glucose ≤ 70 mg/dL)	Gastrointestinal disorders	Nausea	Diarrhoea	Vomiting	Pancreatitis	Injection site reactions
Dulaglutide study														
AWARD-5	Yes	No[a]	No[b]	Yes	Yes	Yes	No[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Glimepiride study														
HARMONY 3	Yes	No[a]	No[b]	Yes	Yes	Yes	No[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: No relevant data were available; for reasons, see Section 2.8.3.2.5.3 of the full dossier assessment.
b: The outcome was recorded in the AWARD-5 study, but not in the HARMONY 3 study, and could not be included in the indirect comparison.
c: The data were not published for the HARMONY 3 study; the outcome could therefore not be included in the indirect comparison.
AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.4.2.2 Risk of bias

Table 11 shows the risk of bias for the relevant outcomes.

Table 11: Risk of bias at study and outcome level – RCT, indirect comparison: dulaglutide + metformin vs. glimepiride + metformin (research question B)

Study	Study level	Outcomes													
		All-cause mortality	Morbidity (micro- and macrovascular late complications)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe hypoglycaemia	Symptomatic hypoglycaemia (blood glucose ≤ 54 mg/dL)	Symptomatic hypoglycaemia (blood glucose ≤ 70 mg/dL)	Gastrointestinal disorders	Nausea	Diarrhoea	Vomiting	Pancreatitis	Injection site reactions
Dulaglutide study															
AWARD-5	L	L	–[a]	–[b]	L	L	L	–[d]	L	L	L	L	L	L	L
Glimepiride study															
HARMONY 3	L	L	–[a]	–[b]	L	L	H[c]	–[d]	H[c]	L	L	L	L	L	L

a: No relevant data were available.
b: The outcome was recorded in the AWARD-5 study, but not in the HARMONY 3 study, and could not be included in the indirect comparison.
c: Due to the uncertainties regarding the use of glimepiride assessed as having a high risk of bias (see Section 2.4.1.2).
d: The outcome was recorded in both studies, but not published in the HARMONY 3 study, and could not be included in the indirect comparison.
AE: adverse event; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

For the AWARD-5 study, the assessment of the risk of bias at outcome level is consistent with the one of the company.

For the HARMONY 3 study, the risk of bias was rated as low for all outcomes except for severe and symptomatic hypoglycaemia (blood glucose < 70 mg/dL). The outcomes of severe and symptomatic hypoglycaemia were rated as having a high risk of bias because of the uncertainties on the use of glimepiride in the study described (see Section 2.4.1.2).

Except for the outcomes of severe and symptomatic hypoglycaemia, this deviates from the company's assessment. Due to the risk of bias at study level assessed as high by the company, the company also rated the risk of bias of all outcomes of this study as high.

Detailed reasons for the assessment of the risk of bias can be found in Section 2.8.3.2.5.2 of the full dossier assessment.

2.4.2.3 Results

Table 12 and Table 13 contain the results on the comparison of dulaglutide with sitagliptin (each with metformin) and on the comparison of glimepiride with sitagliptin (each with metformin) as well as the results on the adjusted indirect comparisons of dulaglutide with glimepiride based on these studies. Where necessary, the data from the company's Module 4 B were supplemented by the Institute's calculations.

Rescue medication during the study was not allowed in the AWARD-5 study; persistent hyperglycaemia resulted in discontinuation of the study. In the HARMONY 3 study, in contrast, rescue medication was allowed. Different periods of analysis depending on the outcome were available for this study: Only analyses up to the use of rescue medication were available for the outcomes of hypoglycaemia; for the outcomes "diarrhoea" and "nausea", both results up to the use of rescue medication and for the total study duration were available. Only results for the total study duration were available for the remaining outcomes. In general, also events under and after rescue medication are of interest. Since rescue medication was not possible in the AWARD-5 study, the results up to rescue medication were used for the outcomes for which analyses at both time points (up to the rescue medication or total study duration) were available (diarrhoea and nausea) (see Section 2.8.3.2.5.3 of the full dossier assessment). The results on both time points did not differ considerably for the outcomes mentioned, however, so that the choice of the period of analysis had not relevant consequences for the result.

Since an adjusted indirect comparison according to Bucher with only one study each was used for research question B, and no direct comparison was available, it was not possible to check homogeneity and consistency. Hence at most hints of added benefit or harm were derived from the available data.

Table 12: Results (mortality, AEs) – RCT, indirect comparison: dulaglutide + metformin vs. glimepiride + metformin (research question B)

Outcome category Outcome Study	Dulaglutide (1.5 mg)[a] or glimepiride[a]		Sitagliptin[a]		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality					
Dulaglutide (1.5 mg) vs. sitagliptin					
AWARD-5	304	1 (0.3)	315	2 (0.6)	0.52 [0.05; 5.68]; > 0.999
Glimepiride vs. sitagliptin					
HARMONY 3	307	3 (1.0)	302	1 (0.3)	2.95 [0.31; 28.21]; 0.624
Adjusted indirect comparison[b]					
Dulaglutide vs. glimepiride					0.18 [0.01; 4.72]; 0.300
Adverse events					
AEs					
Dulaglutide (1.5 mg) vs. sitagliptin					
AWARD-5	304	260 (85.5)	315	243 (77.1)	
Glimepiride vs. sitagliptin					
HARMONY 3	307	248[c] (80.8)	302	228[c] (75.5)	
SAEs					
Dulaglutide (1.5 mg) vs. sitagliptin					
AWARD-5[d]	304	36 (11.8)	315	32 (10.2)	1.17 [0.74; 1.83]; 0.503
Glimepiride vs. sitagliptin					
HARMONY 3[d]	307	29 (9.4)	302	27 (8.9)	1.06 [0.64; 1.74]; 0.829
Adjusted indirect comparison[b]					
Dulaglutide vs. glimepiride					1.10 [0.56; 2.16]; 0.774
Discontinuation due to AEs					
Dulaglutide (1.5 mg) vs. sitagliptin					
AWARD-5[e]	304	63 (20.7)	315	65 (20.6)	0.99 [0.73; 1.34]; 0.947
Glimepiride vs. sitagliptin					
HARMONY 3[e]	307	14 (4.6)	302	11 (3.6)	1.25 [0.58; 2.71]; 0.568
Adjusted indirect comparison[b]					
Dulaglutide vs. glimepiride					0.79 [0.34; 1.82]; 0.579

(continued)

Table 12: Results (mortality, AEs) – RCT, indirect comparison: dulaglutide + metformin vs. glimepiride + metformin (research question B) (continued)

Outcome category Outcome Study	Dulaglutide (1.5 mg)[a] or glimepiride[a]		Sitagliptin[a]		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Adverse events					
Severe hypoglycaemia					
Dulaglutide (1.5 mg) vs. sitagliptin					
AWARD-5	304	0 (0)	315	0 (0)	NC
Glimepiride vs. sitagliptin					
HARMONY 3	307	0 (0)	302	0 (0)	NC
Adjusted indirect comparison[b]					
Dulaglutide vs. glimepiride					NC
Symptomatic hypoglycaemia (blood glucose ≤ 54 mg/dL)	There were no evaluable data.				
Symptomatic hypoglycaemia (blood glucose ≤ 70 mg/dL)					
Dulaglutide (1.5 mg) vs. sitagliptin					
AWARD-5	304	33 (10.9)	315	18 (5.7)	1.90 [1.09; 3.30]; 0.020
Glimepiride vs. sitagliptin					
HARMONY 3	307	55 (17.9)	302	5 (1.7)	10.82 [4.39; 26.66]; < 0.001
Adjusted indirect comparison[b]					
Dulaglutide vs. glimepiride					0.18 [0.06; 0.51]; 0.001
Gastrointestinal disorders					
Dulaglutide (1.5 mg) vs. sitagliptin					
AWARD-5	304	139 (45.7)	315	94 (29.8)	1.53 [1.24; 1.89][c]; < 0.001[f]
Glimepiride vs. sitagliptin					
HARMONY 3	307	85 (27.7)	302	75 (24.8)	1.11 [0.85; 1.46][c]; 0.474[f]
Adjusted indirect comparison[b, c]					
Dulaglutide vs. glimepiride					1.37 [0.98; 1.93]; 0.066
Nausea					
Dulaglutide (1.5 mg) vs. sitagliptin					
AWARD-5	304	53 (17.4)	315	21 (6.7)	2.62 [1.62; 4.23]; < 0.001
Glimepiride vs. sitagliptin					
HARMONY 3	307	16[c] (5.2)	302	19[c] (6.3)	0.79 [0.42; 1.49]; 0.461
Adjusted indirect comparison[b]					
Dulaglutide vs. glimepiride					3.32 [1.50; 7.38]; 0.003

(continued)

Table 12: Results (mortality, AEs) – RCT, indirect comparison: dulaglutide + metformin vs. glimepiride + metformin (research question B) (continued)

Outcome category Outcome Study	Dulaglutide (1.5 mg)[a] or glimepiride[a]		Sitagliptin[a]		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Adverse events					
Diarrhoea					
Dulaglutide (1.5 mg) vs. sitagliptin					
AWARD-5	304	49 (16.1)	315	18 (5.7)	2.82 [1.68; 4.73]; < 0.001
Glimepiride vs. sitagliptin					
HARMONY 3	307	24[c] (7.8)	302	26[c] (8.6)	0.91 [0.53; 1.55]; 0.722
Adjusted indirect comparison[b]					
Dulaglutide vs. glimepiride					3.11 [1.48; 6.52]; 0.003
Vomiting					
Dulaglutide (1.5 mg) vs. sitagliptin					
AWARD-5	304	41 (13.5)	315	11 (3.5)	3.86 [2.02; 7.37][c]; <0.001[f]
Glimepiride vs. sitagliptin					
HARMONY 3	307	11[c] (3.6)	302	13[c] (4.3)	0.83 [0.38; 1.83][c]; 0.666[f]
Adjusted indirect comparison[b, c]					
Dulaglutide vs. glimepiride					4.64 [1.68; 12.85]; 0.003
Pancreatitis					
Dulaglutide (1.5 mg) vs. sitagliptin					
AWARD-5	304	0 (0)	315	2 (0.6)	0.14 [0.01; 2.24]; 0.499[g]
Glimepiride vs. sitagliptin					
HARMONY 3[h]	307	0 (0)	302	0 (0)	NC
Adjusted indirect comparison[b]					
Dulaglutide vs. glimepiride					NC
Injection site reactions					
Dulaglutide (1.5 mg) vs. sitagliptin					
AWARD-5	304	4 (1.3)	315	3 (1.0)	1.38 [0.31; 6.12][c]; 0.694[f]
Glimepiride vs. sitagliptin					
HARMONY 3	307	24 (7.8)	302	19 (6.3)	1.24 [0.70; 2.22][c]; 0.497[f]
Adjusted indirect comparison[b, c]					
Dulaglutide vs. glimepiride					1.11 [0.23; 5.50]; 0.897

(continued)

Table 12: Results (mortality, AEs) – RCT, indirect comparison: dulaglutide + metformin vs. glimepiride + metformin (research question B) (continued)

a: Plus metformin.
b: Indirect comparison according to Bucher [6].
c: Institute's calculation.
d: Hypoglycaemic events were also recorded here. No severe hypoglycaemia occurred in both studies.
e: Hypoglycaemic events were also recorded here. In the AWARD-5 study, no patient in the total population discontinued treatment due to hypoglycaemia. No corresponding data were available for the HARMONY 3 study, but no severe hypoglycaemia occurred.
f: Institute's calculation, unconditional exact test (CSZ method according to [7]).
g: Peto OR.
h: 2 cases of suspected pancreatitis under glimepiride occurred in the HARMONY 3 study, which were not confirmed in the adjudication procedure.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event (at least one); NC: not calculable; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 13: Results (morbidity, health-related quality of life, supplementary outcome) – RCT, indirect comparison: dulaglutide + metformin vs. glimepiride + metformin (research question B)

Outcome category / **Outcome** / **Study**	**Dulaglutide (1.5 mg)[a] or glimepiride[a]**			**Sitagliptin[a]**			**Group difference**
	N[b]	**Baseline values mean (SD)**	**Change at end of study mean[c] (SE)**	**N[b]**	**Baseline values mean (SD)**	**Change at end of study mean[c] (SE)**	**Mean difference [95% CI]; p-value**
Morbidity (micro- and macrovascular late complications)							
There were no evaluable data.							
Health-related quality of life							
There were no evaluable data.							
Supplementary outcome "body weight" (kg)							
Dulaglutide (1.5 mg) vs. sitagliptin							
AWARD-5	303	86.67 (17.45)	-2.88 (0.25)	314	85.97 (16.91)	-1.75 (0.25)	-1.14 [-1.78; -0.49]; < 0.001
Glimepiride vs. sitagliptin							
HARMONY 3	302	91.8 (20.4)	1.17 (0.24)	300	90.3 (19.1)	-0.86 (0.24)	2.03 [1.37; 2.69]; < 0.001
Adjusted indirect comparison[d]							
Dulaglutide vs. glimepiride							-3.17 [-4.09; -2.25]; < 0.001

a: Plus metformin.
b: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
c: Unless stated otherwise, LOCF analysis of the ITT population.
d: Indirect comparison according to Bucher [6].
CI: confidence interval; ITT: intention to treat; LOCF: last observation carried forward; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

Mortality

All-cause mortality

There was no statistically significant difference between dulaglutide + metformin and glimepiride + metformin for the outcome "all-cause mortality". Hence there is no hint of an added benefit of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride). An added benefit for this outcome is therefore not proven. This concurs with the company's assessment.

Morbidity

No data evaluable for a direct or indirect comparison were available on micro- and macrovascular late complications. Hence there is no hint of an added benefit of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride); an added benefit is therefore not proven for patient-relevant outcomes from the category "morbidity". This deviates from the company's assessment, which derived an indication of a minor added benefit on the basis of glycaemic control, change in body weight and in abdominal girth.

Health-related quality of life

No data evaluable for a direct or indirect comparison were available on health-related quality of life. Hence there is no hint of an added benefit of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride). An added benefit for this outcome is therefore not proven. This concurs with the company's assessment.

Adverse events

Serious adverse events and discontinuation due to adverse events

The indirect comparison showed no statistically significant differences between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". Hence there is no hint of greater or lesser harm of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride). An added benefit for this outcome is therefore not proven. This concurs with the company's assessment.

Severe hypoglycaemia

No severe hypoglycaemia occurred in the relevant treatment arms of both studies. Hence there is no hint of greater or lesser harm of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride); an added benefit for these outcomes is therefore not proven.

The company presented no data on severe hypoglycaemia in the HARMONY 3 study, and claimed no added benefit for this outcome.

Symptomatic hypoglycaemia

Only results on a blood glucose threshold of ≤ 70 mg/dL were available for the outcome "symptomatic hypoglycaemia". Analyses on hypoglycaemia with a lower blood glucose threshold (≤ 54 mg/dL) were not published for the HARMONY 3 study and were not presented by the company.

There was a statistically significant difference in favour of dulaglutide + metformin versus glimepiride + metformin for symptomatic hypoglycaemia with a blood glucose threshold of ≤ 70 mg/dL. This results in a hint of lesser harm of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride).

This deviates from the company's assessment, which derived an indication of lesser harm of dulaglutide for this outcome.

Gastrointestinal disorders

The indirect comparison showed no statistically significant difference between the treatment groups for the outcome "gastrointestinal disorders (System Organ Class [SOC] according to the Medical Dictionary for Regulatory Activities [MedDRA])". Hence there is no hint of greater or lesser harm of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride). An added benefit for this outcome is therefore not proven.

The company presented no analysis on the SOC "gastrointestinal disorders" in Module 4 B of the dossier for the AWARD-5 and HARMONY 3 studies included in the comparison.

Nausea, diarrhoea and vomiting

There was a statistically significant difference to the disadvantage of dulaglutide + metformin in comparison with glimepiride + metformin for the outcomes "nausea", "diarrhoea" and "vomiting". This results in hints of greater harm of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride).

For the outcomes "nausea" and "diarrhoea", this deviates from the company's assessment, which derived an indication of greater harm. The company presented no analyses on the outcome "vomiting".

Pancreatitis

No pancreatitis confirmed by an independent committee occurred in any of the patients in both relevant treatment arms, dulaglutide + metformin and glimepiride + metformin. Hence there is no hint of greater or lesser harm of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride). An added benefit for this outcome is therefore not proven.

This concurs with the company's assessment, which presented the study results, but did not use them for an indirect comparison, and which claimed no added benefit for this outcome.

Injection site reactions

The indirect comparison showed no statistically significant difference between the treatment groups for the outcome "injection site reactions (SOC)". Hence there is no hint of greater or lesser harm of dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride). An added benefit for this outcome is therefore not proven.

The fact that the patients in the glimepiride arm received placebo injections has to be taken into account. Hence the available results represent the substance-specific difference – injection with dulaglutide 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 can be assumed that results for this outcome cannot occur at all under the use of glimepiride. The actual difference between the interventions is underestimated as a result. Since the proportion of events in the dulaglutide was low (1.3%) and also below the proportion of events in the glimepiride study (7.8%), this has no consequences for the present benefit assessment.

The assessment of added benefit concurs with that of the company, which presented no analysis on this outcome.

2.4.2.4 Subgroups and other effect modifiers

No subgroup analyses were considered for the present benefit assessment of dulaglutide (see Section 2.8.3.2.2 of the full dossier assessment). This corresponds to the company's approach in Module 4 B of the dossier.

2.4.3 Extent and probability of added benefit

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

The data availability presented in Section 2.4.2 resulted both in a hint of lesser harm from the combination dulaglutide + metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride) for symptomatic hypoglycaemia (blood glucose $\leq$ 70 mg/dL) and in a hint of greater harm for the outcomes "nausea", "diarrhoea" and "vomiting".

The extent of the respective added benefit at outcome level was estimated from these results (see Table 14).

Table 14: Extent of added benefit at outcome level: dulaglutide + metformin vs. metformin + sulfonylurea (glibenclamide or glimepiride) (research question B)

Outcome category **Outcome**	**Dulaglutide + metformin vs. sitagliptin + metformin** **effect estimate [95% CI][a]** **p-value[a]** **probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	RR: 0.18 [0.01; 4.72] p = 0.300	Added benefit not proven
Morbidity (micro- and macrovascular late complications)		
	There were no evaluable data.	
Health-related quality of life		
	There were no evaluable data.	
Adverse events		
SAEs	RR: 1.10 [0.56; 2.16] p = 0.774	Greater/lesser harm not proven
Discontinuation due to AEs	RR: 0.79 [0.34; 1.82] p = 0.579	Greater/lesser harm not proven
Severe hypoglycaemia[d]	RR: NC p = NC	Greater/lesser harm not proven
Symptomatic hypoglycaemia (blood glucose ≤ 54 mg/dL)	There were no evaluable data.	
Symptomatic hypoglycaemia (blood glucose ≤ 70 mg/dL)	RR: 0.18 [0.06; 0.51] p = 0.001 probability: “hint”	Outcome category: non-serious/non-severe AEs CI_u < 0.80 lesser harm, extent: “considerable”
Gastrointestinal disorders	RR: 1.37 [0.98; 1.93] p = 0.066	Greater/lesser harm not proven
Nausea	RR: 3.32 [1.50; 7.38] RR: 0.30 [0.14; 0.67][e] p = 0.003 probability: “hint”	Outcome category: non-serious/non-severe AEs CI_u < 0.80 greater harm, extent: “considerable”
Diarrhoea	RR: 3.11 [1.48; 6.52] RR: 0.32 [0.15; 0.68][e] p = 0.003 probability: “hint”	Outcome category: non-serious/non-severe AEs CI_u < 0.80 greater harm, extent: “considerable”

(continued)

Table 14: Extent of added benefit at outcome level: dulaglutide + metformin vs. metformin + sulfonylurea (glibenclamide or glimepiride) (research question B) (continued)

Outcome category **Outcome**	**Dulaglutide + metformin vs. sitagliptin + metformin** **effect estimate [95% CI][a]** **p-value[a]** **probability[b]**	**Derivation of extent[c]**
Adverse events		
Vomiting	RR: 4.64 [1.68; 12.85] RR: 0.22 [0.08; 0.60][e] p = 0.003 probability: "hint"	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm, extent: "considerable"
Pancreatitis	RR: NC p = NC	Greater/lesser harm not proven
Injection site reactions	RR: 1.11 [0.23; 5.50] p = 0.897	Greater/lesser harm not proven

a: Indirect comparison according to Bucher [6].
b: Probability given if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: No severe hypoglycaemia occurred in both studies.
e: Institute's calculation: reversed direction of effect to enable direct use of limits to derive added benefit.
AE: adverse event; CI: confidence interval; CI_u: upper limit of the CI; NC: not calculable; RR: relative risk; SAE: serious adverse event; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Dulaglutide in dual combination with metformin

Table 15 summarizes the results considered in the overall conclusion on extent of added benefit.

Table 15: Positive and negative effects from the assessment of dulaglutide in comparison with metformin + sulfonylurea (glibenclamide or glimepiride) (research question B)

Positive effects	**Negative effects**
Hint of lesser harm – extent: "considerable" (non-serious/non-severe adverse events: symptomatic hypoglycaemia [blood glucose ≤ 70 mg/dL])	Hint of greater harm – extent: "considerable" (non-serious/non-severe adverse events: nausea, diarrhoea, vomiting)
No sufficient data were available on micro- and macrovascular late complications.	

Overall, one positive effect and several negative effects with the same certainty of results and the same extent remain.

The positive effect was shown in the outcome category "non-serious/non-severe AEs" for confirmed symptomatic hypoglycaemia (blood glucose ≤ 70mg/dL) with a hint of lesser harm (extent: "considerable").

Negative effects were shown in the outcome category "non-serious/non-severe AEs" for the 3 outcomes "nausea", "vomiting" and "diarrhoea" with hints of greater harm (extent: in each case "considerable").

Furthermore, no sufficient data were available on micro- and macrovascular late complications.

In summary, there is therefore no proof of added benefit of dulaglutide in the dual combination with metformin versus the ACT metformin + sulfonylurea (glibenclamide or glimepiride) for patients with type 2 diabetes mellitus.

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

Dulaglutide in dual combination with an OAD other than metformin

There is also no proof of added benefit of the dual combination of dulaglutide with oral blood-glucose lowering drugs other than metformin in comparison with the ACT metformin + sulfonylurea (glibenclamide or glimepiride). The company presented no data for other combinations.

Summary

The result of the assessment of the added benefit of dulaglutide in comparison with the ACT is summarized in Table 16.

Table 16: Dulaglutide – extent and probability of added benefit (research question B)

Research question	**Subindication**	**ACT**[a]	**Extent and probability of added benefit**
B	Dulaglutide + metformin	Metformin + sulfonylurea (glibenclamide or **glimepiride**[b]) *(note: if metformin is considered inappropriate according to the SPC, human insulin is to be used as treatment option)*	Added benefit not proven
	Dulaglutide + OAD other than metformin 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: The company chose no option, but presented studies versus glimepiride. Hence glimepiride is the ACT and is printed in **bold**.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetic; SPC: Summary of Product Characteristics

2.4.4 List of included studies

AWARD-5

Eli Lilly and Company. H9X-MC-GBCF (AWARD-5): post-hoc Analysen [unpublished]. 2014.

Eli Lilly and Company. A phase 2/3, placebo-controlled, efficacy and safety study of once-weekly, subcutaneous LY2189265 compared to sitagliptin in patients with type 2 diabetes mellitus on metformin [online]. In: EU Clinical Trials Register. [Accessed: 4 December 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=+H9X-MC-GBCF.

Eli Lilly and Company. A phase 2/3, placebo-controlled, efficacy and safety study of once-weekly, subcutaneous LY2189265 compared to sitagliptin in patients with type 2 diabetes mellitus on metformin: study H9X-MC-GBCF; clinical study report [unpublished]. 2013.

Eli Lilly and Company. Protocol H9X-MC-GBCF (b): a phase 2/3, placebo-controlled, efficacy and safety study once-weekly, subcutaneous LY2189265 compared to sitagliptin in patients with type 2 diabetes mellitus on metformin [unpublished]. 2009.

Eli Lilly and Company. A study of LY2189265 compared to sitagliptin in patients with type 2 diabetes mellitus on metformin: full text view [online]. In: ClinicalTrials.gov. 9 August 2012 [accessed: 3 December 2014]. URL: https://clinicaltrials.gov/ct2/show/NCT00734474.

Eli Lilly and Company. A study of LY2189265 compared to sitagliptin in patients with type 2 diabetes mellitus on metformin: study results [online]. In: ClinicalTrials.gov. 26 January 2015 [accessed: 9 March 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00734474.

Icon Health Economics. H9X-MC-GBCF und H9X-MC-GBDE (AWARD-5 und AWARD-6) Analysen: indirekter Vergleich [unpublished]. 2014.

Lilly Deutschland. H9X-MC-GBCF und H9X-MC-GBDE (AWARD-5 und AWARD-6) Analysen: indirekter Vergleich [unpublished]. 2014.

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: full text view [online]. In: ClinicalTrials.gov. 11 August 2014 [accessed: 4 December 2014]. URL: https://clinicaltrials.gov/ct2/show/NCT00838903.

GlaxoSmithKline. Efficacy and safety of albiglutide in treatment of type 2 diabetes: study results [online]. In: ClinicalTrials.gov. 11 August 2014 [accessed: 22 April 2015]. URL: https://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. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2008-007660-41.

2.5 Research question C: dulaglutide in triple combination therapy with 2 oral antidiabetics

2.5.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on dulaglutide (studies completed up to 1 December 2014)
- bibliographical literature search on dulaglutide (last search on 1 December 2014)
- search in trial registries for studies on dulaglutide (last search on 1 December 2014)
- bibliographical literature search on the ACT (last search on 21 November 2014)
- search in trial registries for studies on the ACT (last search on 1 December 2014)

To check the completeness of the study pool:

- search in trial registries for studies on dulaglutide (last search on 21 January 2015)

No relevant study of direct comparison was identified from the check.

From the steps of information retrieval mentioned, the company identified the 2 studies H9X-MC-GBDB (AWARD-2) [8] and LAPTOP [9], which it used for an indirect comparison.

The adjusted indirect comparison presented by the company is unsuitable to derive conclusions on the added benefit of dulaglutide in triple combination therapy with 2 OADs in comparison with the ACT specified by the G-BA. This is justified below.

Comparability of the common comparator and the study populations

The company presented the studies AWARD-2 and LAPTOP for the indirect comparison to investigate the research question dulaglutide + metformin + glimepiride versus metformin + human insulin. The common comparator was insulin glargine + metformin + glimepiride.

The AWARD-2 study was a 1:1:1 randomized, open-label study with a treatment duration of 52 weeks, in which 810 patients were included (535 patients in the arms relevant for the benefit assessment). Dulaglutide + metformin + glimepiride was investigated in comparison with insulin glargine + metformin + glimepiride in the study. The LAPTOP study was a 1:1 randomized, open-label study with a treatment duration of 24 weeks, in which 371 patients were included. Administration of premixed insulin (30% normal insulin/70% NPH insulin) was compared with insulin glargine + metformin + glimepiride in the study.

The 2 studies AWARD-2 and LAPTOP are not comparable regarding the common comparator (insulin glargine + metformin + glimepiride) and regarding the study population. This is explained below.

Common comparator

The differences refer to the insulin titration schedule of both studies used in the common comparator arm of the studies.

The titration schedule for insulin glargine in the studies AWARD-2 and LAPTOP is described in Table 17.

Table 17: Comparison of the titration schedules for insulin glargine in the studies AWARD-2 and LAPTOP (research question C)

Titration schedule	**AWARD-2** **fasting plasma glucose levels [mg/dL]**	**LAPTOP** **fasting plasma glucose levels [mg/dL]**
Insulin glargine	≥ 100 to < 120 mg/dL **+ 0 to 2 units** ≥ 120 to < 140 mg/dL **+ 2 units** ≥ 140 to < 160 mg/dL **+ 4 units** ≥ 160 to <180 mg/dL **+ 6 units** ≥ 180 mg/dL **+ 8 units**	> 100 to 120 mg/dL **+ 2 units** > 120 to 140 mg/dL **+ 4 units** > 140 to 160 mg/dL **+ 6 units** > 160 mg/dL **+ 8 units**

As shown in Table 17, the patients in the LAPTOP study received a more intense insulin dose increase on exceeding predefined target levels and were therefore treated with a more stringent insulin titration schedule than patients in the AWARD-2 study.

This is reflected in a notably larger HbA1c reduction in the common comparator arm of the LAPTOP study compared with the AWARD-2 study (-1.64% versus -0.65% after 24 and 26 weeks) and a larger proportion of patients with an HbA1c value of ≤ 7% (approximately half versus approximately one third) (see Table 18).

Table 18: Comparison of the HbA1c values in the common comparator arm (insulin glargine + metformin + glimepiride) of the studies AWARD-2 vs. LAPTOP (research question C)

Criterion	**AWARD-2 (total) N = 262**	**LAPTOP (total) N = 177**	**AWARD-2 (sensitivity analysis[a]) N = 89**
HbA1c value (%), start of study mean (SD)	8.10 (0.95)	8.85 (0.95)	8.41 (0.69)
HbA1c value (%), week 26 and 24 mean (SD)	7.48 (0.95)	7.15 (0.90)	7.71 (0.83)
HbA1c value (%), change at week 26 and 24 mean (SE)[b]	-0.65 (0.06)	-1.64 (0.07)	-0.81 (0.11)
HbA1c value (patients ≤ 7%), week 26 and 24 n (%)	84 (32.6)[c]	87 (49.4)	17 (19.3)

a: The sensitivity analysis was conducted under consideration of the following criteria: age ≥ 35 and ≤ 75 years, BMI ≤ 35 kg/m², HbA1c value ≥ 7.5 ≤ 10.5% and glimepiride dosage ≤ 6 mg/day.
b: Analysis with ANCOVA.
c: Referring to patients with HbA1c < 7%.
ANCOVA: analysis of covariance; HbA1c: haemoglobin A1c; N: number of randomized patients; or number of patients considered in the sensitivity analysis; n: number of patients with event; SD: standard deviation; SE: standard error; vs.: versus

The different insulin regimens alone already resulted in noninterpretability of the indirect comparison. This was not resolved with the sensitivity analyses conducted by the company (see next section) either.

Study population

In addition, the studies AWARD-2 and LAPTOP were based on different inclusion criteria (e.g. age, BMI, HbA1c value, glimepiride dosage and metformin dosage), which in this case resulted in incomparable study populations in both studies. This was particularly reflected in the mean baseline HbA1c. Patients in the common comparator arms had a baseline HbA1c value of 8.10% in the AWARD-2 study, and, of 8.85% in the LAPTOP study (see Table 18).

The company conducted sensitivity analyses to increase the comparability of the study population between the studies AWARD-2 and the LAPTOP. The aim of these sensitivity analyses was to adjust the population of the AWARD-2 study to the population of the LAPTOP study.

The inclusion criteria (AWARD-2 and LAPTOP) and the criteria of the sensitivity analyses conducted by the company to increase the comparability of the studies AWARD-2 and LAPTOP are shown in Table 19.

Table 19: Inclusion criteria (AWARD-2 and LAPTOP) and criteria of the sensitivity analyses conducted by the company to increase the comparability of the studies AWARD-2 and LAPTOP (research question C)

Criterion	**Inclusion criterion AWARD-2**	**Inclusion criterion LAPTOP**	**Criterion of the company's sensitivity analysis (based on the inclusion criteria of the LAPTOP study)**
Age	≥ 18 years	35 to 75 years	≥ 35 years and ≤ 75 years
BMI	≥ 23 and ≤ 45 kg/m^2	≤ 35 kg/m^2	≤ 35 kg/m²
HbA1c	≥ 7.0% and ≤ 11%	≥ 7.5% and ≤ 10.5%	≥ 7.5 and ≤ 10.5%
Glimepiride dosage	≥ 4 mg/day	3 or 4 mg/day dosage was to be maintained in the course of the study	≤ 6 mg/day (within the first 26 weeks)
Metformin dosage	≥ 1.500 mg/day	≥ 850 mg/day dose was to be maintained in the course of the study	≥ 850 mg/day (within the first 26 weeks)
BMI: body mass index; HbA1c: haemoglobin A1c			

Conducting sensitivity analyses generally is a meaningful approach. The company also used relevant parameters. However, the company conducted no complete sensitivity analyses. In the LAPTOP study, patients were included who received either 3 or 4 mg glimepiride (no change in dosing in the course of the study was envisaged). In the AWARD-2 study, patients were included who received at least 4 mg glimepiride. It is not possible to completely adjust the population of the AWARD-2 study to the LAPTOP study because of the dose of 3 mg glimepiride/day, which was not used in the AWARD-2 study. It would have been possible however to limit the dose to 4 mg glimepiride/day. It is unclear why the company dispensed with greater comparability here.

Population in the LAPTOP study does not concur with the target population

Besides the lack of comparability of the common comparator of the 2 studies, the suitability of the LAPTOP study for the indirect comparison is questionable. 371 adult patients with type 2 diabetes mellitus (≥ 1 year) with insufficient glycaemic control despite stable dosage of sulfonylurea and metformin (at least 850 mg/day) were included in the LAPTOP study. Based on the respective inclusion criterion, patients had to have an HbA1c value of ≥ 7.5% and ≤ 10.5%. According to the inclusion criteria, patients were included in the LAPTOP study already with a minimum daily dosage of 850 mg metformin. The study contained no lead-in phase, in which the patients' metformin dose was up-titrated. The metformin dose used at study entry of the patients remained unchanged during the course of the study. The mean daily metformin dose of the patients was 1894.5 ± 475.1 mg.

It is unclear from the available documents how large the proportion of patients was who had been pretreated with the maximum tolerated dose of metformin and who had achieved no

sufficient glycaemic control under this treatment. It is therefore not guaranteed that the majority of the patients included in the LAPTOP study correspond to the target population (inadequate glycaemic control under maximum tolerated dose of metformin).

Summary

The indirect comparison presented by the company for research question C is unsuitable for the present benefit assessment because the 2 studies AWARD-2 and LAPTOP are not comparable regarding the common comparator (insulin glargine + metformin + glimepiride) and the study population. The sensitivity analyses conducted by the company are unsuitable to remove the lack of comparability of the common comparator or of the study populations of the studies AWARD-2 and LAPTOP. In addition, the suitability of the LAPTOP study for the indirect comparison is doubtful because it is not guaranteed that the majority of the patients included in the LAPTOP study correspond to the target population (inadequate glycaemic control under maximum tolerated dose of metformin).

2.5.2 Results on added benefit

No relevant data were available for research question C on the triple combination therapy with 2 OADs. Hence there is no proof of an added benefit of dulaglutide in the triple combination with 2 OADs in comparison with the ACT metformin + human insulin.

2.5.3 Extent and probability of added benefit

No relevant study was presented for the benefit assessment. Hence there is no proof of an added benefit of dulaglutide in the triple combination with 2 OADs in comparison with the ACT metformin + human insulin (or treatment only with human insulin if metformin is not tolerated or not sufficiently effective according to the SPC). Hence there are also no patient groups for whom a therapeutically important added benefit can be derived. This assessment deviates from that of the company. The company overall derived a hint of a minor added benefit in comparison with premixed insulin.

2.5.4 List of included studies

Not applicable as the company presented no relevant studies on the comparison of dulaglutide in the triple combination therapy with 2 OADs in comparison with the ACT specified by the G-BA in its assessment.

2.6 Research question D: dulaglutide in combination with insulin with or without oral antidiabetic

2.6.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on dulaglutide (studies completed up to 1 December 2014)
- bibliographical literature search on dulaglutide (last search on 1 December 2014)
- search in trial registries for studies on dulaglutide (last search on 1 December 2014)

To check the completeness of the study pool:

- search in trial registries for studies on dulaglutide (last search on 21 January 2015)

No additional relevant study was identified from the check.

2.6.1.1 Studies included

Dulaglutide in combination with a short-acting insulin with or without metformin

The AWARD-4 study listed in the following Table 20 was included on the combination of dulaglutide with a short-acting insulin with or without metformin.

Table 20: Study pool – RCT, direct comparison: dulaglutide + insulin lispro with or without metformin vs. insulin glargine + insulin lispro with or without metformin (research question D)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
H9X-MC-GBDD (AWARD-4)[b]	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. b: Hereinafter referred to as "AWARD-4". RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of dulaglutide in combination with insulin, with or without OAD, concurs with that of the company. It included the H9X-MC-GBDD study (hereinafter referred to as "AWARD-4"). Dulaglutide (0.75 mg/week and 1.5 mg/week) + insulin lispro and insulin glargine + insulin lispro, each with or without metformin, were compared in the study. Deviating from the company, only the dulaglutide arm with the dosage of 1.5 mg/week was used for the present benefit assessment because, according to the SPC,

the dosage of 0.75 mg in combination with dulaglutide is only approved for potentially vulnerable patients. This was not an inclusion criterion of the AWARD-4 study, however.

Section 2.6.4 contains a reference list for the study included.

Dulaglutide in combination with a long-acting insulin with or without oral antidiabetic

No relevant studies were identified on the combination of dulaglutide with a long-acting insulin with or without OAD. This concurs with the company's assessment.

2.6.1.2 Study characteristics

Table 21 and Table 22 describe the study used for the benefit assessment.

Table 21: Characteristics of the studies included – RCT, direct comparison: dulaglutide + insulin lispro with or without metformin vs. insulin glargine + insulin lispro with or without metformin (research question D)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
AWARD-4	RCT, double-blind for different dosages of the experimental intervention, open-label for comparator intervention, parallel, active-controlled	Adult patients with type 2 diabetes mellitus with HbA1c ≥ 7% and ≤ 11% despite optimized and stable insulin dosage under conventional insulin treatment[b], alone or in combination with OAD treatment for ≥ 3 months.	Each in combination with insulin lispro with or without metformin: ▪ dulaglutide (0.75 mg)[c] (N = 293) ▪ dulaglutide (1.5 mg) (N = 295) ▪ insulin glargine (N = 296)	▪ Lead-in phase: 9 weeks ▪ Treatment phase: 52 weeks ▪ Follow-up phase: 4 weeks	105 study centres in 15 countries: Argentina, Australia, Belgium, Brazil, Canada, Denmark, Greece, Hungary, Mexico, Poland, Puerto Rico, Russia, Spain, Sweden, Taiwan, United States of America 10/2010 – 9/2012	Primary: change in HbA1c after 26 weeks of treatment Secondary: morbidity, health-related quality of life, AEs, hypoglycaemia

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: ≤ 2 insulin injections daily (basal, basal and prandial or premixed insulin)
c: The treatment arm is not relevant for the assessment and is not shown in the following tables.
AE: adverse event; HbA1c: glycosylated haemoglobin A1c; N: number of randomized patients; OAD: oral antidiabetic; RCT: randomized controlled trial; vs.: versus

Table 22: Characteristics of the interventions – RCT, direct comparison: dulaglutide + insulin lispro with or without metformin vs. insulin glargine + insulin lispro with or without metformin (research question D)

Study	Intervention	Comparison	Concomitant medication
AWARD-4	Dulaglutide (1.5 mg), once weekly, subcutaneous injection + insulin lispro, titrated to target, 3x/day, prandial, subcutaneous injection with or without metformin ≥ 1500 mg, once/day, orally (OAD treatment as described in the column "concomitant medication")	Insulin glargine, titrated to target, once/day at bedtime, subcutaneous injection + insulin lispro, titrated to target, 3x/day, prandial, subcutaneous injection with or without metformin ≥ 1500 mg, once/day, orally (OAD treatment as described in the column "concomitant medication")	▪ *Lead-in phase, 9 weeks:* ▫ The patients were instructed to discontinue all OADs except metformin. ▪ *Prohibited medication:* ▫ GLP-1 receptor agonists not used in the study ▫ drugs to promote weight loss ▫ use of systemic glucocorticoids for more than 14 consecutive days ▫ further insulins (other than the study medication)

GLP-1: glucagon-like peptide 1, OAD: oral antidiabetic; RCT: randomized controlled trial; vs.: versus

The AWARD-4 study was a randomized, active-controlled study sponsored by the company with a treatment phase of 52 weeks. The study design was open-label with patients and outcome assessors being blinded with regard to the different dulaglutide doses (0.75 mg/1.5 mg) used in the study.

After the screening phase, the study consisted of 3 study phases: a 9-week lead-in phase, a 52-week treatment phase and a 4-week follow-up phase.

Adult patients (≥ 18 years) with type 2 diabetes mellitus with inadequate glycaemic control under optimized and stable insulin dosage in conventional insulin treatment alone or in combination with OAD treatment together with diet and exercise were enrolled. Conventional insulin treatment was defined as administration of ≤ 2 insulin injections (basal, basal and prandial or premixed insulins).

A total of 884 patients were randomly assigned in a ratio of 1:1:1 to 3 treatment arms: dulaglutide 0.75 mg daily (293 patients), dulaglutide 1.5 mg daily (295 patients) und insulin glargine (296 patients), each + insulin lispro with or without metformin.

The primary outcome of the study was the change in HbA1c after 26 weeks of treatment.

Treatment regimen and dose adjustments

In the lead-in phase, the patients' current insulin dosage was adapted according to clinical need. In addition, the patients were instructed to discontinue all OAD except metformin. Only patients with stable insulin treatment at randomization and with a minimum daily metformin dosage of 1500 mg as well as patients who were not taking metformin were allowed to participate in the study.

The treatment aim in the AWARD-4 study was to achieve an HbA1c value of < 7%. Insulin treatment with insulin glargine and insulin lispro was optimized with defined algorithms in the course of the study. The insulin glargine dose was adapted on the basis of 3 previous fasting plasma glucose levels, aiming at a target value between 71 and 99 mg/dL. The insulin lispro doses for administration before breakfast, before lunch and before the evening meal was also adapted (for all treatment groups equally) according to a prespecified algorithm based on the 3 last fasting plasma glucose levels before lunch, before the evening meal and before bedtime. The target values were between 71 and 100 mg/dL (before lunch, before the evening meal) and between 71 and 130 mg/dL (before bedtime). Overall, the AWARD-4 study was a study with intensive insulin therapy targeted at near-normal blood-glucose levels.

Hence insulin therapy directed towards a target level was used in both treatment groups. There was no detailed information on the time course of HbA1c values during the study. Data were only available for the time points 0, 26 and 52 weeks. However, no indications of notable differences in blood glucose lowering between the dulaglutide treatment arm and the insulin treatment arm resulted from the number of patients with HbA1c < 6.5 and < 7 (at

week 52: 36.7% and 58.5% in the 1.5 mg dulaglutide arm versus 30.4% and 49.3% in the insulin glargine treatment arm). Limited interpretability of the study results (e.g. for the outcome “hypoglycaemia”) can therefore not be assumed.

Continued treatment with ongoing metformin was also allowed during the treatment phase if a minimum dosage of 1500 mg daily was maintained and the respective maximum approved or maximum tolerated dose was not exceeded. Discontinuation of metformin treatment was allowed if events defined in the study protocol occurred that required dose reduction or discontinuation of treatment.

It was clear from the information on the study that patients were included in the comparator arm of the AWARD-4 study who received combination therapy of insulin glargine + insulin lispro either with metformin (72.3%) or without metformin (27.7%) (see Table 23). For the present assessment, treatment only with human insulin was used as ACT according to the G-BA’s specifications only for patients in whom metformin is not tolerated or not sufficiently effective according to the SPC. According to the treatment escalation, however, it was assumed that the majority of the patients without metformin in the history of their disease who were included had already received metformin. This therefore had no consequence for the present benefit assessment.

Characteristics of the study population

Table 23 shows the characteristics of the patients in the study included.

Table 23: Characteristics of the study populations – RCT, direct comparison: dulaglutide + insulin lispro with or without metformin vs. insulin glargine + insulin lispro with or without metformin (research question D)

Study Group	N	Age [years] mean (SD)	Sex [F/M] %	Body weight [kg] mean (SD)	BMI [kg/m^2] mean (SD)	Duration of diabetes [years] mean (SD)	HbA1c value [%] mean (SD)	Background metformin treatment n (%)	Ethnicity [white/non-white[a]] %	Treatment discontin-uations n (%)
AWARD-4										
Dulaglutide 1.5 mg[b]	295	59 (10)	46/54	91.0 (18.2)	32.0 (5.1)	12.8 (7.2)	8.5 (1.1)	216 (73.2)	78/22[c]	73 (24.7)
Insulin glargine[b]	296	60 (9)	44/56	90.8 (18.9)	32.4 (5.3)	13.0 (6.8)	8.5 (1.0)	214 (72.3)	78/22[c]	60 (20.3)

a: This group includes native American Indians/Alaskans, Asians, African Americans, multiple ethnicity, native Hawaiians/Pacific.
b: + insulin lispro with or without metformin.
c: Institute's calculation.

BMI: body mass index; F: female; HbA1c: glycosylated haemoglobin A1c; M: male; N: number of randomized patients; n: number of patients with event; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patients in both treatment arms relevant for the present benefit assessment were comparable with regard to the characteristics presented in Table 23. Patients in both study arms had a mean age of approximately 60 years, a BMI of approximately 32 kg/m^2 and a body weight of approximately 91 kg. About half of the patients in the treatment arms were women and half were men. The patients' mean disease duration with type 2 diabetes mellitus was approximately 13 years. Approximately 73% of the patients in both treatment arms received metformin in addition to dulaglutide + insulin lispro or in addition to insulin glargine + insulin lispro.

The mean baseline HbA1c (long-term maker for the average blood glucose level) at the start of the study was 8.5% in both treatment arms included (dulaglutide 1.5 mg/insulin glargine), and under 8.5% in about 55% of the patients. According to the inclusion criteria, patients with an HbA1c value $\geq 7.0\%$ and $\leq 11.0\%$ were included in the AWARD-4 study. For this study, the company additionally presented sensitivity analyses for a subpopulation of patients with a baseline HbA1c value $\geq 7.5\%$ and $\leq 11.0\%$. It justified this by claiming that an HbA1c value of 7.0% already lies within the target range recommended by the National Care Guideline (NVL) [10].

Baseline HbA1c value at the start of the study can increase the probability of hypoglycaemia, i.e. patients with a lower baseline value may have a higher probability of hypoglycaemia. In addition, the baseline HbA1c value at the start of the study was relevant for the decision regarding treatment escalation (yes/no). It is meaningful to conduct subgroup analyses based on baseline HbA1c values (e.g. baseline HbA1c $< 7.5\%, \geq 7.5\%$ or $< 8\%, \geq 8\%$) and to compare the results with those of the total population. Such analyses were not submitted by the company in Module 4 D, however. The analyses conducted by the company were not subgroup analyses, but the analysis of the patient population with a baseline HbA1c value in the range between $\geq 7.5\%$ and $\leq 11.0\%$ defined post hoc. The analyses conducted by the company were therefore not used for the present assessment.

Risk of bias at study level

Table 24 shows the risk of bias at study level.

Table 24: Risk of bias at study level – RCT, direct comparison: dulaglutide + insulin lispro with or without metformin vs. insulin glargine + insulin lispro with or without metformin (research question D)

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			
AWARD-4	Yes	Yes	No[a]	No[a]	Yes	Yes	Low

a: The study was double-blinded only with regard to both dulaglutide dosages (0.75 mg and 1.5 mg daily).
RCT: randomized controlled trial; vs.: versus

The risk of bias at study level was rated as low. This contradicts the company's assessment, which rated the overall risk of bias at study level as high because of the open-label (versus the active comparator substance) design.

Lack of blinding at study level does not per se lead to a high risk of bias. However, lack of blinding can have an effect at outcome level, depending on whether the corresponding outcome is recorded objectively or subjectively. In subjectively reported outcomes, the outcome-specific risk of bias is rated as high (see Section 2.6.2.2).

2.6.2 Results on added benefit

2.6.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.8.5.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - health status (EQ-5D VAS)
  - micro- and macrovascular late complications
- Health-related quality of life
- Adverse events
  - SAEs
  - discontinuation due to AEs
  - severe hypoglycaemia
  - symptomatic hypoglycaemia (blood glucose < 54 mg/dL; blood glucose ≤ 70 mg/dL)
  - gastrointestinal disorders
    - nausea
    - diarrhoea
    - vomiting
    - dyspepsia
    - appetite loss
  - pancreatitis
  - injection site reactions

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 D). Reasons for the choice of outcomes are given in Section 2.8.5.2.4.3 of the full dossier assessment.

Table 25 shows for which outcomes data were available in the study included.

Table 25: Matrix of outcomes – RCT, direct comparison: dulaglutide + insulin lispro with or without metformin vs. insulin glargine + insulin lispro with or without metformin (research question D)

Study	Outcomes																
	All-cause mortality	Health status (EQ-5D VAS)	Micro- and macrovascular late complications	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe hypoglycaemia	Symptomatic hypoglycaemia (blood glucose < 54 mg/dL)	Symptomatic hypoglycaemia (blood glucose ≤ 70 mg/dL)	Gastrointestinal disorders	Nausea	Diarrhoea	Vomiting	Dyspepsia	Appetite loss	Pancreatitis	Injection site reactions
AWARD-4	Yes	Yes	No[a]	No[a]	Yes	Yes	No[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: No evaluable data; for reasons, see Section 2.8.5.2.4.3 of the full dossier assessment.

AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.6.2.2 Risk of bias

Table 26 shows the risk of bias for the relevant outcomes.

Table 26: Risk of bias at study and outcome level – RCT, direct comparison: dulaglutide + insulin lispro with or without metformin vs. insulin glargine + insulin lispro with or without metformin (research question D)

Study		Outcomes																
	Study level	All-cause mortality	Health status (EQ-5D VAS)	Micro- and macrovascular late complications	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe hypoglycaemia	Symptomatic hypoglycaemia (blood glucose < 54 mg/dL)	Symptomatic hypoglycaemia (blood glucose ≤ 70 mg/dL)	Gastrointestinal disorders	Nausea	Diarrhoea	Vomiting	Dyspepsia	Appetite loss	Pancreatitis	Injection site reactions
AWARD-4	L	L	H	–[a]	–[a]	L	H	–[a]	H	H	H	H	H	H	H	H	H	H

a: There were no evaluable data.

AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The assessment of the risk of bias at outcome level deviated from the company's assessment as follows:

- The company rated the risk of bias as low for the following outcomes on AEs: discontinuation due to AEs, symptomatic hypoglycaemia (blood glucose < 54 mg/dL and blood glucose ≤ 70 mg/dL), nausea, diarrhoea, vomiting, appetite loss and pancreatitis. Deviating from this assessment, the risk of bias was rated as high for these outcomes because of the subjective component (e.g. symptoms as subjective component in the outcome "symptomatic hypoglycaemia") in an open-label study design.
- Apart from the outcomes presented by the company, the outcomes "gastrointestinal disorders (based on the overall SOC rate)", "dyspepsia" and "injection site reactions" were additionally used for the assessment. For these outcomes, the risk of bias was also rated as high because of the subjective component in an open-label study design.

Detailed reasons for the assessment of the risk of bias can be found in Section 2.8.5.2.4.2 of the full dossier assessment.

2.6.2.3 Results

Table 27 and Table 28 summarize the results on the comparison of dulaglutide + insulin lispro with or without metformin in comparison with insulin glargine + insulin lispro with or without metformin for patients with type 2 diabetes mellitus in whom insulin (with or without OAD), together with diet and exercise, does not provide adequate glycaemic control. Where necessary, the data from Module 4 D of the dossier were supplemented by the Institute's calculations.

As described in Section 2.8.5.2.4.3 of the full dossier assessment, analyses on several time periods were partly available. For the present assessment, the analysis of the longest available time period was used for each outcome. Hence analyses at the time point 52 weeks were included in the assessment for most outcomes. In addition, for some of the outcomes used by the company for the assessment (e.g. hypoglycaemia), the company only considered the event rates up to the time point of administration of rescue medication. The company did not consider events after this time point for these outcomes in Module 4 D. This approach was not accepted for the present assessment and, where possible, data for the longest available time period (also after administration of rescue medication) were considered.

The following descriptions include results from the subgroup analyses only in cases where these affect the derivation of the conclusion on the added benefit for the respective outcome. See Section 2.6.2.4 for a detailed presentation of the results from subgroup analyses.

Table 27: Results (mortality, AEs) – RCT, direct comparison: dulaglutide + insulin lispro with or without metformin vs. insulin glargine + insulin lispro with or without metformin (research question D)

Study Outcome category Outcome	Dulaglutide (1.5 mg)[a]		Insulin glargine[a]		Dulaglutide (1.5 mg)[a] vs. insulin glargine[a]
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
AWARD-4					
Mortality					
All-cause mortality	295	1 (0.3)	296	3 (1.0)	0.37 [0.05; 2.62]; 0.624[b]
Adverse events					
AEs	295	223 (75.6)	296	211 (71.3)	
SAEs[c, d]	295	27 (9.2)	296	54 (18.2)	0.50 [0.33; 0.77]; 0.001
Discontinuation due to AEs[d, e]	295	31 (10.5)	296	9 (3.0)	3.46 [1.67; 7.13][f]; < 0.001[g]
Severe hypoglycaemia[h]	There were no evaluable data.				
Symptomatic hypoglycaemia[i] (blood glucose < 54 mg/dL)	295	198 (68.0)	296	204 (69.2)	0.98 [0.88; 1.10]; 0.772
Symptomatic hypoglycaemia (blood glucose ≤ 70 mg/dL)	295	237 (80.3)	296	247 (83.4)	0.96 [0.89; 1.04][f]; 0.391[g]
Gastrointestinal disorders	295	142 (48.1)	296	54 (18.2)	2.64 [2.02; 3.45][f]; < 0.001[g]
Nausea	295	76 (25.8)	296	10 (3.4)	7.63 [4.02; 14.45][f]; < 0.001[g]
Diarrhoea	295	50 (16.9)	296	18 (6.1)	2.79 [1.67; 4.66][f]; < 0.001[g]
Vomiting	295	36 (12.2)	296	5 (1.7)	7.22 [2.88; 18.15][f]; < 0.001[g]
Dyspepsia	295	27 (9.2)	296	1 (0.3)	27.09 [3.71; 198.07][f]; < 0.001[g]
Appetite loss	295	27 (9.2)	296	0 (0)	55.19 [3.38; 900.51][j]; < 0.001[g]
Pancreatitis	295	0 (0)	296	0 (0)	NC
Injection site reactions	295	1 (0.3)	296	0 (0.0)	3.01 [0.12; 73.59][j]; 0.349[g]

(continued)

Table 27: Results (mortality, AEs) – RCT, direct comparison: dulaglutide + insulin lispro with or without metformin vs. insulin glargine + insulin lispro with or without metformin (research question D) (continued)

a: + insulin lispro with or without metformin.
b: Peto OR.
c: Hypoglycaemic events were also recorded here. However, the available study documents showed no sign that the result differed under inclusion of the events on hypoglycaemia.
d: Results up to week 52.
e: Hypoglycaemic events were also recorded here. In the outcome "discontinuations due to AEs", 0 versus 1 patient in the dulaglutide and insulin glargine treatment arms discontinued treatment due to hypoglycaemia. Without these patients with event, there is an effect of RR 3.89 [1.82; 8.32][f]; p = < 0.001[g].
f: Institute's calculation.
g: Institute's calculation, unconditional exact test (CSZ method according to [7]).
h: Results for severe hypoglycaemic events could not be inferred from the available operationalizations.
i: Results up to week 52 without consideration of the observations after rescue medication.
j: Institute's calculation, RR with 0.5 correction.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event (at least one); NC: not calculable; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 28: Results (morbidity, health-related quality of life, supplementary outcomes) – RCT, direct comparison: dulaglutide + insulin lispro with or without metformin vs. insulin glargine + insulin lispro with or without metformin (research question D)

Study **Outcome category** **Outcome**	**Dulaglutide (1.5 mg)[a]**			**Insulin glargine[a]**			**Dulaglutide (1.5 mg)[a] vs. insulin glargine[a]**
	N[b]	**Baseline values mean (SD)**	**Change at end of study mean (SE)**	**N[b]**	**Baseline values mean (SD)**	**Change at end of study mean (SE)**	**Mean difference [95% CI]; p-value**
AWARD-4							
Morbidity							
Health status (EQ-5D VAS)	279	76.93 (15.35)	-0.46[c] (1.01)	282	76.77 (15.49)	-0.18[c] (1.01)	-0.28 [-3.08; 2.52][d]; 0.815
	N	**Patients with event n (%)**		**N**	**Patients with event n (%)**		**RR [95% CI]; p-value**
Cardiovascular morbidity[e]	295	5 (1.7)		296	12 (4.1)		
Health-related quality of life							
There were no evaluable data.							
Supplementary outcomes							
Body weight (kg)	225	91.00 (18.24)	0.34[f] (0.32)	232	90.75 (18.87)	3.65[f] (0.31)	-3.31 [-4.17; -2.45]; < 0.001

a: + insulin lispro with or without metformin.
b: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
c: Change at end of study calculated with ANCOVA model with LOCF on the difference of the changes to baseline between the treatment arms, adjusted for baseline value, country and metformin treatment.
d: Institute's calculation.
e: Data on cardiovascular morbidity and on further micro-and macrovascular late complications are not evaluable for the assessment of the added benefit or are not available (see Section 2.8.5.2.4.3 of the full dossier assessment). Only the event rates are presented for the outcome "cardiovascular morbidity".
f: MMRM analysis of the ITT population.
ANCOVA: analysis of covariance; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; ITT: intention to treat; LOCF: last observation carried forward; MMRM: mixed-effects model repeated measures; N: number of analysed patients; n: number of patients with event (at least one); RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Mortality

All-cause mortality

A total of 1 death occurred under dulaglutide + insulin lispro with or without metformin, and 3 deaths under insulin glargine + insulin lispro in the AWARD 4 study for the period up to week 52. There was no statistically significant difference between the treatment groups. Hence there is no hint of an added benefit of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). An added benefit for this outcome is therefore not proven.

This concurs with the company's assessment.

Morbidity

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups (week 0 to week 52) for the outcome "health status", which was recorded with the EQ-5D VAS. Hence there is no hint of an added benefit of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). An added benefit for this outcome is therefore not proven.

This concurs with the company's assessment.

Micro- and macrovascular late complications

No evaluable data were available on the outcome "cardiovascular morbidity" and on further micro- and macrovascular late complications. Hence there is no hint of an added benefit of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). An added benefit for this outcome is therefore not proven.

This concurs with the company's assessment, which derived no added benefit of dulaglutide + insulin lispro with or without metformin in comparison with the combination therapy with insulin glargine + insulin lispro with or without metformin for the outcomes on micro- and macrovascular late complications.

Health-related quality of life

The outcome "health-related quality of life" was not included in the present benefit assessment because there was no adequate validation for the target population of the measurement instruments (EQ-5D, Ability to Perform Physical Activities of Daily Living [APPADL]/Impact of Weight on Self-Perception [IW-SP] and Low Blood Sugar Survey [LBSS]) used in the AWARD-4 study. Hence there is no hint of an added benefit of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). An added benefit for this outcome is therefore not proven.

This concurs with the company's assessment, which overall derived no hint of added benefit of dulaglutide + insulin lispro with or without metformin in comparison with the combination therapy with insulin glargine + insulin lispro with or without metformin for the outcome "health-related quality of life" based on the measurement instruments used by the company for the assessment (EQ-5D, APPADL/IW-SP and LBSS).

Adverse events

The AEs, SAEs and discontinuations due to AEs that most commonly occurred in the AWARD 4 study are presented in Appendix B of the full dossier assessment.

Serious adverse events

For the outcome "SAEs", there was a statistically significant difference in favour of dulaglutide + insulin lispro with or without metformin in comparison with insulin glargine + insulin lispro with or without metformin for the time period of up to week 52. Hypoglycaemic events were also recorded under the outcome "SAEs". However, the available study documents showed no sign that the result differed under inclusion of the events on hypoglycaemia. Events occurred across all organ classes without increase in any area.

Overall, there is therefore an indication of lesser harm of the combination of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin) for the outcome "SAEs".

This concurs with the company's assessment, which considered this outcome at the time points of both 26 weeks and 52 weeks and overall derived an indication of lesser harm of dulaglutide.

Discontinuation due to adverse events

Treatment with dulaglutide + insulin lispro with or without metformin in comparison with the combination therapy with insulin glargine + insulin lispro with or without metformin resulted in a statistically significantly greater proportion of patients with discontinuation due to AEs for the time period up to week 52. Hypoglycaemic events were also recorded under the outcome "discontinuation due to AEs", but the result remained statistically significant also without these patients.

Deviating from the company's assessment, the risk of bias was rated as high for the outcome "discontinuation due to AEs". This was done because it was not clear from the available data on the AWARD-4 study that only serious events were recorded under this outcome. According to the recordings of the most common AEs for the AWARD-4 study (Appendix B of the full dossier assessment), nausea and dyspepsia from the SOC "gastrointestinal disorders" were the most common reasons for discontinuation due to AEs (8 and 3 patients in the 1.5 mg dulaglutide arm). It is also clear from the lists of the most common SAEs that only 3 patients in total had an SAE from the SOC "gastrointestinal disorders" (all of them in the dulaglutide arm). Hence the majority of the events of both Preferred Terms (PTs) "nausea" and "dyspepsia" can be classified as "non-serious".

Overall, there is a hint of greater harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin) for the outcome "discontinuation due to AEs".

This deviates from the company's assessment, which derived an indication of greater harm of dulaglutide + insulin lispro with or without metformin in comparison with the combination therapy of insulin glargine + insulin lispro with or without metformin. As a basis for its

assessment on this outcome, the company also recorded treatment discontinuations due to death.

Severe hypoglycaemia

No evaluable data were available for this outcome. Hence there is no hint of greater or lesser harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). An added benefit for this outcome is therefore not proven.

This concurs with the company's assessment.

Symptomatic hypoglycaemia (blood glucose < 54 mg/dL and blood glucose ≤ 70 mg/dL)

There was no statistically significant difference between the treatment groups for the period up to week 52 for the outcomes on symptomatic hypoglycaemia. Hence there is no hint of greater or lesser harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). An added benefit for these outcomes is therefore not proven.

For the outcome "symptomatic hypoglycaemia with a blood glucose level of ≤ 70 mg/dL", this deviates from the company's assessment, which derived an indication of minor harm for this outcome based on the annual rate of hypoglycaemia per patient. Overall, the company derived its conclusions on the added benefit from a superordinate outcome "hypoglycaemia", which includes: hypoglycaemic events in total, confirmed symptomatic, asymptomatic, nocturnal, non-nocturnal and severe hypoglycaemic events, each presented as proportion of patients with ≥ 1 corresponding hypoglycaemic episode and as annual rate of hypoglycaemia per patient. Overall, it derived an indication of lesser harm of dulaglutide + insulin lispro with or without metformin in comparison with insulin glargine + insulin lispro with or without metformin.

Gastrointestinal disorders, nausea, diarrhoea and dyspepsia

There was a statistically significant difference to the disadvantage of treatment with dulaglutide + insulin lispro with or without metformin in comparison with insulin glargine + insulin lispro with or without metformin for the outcomes "gastrointestinal disorders", "nausea", "diarrhoea" and "dyspepsia". In each case this resulted in a hint of greater harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin).

This assessment deviates from that of the company, which overall derived an indication of greater harm of dulaglutide + insulin lispro with or without metformin in comparison with insulin glargine + insulin lispro with or without metformin for the outcome "events affecting the gastrointestinal tract of particular interest".

Vomiting

There was a statistically significant difference to the disadvantage of treatment with dulaglutide + insulin lispro with or without metformin in comparison with insulin glargine + insulin lispro with or without metformin for the outcome "vomiting". In addition, there was proof of an effect modification by the characteristic "age" for this outcome. For patients < 65 years, this resulted in a hint of greater harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). For patients ≥ 65 years, there is no hint of greater harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). An added benefit for this patient group is therefore not proven.

This assessment deviates from that of the company, which identified an indication of relevant effect modification for the characteristic "age" (< 65 years versus ≥ 65 years), but overall derived its conclusions on the added benefit for the superordinate outcome "events affecting the gastrointestinal tract" (indication of greater harm of dulaglutide).

Appetite loss

There was a statistically significant difference to the disadvantage of treatment with dulaglutide + insulin lispro with or without metformin in comparison with insulin glargine + insulin lispro with or without metformin for the outcome "appetite loss". This resulted in a hint of greater harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin).

This deviates from the company's assessment, which derived an indication of greater harm of dulaglutide + insulin lispro with or without metformin in comparison with insulin glargine + insulin lispro with or without metformin.

Pancreatitis

Regarding the proportion of patients with pancreatitis, no events occurred under treatment with dulaglutide + insulin lispro with or without metformin or under treatment with insulin glargine + insulin lispro with or without metformin. Hence there is no hint of greater or lesser harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). An added benefit for this outcome is therefore not proven.

This concurs with the company's assessment.

Injection site reactions

There was no statistically significant difference between the treatment groups for the outcome "injection site reactions". Hence there is no hint of greater or lesser harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin). An added benefit for this outcome is therefore not proven.

The company did not record this outcome in its analyses in the dossier and therefore also derived no conclusions on added benefit.

2.6.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were included in the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)

The subgroup analyses for the patient-relevant outcomes included in the present benefit assessment were conducted post hoc for both characteristics.

Only 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 ≥ 0.05 and < 0.2 provides an indication of an effect modification.

Adverse events

Vomiting

The subgroup results for the outcome "vomiting" are presented in Table 29.

Table 29: Subgroups: outcome "vomiting" by age, dulaglutide + insulin lispro with or without metformin vs. insulin glargine + insulin lispro with or without metformin (research question D)

Study Outcome	Dulaglutide (1.5 mg)[a]		Insulin glargine[a]		Dulaglutide (1.5 mg)[a] vs. insulin glargine[a]	
Characteristic Subgroup	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
AWARD-4						
Vomiting						
Age						
< 65 years	218	31 (14.2)	206	3 (1.5)	9.76 [3.03; 31.45]	< 0.001
≥ 65 years	77	5 (6.5)	90	2 (2.2)	2.92 [0.58; 14.64]	0.250
					Interaction:	0.034[b]

a: + insulin lispro with or without metformin.
b: Calculated from meta-analysis (Cochran's Q test).
CI: confidence interval; N: number of analysed patients; n: number of patients with event (at least one); RCT: randomized controlled trial; RR: relative risk; vs.: versus

There was proof ($p < 0.05$) of an effect modification by the characteristic "age" (interaction test $p = 0.034$) for the outcome "vomiting".

There was a statistically significant difference to the disadvantage of treatment with dulaglutide + insulin lispro with or without metformin for patients < 65 years. Since there is proof of an effect modification, there is a hint of greater harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin) for the outcome "vomiting" in patients < 65 years.

In patients ≥ 65 years, the effect takes the same direction, but the proportions of patients with vomiting did not differ statistically significantly between the 2 treatment arms. This results in no hint of greater harm of dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin); greater harm of dulaglutide for the patient group ≥ 65 years is therefore not proven.

This assessment deviates from that of the company, which identified an indication of relevant effect modification, but derived the harm for the superordinate outcome "events affecting the gastrointestinal tract" (indication of greater harm).

2.6.3 Extent and probability of added benefit

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.

2.6.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.6.2 result in an indication of lesser harm of dulaglutide + insulin lispro with or without metformin in comparison with insulin glargine + insulin lispro with or without metformin for the outcome "SAEs". However, there are also hints of greater harm under dulaglutide + insulin lispro with or without metformin in comparison with the ACT (metformin + human insulin) for the following outcomes: discontinuation due to AEs, gastrointestinal disorders, nausea, diarrhoea, vomiting, dyspepsia and appetite loss.

In addition, there was proof of an effect modification by the subgroup characteristic "age (< 65 years versus ≥ 65 years)" for the outcome "vomiting".

The extent of the respective added benefit at outcome level was estimated from these results (see Table 30).

Table 30: Extent of added benefit at outcome level: dulaglutide + insulin lispro with or without metformin vs. metformin + human insulin (research question D)

Outcome category **Outcome**	**Dulaglutide + insulin lispro with or without metformin vs.** **insulin glargine + insulin lispro with or without metformin** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0.3% vs. 1.0% RR: 0.37 [0.05; 2.62] p = 0.624[c]	Added benefit not proven
Morbidity		
Health status (EQ-5D VAS)	MD: -0.28 [-3.08; 2.52][d] p = 0.815	Added benefit not proven
Cardiovascular morbidity[e]	There were no evaluable data.	
Health-related quality of life		
	There were no evaluable data.	
Adverse events		
SAEs	9.2% vs. 18.2% RR: 0.50 [0.33; 0.77] p = 0.001 probability: "indication"	Outcome category: serious/severe AEs $CI_u < 0.90$ lesser harm, extent: "considerable"
Discontinuation due to AEs	10.5% vs. 3.0% RR: 3.46 [1.67; 7.13][d] RR: 0.29 [0.14; 0.60][f] p < 0.001[g] probability: "hint"	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm, extent: "considerable"
Severe hypoglycaemia	There were no evaluable data.	
Symptomatic hypoglycaemia (blood glucose < 54 mg/dL)	68.0% vs. 69.2% RR: 0.98 [0.88; 1.10]; p = 0.772	Greater/lesser harm not proven
Symptomatic hypoglycaemia (blood glucose ≤ 70 mg/dL)	80.3% vs. 83.4% RR: 0.96 [0.89; 1.04][d] p = 0.391[g]	Greater/lesser harm not proven

(continued)

Table 30: Extent of added benefit at outcome level: dulaglutide + insulin lispro with or without metformin vs. metformin + human insulin (research question D) (continued)

Outcome category **Outcome**	**Dulaglutide + insulin lispro with or without metformin vs.** **insulin glargine + insulin lispro with or without metformin** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Adverse events		
Gastrointestinal disorders	48.1% vs. 18.2% RR: 2.64 [2.02; 3.45][d] RR: 0.38 [0.29; 0.50][f] p < 0.001[g] probability: "hint"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 greater harm, extent: "considerable"
Nausea	25.8% vs. 3.4% RR: 7.63 [4.02; 14.45][d] RR: 0.13 [0.07; 0.25][f] p < 0.001[g] probability: "hint"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 greater harm, extent: "considerable"
Diarrhoea	16.9% vs. 6.1% RR: 2.79 [1.67; 4.66][d] RR: 0.36 [0.21; 0.60][f] p < 0.001[g] probability: "hint"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 greater harm, extent: "considerable"
Vomiting < 65 years	14.2% vs. 1.46% RR: 9.76 [3.03; 31.45] RR: 0.10 [0.03; 0.33][f] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 greater harm, extent: "considerable"
≥ 65 years	6.5% vs. 2.2% RR 2.92 [0.58; 14.64] p = 0.250	Greater/lesser harm not proven
Dyspepsia	9.2% vs. 0.3% RR: 27.09 [3.71; 198.07][d] RR: 0.04 [0.01; 0.27][f] p < 0.001[g] probability: "hint"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 greater harm, extent: "considerable"

(continued)

Table 30: Extent of added benefit at outcome level: dulaglutide + insulin lispro with or without metformin vs. metformin + human insulin (research question D) (continued)

Outcome category **Outcome**	**Dulaglutide + insulin lispro with or without metformin vs.** **insulin glargine + insulin lispro with or without metformin** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Adverse events		
Appetite loss	9.2% vs. 0% RR: 55.19 [3.38; 900.51][g] RR: 0.02 [0.00; 0.30][f] $p < 0.001$[g] probability: "hint"	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm, extent: "considerable"
Pancreatitis	0% vs. 0% RR: NC	Greater/lesser harm not proven
Injection site reactions	0.3% vs. 0% RR: 3.01 [0.12; 73.59][h] $p = 0.349$[g]	Greater/lesser harm not proven

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: Peto OR.
d: Institute's calculation.
e: Data on cardiovascular morbidity and on further micro-and macrovascular late complications are not evaluable for the assessment of the added benefit or are not available (see Section 2.8.5.2.4.3 of the full dossier assessment). Only the event rates are presented for the outcome "cardiovascular morbidity".
f: Proportion of events dulaglutide + metformin vs. insulin glargine with or without metformin (reversed direction of effect to enable direct use of limits to derive the extent of added benefit).
g: Institute's calculation, unconditional exact test (CSZ method according to [7]).
h: Institute's calculation, RR with 0.5 correction.
AE: adverse event; CI: confidence interval; CI_u: upper limit of the CI; CSZ: convexity, symmetry, z score; MD: mean difference; NC: not calculable; OR: odds ratio; RR: relative risk; SAE: serious adverse event; vs.: versus

2.6.3.2 Overall conclusion on added benefit

Dulaglutide in combination with a short-acting insulin with or without metformin

Table 31 summarizes the results considered in the overall conclusion on extent of added benefit.

Transferability of the results from studies with insulin analogues to human insulin can be assumed for the outcomes for which positive or negative effects were shown (see Section 2.8.5.1 of the full benefit assessment).

Table 31: Positive and negative effects from the assessment of dulaglutide in comparison with metformin + human insulin (research question D)

Positive effects	**Negative effects**
Indication of lesser harm – extent: "considerable" (serious/severe AEs: SAEs)	Hint of greater harm – extent "considerable" (non-serious/non-severe AEs: discontinuation due to AEs)
	Hint of greater harm – extent: "considerable" (non-serious/non-severe AEs: gastrointestinal disorders, nausea, diarrhoea, dyspepsia, vomiting [only for patients < 65 years])
	Hint of greater harm – extent: "considerable" (non-serious/non-severe AEs: appetite loss)
No sufficient data were available on micro- and macrovascular late complications.	
AE: adverse event; SAE: serious adverse event; vs.: versus	

Overall, one positive effect and several negative effects with different certainty of results, but the same extent, remain.

The positive effect was shown in the outcome category "serious/severe AEs" for the outcome "SAEs" with an indication of lesser harm under dulaglutide + short-acting insulin with or without metformin (extent: "considerable").

There were negative effects in the outcome category "non-serious/non-severe AEs" for the following outcomes: discontinuation due to AEs, gastrointestinal disorders, nausea, diarrhoea, vomiting, dyspepsia and decreased appetite, in each case with a hint of greater harm under dulaglutide + short-acting insulin with or without metformin (extent: "considerable"). For the outcome "vomiting", the negative effect only applies to patients < 65 years.

No sufficient data were available on micro- and macrovascular late complications.

In the balancing of the results, the negative effects for the outcomes "discontinuation due to AEs", "gastrointestinal disorders", "nausea", "diarrhoea", "vomiting", "dyspepsia" and "appetite loss" do not fully outweigh the advantage of dulaglutide regarding SAEs. However, they resulted in a weakening of the advantage so that, overall, there is a hint of a minor added benefit of dulaglutide + short-acting insulin with or without metformin in comparison with the ACT metformin + human insulin.

This deviates from the company's approach, which derived an indication of considerable added benefit of dulaglutide + insulin lispro with or without metformin in comparison with the ACT.

Dulaglutide in combination with a long-acting insulin with or without oral antidiabetic

The company presented no data on other combinations of dulaglutide with a long-acting insulin with or without OAD. Overall, this resulted in no proof of added benefit of dulaglutide + long-acting insulin with or without OAD versus the ACT metformin + human insulin.

Summary

The result of the assessment of the added benefit of dulaglutide + insulin lispro with or without metformin in comparison with the ACT is summarized in Table 32.

Table 32: Dulaglutide – extent and probability of added benefit (research question D)

Research question	Subindication	ACT[a]	Extent and probability of added benefit
D	Dulaglutide + short-acting insulin with or without metformin	Metformin + human insulin *(note: if applicable, treatment only with human insulin if metformin is not tolerated or not sufficiently effective according to the SPC)*	Hint of a minor added benefit
	Dulaglutide + long-acting insulin with or without OAD 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. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAD: oral antidiabetic; SPC: Summary of Product Characteristics			

2.6.4 List of included studies

AWARD-4

Eli Lilly and Company. A study in participants with type 2 diabetes mellitus (AWARD-4): full text view [online]. In: ClinicalTrials.gov. 3 October 2014 [accessed: 3 December 2014]. URL: https://clinicaltrials.gov/ct2/show/NCT01191268.

Eli Lilly and Company. A study in participants with type 2 diabetes mellitus (AWARD-4): study results [online]. In: ClinicalTrials.gov. 3 October 2014 [accessed: 14 April 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01191268.

Eli Lilly and Company. H9X-MC-GBDD (AWARD-4): post-hoc Analysen [unpublished]. 2014.

Eli Lilly and Company. The impact of LY2189265 versus insulin glargine both in combination with insulin lispro for the treatment to target of type 2 diabetes mellitus (AWARD-4: assessment of weekly administration of LY2189265 in diabetes - 4); study H9X-MC-GBDD; clinical study report [unpublished]. 2013.

2.7 Extent and probability of added benefit – summary

The extent and probability of an added benefit of dulaglutide in the individual subindications in comparison with the ACT is presented in Table 33.

Table 33: Dulaglutide – extent and probability of added benefit

Research question	**Subindication**	**ACT**	**Extent and probability of added benefit**
A	Dulaglutide monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications	Sulfonylurea (glibenclamide or glimepiride)	Added benefit not proven
B	Dulaglutide + metformin	Metformin + sulfonylurea (glibenclamide or **glimepiride**[a]) *(note: if metformin is considered inappropriate according to the SPC, human insulin is to be used as treatment option)*	Added benefit not proven
	Dulaglutide + OAD other than metformin when this, together with diet and exercise, does not provide adequate glycaemic control		Added benefit not proven
C	Dulaglutide + 2 OADs when these, together with diet and exercise, do not provide adequate glycaemic control	Metformin + human insulin *(note: if applicable, treatment only with human insulin if metformin is not tolerated or not sufficiently effective according to the SPC)*	Added benefit not proven
D	Dulaglutide + short-acting insulin with or without metformin	Metformin + human insulin *(note: if applicable, treatment only with human insulin if metformin is not tolerated or not sufficiently effective according to the SPC)*	Hint of a minor added benefit
	Dulaglutide + long-acting insulin with or without OAD when this, together with diet and exercise, does not provide adequate glycaemic control		Added benefit not proven

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

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

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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