IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Insulin degludec (new therapeutic indication) – Benefit assessment according to §35a Social Code Book V[1]

Extract

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Insulin degludec

Assessment module I

type 1 diabetes mellitus (children and adolescents)

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
FPG	fasting plasma glucose
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	haemoglobin A1c
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
PT	Preferred Term
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 2 Benefit assessment

I 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 insulin degludec. 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 March 2015.

Research question

The drug insulin degludec is approved for different therapeutic indications. The aim of the present Assessment module I was to assess the added benefit of insulin degludec in combination with short-/rapid-acting insulin in comparison with the appropriate comparator therapy (ACT) in adolescents and children from the age of one year with type 1 diabetes mellitus.

The benefit assessment of insulin degludec in combination with short-/rapid-acting insulin was conducted in comparison with the comparator therapy human insulin specified by the G-BA.

This deviates from the company's approach, which specified insulin analogues (long-acting insulin + bolus insulin) as comparator therapy. However, the company also searched for studies with human insulin. The transferability of the results of the study with insulin analogues used by the company was viewed to be sufficient. Hence this deviation had no consequences for the benefit assessment.

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

Results

The assessment was based on the NN1250-3561 study. In the study, 350 adolescents and children from the age of one year with type 1 diabetes mellitus were randomly assigned to insulin degludec or insulin detemir, each in combination with insulin aspart, in the framework of intensive insulin therapy.

The randomized study phase was 26 weeks, followed by an optional extension phase of another 26 weeks. The assessment was primarily based on the results after 52 weeks.

The risk of bias of the study was rated as low for the time point 26 weeks, and as high for the time point 52 weeks.

Mortality

No deaths occurred in the NN1250-3561 study. There was no hint of an added benefit of insulin degludec in comparison with insulin detemir; an added benefit is therefore not proven.

Morbidity

Change in HbA1c value as sufficiently valid surrogate for microvascular late complications

There was no statistically significant difference between the treatment groups for the outcome "change in haemoglobin A1c (HbA1c value)". There was no hint of an added benefit of insulin degludec in comparison with insulin detemir; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was not investigated in the NN1250-3561 study. There was no hint of an added benefit of insulin degludec in comparison with insulin detemir; an added benefit is therefore not proven.

Adverse events

Serious adverse event

There was no statistically significant difference between the treatment groups for the outcome "serious adverse events (SAEs)". However, there was proof of an effect modification by the characteristic "sex". It was therefore meaningful to consider the results separately for male and female children and adolescents.

For boys, there was no statistically significant difference between the treatment groups. Hence there was no hint of greater or lesser harm from insulin degludec in comparison with insulin detemir for boys; greater or lesser harm is therefore not proven.

For girls, there was a statistically significant result to the disadvantage of insulin degludec. This would result in an indication of greater harm of insulin degludec in girls. However, the result of this subgroup analysis was clearly influenced also by the events in the insulin detemir arm of the study. There is no sign of this kind of sex-specific effect of insulin detemir from other sources of evidence. But the effect was so pronounced that overall this resulted in a hint of greater harm from insulin degludec in girls.

Discontinuation due to adverse events

In the NN1250-3561 study, there was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". Hence there was no hint of greater or lesser harm from insulin degludec in comparison with insulin detemir; greater or lesser harm is therefore not proven.

Severe hypoglycaemia

In the NN1250-3561 study, there was no statistically significant difference between the treatment groups for the outcome "severe hypoglycaemia". Hence there was no hint of greater

or lesser harm from insulin degludec in comparison with insulin detemir; greater or lesser harm is therefore not proven.

Symptomatic hypoglycaemia (plasma glucose ≤ 70 mg/dL and < 56 mg/dL)

For the outcome "symptomatic hypoglycaemia", no statistically significant differences between the treatment groups were shown in the NN1250-3561 study for the plasma glucose threshold of < 56 mg/dL or for the plasma glucose threshold of ≤ 70 mg/dL. Hence there was no hint of greater or lesser harm from insulin degludec in comparison with insulin detemir; greater or lesser harm is therefore not proven.

Symptomatic hyperglycaemia

There were no evaluable data for the outcome "symptomatic hyperglycaemia". Hence there was no hint of greater or lesser harm from insulin degludec in comparison with insulin detemir; greater or lesser harm is therefore not proven.

Ketoacidosis

In the NN1250-3561 study, there was no statistically significant difference between the treatment groups for the outcome "ketoacidosis". Hence there was no hint of greater or lesser harm from insulin degludec in comparison with insulin detemir; greater or lesser harm is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[2]

On the basis of the results presented, the extent and probability of the added benefit of the drug insulin degludec in comparison with the ACT for the therapeutic indication adolescents and children from the age of one year with type 1 diabetes mellitus are assessed as follows:

Overall, only one negative effect in the outcome category "serious/severe AEs" remains for the subgroup of girls, with the probability "hint" and the extent "major". For girls with type 1 diabetes mellitus, this results in a hint of a lesser benefit of insulin degludec in comparison with the ACT.

There are neither positive nor negative effects for boys. Hence the added benefit of insulin degludec versus the ACT for boys with type 1 diabetes mellitus is not proven.

[2] 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].

Table 1 shows a summary of the extent and probability of the added benefit of insulin degludec in the therapeutic indication adolescents and children from the age of one year with type 1 diabetes mellitus.

Table 1: Insulin degludec – extent and probability of added benefit

Therapeutic indication	**ACT**	**Subgroup**	**Extent and probability of added benefit**
Type 1 diabetes mellitus in adolescents and children from the age of one year	Human insulin	Girls	Hint of lesser benefit
		Boys	Added benefit not proven
ACT: appropriate comparator therapy			

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

I 2.2 Research question

The aim of the present Assessment module I was to assess the added benefit of insulin degludec in combination with short-/rapid-acting insulin in comparison with the ACT in adolescents and children from the age of one year with type 1 diabetes mellitus.

The G-BA specified human insulin as ACT for the therapeutic indication.

The G-BA further specified the ACT in so far as the benefit assessment also includes evidence from studies in which insulin analogues were used under consideration of the approval if the results from studies with insulin analogues are transferable to human insulin.

The benefit assessment of insulin degludec in combination with short-/rapid-acting insulin was conducted in comparison with the comparator therapy human insulin specified by the G-BA.

This deviates from the company's approach, which specified insulin analogues (long-acting insulin + bolus insulin) as comparator therapy. However, the company also searched for studies with human insulin. The transferability of the results of the study with insulin analogues used by the company was viewed to be sufficient. Hence this deviation had no consequences for the benefit assessment (see Section I 2.7.1 of the full dossier assessment).

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

I 2.3 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 (studies completed up to 12 January 2015)
- bibliographical literature search on insulin degludec (last search on 12 January 2015)
- search in trial registries for studies on insulin degludec (last search on 12 January 2015)

To check the completeness of the study pool:

- search in trial registries for studies on insulin degludec (last search on 20 March 2015)

No additional relevant study was identified from the check.

I 2.3.1 Studies included

The study listed in the following Table 2 was included in the benefit assessment.

Table 2: Study pool – RCT, direct comparison: insulin degludec + insulin aspart vs. insulin detemir + insulin aspart

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
NN1250-3561	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of insulin degludec corresponded to that of the company. It included the NN1250-3561 study, which compared insulin degludec with insulin detemir (each in combination with insulin aspart).

Section I 2.6 contains a reference list for the study included.

I 2.3.2 Study characteristics

Table 3 and Table 4 describe the study used for the benefit assessment.

Table 3: Characteristics of the studies included – RCT, direct comparison: insulin degludec + insulin aspart vs. insulin detemir + insulin aspart

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
NN1250-3561	RCT, open-label, parallel	Children and adolescents from the age of one year to < 18 years with type 1 diabetes mellitus	IDeg + IAsp (N = 174) IDet + IAsp (N = 176)	▪ Screening: 1 week ▪ Treatment phase: 26 weeks ▪ Follow up: 1 week or optional extension phase ▪ Optional extension phase: 26 weeks ▪ Follow-up: 1 week	72 centres in Europe, Japan, Russia, South Africa, United States 1/2012 – 7/2013	Primary: change in HbA1c after 26 weeks of treatment Secondary: hypoglycaemia, hyperglycaemia, AEs

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.

AE: adverse event; HbA1c: haemoglobin A1c; IAsp: insulin aspart; IDeg: insulin degludec; IDet: insulin detemir; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 4: Characteristics of the interventions – RCT, direct comparison: insulin degludec + insulin aspart vs. insulin detemir + insulin aspart

<table>
<tr><th>Study</th><th>Intervention</th><th>Comparison</th></tr>
<tr><td>NN1250-3561</td><td>Basal insulin: IDeg
once daily, SC,
at approximately the same time
+
bolus insulin: IAsp
2-4 times daily before main meals, SC

The insulin dose at the start of the study (basal and bolus insulin) depended on the previous insulin regimen.

Dose adjustments of basal insulin (IDeg and IDet)[b]
once weekly in the course of the study, based on the lowest fasting plasma glucose level[c] according to the following scheme:
<table><tr><td>Current dose</td><td></td><td>< 5 U</td><td>5–15 U</td><td>> 15 U</td></tr><tr><td colspan="2">Measurements before breakfast or before evening meal</td><td colspan="3">Adjustment (U)</td></tr><tr><td>PG (mmol/L)</td><td>PG (mg/dL)</td><td></td><td></td><td></td></tr><tr><td>< 5.0</td><td>< 90</td><td>- 0.5</td><td>- 1</td><td>- 2</td></tr><tr><td>5.0-8.0</td><td>90-145</td><td>0</td><td>0</td><td>0</td></tr><tr><td>8.1-10.0</td><td>146-180</td><td>+ 0.5</td><td>+ 1</td><td>+ 2</td></tr><tr><td>10.1-15.0</td><td>181-270</td><td>+ 1</td><td>+ 2</td><td>+ 4</td></tr><tr><td>> 15.0</td><td>> 270</td><td>+ 1.5</td><td>+ 3</td><td>+ 6</td></tr></table>
Dose adjustments of bolus insulin (IAsp)[b]
in the course of the study several times daily based on carbohydrate counting or once weekly based on the lowest fasting plasma glucose level/plasma glucose level prior to bedtime[c] according to the following scheme:
<table><tr><td>Current dose</td><td></td><td>≤ 5 U</td><td>> 5 U</td></tr><tr><td colspan="2">Measurements before the next meal or prior to bedtime</td><td colspan="2">Adjustment (U)</td></tr><tr><td>PG (mmol/L)</td><td>PG (mg/dL)</td><td></td><td></td></tr><tr><td>< 5.0</td><td>< 90</td><td>- 1</td><td>- 2</td></tr><tr><td>5.0-8.0</td><td>90-145</td><td>0</td><td>0</td></tr><tr><td>8.1-10.0</td><td>146-180</td><td>+ 0.5</td><td>+ 1</td></tr><tr><td>10.1-15.0</td><td>181-270</td><td>+ 1</td><td>+ 2</td></tr><tr><td>> 15.0</td><td>> 270</td><td>+ 1.5</td><td>+ 3</td></tr></table></td><td>Basal insulin: IDet
once or twice daily[a] (continuing the ongoing dosing scheme), SC
+
bolus insulin: IAsp
2-4 times daily before main meals, SC</td></tr>
<tr><td></td><td colspan="2">▪ Pretreatment:
insulin therapy for at least 3 months with a daily insulin dose of ≤ 2 U/kg
▪ Concomitant medication prohibited
antidiabetic medication except study medication</td></tr>
</table>

(continued)

Table 4: Characteristics of the interventions – RCT, direct comparison: insulin degludec + insulin aspart vs. insulin detemir + insulin aspart (continued)

a: A second daily dose could be administered according to the specifications for titration in the study protocol on the basis of the average fasting plasma glucose levels.
b: Dose adjustments were conducted after clinical assessment and balancing the safety risk at the investigator's discretion. Dose adjustments were also possible outside the titration guidelines.
c: Based on the lowest plasma glucose level measured by the patient within 3 days.
IAsp: insulin aspart; IDeg: insulin degludec; IDet: insulin detemir; PG: plasma glucose; RCT: randomized controlled trials; SC: subcutaneously; U: units; vs.: versus

Study design

The NN1250-3561 study was an open-label, parallel, active-controlled phase 3 study. It was a multicentre study conducted in countries in Europe, Japan, Russia, South Africa and the United States. Adolescents and children from the age of one year with type 1 diabetes mellitus who had had insulin treatment for at least 3 months were included in the study. The randomized study phase was 26 weeks, followed by an optional extension phase of another 26 weeks. The assessment was primarily based on the results after 52 weeks.

350 patients were randomly assigned in a ratio of 1:1 to the 2 treatment arms insulin degludec (N = 174) and insulin detemir (N = 176), each plus insulin aspart. Randomization was stratified by age group (1 to 5 years, 6 to 11 years, 12 to 17 years).

Characteristics of the interventions

The patients in the study received insulin degludec or insulin detemir as basal insulin, and insulin aspart as bolus insulin in both treatment arms. The starting dose of both basal and bolus insulin depended on the prior insulin regimen.

The specifications for dose adjustment were identical for insulin degludec and insulin detemir and were based on a target fasting plasma glucose (FPG) level. Possible dose adjustments were conducted once weekly.

The dose of the bolus insulin used in both treatment arms was adapted either several times daily based on carbohydrate counting or once weekly based on the target FPG level.

Dose adjustment of both basal and bolus insulin could be conducted at the investigator's discretion also outside the titration guidelines.

Table 5 shows the characteristics of the patients in the studies included.

Table 5: Characteristics of the study populations – RCT, direct comparison: insulin degludec + insulin aspart vs. insulin detemir + insulin aspart

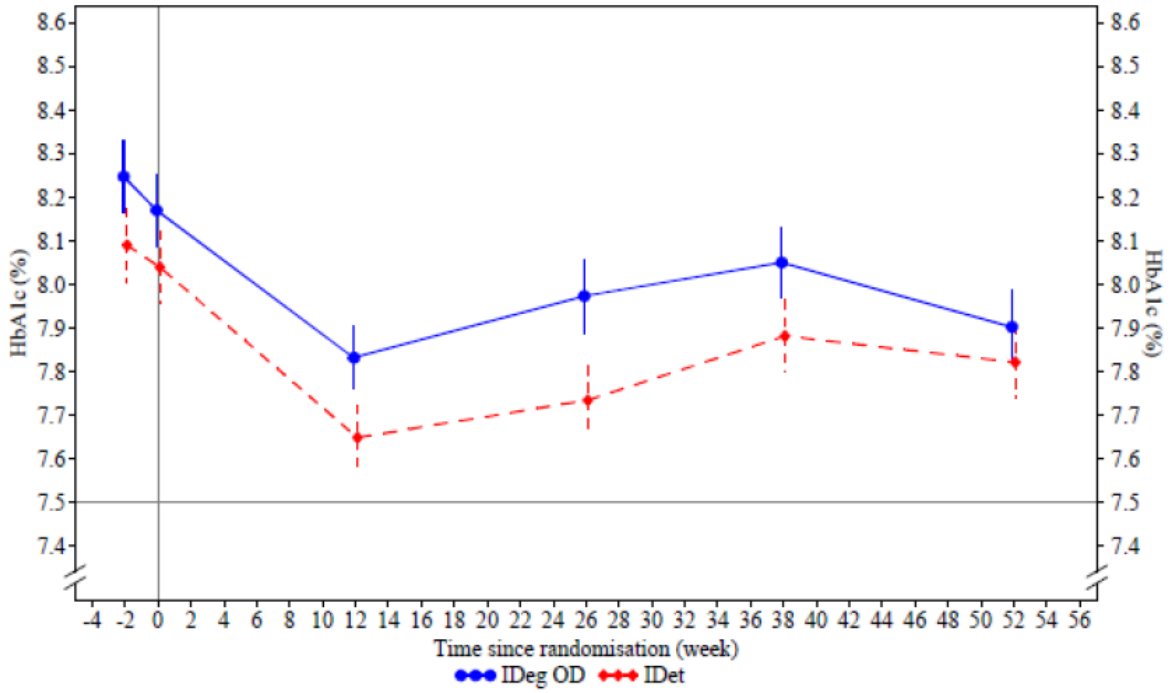
Study **Characteristics** **Category**	**Insulin degludec + insulin aspart** **N = 174[a]**	**Insulin detemir + insulin aspart** **N = 176[a]**
NN1250-3561		
Age [years]: mean (SD)	10.0 (4.4)	10.0 (4.4)
adolescents (12-17 years), n (%)	61 (35.1)	66 (37.5)
children (6-11 years), n (%)	70 (40.2)	68 (38.6)
children (1-5 years), n (%)	43 (24.7)	42 (23.9)
Sex: [F/M], %	45/55	44/56
BMI (kg/m²): mean (SD)	18.7 (3.6)	18.5 (3.6)
Duration of diabetes [years]: mean (SD)	3.9 (3.6)	4.0 (3.4)
HbA1c value [%]: mean (SD)	8.2 (1.1)	8.0 (1.1)
Ethnicity, n (%)		
white	136 (78.2)	125 (71.0)
non-white[b]	38 (21.8)[c]	51 (29.0)[c]
Geographical region, n (%)		
Europe	66 (37.9)[c]	65 (36.9)[c]
Japan	23 (13.2)	32 (18.2)
Russia	23 (13.2)	28 (15.9)
South Africa	5 (2.9)	7 (4.0)
United States	57 (32.8)	44 (25.0)
Treatment discontinuations[d], n (%)	4 (2.3)[c]	11 (6.3)[c]
Treatment discontinuations[e], n (%)	23 (13.2)[c]	54 (30.7)[c]

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: This group includes black or Afro-American, Asia - Indian origin, Asia non-Indian origin; American Indian or native Alaskan, native Hawaiian or other pacific islanders and others.
c: Institute's calculation.
d: Up to week 26.
e: Up to week 52
BMI: body mass index; F: female; HbA1c: haemoglobin A1c; M: male; N: number of randomized patients; n: number of patients with event; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

There were no important differences between the treatment arms with regard to age, sex, duration of diabetes and ethnicity. The average age of the patients was 10 years. Approximately the same number of girls and boys were included in both study arms.

Baseline HbA1c was approximately 0.2 percentage points higher in the insulin degludec arm than in the insulin detemir arm. This difference persisted over the entire course of the study.

Figure 1 shows the course of change in HbA1c up to week 52 in the NN1250-3561 study. Missing values were replaced with the last observation carried forward (LOCF).



HbA1c: haemoglobin A1c; IDeg OD: insulin degludec once daily; IDet: insulin detemir

Figure 1: course of change in HbA1c up to week 52 in the NN1250-3561 study

Table 6 shows the risk of bias at study level.

Table 6: Risk of bias at study level – RCT, direct comparison: insulin degludec + insulin aspart vs. insulin detemir + insulin aspart

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			
NN1250-3561 (main study, W 26)	Yes	Yes	No	No	Yes	Yes	Low
NN1250-3561 (extension phase, W 52)	Yes	Yes	No	No	Yes	No[a]	High

a: Original randomization no longer fully guaranteed.
RCT: randomized controlled trial; vs.: versus; W: week

The risk of bias at the study level was rated as low for the main study. After completion of the main study, patients had the option to continue their ongoing treatment in the extension phase. They were not re-randomized. 18 patients (10.3%) in the insulin degludec arm and 37 patients

(21.0%) in the insulin detemir arm decided against participation in the extension phase. Due to this high number of patients who discontinued, which also differed between the treatment groups, and the lacking re-randomization, the extension phase was rated as having a high risk of bias. However, enough patients continued the study to produce informative results. The data of the extension phase can therefore be used for the benefit assessment. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section I 2.4.2 with the outcome-specific risk of bias.

I 2.4 Results on added benefit

I 2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section I 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - change in HbA1c value as sufficiently valid surrogate for microvascular late complications
- Health-related quality of life
- Adverse events
  - SAEs
  - discontinuation due to AEs
  - hypoglycaemia
    - severe hypoglycaemia
    - symptomatic hypoglycaemia (plasma glucose ≤ 70 mg/dL and < 56 mg/dL)
  - symptomatic hyperglycaemia
  - ketoacidosis (Preferred Term [PT])

The following outcomes are presented as additional information (see Section I 2.7.2.4.3 of the full dossier assessment for reasons): AEs, severe nocturnal hypoglycaemia (plasma glucose ≤ 70 mg/dL and < 56 mg/dL) and body mass index (BMI).

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 E) (see Section I 2.7.2.4.3 of the full dossier assessment).

Table 7 shows for which outcomes data were available in the studies included.

Table 7: Matrix of outcomes – RCT, direct comparison: insulin degludec + insulin aspart vs. insulin detemir + insulin aspart

Study	Outcomes									
	All-cause mortality	Change in HbA1c value	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe hypoglycaemia	Symptomatic hypoglycaemia (plasma glucose < 56 mg/dL)	Symptomatic hypoglycaemia (plasma glucose ≤ 70 mg/dL)	Symptomatic hyperglycaemia	Ketoacidosis
NN1250-3561	Yes	Yes	No[a]	Yes	Yes	Yes	Yes	Yes	No[b]	Yes

a: Outcome was not recorded in the study.
b: No evaluable data available (for reasons, see Section I 2.7.2.4.3 of the full dossier assessment).
AE: adverse event; HbA1c: haemoglobin A1c; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

I 2.4.2 Risk of bias

Table 8 shows the risk of bias for the relevant outcomes.

Table 8: Risk of bias at study and outcome level – RCT, direct comparison: insulin degludec + insulin aspart vs. insulin detemir + insulin aspart

Study	Study level	Outcome									
		All-cause mortality	Change in HbA1c value	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe hypoglycaemia	Symptomatic hypoglycaemia (plasma glucose < 56 mg/dL)	Symptomatic hypoglycaemia (plasma glucose ≤ 70 mg/dL)	Symptomatic hyperglycaemia	Ketoacidosis
NN1250-3561 (main study, W 26)	L	L	L	–[a]	L	H	L	H	H	–[b]	L
NN1250-3561 (extension phase, W 52)	H	H	H	–[a]	H	H	H	H	H	–[b]	H

a: Outcome was not recorded in the study.
b: No evaluable data available.
AE: adverse event; H: high; HbA1c: haemoglobin A1c; L: low; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus; W: week

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

Deviating from the company, the outcome “all-cause mortality” was rated as having a high risk of bias also at the data cut-off at 52 weeks because of the potential selection bias at study level. Due to the open-label study design, the outcome “discontinuation due to AEs” was rated as having a high risk of bias already at the data cut-off at 26 weeks.

Symptomatic hypoglycaemia was also rated as having a high risk of bias at both data cut-off dates. The company included this outcome on the basis of a different operationalization.

Ketoacidosis was rated as having a low risk of bias at the data cut-off at 26 weeks, and as having a high risk of bias at the data cut-off at 52 weeks. The company did not include this outcome in its dossier.

Detailed reasons for the assessment of the risk of bias can be found in Section I 2.7.2.4.2 of the full dossier assessment.

I 2.4.3 Results

Table 9 and Table 10 summarize the results on the comparison of insulin degludec with insulin detemir (each in combination with insulin aspart) in adolescents and children from the age of one year with type 1 diabetes mellitus. Where necessary, the data from the company’s dossier were supplemented by the Institute’s calculations.

The data recorded after 52 weeks were primarily used in the benefit assessment. Since these data have a high risk of bias, at most hints can initially be derived. The corresponding results at the time point 26 weeks were considered additionally. If these were consistent with the 52-week data and if the respective outcome had a low risk of bias at the time point 26 weeks, the certainty of results of the 52-week data was upgraded from “hint” to “indication” (see Section I 2.7.2.8.1 of the full dossier assessment).

Table 9: Results (dichotomous outcomes) – RCT, direct comparison: insulin degludec + insulin aspart vs. insulin detemir + insulin aspart

Study **Outcome category** **Outcome** **Time point**	**Insulin degludec + insulin aspart**		**Insulin detemir + insulin aspart**		**Insulin degludec + insulin aspart vs. insulin detemir + insulin aspart**
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI]; p-value**
NN1250-3561					
Mortality					
All-cause mortality					
26 weeks	174	0 (0)	175	0 (0)	NC; > 0.999
52 weeks	174	0 (0)	175	0 (0)	NC; > 0.999
Health-related quality of life	Outcome not recorded				
Adverse events					
AEs					
26 weeks	174	145 (83.3)	175	142 (81.1)	
52 weeks	174	161 (92.5)	175	157 (89.7)	
SAEs					
26 weeks	174	12 (6.9)	175	11 (6.3)	1.10 [0.50; 2.42]; 0.877[a]
52 weeks	174	18 (10.3)	175	16 (9.1)	1.13 [0.60; 2.15]; 0.762[a]
Discontinuation due to AEs					
26 weeks	174	0 (0)	175	2 (1.1)	0.20 [0.01; 4.16][b, c]; 0.170[a]
52 weeks	174	0 (0)	175	3 (1.7)	0.14 [0.01; 2.76][b, c]; 0.087[a]
Severe hypoglycaemia					
26 weeks	174	24 (13.8)	175	17 (9.7)	1.38 [0.77; 2.49][d]; 0.246[a]
52 weeks	174	31 (17.8)	175	24 (13.7)	1.22 [0.75; 1.98][d]; 0.301[a]
Additional: severe nocturnal hypoglycaemia					
26 weeks	174	5 (2.9)	175	5 (2.9)	1.01 [0.30; 3.41]; > 0.999[a]
52 weeks	174	10 (5.7)	175	9 (5.1)	1.12 [0.47; 2.68]; 0.868[a]
Symptomatic hypoglycaemia					
plasma glucose < 56 mg/dL					
26 weeks	174	156 (89.7)	175	152 (86.9)	1.03 [0.96; 1.11]; 0.497[a]
52 weeks	174	163 (93.7)	175	160 (91.4)	1.02 [0.97; 1.09]; 0.497[a]
plasma glucose ≤ 70 mg/dL					
26 weeks	174	161 (92.5)	175	159 (90.9)	1.02 [0.96; 1.08][b]; 0.669[a]
52 weeks	174	166 (95.4)	175	163 (93.1)	1.02 [0.97; 1.08][b]; 0.461[a]

(continued)

Table 9: Results (dichotomous outcomes) – RCT, direct comparison: insulin degludec + insulin aspart vs. insulin detemir + insulin aspart (continued)

Study **Outcome category** **Outcome** **Time point**	**Insulin degludec + insulin aspart**		**Insulin detemir + insulin aspart**		**Insulin degludec + insulin aspart vs. insulin detemir + insulin aspart**
	N	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI]; p-value**
Additional: symptomatic nocturnal hypoglycaemia					
plasma glucose < 56 mg/dL					
26 weeks	174	76 (43.7)	175	71 (40.6)	1.11 [0.89; 1.38][d]; 0.580[a]
52 weeks	174	101 (58.0)	175	82 (46.9)	1.22 [1.02; 1.46][d]; 0.039[a]
plasma glucose ≤ 70 mg/dL					
26 weeks	174	94 (54.0)	175	99 (56.6)	0.95 [0.79; 1.15][b]; 0.669[a]
52 weeks	174	118 (67.8)	175	107 (61.1)	1.11 [0.95; 1.30][b]; 0.246[a]
Symptomatic hyperglycaemia	No evaluable data available				
Ketoacidosis					
26 weeks	174	0 (0)	175	0 (0)	NC; > 0.999
52 weeks	174	2 (1.1)	175	0 (0)	5.03 [0.24; 103.99][b, c]; 0.169[a]

a: Institute's calculation, unconditional exact test (CSZ method according to [3]).
b: Institute's calculation (asymptotic).
c: Correction factor 0.5.
d: Logistic regression model (log-link function), adjusted for treatment, sex, geographical region and age group.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; NC: not calculable; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 10: Results (continuous outcomes) – RCT, direct comparison: insulin degludec + insulin aspart vs. insulin detemir + insulin aspart

Study Outcome category Outcome Time point	Insulin degludec + insulin aspart			Insulin detemir + insulin aspart			Insulin degludec + insulin aspart vs. insulin detemir + insulin aspart
	N	Baseline values mean (SD)	Values at end of study mean[a] (SD)	N	Baseline values mean (SD)	Values at end of study mean[a] (SD)	Mean difference [95% CI]; p-value
NN1250-3561							
Morbidity							
Change in HbA1c value[b]							
26 weeks	174	8.2 (1.1)	8.0 (1.1)	176	8.0 (1.1)	7.7 (1.0)	0.15 [-0.03; 0.32][c]; ND
52 weeks	174	8.2 (1.1)	7.9 (1.1)	176	8.0 (1.1)	7.8 (1.1)	-0.01 [-0.20; 0.19][c]; ND
Additional: BMI							
26 weeks	174	18.7 (3.6)	19.1 (3.8)	175	18.5 (3.5)	18.6 (3.6)	0.50 [-0.28; 1.28]; 0.208[d]
52 weeks	174	18.7 (3.6)	19.4 (3.9)	175	18.5 (3.5)	18.7 (3.7)	0.70 [-0.10; 1.50]; 0.086[d]

a: LOCF analysis of the ITT population.
b: Sufficiently valid surrogate for microvascular late complications
c: ANOVA model, adjusted for treatment, sex, region, age group and baseline value.
d: Institute's calculation: t-test.

ANOVA: analysis of variance; BMI: body mass index; CI: confidence interval; HbA1c: haemoglobin A1c; ITT: intention to treat; LOCF: last observation carried forward; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Mortality

No deaths occurred in the NN1250-3561 study. There was no hint of an added benefit of insulin degludec in comparison with insulin detemir; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Change in HbA1c value as sufficiently valid surrogate for microvascular late complications

There was no statistically significant difference between the treatment groups for the outcome "change in HbA1c value". There was no hint of an added benefit of insulin degludec in comparison with insulin detemir; an added benefit is therefore not proven.

The company presented the change in HbA1c value in the dossier, but did not use the outcome in its assessment.

Health-related quality of life

Health-related quality of life was not investigated in the NN1250-3561 study. There was no hint of an added benefit of insulin degludec in comparison with insulin detemir; an added benefit is therefore not proven.

The company did not use health-related quality of life in its assessment.

Adverse events

The AEs and SAEs that most commonly occurred in the NN1250-3561 study are presented in I Appendix A of the full dossier assessment.

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs".

However, there was proof of an effect modification by the characteristic "sex" for the outcome "SAEs". It was therefore meaningful to consider the results separately for male and female children and adolescents. The subgroup analyses showed a hint of greater harm from insulin degludec in comparison with insulin detemir (each in combination with insulin aspart) for girls (see Section I 2.4.4). For boys, there was no statistically significant difference between the treatment groups (see Table 12).

This assessment deviates from that of the company, which, on the basis of the total population, derived no effect and did not consider the proof of an effect modification by the characteristic "sex".

Discontinuation due to adverse events

In the NN1250-3561 study, there was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". Hence there was no hint of greater or lesser harm from insulin degludec in comparison with insulin detemir; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Severe hypoglycaemia

In the NN1250-3561 study, there was no statistically significant difference between the treatment groups for the outcome "severe hypoglycaemia". Hence there was no hint of greater or lesser harm from insulin degludec in comparison with insulin detemir; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Symptomatic hypoglycaemia (plasma glucose ≤ 70 mg/dL and < 56 mg/dL)

For the outcome "symptomatic hypoglycaemia", no statistically significant differences between the treatment groups were shown in the NN1250-3561 study for the plasma glucose threshold of < 56 mg/dL or for the plasma glucose threshold of ≤ 70 mg/dL. However, there was proof of an effect modification by the characteristic "sex" for symptomatic hypoglycaemia < 56 mg/dL. The results of the subgroup analyses on this outcome are presented in the following Section I 2.4.4.

In summary, there was no hint of greater or lesser harm from insulin degludec in comparison with insulin detemir; greater or lesser harm is therefore not proven.

This concurs with the company's assessment, which considered only symptomatic hypoglycaemia with a plasma glucose threshold of < 56 mg/dL in its dossier, however.

Symptomatic hyperglycaemia

There were no evaluable data for the outcome "symptomatic hyperglycaemia". Hence there was no hint of greater or lesser harm from insulin degludec in comparison with insulin detemir; greater or lesser harm is therefore not proven.

The company did not use the outcome in its assessment.

Ketoacidosis

In the NN1250-3561 study, there was no statistically significant difference between the treatment groups for the outcome "ketoacidosis". Hence there was no hint of greater or lesser harm from insulin degludec in comparison with insulin detemir; greater or lesser harm is therefore not proven.

The company did not use the outcome in its assessment.

I 2.4.4 Subgroups and other effect modifiers

Selected subgroups were investigated for the presence of heterogeneous treatment effects in order to identify possible effect modifications. The company presented the corresponding analyses for the outcomes it rated as relevant. Where necessary, these were supplemented by the Institute's calculations. There were no subgroup analyses for the outcomes "symptomatic hypoglycaemia (plasma glucose ≤ 70 mg/dL)" and "ketoacidosis", which were additionally rated as relevant, and they could also not be subsequently calculated from the available documents. Subgroup analyses on symptomatic hypoglycaemia (plasma glucose ≤ 70 mg/dL) would be important to answer the question whether the effect modification is confirmed in symptomatic hypoglycaemia (plasma glucose < 56 mg/dL). The lack of subgroup analyses for the outcome "ketoacidosis" is not important, however, because only 2 events in total occurred.

Subgroup analyses for the following characteristics were considered:

- age (1 to 5 years, 6 to 11 years, 12 to 17 years)
- sex (male versus female)
- region (Europe, Japan, North America, South Africa)
- baseline HbA1c (< 8.0%; ≥ 8.0%)

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

Table 11 shows the results of the subgroup analyses.

Table 11: Subgroups with at least indications of interaction – RCT, direct comparison: insulin degludec + insulin aspart vs. insulin detemir + insulin aspart

Study Outcome Characteristic Time point Subgroup	Insulin degludec + insulin aspart		Insulin detemir + insulin aspart		Insulin degludec + insulin aspart vs. insulin detemir + insulin aspart	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]	p-value
NN1250-3561						
SAEs						
Sex						
26 weeks						
male	96	6 (6.3)	98	10 (10.2)	0.61 [0.23; 1.62]	0.363[a]
female	78	6 (7.7)	77	1 (1.3)	5.92 [0.73; 48.05]	0.058[a]
					Interaction:	0.054[b]
52 weeks						
male	96	6 (6.3)	98	14 (14.3)	0.44 [0.18; 1.09]	0.072[a]
female	78	12 (15.4)	77	2 (2.6)	5.92 [1.37; 25.59]	0.006[a]
					Interaction:	0.003[b]
Hypoglycaemia (symptomatic + < 56 mg/dL)						
Sex						
26 weeks						
male	96	84 (87.5)	98	88 (89.8)	0.97 [0.88; 1.08][c]	0.663[a]
female	78	72 (92.3)	77	64 (83.1)	1.11 [0.99; 1.25][c]	0.084[a]
					Interaction:	0.101[b]
52 weeks						
male	96	88 (91.7)	98	93 (94.9)	0.97 [0.90; 1.04]	0.526[a]
female	78	75 (96.2)	77	67 (87.0)	1.11 [1.00; 1.22]	0.042[a]
					Interaction:	0.032[b]

a: Institute's calculation, unconditional exact test (CSZ method according to [3]).
b: Institute's calculation from meta-analysis (Cochran's Q test).
c: Institute's calculation (asymptotic).
CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; SAE: severe adverse event; vs.: versus

Serious adverse events

For the outcome "SAEs", an indication of effect modification by the characteristic "sex" was shown after 26 weeks, and proof after 52 weeks; hence overall there was proof of an effect modification.

For boys, there was no statistically significant difference between the treatment groups. Hence there was no hint of greater or lesser harm from insulin degludec in comparison with insulin detemir for boys; greater or lesser harm is therefore not proven.

For girls, there was a statistically significant result to the disadvantage of insulin degludec after 52 weeks. After 26 weeks, the effect already pointed in the same direction with an identical effect estimate for relative risk; however the result was less precise and not statistically significant. Overall, the results after 26 weeks and after 52 weeks were consistent so that this would result in an indication of greater harm from insulin degludec in girls.

However, the result of this subgroup analysis was clearly influenced also by the events in the insulin detemir arm of the study (n = 14 SAEs in boys versus n = 2 SAEs in girls). Such a sex-specific effect of insulin detemir is neither supported by the guidelines [4], nor previous IQWiG assessments [5] nor the Summary of Product Characteristics (SPC) [6]. The certainty of results was therefore downgraded from “indication” to “hint”.

But the effect was so pronounced that overall this resulted in a hint of greater harm from insulin degludec in girls.

This assessment deviates from that of the company, which, on the basis of the results of the total population, derived no greater harm of insulin degludec for this outcome and did not consider the proof of effect modification.

Symptomatic hypoglycaemia (plasma glucose < 56 mg/dL)

For the outcome “symptomatic hypoglycaemia (plasma glucose < 56 mg/dL)”, an indication of effect modification by the characteristic “sex” was shown after 26 weeks, and proof after 52 weeks; hence overall there was proof of an effect modification.

For boys, there was no statistically significant difference between the treatment groups. Hence there was no hint of greater or lesser harm from insulin degludec in comparison with insulin detemir for boys; greater or lesser harm is therefore not proven.

In girls, there was a statistically significant result to the disadvantage of insulin degludec, which was of only marginal effect size (the upper confidence interval is above the threshold of 0.9; outcome category “non-severe/non-serious AEs [1]) so that greater/lesser harm from insulin degludec is not proven. Hence the effect modification by the characteristic “sex” is not considered further for this outcome.

I 2.5 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.

I 2.5.1 Assessment of added benefit at outcome level

The data availability presented in Section I 2.4resulted in a hint of greater harm from insulin degludec in comparison with insulin detemir for the outcome “SAEs” (only for girls).

The extent of the respective added benefit at outcome level was estimated from these results (see Table 12).

Table 12: Extent of added benefit at outcome level: Insulin degludec + insulin aspart vs. insulin detemir + insulin aspart

Outcome category **Outcome**	**Insulin degludec + insulin aspart vs. insulin detemir + insulin aspart** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: NC p > 0.999	Added benefit not proven
Morbidity		
Change in HbA1c value[c]	MD: -0.01 [-0.20; 0.19][d] ND	Added benefit not proven
Health-related quality of life	Outcome not recorded	
Adverse events		
SAEs male	6.3% vs. 14.3% RR: 0.44 [0.18; 1.09] p = 0.072[e]	Greater/lesser harm not proven
female	15.4% vs. 2.6% RR: 5.92 [1.37; 25.59] RR: 0.17 [0.04; 0.73][f] p = 0.006[e] probability: “hint”	Outcome category: serious/severe AEs CI_u < 0.75 Greater harm extent: “major”
Discontinuation due to AEs	0% vs. 1.7% RR: 0.14 [0.01; 2.76][g, h] p = 0.087[e]	Greater/lesser harm not proven
Severe hypoglycaemia	17.8% vs. 13.7% RR: 1.22 [0.75; 1.98][i] p = 0.301[e]	Greater/lesser harm not proven
Symptomatic hypoglycaemia		
plasma glucose < 56 mg/dL	93.7% vs. 91.4% RR: 1.02 [0.97; 1.09] p = 0.497[e]	Greater/lesser harm not proven
plasma glucose ≤ 70 mg/dL	95.4% vs. 93.1% RR: 1.02 [0.97; 1.08][g] p = 0.461[e]	Greater/lesser harm not proven
Symptomatic hyperglycaemia	No evaluable data available	

(continued)

Table 12: Extent of added benefit at outcome level: Insulin degludec + insulin aspart vs. insulin detemir + insulin aspart (continued)

Outcome category **Outcome**	**Insulin degludec + insulin aspart vs. insulin detemir + insulin aspart** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Ketoacidosis	1.1% vs. 0% RR: 5.03 [0.24; 103.99][g, h] p = 0.169[e]	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: Sufficiently valid surrogate for microvascular late complications.
d: ANOVA model, adjusted for treatment, sex, region, age group and baseline value; LOCF.
e: Institute‘s calculation, unconditional exact test (CSZ method according to [3]).
f: Institute’s calculation: reversed direction of effect to enable use of limits to derive the added benefit.
g: Institute’s calculation (asymptotic).
h: Correction factor 0.5.
i: Logistic regression model (log-link function), adjusted for treatment, sex, geographical region and age group.
AE: adverse event; ANOVA: analysis of variance; CI: confidence interval; CI_u: upper limit of confidence interval; LOCF: last observation carried forward; MD: mean difference; ND: no data; RR: relative risk; SAE: serious adverse event; vs.: versus

I 2.5.2 Overall conclusion on added benefit

Table 13 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 13: Positive and negative effects from the assessment of insulin degludec + insulin aspart in comparison with insulin detemir + insulin aspart

Positive effects	**Negative effects**
	Sex – female ▪ hint of greater harm – extent “major” (serious/severe adverse events: serious adverse events)

Overall, only one negative effect in the outcome category “serious/severe AEs” remains for the subgroup of girls, with the probability “hint” and the extent “major”. For girls with type 1 diabetes mellitus, this results in a hint of a lesser benefit of insulin degludec in comparison with the ACT.

There are neither positive nor negative effects for boys. Hence the added benefit of insulin degludec versus the ACT for boys with type 1 diabetes mellitus is not proven.

The result of the assessment of the added benefit of insulin degludec in comparison with the ACT is summarized in Table 14.

Table 14: Insulin degludec – extent and probability of added benefit

Therapeutic indication	ACT	Subgroup	Extent and probability of added benefit
Type 1 diabetes mellitus in adolescents and children from the age of one year	Human insulin	Girls	Hint of lesser benefit
		Boys	Added benefit not proven

This result deviates from the company's assessment, which derived an indication of added benefit with the extent "considerable" for adolescents and children from the age of one year with type 1 diabetes mellitus.

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

I 2.6 List of included studies

NN1250-3561

Novo Nordisk. A 26-week, multinational, multi-centre, open-labelled, randomised, parallel, efficacy and safety comparison of insulin degludec and insulin detemir in children and adolescents 1 to less than 18 years with type 1 diabetes mellitus on a basal-bolus regimen with insulin aspart as bolus insulin followed by a 26-week extension investigating long term safety [online]. In: EU Clinical Trials Register. [Accessed: 12 January 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-003148-39/DE.

Novo Nordisk. A 26-week, multinational, multi-centre, open-labelled, randomised, parallel, efficacy and safety comparison of insulin degludec and insulin detemir in children and adolescents 1 to less than 18 years with type 1 diabetes mellitus on a basal-bolus regimen with insulin aspart as bolus insulin, followed by a 26-week extension investigating long term safety: study NN1250-3561; clinical trial report [unpublished]. 2013.

Novo Nordisk. A 26-week, multinational, multi-centre, open-labelled, randomised, parallel, efficacy and safety comparison of insulin degludec and insulin detemir in children and adolescents 1 to less than 18 years with type 1 diabetes mellitus on a basal-bolus regimen with insulin aspart as bolus insulin, followed by a 26-week extension investigating long term safety: study NN1250-3561; clinical trial report [unpublished]. 2014.

Novo Nordisk. A trial investigating the efficacy and safety of insulin degludec in children and adolescents with type 1 diabetes mellitus (BEGINT): full text view [online]. In: ClinicalTrials.gov. 20 August 2014 [accessed: 12 January 2015]. URL: https://clinicaltrials.gov/ct2/show/NCT01513473.

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Insulin degludec

Assessment module II

type 2 diabetes mellitus (children and adolescents)

Medical and scientific advice:

- Matthias Breidert, Hospitals in the Altmühltal Nature Park, Kösching, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the benefit assessment. However, the advisor was not involved in the actual preparation of the benefit assessment. The responsibility for the contents of the benefit assessment lies solely with IQWiG.

IQWiG employees involved in the benefit assessment[1]:

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- Marco Knelangen
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- Ulrike Seay

Keywords: insulin degludec, diabetes mellitus – type 2, child, adolescent, benefit assessment

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

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List of tables

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Table 1: Insulin degludec – extent and probability of added benefit II.2

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)

II 2 Benefit assessment

II 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 insulin degludec. 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 March 2015.

Research question

The drug insulin degludec is approved for different therapeutic indications. The aim of the present Assessment module II was to assess the added benefit of insulin degludec in comparison with the appropriate comparator therapy (ACT) in adolescents and children from the age of one year with type 2 diabetes mellitus.

Two subindications resulted from this, for which the G-BA specified the following ACTs:

- in monotherapy: human insulin
- in combination with other antidiabetics: human insulin plus metformin

The G-BA further specified the ACT in so far as the benefit assessment also includes evidence from studies in which insulin analogues were used under consideration of the approval if the results from studies with insulin analogues are transferable to human insulin.

The benefit assessment of insulin degludec in adolescents and children from the age of one year with type 2 diabetes mellitus was conducted for both subindications in comparison with the ACT specified by the G-BA.

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

Results

The company presented no data for adolescents and children from the age of one year with type 2 diabetes mellitus. There was no hint of an added benefit of insulin degludec in comparison with the ACT; an added benefit is therefore not proven.

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

On the basis of the results presented, the extent and probability of the added benefit of the drug insulin degludec compared with the ACT for the therapeutic indication type 2 diabetes mellitus (children and adolescents) is assessed as follows:

Table 1: Insulin degludec – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy**	**Extent and probability of added benefit**
Type 2 diabetes mellitus in adolescents and children from the age of one year	▪ in monotherapy: human insulin ▪ in combination with other antidiabetics: human insulin plus metformin	Added benefit not proven

The G-BA decides on the added benefit.

II 2.2 Research question

The aim of the present Assessment module II was to assess the added benefit of insulin degludec in comparison with the ACT in adolescents and children from the age of one year with type 2 diabetes mellitus.

Two subindications resulted from this, for which the G-BA specified the following ACTs:

- in monotherapy: human insulin
- in combination with other antidiabetics: human insulin plus metformin

The G-BA further specified the ACT in so far as the benefit assessment also includes evidence from studies in which insulin analogues were used under consideration of the approval if the results from studies with insulin analogues are transferable to human insulin.

The benefit assessment of insulin degludec in adolescents and children from the age of one year with type 2 diabetes mellitus was conducted for both subindications in comparison with the ACT specified by the G-BA.

In its research question, the company did not differentiate monotherapy and combination with other antidiabetics. It deviated from the ACT specified by the G-BA and cited insulin analogues (long-acting insulin + bolus insulin) as general comparator therapy for both subindications. However, the company also searched for studies with human insulin. Hence this deviation had no consequences for the benefit assessment (see Section II 2.7.1 of the full dossier assessment).

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

II 2.3 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 (studies completed up to 12 January 2015)
- bibliographical literature search on insulin degludec (last search on 12 January 2015)
- search in trial registries for studies on insulin degludec (last search on 12 January 2015)

To check the completeness of the study pool:

- search in trial registries for studies on insulin degludec (last search on 20 March 2015)

The company did not identify any relevant studies. No relevant study was identified from the check either.

II 2.4 Results on added benefit

The company presented no data for adolescents and children from the age of one year with type 2 diabetes mellitus. There was no hint of an added benefit of insulin degludec in comparison with the ACT; an added benefit is therefore not proven.

II 2.5 Extent and probability of added benefit

Since the company presented no data for adolescents and children from the age of one year with type 2 diabetes mellitus, an added benefit is not proven.

The G-BA decides on the added benefit.

II 2.6 List of included studies

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

References for English extract

Please see full assessment for full reference list.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a15-10-insulin-degludec-neues-anwendungsgebiet-nutzenbewertung-gemass-35a-sgb-v-dossierbewertung.6641.html.