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Insulin degludec/liraglutide – Benefit assessment according to §35a Social Code Book V¹

Extract

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BOT	basal supported oral therapy
CPG	clinical practice guideline
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLP-1	glucagon-like peptide 1
HbA1c	glycosylated haemoglobin A1c
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NVL	Nationale VersorgungsLeitlinie (National Care Guideline)
OAD	oral antidiabetic
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SHI	statutory health insurance

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 combination insulin degludec/liraglutide. 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 29 April 2015.

Research question

The aim of this report was to assess the added benefit of the fixed combination of insulin degludec/liraglutide in combination with oral antidiabetics (OADs) in comparison with the appropriate comparator therapy (ACT) in adult patients with type 2 diabetes mellitus when OADs alone or combined with basal insulin do not provide adequate glycaemic control.

From the G-BA’s specification of the ACT, the following 2 research questions result for the benefit assessment (Table 2).

Table 2: Subindications and ACTs on insulin degludec/liraglutide considered in the benefit assessment

Research question	Subindication ^a	Appropriate comparator therapy
	Combination with oral antidiabetics:	
A1	<ul style="list-style-type: none"> ▪ When oral antidiabetic combination therapy does not provide adequate glycaemic control 	Metformin + human insulin <i>(Note: If metformin is considered inappropriate according to the SPC, human insulin is to be used as treatment option.)</i>
A2	<ul style="list-style-type: none"> ▪ When oral antidiabetics in combination with basal insulin do not provide adequate glycaemic control 	Human insulin + metformin if applicable <i>(Additional administration of metformin is not generally indicated in the framework of an ICT.)</i>
a: Subdivisions of the therapeutic indication according to the G-BA. G-BA: Federal Joint Committee; ICT: intensified insulin therapy; SPC: Summary of Product Characteristics		

The G-BA assumed that oral antidiabetic therapy alone is not an option in the antidiabetic treatment situation for which the ACT was specified. It also specified that the benefit assessment also considers evidence from studies in which insulin analogues were used if the results from studies with insulin analogues are transferable to human insulin.

The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company in the dossier.

Results

Research question A1:

For research question A1, the study pool of the company to prove the added benefit consisted of the DUAL I study (including extension). This study was unsuitable to derive conclusions on the added benefit of insulin degludec/liraglutide in combination with OADs versus the ACT specified by the G-BA. The patients in the study did not concur with the patient population for this research question. Moreover, the ACT specified by the G-BA was not implemented in the study.

Patients in the study did not concur with the patient population for research question A1

Patients with type 2 diabetes mellitus and inadequate glycaemic control ($7\% \leq$ glycosylated haemoglobin A1c [HbA1c] $\leq 10\%$) despite treatment with metformin, with or without pioglitazone, were included in the DUAL I study. The patients were randomly assigned to additional treatment with insulin degludec/liraglutide or insulin degludec or liraglutide, in each case in addition to their ongoing treatment with metformin \pm pioglitazone.

83% of the patients in both study arms had been pretreated only with metformin monotherapy, however, and therefore did not concur with the population in research question A1, who are defined by pretreatment with OAD combination therapy. It cannot be assumed that patients with inadequate treatment under OAD monotherapy cannot be treated adequately with OAD combination therapy.

Only 17% of the patients in both study arms received inadequate treatment under OAD combination therapy with metformin + pioglitazone. However, the drug pioglitazone is not reimbursable within the German statutory health insurance (SHI). Hence data on patients with pioglitazone treatment are not relevant for the benefit assessment.

Appropriate comparator therapy not implemented in the DUAL I study

The ACT was not implemented in the DUAL I study because the patients in the insulin comparator arm received the analogue insulin degludec as insulin component. However, the company did not show the transferability of insulin degludec to the ACT human insulin. Moreover, patients who had been pretreated with OAD combination therapy continued their ongoing treatment with the 2 OADs metformin and pioglitazone during the study. This does not represent the G-BA's specification, however, which determined only metformin as OAD component of the ACT.

Research question A2:

For research question A2, the study pool of the company to prove the added benefit consisted of the studies DUAL II and DUAL V. These studies were unsuitable to derive conclusions on the added benefit of insulin degludec/liraglutide in combination with OADs versus the ACT specified by the G-BA. Patients in the comparator arms of both studies received no

meaningful escalation of their insulin therapy. In addition, the ACT was not implemented in the DUAL II study.

Study DUAL V

Adult patients with type 2 diabetes mellitus and inadequate glycaemic control ($7.0\% \leq \text{HbA1c} \leq 10\%$) despite treatment with insulin glargine + metformin were included in the DUAL V study. According to the inclusion criterion of the study, the patients in the study had been pretreated with insulin glargine (basal insulin) + metformin for at least 90 days, 56 days of which at a relatively stable daily dose of 20 to 50 units of insulin glargine.

No change in therapeutic strategy in the comparator arm

Whereas the patients in the intervention arm of the DUAL V study received an intensification of their therapy by the additional administration of liraglutide (in addition to basal insulin and metformin), the therapeutic strategy in the comparator arm remained unchanged. Treatment with basal insulin (insulin glargine) + metformin was continued; the dose of basal insulin, on the basis of the fasting plasma glucose levels, was titrated analogously to the intervention arm. Continuing the ongoing therapeutic strategy in the comparator arm is not meaningful in the present situation, however, and resulted in an unfair comparison because this therapeutic strategy had already been obviously inadequate before.

This assessment is also in line with treatment recommendations in clinical practice guidelines (CPGs), in which a change in therapeutic strategy is considered to be meaningful and necessary when patients have not reached their target blood glucose level after about 3 months (or 3 to 6 months) of treatment. According to the CPG recommendations, this change in strategy can be done in the present treatment situation by intensifying insulin therapy such as conventional insulin therapy (e.g. with mixed insulin) or intensified insulin therapy. These recommendations were implemented only in the intervention arm by the additional administration of the glucagon-like peptide 1 (GLP-1) receptor antagonist liraglutide, but not in the comparator arm. Hence the therapeutic strategy was not changed for patients in the comparator arm, although these patients would have required a change in strategy according to the CPGs.

In summary, the DUAL V study investigated the research question of the approval (efficacy: escalation with insulin degludec/liraglutide versus continuation of inadequate treatment), but not the research question of the benefit assessment (added benefit: escalation with insulin degludec/liraglutide versus escalation with the ACT).

Study DUAL II

Adult patients with type 2 diabetes mellitus and inadequate glycaemic control ($7.5\% \leq \text{HbA1c} \leq 10\%$) despite treatment with a stable dose of a basal insulin + 1 to 2 OADs (metformin ± sulfonylurea or glinides) were included in the DUAL II study. The patients were randomly assigned to basal insulin treatment with insulin degludec or to treatment with insulin degludec/liraglutide. Ongoing treatment with basal insulin, sulfonylureas or glinides

was discontinued at the start of the study. Patients in both study arms continued their ongoing treatment with metformin at the same dosage and frequency as before the start of the study.

No change in therapeutic strategy in the comparator arm

As in the DUAL V study, patients of the DUAL II study did not receive adequate treatment in the comparator arm and would have required a change in therapeutic strategy.

In summary, the DUAL II study also investigated the question of the approval (efficacy: escalation with insulin degludec/liraglutide versus continuation or even reduction of inadequate treatment), but not the research question of the benefit assessment (added benefit: escalation with insulin degludec/liraglutide versus escalation with the ACT).

ACT not implemented in the DUAL II study

In addition, the ACT was not implemented in the DUAL II study because the patients in the comparator arm received the insulin analogue insulin degludec as insulin component. However, the company did not show the transferability of insulin degludec to the ACT human insulin.

Hence the company presented no suitable studies for both research questions to assess the added benefit of insulin degludec/liraglutide in combination with OADs versus the ACT specified by the G-BA.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

On the basis of the results presented, the extent and probability of the added benefit of the drug insulin degludec/liraglutide versus the ACT is assessed as follows:

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

Table 3: Insulin degludec/liraglutide – extent and probability of added benefit

Research question	Subindication ^a	ACT	Extent and probability of added benefit
	Combination with oral antidiabetics:		
A1	<ul style="list-style-type: none"> ▪ When oral antidiabetic combination therapy does not provide adequate glycaemic control 	Metformin + human insulin <i>(Note: If metformin is considered inappropriate according to the SPC, human insulin is to be used as treatment option.)</i>	Added benefit not proven
A2	<ul style="list-style-type: none"> ▪ When oral antidiabetics in combination with basal insulin do not provide adequate glycaemic control 	Human insulin + metformin if applicable <i>(Additional administration of metformin is not generally indicated in the framework of an ICT.)</i>	Added benefit not proven
a: Subdivisions of the therapeutic indication according to the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; ICT: intensified insulin therapy			

The G-BA decides on the added benefit.

2.2 Research questions

The aim of this report was to assess the added benefit of the fixed combination of insulin degludec/liraglutide in combination with OADs in comparison with the ACT in adult patients with type 2 diabetes mellitus when OADs alone or combined with basal insulin do not provide adequate glycaemic control.

From the G-BA's specification of the ACT, the following 2 research questions result for the benefit assessment (Table 4).

Table 4: Subindications and ACTs on insulin degludec/liraglutide considered in the benefit assessment

Research question	Subindication ^a	ACT
	Combination with oral antidiabetics:	
A1	<ul style="list-style-type: none"> ▪ When oral antidiabetic combination therapy does not provide adequate glycaemic control 	Metformin + human insulin <i>(Note: If metformin is considered inappropriate according to the SPC, human insulin is to be used as treatment option.)</i>
A2	<ul style="list-style-type: none"> ▪ When oral antidiabetics in combination with basal insulin do not provide adequate glycaemic control 	Human insulin + metformin if applicable <i>(Additional administration of metformin is not generally indicated in the framework of an ICT.)</i>
a: Subdivisions of the therapeutic indication according to the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; ICT: intensified insulin therapy		

The G-BA assumed that oral antidiabetic therapy alone is not an option in the antidiabetic treatment situation for which the ACT was specified. It also specified that the benefit assessment also considers evidence from studies in which insulin analogues were used if the results from studies with insulin analogues are transferable to human insulin.

Appropriate comparator therapy

In the present assessment, the benefit assessment of insulin degludec/liraglutide in combination with OADs was conducted for both research questions in comparison with the ACT specified by the G-BA. The G-BA specified human insulin as insulin component in each case. The company deviated from the G-BA's specification and named insulin analogues instead of human insulin as ACT for both research questions (A1 and A2). The company argued on the transferability of the results on insulin analogues to human insulin, and on the transferability of the results on insulin analogues (insulin detemir, insulin glargine, insulin degludec) between one another.

The company's deviation from the ACT was not accepted.

The available evidence on longterm data supports human insulin as ACT. No general transferability of the results of studies with insulin analogues to human insulin can be

assumed because there is a lack of data on late complications. On the basis of the IQWiG assessment [3], transferability can be assumed for the 2 insulin analogues insulin detemir and insulin glargine for other outcomes (see Section 2.6.1 of the full dossier assessment).

This does not apply to the insulin analogue insulin degludec, however, for which the company did not show transferability to the ACT human insulin. Hence studies in comparison with insulin degludec were not used for the present assessment (see Section 2.6.1 of the full dossier assessment). This had no consequence for the present assessment insofar as the studies used by the company, in which insulin degludec was investigated in the comparator arm, were not relevant for the benefit assessment also for other reasons (see Sections 2.3.1 and 2.4.1).

Relevant patients in research question A1

In research question A1, the benefit assessment of insulin degludec/liraglutide was conducted for patients for whom oral antidiabetic combination therapy does not provide adequate glycaemic control and followed the specifications by the G-BA. The company considered the therapeutic indication to be not fully represented by the G-BA's specification. It expanded the population in research question A1 to also include patients who have received OAD monotherapy (see Table 5).

Table 5: Definition of the population in research question A1

Source	Research question A1
SPC Xultophy [4]	▪ When oral glucose-lowering medicinal products do not provide adequate glycaemic control
G-BA	▪ When oral antidiabetic combination therapy does not provide adequate glycaemic control
Company	▪ When oral antidiabetic therapy does not provide adequate glycaemic control
G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics	

The company's expansion of the patient population was not followed because the subdivisions of the therapeutic indication according to the G-BA is comprehensible and also supported by the National Care Guideline (NVL) for the treatment of type 2 diabetes [5], for example: According to the algorithm of the NVL for the treatment of type 2 diabetes [5], patients do not continue treatment with a combination of 3 drugs, such as administration of the fixed combination of insulin degludec/liraglutide in addition to an OAD, after failure of pharmaceutical monotherapy. According to the algorithm of the NVL for the treatment of type 2 diabetes, either treatment with a dual pharmaceutical combination (e.g. 2 OADs or insulin + metformin) or insulin alone is to be administered after failure of pharmaceutical monotherapy (see Section 2.6.2.1 of the full dossier assessment).

Consequences for the assessment

The present dossier assessment was conducted for both research questions resulting from the G-BA specification in comparison with the ACTs specified by the G-BA. Evidence from studies investigating the 2 insulin analogues insulin detemir or insulin glargine was also

considered if these studies were not targeted at late complications. The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company in the dossier.

2.3 Research question A1

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 insulin degludec/liraglutide (status: 2 March 2015)
- bibliographical literature search on insulin degludec/liraglutide (last search on 17 February 2015)
- search in trial registries for studies on insulin degludec/liraglutide (last search on 26 February 2015)

To check the completeness of the study pool:

- search in trial registries for studies on insulin degludec/liraglutide (last search on 6 May 2015)

No relevant study was identified from the check.

From the steps of information retrieval mentioned, the company identified one randomized controlled trial (RCT), the NN9068-3697 study (DUAL I including extension [6]), hereinafter referred to as “DUAL I”. This study was unsuitable to derive conclusions on the added benefit of insulin degludec/liraglutide in combination with OADs versus the ACT specified by the G-BA. The reasons were as follows:

Patients in the study did not concur with the patient population for research question A1

Patients with type 2 diabetes mellitus and inadequate glycaemic control ($7\% \leq \text{HbA1c} \leq 10\%$) despite treatment with metformin, with or without pioglitazone, were included in the DUAL I study. The patients were randomly assigned to additional treatment with insulin degludec/liraglutide or insulin degludec or liraglutide, in each case in addition to their ongoing treatment with metformin \pm pioglitazone.

83% of the patients in both study arms had been pretreated only with metformin monotherapy, however, and therefore did not concur with the population in research question A1, who are defined by pretreatment with OAD combination therapy (see Section 2.2 and Section 2.6.2.1 of the full dossier assessment). It cannot be assumed that patients with inadequate treatment under OAD monotherapy cannot be treated adequately with OAD combination therapy.

Only 17% of the patients in both study arms received inadequate treatment under OAD combination therapy with metformin + pioglitazone. However, the drug pioglitazone is not reimbursable within the German SHI [7]. Hence data on patients with pioglitazone treatment are not relevant for the benefit assessment.

Appropriate comparator therapy not implemented in the DUAL I study

The ACT was not implemented in the DUAL I study. The G-BA specified metformin + human insulin as ACT for patients in whom oral antidiabetic combination therapy does not provide adequate glycaemic control. Patients in the insulin comparator arm received the analogue insulin degludec as insulin component. As described in Section 2.2 and in Section 2.6.1 of the full dossier assessment, studies investigating the insulin analogue insulin detemir or insulin glargine as insulin component in the comparator arm would have also been included in the benefit assessment. This assumption of transferability to human insulin does not apply to the insulin analogue insulin degludec, however. Moreover, patients who had been pretreated with OAD combination therapy continued their ongoing treatment with the 2 OADs metformin and pioglitazone during the study. This does not represent the G-BA's specification, however, which determined only metformin as OAD component of the ACT.

Information on the study design and the study population of the DUAL I study can be found in Appendix A, Table 11 to Table 13, of the full dossier assessment.

2.3.2 Results on added benefit

No suitable data were available for research question A1 – insulin degludec/liraglutide in combination with OADs for patients in whom oral antidiabetic combination therapy is inadequate. There was no hint of an added benefit of insulin degludec/liraglutide in combination with OADs in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

Since no suitable study was presented for the benefit assessment, an added benefit of insulin degludec/liraglutide in combination with OADs – for patients in whom oral antidiabetic combination therapy is inadequate – in comparison with the ACT specified by the G-BA (metformin + human insulin) is not proven. 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 derived an indication of considerable added benefit for the population it considered in its research question (see Section 2.6.2.1 of the full dossier assessment) in comparison with the insulin analogue insulin degludec.

2.3.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.4 Research question A2

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 insulin degludec/liraglutide (status: 2 March 2015)
- bibliographical literature search on insulin degludec/liraglutide (last search on 17 February 2015)
- search in trial registries for studies on insulin degludec/liraglutide (last search on 26 February 2015)

To check the completeness of the study pool:

- search in trial registries for studies on insulin degludec/liraglutide (last search on 6 May 2015)

No relevant study was identified from the check.

From the steps of information retrieval mentioned, the company identified 2 RCTs, NN9068-3912 (DUAL II [8]) and NN9068-3952 (DUAL V [9]), hereinafter referred to as “DUAL II” and “DUAL V”. Both studies were unsuitable for the assessment of the added benefit of insulin degludec/liraglutide in comparison with the ACT, particularly because in both studies the patients in the comparator arm received no meaningful escalation of their insulin treatment. In addition, the ACT was not implemented in the DUAL II study. Detailed reasons for exclusion are given below.

Study DUAL V

Patients included concur with research question A2 (prior treatment with OAD and basal insulin inadequate)

Adult patients with type 2 diabetes mellitus and inadequate glycaemic control ($7.0\% \leq \text{HbA1c} \leq 10\%$) despite treatment with insulin glargine + metformin were included in the DUAL V study. The patients were randomly assigned to continuing their inadequate basal insulin treatment with insulin glargine or to treatment with insulin degludec/liraglutide. In the study, patients in both study arms continued their previous treatment with the OAD metformin with the same dosage and frequency as before the start of the study.

The starting dose of insulin degludec/liraglutide in the intervention arm was 16 dose steps, which corresponds to the recommended starting dose when changing from basal insulin therapy [4]. The starting dose of insulin glargine in the comparator arm corresponded to the dose administered before the start of the study. In both study arms, the dose was titrated twice

weekly on the basis of the fasting plasma glucose to a target level of 4.5 to 5.0 mmol/L (72 to 90 mg/dL).

Patients in whom OADs in combination with basal insulin do not provide adequate glycaemic control were considered in the present research question A2. For the DUAL V study, there was no information since when the patients had already received basal insulin. However, according to the inclusion criterion of the study, the patients in the study had been pretreated with insulin glargine (basal insulin) + metformin for at least 90 days, 56 days of which at a relatively stable daily dose of 20 to 50 units of insulin glargine. It can be assumed on the basis of this information that the patients in the study were mainly patients who are not just beginning their insulin treatment, but patients who cannot achieve further target blood glucose levels with a treatment of basal insulin + metformin, with a mean baseline HbA1c of about 8.3%. Hence the patients concurred with research question A2. This would not be the case if the patients were just beginning their basal insulin therapy, and further escalations within this therapeutic strategy would still be meaningful to achieve target blood glucose levels. In this case, the population included would not be relevant for research question A2, however.

No change in therapeutic strategy in the comparator arm

Whereas the patients in the intervention arm of the DUAL V study received an intensification of their therapy by the additional administration of liraglutide (in addition to basal insulin and metformin), the therapeutic strategy in the comparator arm remained unchanged. Treatment with basal insulin (insulin glargine) + metformin was continued; the dose of basal insulin, on the basis of the fasting plasma glucose levels, was titrated analogously to the intervention arm. Continuation of the ongoing therapeutic strategy in the comparator arm is not meaningful in the present situation, however, and resulted in an unfair comparison because this therapeutic strategy had already been obviously inadequate before.

This assessment is also in line with treatment recommendations in CPGs [5,10,11], in which a change in therapeutic strategy is considered to be meaningful and necessary when patients have not reached their target blood glucose level after about 3 months (or 3 to 6 months [5]) of treatment. Changing their therapeutic strategy or moving to the next level of treatment is considered necessary for these patients.

According to the CPGs, this change in strategy can be done in the present treatment situation by intensifying insulin therapy such as conventional insulin therapy (e.g. with mixed insulin) or intensified insulin therapy [5,10]. In patients with persistent uncontrolled blood glucose levels, although they achieve their target fasting plasma glucose level under their current treatment with basal insulin + OAD, this intensification can also be achieved by adding a prandial insulin or a GLP-1 receptor agonist or by switching to mixed insulin, according to the recommendations from the current guideline of the European Association for the Study of Diabetes (EASD) und der American Diabetes Association (ADA) [10]. These recommendations were implemented only in the intervention arm by the additional administration of the GLP-1 receptor antagonist liraglutide, but not in the comparator arm.

Hence the therapeutic strategy was not changed for patients in the comparator arm, although these patients would have required a change in strategy according to the CPGs.

The company's rationale in Sections 3.1.2 (Module 3 A) and 4.3.1.2.1 (Module 4 A) stating that both the G-BA's specification and the recommendations of the NVL on the treatment of type 2 diabetes include several insulin treatment regimens (e.g. conventional treatment, intensified conventional treatment, or basal supported oral therapy [BOT]) cannot solve this problem either. Instead, in the respective study situation, an intensification of treatment that is adequate for the patients has to be conducted in both study arms to provide a fair comparison of 2 therapeutic options that is relevant for the benefit assessment.

In summary, the DUAL V study investigated the research question of the approval (efficacy: escalation with insulin degludec/liraglutide versus continuation of inadequate treatment), but not the research question of the benefit assessment (added benefit: escalation with insulin degludec/liraglutide versus escalation with the ACT).

Study DUAL II

Patients included concur with research question A2 (prior treatment with OAD and basal insulin inadequate)

Adult patients with type 2 diabetes mellitus and inadequate glycaemic control ($7.5\% \leq \text{HbA1c} \leq 10\%$) despite treatment with a stable dose of a basal insulin + 1 to 2 OADs (metformin ± sulfonylurea or glinides) were included in the DUAL II study. The patients were randomly assigned to basal insulin treatment with insulin degludec or to treatment with insulin degludec/liraglutide. Ongoing treatment with basal insulin, sulfonylureas or glinides was discontinued at the start of the study. Patients in both study arms continued their ongoing treatment with metformin at the same dosage and frequency as before the start of the study.

After randomization, the patients received either insulin degludec/liraglutide or insulin degludec once daily subcutaneously. The starting dose was 16 dose steps insulin degludec/liraglutide (this corresponds to the recommended starting dose when changing from basal insulin treatment [4]). The starting dose of insulin degludec in the comparator arm was analogous to the intervention arm and also consisted of 16 units, irrespective of the previous insulin dose. Deviating from this, the SPC of insulin degludec proposes that changing from another basal insulin to insulin degludec can be done unit-to-unit based on the previous basal insulin dose [12]. In both study arms, the dose was titrated twice weekly on the basis of the fasting plasma glucose to a target level of 4.5 to 5.0 mmol/L (72 to 90 mg/dL).

No change in therapeutic strategy in the comparator arm

As in the DUAL V study, patients of the DUAL II study did not receive adequate treatment in the comparator arm and would have required a change in therapeutic strategy.

According to the inclusion criteria of the study, the patients had already received a stable dose of basal insulin for at least 90 days before screening. Hence, similarly to the DUAL V study,

it can be assumed that these were patients who cannot achieve their target blood glucose levels with their previous treatment regimen of basal insulin + OAD, therefore corresponding to research question A2. As described for the DUAL V study, continuing the ongoing therapeutic strategy with basal insulin is not meaningful in this situation because this strategy had already been obviously inadequate before. This assessment is also in line with treatment recommendations in CPGs [5,10,11], in which a change in therapeutic strategy is considered to be meaningful and necessary when patients have not reached their target blood glucose level after about 3 months (or 3 to 6 months [5]) of treatment (see also the explanations on the DUAL V study).

Moreover, the fixed starting dose of 16 units insulin degludec specified in the study, in the comparator arm led to reduction of the insulin dose instead of treatment escalation in all patients. According to the inclusion criteria of the study, all patients had a basal insulin dose between 20 and 40 units at the start of the study, and the median of their daily insulin dose was between 28 and 30 units, depending on the type of insulin. In addition, the insulin degludec dose was only allowed to be increased up to a maximum daily dose of 50 units in the study. In contrast, the SPC of insulin degludec proposes using the current dose as the starting dose when changing from another basal insulin, and specifies no maximum daily dose [12].

The company justifies this by explaining in Section 4.3.1.2.1 (Module 4 A) that the DUAL II study was conducted to demonstrate the additional effect of the liraglutide component of insulin degludec/liraglutide in comparison with insulin degludec. For the same reason, the same maximum dose of 50 dose steps or units was specified, which, according to the company, corresponds to the approved maximum daily dose of insulin degludec/liraglutide. Furthermore, an identical starting dose would allow maintaining adequate blinding of the study medication. This approach might be suitable to provide proof of efficacy of the liraglutide component required for the approval, but it also leads to the DUAL II study being unsuitable for the present research question.

In summary, the DUAL II study also investigated the question of the approval (efficacy: escalation with insulin degludec/liraglutide versus continuation or even reduction of inadequate treatment), but not the research question of the benefit assessment (added benefit: escalation with insulin degludec/liraglutide versus escalation with the ACT).

ACT not implemented in the DUAL II study

In addition, the ACT was not implemented in the DUAL II study. The G-BA specified human insulin + metformin, if applicable, as ACT for patients in whom OADs in combination with basal insulin do not provide adequate glycaemic control. Patients in the comparator arm received the insulin analogue insulin degludec as insulin component. As described in Section 2.2 and in Section 2.6.1 of the full dossier assessment, studies investigating the insulin analogue insulin detemir or insulin glargine as insulin component in the comparator arm would have also been included in the benefit assessment (if these studies were not

targeted at late complications). This assumption of transferability to human insulin does not apply to the insulin analogue insulin degludec, however.

Information on the study design and the study population of the studies DUAL II and DUAL V can be found in Appendix A, Table 13 to Table 15, of the full dossier assessment.

2.4.2 Results on added benefit

No suitable data were available for research question A2 – insulin degludec/liraglutide in combination with OADs for patients in whom OADs in combination with basal insulin do not provide adequate glycaemic control. There was no hint of an added benefit of insulin degludec/liraglutide in combination with OADs in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

Since no suitable study was presented for the benefit assessment, an added benefit of insulin degludec/liraglutide in combination with OADs – for patients in whom OADs in combination with basal insulin do not provide adequate glycaemic control – in comparison with the ACT specified by the G-BA (human insulin + metformin, if applicable) is not proven. 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 derived an indication of considerable added benefit in comparison with the 2 insulin analogues insulin degludec and insulin glargine.

2.4.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.5 Extent and probability of added benefit – summary

An overview of the extent and probability of added benefit for the different subindications of insulin degludec/liraglutide in comparison with the corresponding ACTs is given Table 6.

Table 6: Insulin degludec/liraglutide – extent and probability of added benefit

Research question	Subindication ^a	Appropriate comparator therapy	Extent and probability of added benefit
	Combination with oral antidiabetics:		
A1	<ul style="list-style-type: none"> ▪ When oral antidiabetic combination therapy does not provide adequate glycaemic control 	Metformin + human insulin <i>(Note: If metformin is considered inappropriate according to the SPC, human insulin is to be used as treatment option.)</i>	Added benefit not proven
A2	<ul style="list-style-type: none"> ▪ When oral antidiabetics in combination with basal insulin do not provide adequate glycaemic control 	Human insulin + metformin if applicable <i>(Additional administration of metformin is not generally indicated in the framework of an ICT.)</i>	Added benefit not proven
a: Subdivisions of the therapeutic indication according to the G-BA. G-BA: Federal Joint Committee; ICT: intensified insulin therapy; SPC: Summary of Product Characteristics			

This assessment deviates from that of the company, which derived an indication of considerable added benefit for insulin degludec/liraglutide on the basis of the studies included by the company.

The G-BA decides on the added benefit.

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Please see full dossier assessment for full reference list.

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