IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Insulin degludec (type 2 diabetes mellitus) –

Benefit assessment according to §35a Social Code Book V[1] (new scientific findings)

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Insulin degludec (Diabetes mellitus Typ 2) – Nutzenbewertung gemäß § 35a SGB V (neue wissenschaftliche Erkenntnisse)* (Version 1.0; Status: 27 February 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CI	confidence interval
DPP-4	dipeptidyl peptidase-4
FPG	fasting plasma glucose
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycosylated haemoglobin A1c
ICT	intensified insulin therapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MACE	major adverse cardiovascular events
MCS	Mental Component Summary
OAD	oral antidiabetic
PCS	Physical Component Summary
PG	plasma glucose
PT	Preferred Term
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SGLT	sodium-glucose cotransporter
SOC	System Organ Class
SPC	Summary of Product Characteristics
TRIM-D	Treatment-Related Impact Measure for Diabetes

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 insulin degludec. The pharmaceutical company (hereinafter referred to as "the company") submitted a first dossier on the drug to be evaluated on 1 May 2014 for the early benefit assessment. Due to new scientific findings, the G-BA now initiated a new benefit assessment for a subindication – treatment of type 2 diabetes mellitus in adults – under inclusion of the DEVOTE study. 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 November 2018.

Research question

The aim of the present report was the assessment of the added benefit of insulin degludec in monotherapy or combination therapy for the treatment of type 2 diabetes mellitus in adults.

Insulin degludec is also approved for the treatment of type 1 diabetes mellitus and for the treatment of type 2 diabetes mellitus in adolescents and children from the age of 1 year. These subindications are not subject of the present assessment.

The G-BA distinguished between different patient groups in its specification of the ACT. This resulted in 2 research questions for the assessment. These are shown in Table 2.

Table 2: Research questions of the benefit assessment of insulin degludec in type 2 diabetes mellitus in adults

Research question[a]	**Subindication**	**ACT**[b]
A	Patients inadequately controlled by treatment with at least 2 blood-glucose lowering drugs (except insulin)[c]	Human insulin + metformin or human insulin + empagliflozin[d] or human insulin + liraglutide[d] or human insulin[e]
B	Patients inadequately controlled by treatment with insulin with or without another blood-glucose lowering drug[f]	Optimization of the human insulin regimen (possibly + metformin or empagliflozin[d] or liraglutide[d])

a: Insulin degludec is approved for type 2 diabetes mellitus irrespective of pretreatment; hence, the research questions do not cover the complete approved therapeutic indication. According to the G-BA, therapeutic situations in which oral antidiabetic therapy would be the only option for the ACT are not considered as insulin is generally not indicated in these therapeutic situations.
b: Presentation of the respective ACT specified by the G-BA.
c: In the assessment referred to as "patients pretreated with at least 2 antidiabetics except insulin".
d: Empagliflozin or liraglutide, each in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for the operationalization, see study protocols of the respective outcome studies [1,2]).
e: If, according to the SPC, metformin and empagliflozin[d] and liraglutide[d] are not tolerated or contraindicated or are not sufficiently effective due to advanced type 2 diabetes mellitus.
f: In the assessment referred to as "patients pretreated with insulin".
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

For easier presentation and better readability, the report uses the following terms for the 2 research questions:

- patients pretreated with at least 2 antidiabetics except insulin (research question A)
- patients pretreated with insulin (research question B)

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results for research question A (patients pretreated with at least 2 antidiabetics except insulin)

Study pool and study characteristics

The study pool for the benefit assessment of insulin degludec in comparison with the ACT consisted of the randomized controlled trials (RCTs) NN1250-3579 (with the extension study 3579Ext), NN1250-3587 and NN1250-3672.

The studies were 2-arm, open-label phase 3 studies with treatment durations of 52 (NN1250-3579) or 26 weeks (NN1250-3587 and NN1250-3672). Patients in the NN1250-3579 study could additionally participate in a 52-week extension study (3579Ext) after the follow-up phase.

All studies included insulin-naive adults with type 2 diabetes mellitus in whom pretreatment with metformin alone or in combination with further antidiabetics of at least 3 months at unchanged dosages did not provide adequate glycaemic control. All studies investigated the comparison of insulin degludec versus insulin glargine.

The subpopulations of the studies relevant for the assessment comprised patients pretreated with at least 2 blood-glucose lowering drugs and whose study medication consisted of the respective insulin component and metformin based on their pretreatment. These subpopulations comprised 60 to 67% of the respective total population, depending on the study.

Insulin degludec and insulin glargine were used in compliance with their Summaries of Product Characteristics (SPCs) in all studies. The basal insulin was injected at different time points, however: Insulin degludec was to be administered once daily with the evening meal, whereas insulin glargine was to be administered once daily at the same time of day. In addition, all studies had a treat-to-target design, in which fasting plasma glucose (FPG) was titrated to a specified goal. It was unclear whether the patients included in the studies NN1250-3579, NN1250-3587 and NN1250-3672 were candidates for near-normal blood-glucose levels. Hence, based on the results of these studies, conclusions can only be drawn for patients with the treatment goal of near-normal blood-glucose levels in whom this aim is initially to be achieved with basal supported oral therapy if oral therapy is inadequate.

Primary outcome of all 3 studies was the change in glycosylated haemoglobin A1c (HbA1c) from baseline to week 52 (NN1250-3579) or 26 (NN1250-3587 and NN1250-3672). Patient-relevant secondary outcomes were all-cause mortality as well as outcomes on morbidity, health-related quality of life and adverse events (AEs) including hypoglycaemia.

Risk of bias and overall assessment of the certainty of conclusions

The risk of bias at study level was rated as low for the studies NN1250-3579, NN1250-3587 and NN1250-3672. For the studies NN1250-3579, NN1250-3587 and NN1250-3672, the risk of bias was rated as low for the results on the outcomes “all-cause mortality”, “cardiovascular events (major adverse cardiovascular events [MACE])” including the components “cardiovascular death”, “nonfatal stroke” and “acute coronary syndrome”, as well as on the side effect outcomes “serious adverse events (SAEs)”, “severe hypoglycaemia” and “renal function disorder”. The risk of bias was rated as high for the results on all other outcomes (health status measured with the instrument Treatment-Related Impact Measure for Diabetes [TRIM-D], health-related quality of life measured with the instrument Short Form (36) Health Survey [SF-36], discontinuation due to AEs, non-severe symptomatic hypoglycaemic episodes in total [plasma glucose (PG) < 56 mg/dL] and further specific AEs). For the 3579Ext extension study, the risk of bias was rated as high for the results on all outcomes.

The results from the meta-analysis of the studies NN1250-3587, NN1250-3672 and NN1250-3579 at week 26 or week 52 respectively, as well as the results from the 3579Ext extension study at week 104 were used for the benefit assessment and considered jointly in qualitative

terms. Proof can be derived from the meta-analysis and at most hints from the extension study due to the high risk of bias of all outcomes. In addition, an outcome-specific joint qualitative consideration of the results of the meta-analysis and of the extension study was conducted, which was included in the balancing of the certainty of conclusions. The time course was also taken into account. In case of differing results from the meta-analysis and the extension, this can lead to a limitation of the certainty of conclusions.

Results

Mortality

- All-cause mortality

Only few deaths occurred in both treatment arms of all studies. Neither the meta-analysis nor the extension study showed a statistically significant difference between insulin degludec + metformin and insulin glargine + metformin for the outcome "all-cause mortality". This resulted in no hint of an added benefit of insulin degludec + metformin in comparison with insulin glargine + metformin; an added benefit is therefore not proven.

Morbidity

- Cardiovascular events (MACE, including the components "cardiovascular death", "nonfatal stroke" and "acute coronary syndrome")

Neither the meta-analysis nor the extension study showed a statistically significant difference between the treatment arms for the composite outcome "cardiovascular events (MACE)" or the 2 components "cardiovascular death" and "nonfatal stroke". This resulted in no hint of an added benefit of insulin degludec + metformin in comparison with insulin glargine + metformin; an added benefit is therefore not proven.

The extension study showed a statistically significant effect to the disadvantage of insulin degludec + metformin for the outcome "acute coronary syndrome". In the meta-analysis, the effect was not statistically significant, but the direction of the effect was consistent. The joint consideration of the results showed that the events occurred mostly in the study with longer study duration (NN1250-3579 and its extension study). This resulted in a hint of lesser benefit of insulin degludec + metformin versus insulin glargine + metformin for this outcome.

- Health status (TRIM-D domains of daily life and psychological health)

The meta-analysis showed no statistically significant difference between the treatment arms for the outcome "health status", measured with the domains of daily life and psychological health of the TRIM-D questionnaire. The outcome was not recorded in the extension study. This resulted in no hint of an added benefit of insulin degludec + metformin in comparison with insulin glargine + metformin; an added benefit is therefore not proven.

Health-related quality of life

- SF-36 − Physical Component Summary (PCS) and Mental Component Summary (MCS)

The mean changes at the end of study versus baseline were considered for the SF-36 MCS and PCS.

The meta-analysis and the extension study showed no statistically significant differences between the treatment arms for the MCS.

For the PCS, there was a statistically significant result for the change from baseline in the meta-analysis, with homogeneous data situation. No relevant effect could be derived from the standardized mean difference estimated with the Hedges' g effect measure. For the Hedges' g effect measure, there was heterogeneity between the studies of the meta-analysis ($p < 0.05$). The consideration of the results of the individual studies produced no effect in the same direction. A statistically significant effect in favour of insulin degludec + metformin was only present in the NN1250-3579 study. This observed effect, assessed with Hedges' g, was not relevant, however. There was no statistically significant difference between the treatment groups in either of the studies NN1250-3587 and NN1250-3672. Hence, the effects were not in the same direction. The 3579Ext extension study showed a statistically significant difference in favour of insulin degludec + metformin for the PCS. The confidence interval (CI) for Hedges' g was not fully outside the irrelevance range [−0.2; 0.2] also for the 3579Ext extension study. It can therefore not be inferred that the effect is relevant.

This resulted in no hint of an added benefit of insulin degludec + metformin in comparison with insulin glargine + metformin for the MCS or for the PCS; an added benefit is therefore not proven.

Side effects

- Serious adverse events

Neither the meta-analysis nor the extension study showed a statistically significant difference between the treatment arms for the outcome "SAEs".

This resulted in no hint of an added benefit of insulin degludec + metformin in comparison with insulin glargine + metformin for this outcome; an added benefit is therefore not proven.

- Discontinuation due to adverse events and renal function disorder (SAE, System Organ Class [SOC])

Neither the meta-analysis nor the extension study showed statistically significant differences between the treatment groups for the outcomes "discontinuation due to AEs" and "renal function disorder". Hence, for these outcomes, there was no hint of greater or lesser harm from insulin degludec + metformin in comparison with insulin glargine + metformin; greater or lesser harm is therefore not proven.

- Non-severe hypoglycaemia

Neither the meta-analysis nor the extension study showed a statistically significant difference between the treatment arms for the outcome "non-severe confirmed symptomatic hypoglycaemic episodes in total (PG < 56 mg/dL)". Overall, there was no hint of greater or lesser harm from insulin degludec + metformin in comparison with insulin glargine + metformin for non-severe confirmed symptomatic hypoglycaemic episodes; greater or lesser harm is therefore not proven.

- Severe hypoglycaemia

As an auxiliary measure, the company operationalized severe hypoglycaemic episodes as hypoglycaemic episodes documented as SAEs. Neither the meta-analysis nor the extension study showed statistically significant differences between the treatment groups for the outcome "severe hypoglycaemic episodes (SAEs)". Hence, for this outcome, there was no hint of greater or lesser harm from insulin degludec + metformin in comparison with insulin glargine + metformin; greater or lesser harm is therefore not proven.

- Vomiting (Preferred Term [PT])

In the meta-analysis, there was no statistically significant effect between the treatment arms for the outcome "vomiting". In the extension study, however, there was a statistically significant difference in favour of insulin degludec + metformin for this outcome. The joint consideration of the results showed that the events occurred mostly in the study with longer study duration (NN1250-3579) and continued to increase in the second year of the study (extension study) with the same direction of effect.

Due to the high risk of bias for the results on this outcome in the extension study, there was overall a hint of lesser harm from insulin degludec + metformin versus insulin glargine + metformin.

- Depression (PT)

In the meta-analysis, there was no statistically significant effect between the treatment arms for the outcome "depression (PT)". In the extension study, however, there was a statistically significant difference to the disadvantage of insulin degludec + metformin for this outcome.

The joint consideration of the results showed that the events occurred mostly in the study with longer study duration (NN1250-3579) and also in the second year of the study (extension study).

Due to the high risk of bias for the results on this outcome in the extension study, there was overall a hint of greater harm from insulin degludec + metformin versus insulin glargine + metformin.

Results for research question B (patients pretreated with insulin)

Study pool of the company

The company identified the RCTs NN1250-3582 (including its extension study NN1250-3667), NN1250-3668 and NN1250-3998. For the present research question, only study NN1250-3582 and its extension study NN1250-3667 were relevant for the benefit assessment of insulin degludec in comparison with the ACT (see below). The studies NN1250-3668 and NN1250-3998 also used by the company were unsuitable for the present benefit assessment, however. The G-BA defined optimization of the human insulin regimen as ACT for research question B. It further specified that continuation of an inadequate treatment regimen for type 2 diabetes mellitus did not concur with the ACT. The patients in both studies did not receive meaningful escalation of their ongoing insulin therapy, which was demonstrably inadequate.

Study NN1250-3668

The NN1250-3668 study was an open-label, multicentre 3-arm RCT on the comparison of 2 different dosing regimens of insulin degludec (± oral antidiabetics [OADs]) and insulin glargine (± OADs). The study included adult patients with type 2 diabetes mellitus and inadequate glycaemic control (pretreatment with OADs [insulin-naive patients] or with basal insulin ± OADs). The patients in the study were randomly allocated to basal insulin treatment with insulin degludec or insulin glargine. Hence, the therapeutic strategy was unchanged in both treatment arms; only the dose of the basal insulin (insulin degludec or insulin glargine) was uniformly titrated on the basis of FPG levels to reach near-normal blood-glucose levels. The uniform continuation of the therapeutic strategy targeted at near-normal blood glucose levels, which was already in place before study inclusion, was inadequate in the present situation, however.

Study NN1250-3998

The NN1250-3998 study was an open-label, multicentre 2-arm RCT on the comparison of insulin degludec (± OADs) and insulin glargine (± OADs). The study included adult patients with type 2 diabetes mellitus and inadequate glycaemic control (HbA1c ≤ 9.5%) despite treatment with basal insulin ± OADs (metformin ± thiazolidinediones ± sulfonylureas ± glinides ± sodium-glucose cotransporter 2 [SGLT 2] inhibitors). In addition, patients had to have an increased risk of hypoglycaemia. This was operationalized as at least one severe hypoglycaemic episode within the previous year.

The patients received either insulin degludec or insulin glargine once daily subcutaneously as study medication. Hence, also in the NN1250-3998 study, the therapeutic strategy – continuation of basal insulin therapy – was unchanged in both treatment arms. Furthermore, it was notable in this study that the treatment goal in patients with increased risk of hypoglycaemia was a very low blood glucose level, using a therapeutic strategy that was demonstrably unsuitable for these patients.

Study pool and study characteristics

The study pool for the benefit assessment of insulin degludec in comparison with the ACT consisted of the RCT NN1250-3582 with its extension study NN1250-3667.

The NN1250-3582 study was a 2-arm, open-label phase 3 study with a treatment duration of 52 weeks. After a 1-week follow-up phase, the patients could participate in an extension study (NN1250-3667) for another 26 weeks.

Adults with type 2 diabetes mellitus who had received insulin treatment with or without OADs for at least 3 months were included in the NN1250-3582 study.

The NN1250-3582 study investigated the comparison of a combination therapy of insulin degludec and insulin aspart with or without OADs versus a combination therapy of insulin glargine and insulin aspart with or without OADs. A total of 1006 patients were randomly allocated in a 3:1 ratio to the study arms of insulin degludec + insulin aspart (N = 755) and insulin glargine + insulin aspart (N = 251), each in combination with metformin and/or pioglitazone. Of these patients, 75.0% (N = 566) of the patients from the intervention arm and 76.1% (N = 191) of the patients from the control arm continued in the NN1250-3667 extension study without new randomization.

From the study, only a subpopulation of the patients was relevant. Patients receiving metformin only corresponded to the research question if they receive an approval-compliant dosage (1000 to 3000 mg/day). Patients receiving pioglitazone were not relevant for the present research question. The dossier contained no analyses for the relevant subpopulation, however. Since more than 80% of the patients included were relevant for the present research question, however, the data of the total population were used as an auxiliary measure.

Primary outcome was the change in HbA1c from baseline to week 52. Patient-relevant secondary outcomes were all-cause mortality as well as outcomes on morbidity, health-related quality of life and AEs.

Risk of bias and overall assessment of the certainty of conclusions

The risk of bias across outcomes was rated as low both for the main study NN1250-3582 and for its extension study NN1250-3667. For the NN1250-3582 study, the risk of bias was rated as low for the results on the outcomes “all-cause mortality”, “cardiovascular events (MACE)” including the individual components “cardiovascular death”, “nonfatal stroke” and “acute coronary syndrome”, as well as on the side effect outcomes “SAEs”, “severe hypoglycaemia” and “renal function disorder”. The risk of bias was rated as high for the results on all other outcomes (health status measured with the instrument TRIM-D, health-related quality of life measured with the instrument SF-36, discontinuation due to AEs, non-severe symptomatic hypoglycaemic episodes in total [PG < 56 mg/dL]). For the NN1250-3667 extension study, the risk of bias was rated as high for the results on all outcomes.

The data from the NN1250-3667 extension study (78 weeks) – if recorded – were primarily used in the benefit assessment. Since these data had a high risk of bias, at most hints could initially be derived. The corresponding results at the time point 52 weeks from the NN1250-3582 study were additionally considered. If these were consistent with the 78-week data and if the respective outcome had a low risk of bias at the time point 52 weeks, the certainty of results of the 78-week data was upgraded from "hint" to "indication".

Results

Mortality

- All-cause mortality

Only few deaths occurred in both treatment arms. After 78 weeks, the NN1250-3667 extension study showed no statistically significant difference between insulin degludec + insulin aspart ± metformin versus insulin glargine + insulin aspart ± metformin for the outcome "all-cause mortality". This resulted in no hint of an added benefit of insulin degludec + insulin aspart ± metformin in comparison with insulin glargine + insulin aspart ± metformin; an added benefit is therefore not proven.

Morbidity

- Cardiovascular events (MACE, including the components "cardiovascular death", "nonfatal stroke" and "acute coronary syndrome")

The NN1250-3667 extension study showed no statistically significant difference between the treatment arms for the outcome "cardiovascular events (MACE)" and its individual components "cardiovascular death", "nonfatal stroke" and "acute coronary syndrome". This resulted in no hint of an added benefit of insulin degludec + insulin aspart ± metformin in comparison with insulin glargine + insulin aspart ± metformin for these outcomes; an added benefit is therefore not proven.

- Health status (TRIM-D domains of daily life and psychological health)

The NN1250-3582 main study showed no statistically significant difference between the treatment arms for the outcome "health status", measured with the domains of daily life and psychological health of the TRIM-D questionnaire. This resulted in no hint of an added benefit of insulin degludec + insulin aspart ± metformin in comparison with insulin glargine + insulin aspart ± metformin; an added benefit is therefore not proven. The outcome was not recorded in the NN1250-3667 extension study.

Health-related quality of life

- SF-36 − Physical Component Summary (PCS) and Mental Component Summary (MCS)

The mean changes at the end of study versus baseline were considered for the SF-36 MCS and PCS

There were no statistically significant differences between the treatment arms in the NN1250-3582 main study for the MCS or for the PCS. This resulted in no hint of an added benefit of insulin degludec + insulin aspart ± metformin in comparison with insulin glargine + insulin aspart ± metformin; an added benefit is therefore not proven. The outcome was not recorded in the NN1250-3667 extension study.

Side effects

- Serious adverse events

Neither the NN1250-3582 main study nor the NN1250-3667 extension study showed a statistically significant difference between the treatment arms for the outcome "SAEs". This resulted in no hint of greater or lesser harm from insulin degludec + insulin aspart ± metformin versus insulin glargine + insulin aspart ± metformin. Greater or lesser harm is therefore not proven.

- Discontinuation due to adverse events and renal function disorder (SAE, SOC)

The NN1250-3667 extension study showed no statistically significant difference between the treatment groups for the outcomes "discontinuation due to AEs", "severe hypoglycaemic episodes (SAEs)" and "renal function disorder". Hence, for these outcomes, there was no hint of greater or lesser harm from insulin degludec + insulin aspart ± metformin in comparison with insulin glargine + insulin aspart ± metformin; greater or lesser harm is therefore not proven.

- Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 56 mg/dL)

The NN1250-3667 extension study showed no statistically significant difference between the treatment arms for the outcome "non-severe confirmed symptomatic hypoglycaemic episodes in total (PG < 56 mg/dL)". Overall, there was no hint of greater or lesser harm from insulin degludec + insulin aspart ± metformin in comparison with insulin glargine + insulin aspart ± metformin for non-severe confirmed symptomatic hypoglycaemic episodes; greater or lesser harm is therefore not proven.

- Severe hypoglycaemia

The extension study showed no statistically significant difference between the treatment groups for the outcome "severe hypoglycaemic episodes (SAEs)". Hence, for this outcome, there was no hint of greater or lesser harm from insulin degludec + insulin aspart ± metformin in comparison with insulin glargine + insulin aspart ± metformin; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug insulin degludec in comparison with the ACT are assessed as follows:

Research question A (patients pretreated with at least 2 antidiabetics except insulin)

The overall consideration of the data showed both positive and negative effects of insulin degludec + metformin versus insulin glargine + metformin. In summary, the negative effects, particularly the hint of greater harm regarding acute coronary syndrome (outcome category "serious/severe symptoms/late complications") outweighed the positive effects, however. This resulted in a hint of lesser benefit of insulin degludec + metformin versus insulin glargine + metformin.

Due to the therapy targeted at a uniform FPG level between 90 and 125 mg/dL, the conclusions on added benefit or lesser benefit are limited to patients with the treatment goal of near-normal blood glucose levels with basal supported oral therapy. An added benefit or lesser benefit is not proven for patients without this treatment goal.

Research question B (patients pretreated with insulin)

Based on the available and usable results, there are neither positive nor negative effects.

In summary, there is no hint of an added benefit of insulin degludec + insulin aspart ± metformin versus the ACT specified by the G-BA for adult patients with type 2 diabetes mellitus inadequately controlled by treatment with insulin with or without another blood-glucose lowering drug; an added benefit is therefore not proven.

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

[3] 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, added benefit not proven, or less benefit). For further details see [3,4].

Table 3: Insulin degludec – probability and extent of the added benefit in type 2 diabetes mellitus in adults

Research question[a]	**Subindication**	**ACT**[b]	**Probability and extent of added benefit**
A	Patients inadequately controlled by treatment with at least 2 blood-glucose lowering drugs (except insulin)[c]	Human insulin + metformin or human insulin + empagliflozin[d] or human insulin + liraglutide[d] or human insulin[e]	*Treatment goal near normal blood glucose levels:* hint of lesser benefit
			Other treatment goal: added benefit not proven
B	Patients inadequately controlled by treatment with insulin with or without another blood-glucose lowering drug[g]	Optimization of the human insulin regimen (possibly + metformin or empagliflozin[d] or liraglutide[d])	added benefit not proven

a: Insulin degludec is approved for type 2 diabetes mellitus irrespective of pretreatment; hence, the research questions do not cover the complete approved therapeutic indication. According to the G-BA, therapeutic situations in which oral antidiabetic therapy would be the only option for the ACT are not considered as insulin is generally not indicated in these therapeutic situations.
b: Presentation of the respective ACT specified by the G-BA.
c: In the assessment referred to as "patients pretreated with at least 2 antidiabetics except insulin".
d: Empagliflozin or liraglutide, each in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for the operationalization, see study protocols of the respective outcome studies [1,2]).
e: If, according to the SPC, metformin and empagliflozin[d] and liraglutide[d] are not tolerated or contraindicated or are not sufficiently effective due to advanced type 2 diabetes mellitus.
f: At baseline.
g: In the assessment referred to as "patients pretreated with insulin".
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

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

Research question additionally investigated by the company

The company investigated an additional research question in its dossier: determination of the extent of the added benefit of insulin degludec in monotherapy or combination therapy in adult patients with type 2 diabetes mellitus at high risk of cardiovascular events. The company presented the DEVOTE study for this research question.

Adult patients with type 2 diabetes mellitus and a high risk of cardiovascular events are comprised as a subgroup in both research questions mentioned above. Correspondingly, the G-BA specified further options as ACT within the respective research question (combination with empagliflozin or liraglutide). The company did not present such analyses, however.

Due to the design of the DEVOTE study, no subpopulation can be formed for research question A.

For research question B, it would be possible to form a subpopulation from the DEVOTE study because the necessary treatment escalation was performed in the comparator arm. However, treatment in the comparator arm was conducted with an insulin analogue (insulin glargine), and not with human insulin.

Irrespective of this, due to the size and the outcomes investigated (particularly cardiovascular events), the DEVOTE study is described in Appendix A of the full dossier assessment.

2.2 Research question

The aim of the present report was the assessment of the added benefit of insulin degludec in monotherapy or combination therapy for the treatment of type 2 diabetes mellitus in adults.

Insulin degludec is also approved for the treatment of type 1 diabetes mellitus and for the treatment of type 2 diabetes mellitus in adolescents and children from the age of 1 year. These subindications are not subject of the present assessment.

The G-BA distinguished between different patient groups in its specification of the ACT. 2 research questions resulted from this for the assessment; these are presented in Table 4.

Table 4: Research questions of the benefit assessment of insulin degludec in type 2 diabetes mellitus in adults

Research question[a]	**Subindication**	**ACT**[b]
A	Patients inadequately controlled by treatment with at least 2 blood-glucose lowering drugs (except insulin)[c]	Human insulin + metformin or human insulin + empagliflozin[d] or human insulin + liraglutide[d] or human insulin[e]
B	Patients inadequately controlled by treatment with insulin with or without another blood-glucose lowering drug[f]	Optimization of the human insulin regimen (possibly + metformin or empagliflozin[d] or liraglutide[d])

a: Insulin degludec is approved for type 2 diabetes mellitus irrespective of pretreatment; hence, the research questions do not cover the complete approved therapeutic indication. According to the G-BA, therapeutic situations in which oral antidiabetic therapy would be the only option for the ACT are not considered as insulin is generally not indicated in these therapeutic situations.
b: Presentation of the respective ACT specified by the G-BA.
c: In the assessment referred to as "patients pretreated with at least 2 antidiabetics except insulin".
d: Empagliflozin or liraglutide, each in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for the operationalization, see study protocols of the respective outcome studies [1,2]).
e: If, according to the SPC, metformin and empagliflozin[d] and liraglutide[d] are not tolerated or contraindicated or are not sufficiently effective due to advanced type 2 diabetes mellitus.
f: In the assessment referred to as "patients pretreated with insulin".
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

Both research questions presented do not cover the complete approved therapeutic indication of insulin degludec in adults with type 2 diabetes mellitus as insulin is approved irrespective of pretreatment, i.e. also for treatment-naive patients, for example. According to the G-BA, under consideration of the properties of insulin degludec, only patient groups for whom insulin therapy is an option were included in the determination of the ACT. According to the G-BA, therapeutic situations in which oral antidiabetic therapy would be the only option for the ACT were not considered as insulin is generally not indicated in these situations. The company also did not consider this part of the approved therapeutic indication.

For easier presentation and better readability, the report uses the following terms for the 2 research questions:

- patients pretreated with at least 2 antidiabetics except insulin (research question A)
- patients pretreated with insulin (research question B)

The company only partly followed the G-BA's specification of the ACT. According to the company, it additionally used insulin analogues as components of the comparator therapy to prove the added benefit of insulin degludec. From the company's point of view, these should be recognized both for short-term and for long-term outcomes. Deviating from the company's assessment, only human insulin was considered as component of the ACT for the present assessment. Transferability of the results can be assumed for studies with long-acting insulin analogues not targeted at diabetic late complications, however (see Section 2.6.2.1 of the full dossier assessment).

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

Research question additionally investigated by the company

The company investigated an additional research question in its dossier: determination of the extent of the added benefit of insulin degludec in monotherapy or combination therapy in adult patients with type 2 diabetes mellitus at high risk of cardiovascular events. The company presented the DEVOTE study for this research question.

Adult patients with type 2 diabetes mellitus and a high risk of cardiovascular events are comprised as a subgroup in both research questions mentioned above. Correspondingly, the G-BA specified further options as ACT within the respective research question (combination with empagliflozin or liraglutide). The company did not present such analyses, however.

Due to the design of the DEVOTE study, no subpopulation can be formed for research question A.

For research question B, it would be possible to form a subpopulation from the DEVOTE study because the necessary treatment escalation was performed in the comparator arm. However, an insulin analogue (insulin glargine) was used for this instead of human insulin. Information on a possible operationalization of a subpopulation for research question B can be found in Appendix A of the full dossier assessment.

Irrespective of this, due to the size and the outcomes investigated (particularly cardiovascular events), the DEVOTE study is described in Appendix A of the full dossier assessment and the results of the total population are presented.

2.3 Research question A (patients pretreated with at least 2 antidiabetics except insulin)

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 (status: 5 September 2018)
- bibliographical literature search on insulin degludec (last search on 4 September 2018)
- search in trial registries for studies on insulin degludec (last search on 5 September 2018)

To check the completeness of the study pool:

- search in trial registries for studies on insulin degludec (last search on 17 December 2018)

The check identified no additional relevant study.

2.3.1.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, insulin degludec + metformin vs. insulin glargine + metformin (research question A)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
NN1250-3579 (with the NN1250-3643 extension study [3579Ext][b])	Yes	Yes	No
NN1250-3587	Yes	Yes	No
NN1250-3672	Yes	Yes	No

a: Study sponsored by the company.
b: Hereinafter, the study is referred to with this abbreviated form.
RCT: randomized controlled trial; vs.: versus

Section 2.3.4 contains a reference list for the studies included.

2.3.1.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
NN1250-3579 (with the 3579Ext extension study)	RCT, open-label, parallel, treat-to-target	Adults with type 2 diabetes mellitus for ≥ 6 months, insulin-naive and pretreated[b]; without prior cardiovascular disease[c]; HbA1c: 7.0–10.0%	IDeg + metformin ± DPP-4 inhibitors (N = 773) IGlar + metformin ± DPP-4 inhibitors (N = 257) Relevant subpopulation thereof[d]: IDeg + metformin (n = 519) IGlar + metformin (n = 151)	Screening: 1 week Treatment: 52 weeks Follow-up: 1 week[e] 3579Ext extension study: Treatment: 52 weeks Follow-up: 1 week	166 centres in Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Norway, Serbia, Spain, and United States 9/2009–1/2011 Extension: 142 centres in Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Norway, Serbia, Spain, and United States 9/2010–12/2011	Primary outcome: change in HbA1c after 52 weeks Secondary outcomes: all-cause mortality, morbidity, health-related quality of life, hypoglycaemia, AEs
NN1250-3587	RCT, open-label, parallel, treat-to-target	Adults with type 2 diabetes mellitus for ≥ 6 months, insulin-naive and pretreated[b], without prior cardiovascular disease[c]; HbA1c: 7.0–10.0%	IDeg + metformin (N = 555) IGlar + metformin (N = 278) Relevant subpopulation thereof[d]: IDeg + metformin (n = 366) IGlar + metformin (n = 191)	Screening: 1 week Treatment: 26 weeks Follow-up: 1 week[e]	68 centres in Brazil, Canada, China, South Africa, Ukraine, United States 6/2013–5/2014	Primary outcome: change in HbA1c after 26 weeks Secondary outcomes: all-cause mortality, morbidity, health-related quality of life, hypoglycaemia, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A) (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
NN1250-3672	RCT, open-label, parallel, treat-to-target	Adults with type 2 diabetes mellitus for ≥ 6 months, insulin-naive and pretreated[b], without prior cardiovascular disease[c]; HbA1c: 7.0–10.0%	IDeg + metformin ± DPP-4 inhibitors (N = 230) IGlar + metformin ± DPP-4 inhibitors (N = 230) Relevant subpopulation thereof[d]: IDeg + metformin (n = 139) IGlar + metformin (n = 139)	Screening: 1 week Treatment: 26 weeks Follow-up: 1 week[e]	106 centres in Canada, France, Ireland, Russia, South Africa, Ukraine, United Kingdom and United States 3/2010–11/2010	Primary outcome: change in HbA1c after 26 weeks Secondary outcomes: all-cause mortality, morbidity, health-related quality of life, hypoglycaemia, AEs

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
b: At least 3 months before screening pretreatment with metformin in monotherapy or in combination therapy with SUs, glinides, DPP-4 inhibitors, alpha glucosidase inhibitors at unchanged dosages.
c: Within the last 6 months prior to the first study visit; defined as stroke, cardiac failure of NYHA class III or IV, myocardial infarction, unstable angina pectoris, coronary artery bypass or angioplasty.
d: Pretreatment with at least 2 antidiabetics except insulin, and concomitant treatment exclusively with metformin after randomization.
e: The study medication is replaced with NPH insulin during follow-up.

AE: adverse event; DPP-4: dipeptidyl peptidase 4; HbA1c: glycosylated haemoglobin A1c; IDeg: insulin degludec; IGlar: insulin glargine; n: relevant subpopulation; N: number of randomized patients; NPH: neutral protamine Hagedorn; NYHA: New York Heart Association; RCT: randomized controlled trial; SU: sulfonylurea; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A)

<table>
<tr><th>Study</th><th>Intervention</th><th>Comparison</th></tr>
<tr><td rowspan="5">NN1250-3579 (with the 3579Ext extension study)</td><td>Insulin degludec ≥ 10 units
once/day, SC, with evening meal
+</td><td>Insulin glargine ≥ 10 units
once/day, SC, at the same time of day
+</td></tr>
<tr><td colspan="2">metformin (as described under pretreatment) ± DPP-4 inhibitor[a]</td></tr>
<tr><td colspan="2">Starting dose, titration, dose increase
▪ starting dose: 10 units (10 units insulin degludec)
▪ titration based on target value on the basis of FPG according to the following regimen[b]:
<table>
<tr><th colspan="2">Mean FPG (before breakfast)</th><th>Dose adjustment (dose steps or units)</th></tr>
<tr><th>mmol/L</th><th>mg/dL</th><th></th></tr>
<tr><td>< 5.0</td><td>< 90</td><td>No adjustment</td></tr>
<tr><td>< 7.0</td><td>< 126</td><td>+2</td></tr>
<tr><td>< 8.0</td><td>< 144</td><td>+4</td></tr>
<tr><td>< 9.0</td><td>< 162</td><td>+6</td></tr>
<tr><td>≥ 9.0</td><td>≥ 162</td><td>+8</td></tr>
<tr><td>< 3.1 (without evident explanation)</td><td>< 56 (without evident explanation)</td><td>−4</td></tr>
<tr><td>< 3.9 (without evident explanation)</td><td>< 70 (without evident explanation)</td><td>−2</td></tr>
</table></td><td>▪ starting dose: 10 units (10 units insulin glargine)</td></tr>
<tr><td colspan="2">Pretreatment and concomitant treatment:
Permitted pretreatment:
▪ ≤ 90 days before screening 1–2 OADs, either
▫ metformin or
▫ metformin in combination with another antidiabetic (sulfonylurea, glinide, alpha glucosidase inhibitor or DPP-4 inhibitor[a])
▪ other antidiabetics (except metformin and DPP-4 inhibitors[a]) had to be discontinued before randomization
▪ metformin 1500 mg or maximum tolerated dose (≥ 1000 mg)
▪ DPP-4 inhibitor[a]
Non-permitted pretreatment:
▪ insulin
▪ thiazolidinedione, exenatide or liraglutide within the last 3 months before baseline
Allowed concomitant treatment:
▪ inhaled corticosteroids
Non-permitted concomitant medication:
▪ systemic corticosteroids, beta-blockers, monoamine oxidase inhibitors</td></tr>
<tr><td>NN1250-3587</td><td colspan="2">See information on study NN1250-3579 (with the 3579Ext extension study)[c]</td></tr>
<tr><td>NN1250-3672</td><td colspan="2">See information on study NN1250-3579 (with the 3579Ext extension study)</td></tr>
</table>

(continued)

Table 7: Characteristics of the interventions – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A) (continued)

a: Patients whose treatment with DPP-4 inhibitors was continued after randomization are not part of the relevant subpopulations.
b: Adjustments of the insulin dose at the investigator's choice.
c: Continuation of treatment with DPP-4 inhibitors after randomization was not allowed in the NN1250-3587 study.
DPP-4: dipeptidyl peptidase 4; FPG: fasting plasma glucose; OAD: oral antidiabetic; RCT: randomized controlled trial; SC: subcutaneous; vs.: versus

Study characteristics

The studies NN1250-3579, NN1250-3587 and NN1250-3672 were 2-arm, randomized, active-controlled, open-label phase 3 studies with treatment durations of 52 (NN1250-3579) or 26 weeks (NN1250-3587 and NN1250-3672). Patients in the NN1250-3579 study could additionally participate in a 52-week extension study (3579Ext), where they continued their randomly allocated study medication, after the follow-up phase. All studies had a treat-to-target design, in which FPG was titrated to a specified goal (see below).

All studies included insulin-naive adults with type 2 diabetes mellitus in whom pretreatment with metformin alone or in combination with further antidiabetics (sulfonylureas, glinides, dipeptidyl peptidase-4 [DPP-4] inhibitors or alpha glucosidase inhibitors) of at least 3 months at unchanged dosages did not provide adequate glycaemic control. The patients had an HbA1c value of ≥ 7.0% and ≤ 10%. Except metformin (NN1250-3587) and metformin in combination with DPP-4 inhibitors (NN1250-3579 and NN1250-3672), antidiabetics were to be discontinued in all studies at the time point of randomization.

All studies investigated the comparison of insulin degludec versus insulin glargine.

- In the NN1250-3579 study, a total of 1030 patients were randomly allocated in a 3:1 ratio to the study arms of insulin degludec (N = 773) and insulin glargine (N = 257), each in combination with metformin ± DPP-4 inhibitor. The follow-up proportion at the end of study (week 52) was 78.5% (N = 607) in the insulin degludec arm, and 76.7% (N = 197) in the insulin glargine arm. The majority of the patients transitioned to the 3579Ext extension study without new randomization, i.e. 71.3% (N = 551) of the patients in the insulin degludec arm and 67.7% (N = 174) of the patients in the insulin glargine arm.
- The NN1250-3672 study included a total of 460 patients randomly allocated in a 1:1 ratio to the study arms (N = 230 each).
- In the NN1250-3587 study, a total of 833 patients, stratified by region (China/not China), were randomly allocated in a 2:1 ratio to the study arms of insulin degludec (N = 555) and insulin glargine (N = 278), each in combination with metformin.

Primary outcome of all 3 studies was the change in HbA1c from baseline to week 52 (NN1250-3579 with the 3579Ext extension study) or 26 (NN1250-3587 and NN1250-3672). Patient-

relevant secondary outcomes were all-cause mortality as well as outcomes on morbidity, health-related quality of life and AEs including hypoglycaemia.

Relevant subpopulations

All studies also included patients not comprised by research question A (pretreatment with at least 2 antidiabetics, other drug combinations than the ones specified for the ACT). The company therefore presented results of the relevant subpopulations of the studies. It considered patients pretreated with at least 2 blood-glucose lowering drugs and whose study medication consisted of the respective insulin component and metformin based on their pretreatment. In addition, the company only considered patients treated with a metformin dosage that is in compliance with the approval in Germany (1000 to 3000 mg per day) in its subpopulations. The subpopulations adequately formed by the company comprised 60 to 67% of the respective total population, depending on the study.

Treatment with the study medication

Insulin degludec and insulin glargine were used in compliance with their SPCs in all studies [5,6]. The basal insulin was injected at different time points, however: Insulin degludec was to be administered once daily with the evening meal, whereas insulin glargine was to be administered once daily at the same time of day. During the studies, the doses of insulin degludec and insulin glargine in the treatment arms were titrated based on the FPG levels measured by the patients. The treatment goals were not defined for the individual patients, but uniform values between 90 and 125 mg/dL were aimed at. These target values were below the range of 100 to 125 mg/dL recommended as reference values in the currently valid German National Care Guideline (NVL) on the treatment of type 2 diabetes mellitus [7]. It was unclear whether the patients included in the studies NN1250-3579, NN1250-3587 and NN1250-3672 were candidates for near-normal blood-glucose levels. Hence, based on the results of these studies, conclusions can only be drawn for patients with the treatment goal of near-normal blood-glucose levels in whom this aim is initially to be achieved with basal supported oral therapy if oral therapy is inadequate.

Patient characteristics

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

Table 8: Characteristics of the study populations – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A)

Study Characteristics	NN1250-3579 (with the 3579Ext extension study)		NN1250-3587		NN1250-3672	
Category	IDeg + metformin	IGlar + metformin	IDeg + metformin	IGlar + metformin	IDeg + metformin	IGlar + metformin
	N[a] = 519	N[a] = 151	N[a] = 366	N[a] = 191	N[a] = 139	N[a] = 139
Age [years], mean (SD)	60 (9)	60 (9)	57 (9)	57 (9)	59 (8)	58 (9)
Sex [F/M], %	35/65	33/67	46/54	53/47	48/52	48/52
BMI [kg/m²], mean (SD)	30.7 (4.6)	31.5 (4.3)	27.6 (4.9)	26.5 (4.3)	32.0 (5.3)	32.3 (5.4)
Body weight [kg], mean (SD)	88.9 (16.8)	91.6 (15.9)	76.2 (16.5)	72.2 (15.0)	90.3 (17.1)	90.1 (18.0)
Duration of diabetes [years], mean (SD)	10.0 (6.3)	10.0 (5.9)	8.4 (5.2)	9.1 (5.6)	8.8 (5.9)	8.6 (6.2)
HbA1c value [%], mean (SD)	8.2 (0.8)	8.3 (0.8)	8.3 (0.8)	8.3 (0.8)	8.4 (1.0)	8.3 (0.8)
HbA1c value [%], n (%)						
< 8%	231 (44.5)	61 (40.4)	148 (40.4)	79 (41.4)	55 (39.6)	50 (36.0)
≥ 8%	288 (55.5)	90 (59.6)	218 (59.6)	112 (58.6)	84 (60.4)	89 (64.0)
Antidiabetic therapy at screening, n (%)						
Metformin + DPP-4 inhibitor ± SU or glinides ± alpha glucosidase inhibitor	114 (22.0)	38 (25.2)	45 (12.3)[c]	17 (8.9)[c]	16 (11.5)	17 (12.2)
Metformin monotherapy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Metformin ± SU or glinides ± alpha glucosidase inhibitor	405 (78.0)	113 (74.8)	321 (87.7)[d]	174 (91.1)[d]	123 (88.5)	122 (87.8)

(continued)

Table 8: Characteristics of the study populations – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A) (continued)

Study Characteristics	NN1250-3579 (with the 3579Ext extension study)		NN1250-3587		NN1250-3672	
Category	IDeg + metformin	IGlar + metformin	IDeg + metformin	IGlar + metformin	IDeg + metformin	IGlar + metformin
	N[a] = 519	N[a] = 151	N[a] = 366	N[a] = 191	N[a] = 139	N[a] = 139
Prior cardiovascular disease [yes/no][b]	ND	ND	ND	ND	ND	ND
Region, n (%)						
Europe	298 (57.4)	90 (59.6)	48 (13.1)	23 (12.0)	67 (48.2)	69 (49.6)
Non-Europe	221 (42.6)	61 (40.4)	318 (86.9)	168 (88.0)	72 (51.8)	70 (50.4)
Treatment discontinuation, n (%)	ND	ND	ND	ND	ND	ND
Study discontinuation, n (%)						
during study	93 (17.9)	30 (19.9)	19 (5.2)	17 (8.9)	12 (8.6)	16 (11.5)
during extension	27 (5.2)[e]	11 (7.3)[f]	-	-	-	-

a: Number of randomized patients in the relevant subpopulation. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Patients with prior cardiovascular disease (defined as stroke, cardiac failure of NYHA class III or IV, myocardial infarction, unstable angina pectoris, coronary artery bypass or angioplasty) within the last 6 months prior to the first study visit were excluded from participation in the studies. There is no information on the number of included patients with prior cardiovascular disease within > 6 months before the first study visit.
c: Categorization in the NN1250-3587 study: metformin + other.
d: Categorization in the NN1250-3587 study: metformin + SU ± glinides ± other.
e: From the total population, n = 551 (71.3%) of 773 randomized patients enrolled in the extension study. No exact information on this is available for the relevant subpopulation (see Section 2.6.2.4.2 of the full dossier assessment).
f: From the total population, n = 174 (67.7%) of 257 randomized patients enrolled in the extension study. No exact information on this is available for the relevant subpopulation (see Section 2.6.2.4.2 of the full dossier assessment).

BMI: body mass index; DPP-4: dipeptidyl peptidase-4; F: female; HbA1c: glycosylated haemoglobin A1c; IDeg: insulin degludec; IGlar: insulin glargine; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; NYHA: New York Heart Association; RCT: randomized controlled trial; SD: standard deviation; SU: sulfonylurea; vs.: versus

The demographic and clinical characteristics of the patients in these subpopulations were largely balanced and sufficiently similar both between the individual study arms and between the studies.

The mean age of the patients in both study arms of all 3 studies was about 60 years. The proportion of male patients in the NN1250-3579 study (with the 3579Ext extension study) was about 65%, whereas the proportions of men and women in the other 2 studies were balanced (about 50% each). The mean HbA1c value in both study arms of the 3 studies was 8.3% at baseline, and under 8% in approximately 40% of the patients. The proportions of Europeans and non-Europeans in both study arms were evenly balanced (about 50% each) in the studies NN1250-3579 (with the 3579Ext extension study) and NN1250-3672. The proportion of Europeans in the NN1250-3587 study was about 13%. There was no information on treatment discontinuations for the relevant subpopulation or for the total population of all studies. For the extension study, there was no information on the number of patients of the relevant subpopulation who transitioned from the main study to the extension study. The information can be estimated on the basis of the available documents, however (see Section 2.6.2.4.2 of the full dossier assessment).

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
NN1250-3579	Yes	Yes	No	No	Yes	Yes	Low
NN1250-3587	Yes	Yes	No	No	Yes	Yes	Low
NN1250-3672	Yes	Yes	No	No	Yes	Yes	Low
3579Ext[a]	Yes	Yes	No	No	Yes	Yes	Low

a: Extension study to study NN1250-3579.
RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for all studies. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.3.2 with the outcome-specific risk of bias.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.2.4.3.2 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - cardiovascular events (MACE)
    - cardiovascular death
    - nonfatal stroke
    - acute coronary syndrome
  - health status (TRIM-D domains “daily life” and “psychological health”)
- Health-related quality of life
  - SF-36v2
- Side effects
  - SAEs
  - discontinuation due to AEs
  - non-severe confirmed symptomatic hypoglycaemic episodes in total (PG < 56 mg/dL)
  - severe hypoglycaemic episodes (SAEs)
  - renal function disorder (AE)
  - if applicable, further specific AEs

Results at week 26 were available for the studies NN1250-3587 and NN1250-3672, whereas results at week 52 were available for the NN1250-3579 study and at week 104 for the 3579Ext extension study. Consideration of the longer observation period, i.e. 104 weeks, would principally be preferable for the present benefit assessment. A meta-analysis of the results of the studies NN1250-3587 and NN1250-3672 at week 26 with those from the extension study at week 104 (3579Ext) was inadequate due to the notably longer observation period in the 3579Ext study. In order to adequately consider all information from the studies presented, the results from the meta-analysis of the studies NN1250-3587, NN1250-3672 and NN1250-3579 at week 26 or week 52 respectively, as well as the results from the 3579Ext extension study at week 104 were used for the present benefit assessment and considered jointly in qualitative terms (see Section 2.6.2.4.3 of the full dossier assessment).

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A), but did not consider renal function disorder as separate outcome. The results on non-severe confirmed symptomatic diurnal and nocturnal hypoglycaemic episodes (PG < 56 mg/dL), on the overall rate of AEs, and on the change in HbA1c and body weight are shown as additional information in the present assessment. A detailed explanation on the inclusion of outcomes can be found in Section 2.6.2.4.3 of the full dossier assessment.

The company presented analyses on the relative risks (RR) and on the rate ratios for the outcomes on non-severe confirmed hypoglycaemic episodes (PG < 56 mg/dL) and on severe hypoglycaemic episodes. For the present assessment, the results for the effect measure RR were primarily used for these outcomes. The results on the rate ratios are presented as additional information in Appendix B.3 of the full dossier assessment (for reasons, see Section 2.6.2.4.3.2 of the full dossier assessment).

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

Table 10: Matrix of outcomes – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A)

Study	Outcomes												
	All-cause mortality	**Cardiovascular events (MACE)[a]**	**Cardiovascular death**	**Nonfatal stroke**	**Acute coronary syndrome**	**Health status (TRIM-D[b])**	**Health-related quality of life (SF-36v2)[c]**	**SAEs**	**Discontinuation due to AEs[d]**	**Non-severe confirmed symptomatic hypoglycaemic episodes in total (PG < 56 mg/dL)**	**Severe hypoglycaemic episodes (SAEs)**	**Renal function disorder (SOC, SAE)**	**Further specific AEs[e]**
NN1250-3579	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
NN1250-3587	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
NN1250-3672	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3579Ext[f]	Yes	Yes	Yes	Yes	Yes	No[g]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Composite outcome: first occurrence of one of the events “cardiovascular death”, “nonfatal stroke” or “acute coronary syndrome”.
b: The domains “daily life” and “psychological health” are considered.
c: PCS and MCS are considered; there are no data on the individual SF-36 domains for the relevant subpopulations.
d: No analyses by SOC and PT available for the relevant subpopulations.
e: The following events (MedDRA coding) are considered: “vomiting (PT, AE)” and “depression (PT, AE)”.
f: Extension study to study NN1250-3579.
g: Outcome not recorded in the extension study.

AE: adverse event; MACE: major adverse cardiovascular event; MCS: Mental Component Summary; MedDRA: Medical Dictionary for Regulatory Activities; PCS: Physical Component Summary; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; TRIM-D: Treatment-Related Impact Measure for Diabetes; vs.: versus

2.3.2.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A)

Study	Outcomes													
	Study level	All-cause mortality	Cardiovascular events (MACE)[a]	Cardiovascular death	Nonfatal stroke	Acute coronary syndrome	Health status (TRIM-D[b])	Health-related quality of life (SF-36v2)[c]	SAEs	Discontinuation due to AEs[d]	Non-severe confirmed symptomatic diurnal hypoglycaemic episodes (PG < 56 mg/dL)	Severe hypoglycaemic episodes (SAEs)	Renal function disorder (SOC, SAE)	Further specific AEs[e]
NN1250-3579	L	L	L	L	L	L	H[f, g]	H[f, g]	L	H[f]	H[f]	L	L	H[f]
NN1250-3587	L	L	L	L	L	L	H[f]	H[f]	L	H[f]	H[f]	L	L	H[f]
NN1250-3672	L	L	L	L	L	L	H[f, g]	H[f, g]	L	H[f]	H[f]	L	L	H[f]
3579Ext[h]	L	H[i]	H[i]	H[i]	H[i]	H[i]	–[j]	H[f, g]	H[i]	H[f]	H[f, i]	H[i]	H[i]	H[f, i]

a: Composite outcome: first occurrence of one of the events "cardiovascular death", "nonfatal stroke" or "acute coronary syndrome".
b: The domains "daily life" and "psychological health" are considered.
c: PCS and MCS are considered; there are no data on the individual SF-36 domains for the relevant subpopulations.
d: No analyses by SOC and PT available for the relevant subpopulations.
e: The following events (MedDRA coding) are considered: "vomiting (PT, AE)" and "depression (PT, AE)".
f: Due to incomplete blinding in subjective recording of outcomes.
g: The results on Hedges' g are potentially highly biased because the estimation is unclear; proportions of missing values > 10% at end of study.
h: Extension study to study NN1250-3579.
i: Possibly large proportion of patients with incomplete observation.
j: Outcome not recorded in the extension study.
AE: adverse event; H: high; L: low; MACE: major adverse cardiovascular event; MCS: Mental Component Summary; MedDRA: Medical Dictionary for Regulatory Activities; PCS: Physical Component Summary; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; TRIM-D: Treatment-Related Impact Measure for Diabetes; vs.: versus

The following description of the risk of bias at outcome level is separated by the studies of the meta-analysis (NN1250-3579, NN1250-3587 and NN1250-3672) and the 3579Ext study.

For the studies NN1250-3579, NN1250-3587 and NN1250-3672, the risk of bias was rated as low for the results on the outcomes "all-cause mortality", "cardiovascular events (MACE)" including the components "cardiovascular death", "nonfatal stroke" and "acute coronary syndrome", as well as on the side effect outcomes "SAEs" and "severe hypoglycaemia". This

is consistent with the assessment of the company, which determined the risk of bias only for the results on the superordinate composite outcome "cardiovascular events (MACE)" and not for the individual components mentioned above, however. The risk of bias of the result on the outcome "renal function disorder" was also rated as low. The company did not consider this outcome and hence did not rate the risk of bias.

Due to the lack of blinding in subjective recording of outcomes, the risk of bias was rated as high for the results on all other outcomes (health status measured with the instrument TRIM-D, health-related quality of life measured with the instrument SF-36, discontinuation due to AEs, non-severe symptomatic hypoglycaemic episodes in total [PG < 56 mg/dL] and further specific AEs). For the studies NN1250-3579 and NN1250-3672, the risk of bias for the results on the outcomes "health status (TRIM-D)" and "health-related quality of life (SF-36)" was high also because the results on Hedges' g were potentially highly biased due to the unclear estimation. In addition, the proportions of the missing values were > 10% at the end of study. This is largely consistent with the assessment of the company, which also rated the risk of bias as high for the results on these outcomes except non-severe confirmed hypoglycaemia.

For the 3579Ext extension study, the risk of bias was rated as high for the results on all outcomes. This is justified below.

There was a possibly large proportion of patients with incomplete observation for the outcomes "all-cause mortality" and "cardiovascular events" (including the individual components) as well as all side effect outcomes except discontinuation due to AEs. The results on the outcomes "health-related quality of life (SF-36)", "discontinuation due to AEs", "non-severe symptomatic hypoglycaemic episodes in total (PG < 56 mg/dL)" and "further specific AEs" have a high risk of bias due to incomplete blinding in subjective recording of outcomes.

This deviates from the assessment of the company, which rated the risk of bias as low for the results on the outcomes "all-cause mortality", "cardiovascular events", "SAEs", "non-severe symptomatic hypoglycaemic episodes (PG < 56 mg/dL)" and "severe hypoglycaemic episodes". The company did not consider the outcome "renal function disorder" and hence did not rate the risk of bias.

A detailed explanation on the risk of bias can be found in Section 2.6.2.4.2 of the full dossier assessment.

Overall assessment of the certainty of conclusions

Proof can be derived from the meta-analysis and at most hints from the extension study due to the high risk of bias for the results of all outcomes. An outcome-specific joint qualitative consideration of the results of the meta-analysis and of the extension study was conducted, which was included in the balancing of the certainty of conclusions. The time course was also taken into account. In case of differing results from the meta-analysis and the extension, this can lead to a limitation of the certainty of conclusions.

2.3.2.3 Results

Table 12 and Table 13 summarize the results on the comparison of insulin degludec with insulin glargine, each in combination with metformin in patients with type 2 diabetes mellitus pretreated with at least 2 antidiabetics (except insulin). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Forest plots of the meta-analyses calculated by the Institute can be found in Appendix B.2 of the full dossier assessment. The analyses of the rate ratios for the outcomes "non-severe confirmed symptomatic hypoglycaemic episodes (PG < 56 mg/dL)" and "severe hypoglycaemic episodes", as well as the tables on common AEs are presented as additional information in Appendix B.3 and Appendix B.4 of the full dossier assessment. Frequencies are not presented as the frequencies of the SAEs that occurred in the studies NN1250-3587 and NN1250-3672 were low (none of the events was above the limitation of presentation determined) and were mainly based on individual events. Information on the frequencies of discontinuations due to AEs was available for the total population, but not for the relevant subpopulations. Frequencies in the total population are also not presented.

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A)

Outcome category Outcome Study	IDeg + metformin N	 Patients with event n (%)	IGlar + metformin N	 Patients with event n (%)	IDeg + metformin vs. IGlar + metformin RR [95% CI]; p-value
Mortality					
All-cause mortality					
NN1250-3579 (52 W)	519	0 (0)	151	1 (0.7)	NC; 0.225
NN1250-3587 (26 W)	366	0 (0)	191	1 (0.5)	NC; 0.343
NN1250-3672 (26 W)	139	0 (0)	139	1 (0.7)	NC; > 0.999
Total					0.18 [0.03; 1.13]; 0.067
3579Ext[a] (104 W)	519	2 (0.4)	151	1 (0.7)	0.58 [0.05; 6.37]; 0.536
Morbidity					
Cardiovascular events (MACE)					
NN1250-3579 (52 W)	518	9 (1.7)	151	1 (0.7)	2.62 [0.34; 20.54]; 0.470
NN1250-3587 (26 W)	364	0 (0)	191	2 (1.0)	0.11 [0.01; 2.18]; 0.052[b]
NN1250-3672 (26 W)	139	3 (2.2)	139	2 (1.4)	1.50 [0.25; 8.84]; > 0.999
Total					1.18 [0.35; 4.04]; 0.788
3579Ext[a] (104 W)	518	24 (4.6)	151	3 (2.0)	2.33 [0.71; 7.64]; 0.166
Cardiovascular death					
NN1250-3579 (52 W)	518	1 (0.2)	151	0 (0)	0.88 [0.04; 21.46][c]; 0.734[b]
NN1250-3587 (26 W)	364	0 (0)	191	0 (0)	NC
NN1250-3672 (26 W)	139	0 (0)	139	1 (0.7)	0.33 [0.01; 8.11][c]; 0.409[b]
Total					0.52 [0.06; 4.69]; 0.559[d]
3579Ext[a] (104 W)	518	2 (0.4)	151	1 (0.7)	0.58 [0.05; 6.39]; 0.536
Nonfatal stroke					
NN1250-3579 (52 W)	518	1 (0.2)	151	1 (0.7)	0.29 [0.02; 4.63]; 0.401
NN1250-3587 (26 W)	364	0 (0)	191	2 (1.0)	0.11 [0.01; 2.18][c]; 0.052[b]
NN1250-3672 (26 W)	139	0 (0)	139	1 (0.7)	0.33 [0.01; 8.11][c]; 0.409[b]
Total					0.20 [0.04; 1.11]; 0.066[d]
3579Ext[a] (104 W)	518	6 (1.2)	151	2 (1.3)	0.87 [0.18; 4.29]; > 0.999
Acute coronary syndrome					
NN1250-3579 (52 W)	518	7 (1.4)	151	0 (0)	4.39 [0.25; 76.48][c]; 0.158[b]
NN1250-3587 (26 W)	364	0 (0)	191	0 (0)	NC
NN1250-3672 (26 W)	139	3 (2.2)	139	0 (0)	7.00 [0.36; 134.27][c]; 0.087[b]
Total					5.42 [0.70; 41.85]; 0.105[d]
3579Ext[a] (104 W)	518	17 (3.3)	151	0 (0)	OR: 7.21 [1.54; ∞); 0.012[e]

(continued)

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A) (continued)

Outcome category Outcome Study	IDeg + metformin		IGlar + metformin		IDeg + metformin vs. IGlar + metformin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Side effects					
AEs (additional information)					
NN1250-3579 (52 W)	*519*	*392 (75.5)*	*151*	*110 (72.8)*	–
NN1250-3587 (26 W)	*366*	*204 (55.7)*	*191*	*113 (59.2)*	–
NN1250-3672 (26 W)	*139*	*86 (61.9)*	*139*	*95 (68.3)*	–
3579Ext[a] (104 W)	*519*	*421 (81.1)*	*151*	*121 (80.1)*	–
SAEs					
NN1250-3579 (52 W)	519	40 (7.7)	151	18 (11.9)	0.65 [0.38; 1.09]; 0.137
NN1250-3587 (26 W)	366	10 (2.7)	191	9 (4.7)	0.58 [0.24; 1.40]; 0.228
NN1250-3672 (26 W)	139	10 (7.2)	139	8 (5.8)	1.25 [0.51; 3.07]; 0.808
Total					0.72 [0.48; 1.08]; 0.114
3579Ext[a] (104 W)	519	80 (15.4)	151	25 (16.6)	0.93 [0.62; 1.40]; 0.705
Discontinuation due to AEs					
NN1250-3579 (52 W)	519	14 (2.7)	151	2 (1.3)	2.04 [0.47; 8.86]; 0.544
NN1250-3587 (26 W)	366	2 (0.5)	191	2 (1.0)	0.52 [0.07; 3.68]; 0.610
NN1250-3672 (26 W)	139	2 (1.4)	139	2 (1.4)	1.00 [0.14; 7.00]; > 0.999
Total					1.17 [0.43; 3.21]; 0.755
3579Ext[a] (104 W)	519	21 (4.0)	151	4 (2.6)	1.53 [0.53; 4.38]; 0.625
Non-severe confirmed symptomatic hypoglycaemic episodes in total (PG < 56 mg/dL)					
NN1250-3579 (52 W)	519	175 (33.7)	151	57 (37.7)	0.89 [0.70; 1.13]; 0.382
NN1250-3587 (26 W)	366	97 (26.5)	191	55 (28.8)	0.92 [0.70; 1.22]; 0.617
NN1250-3672 (26 W)	139	23 (16.5)	139	29 (20.9)	0.79 [0.48; 1.30]; 0.442
Total					0.89 [0.75; 1.06]; 0.182
3579Ext[a] (104 W)	519	237 (45.7)	151	71 (47.0)	0.97 [0.80; 1.18]; 0.781
Non-severe confirmed symptomatic diurnal hypoglycaemic episodes (PG < 56 mg/dL) (additional information)					
NN1250-3579 (52 W)	*519*	*155 (29.9)*	*151*	*50 (33.1)*	*0.90 [0.69; 1.17]; 0.483*
NN1250-3587 (26 W)	*366*	*79 (21.6)*	*191*	*41 (21.5)*	*1.01 [0.72; 1.40]; > 0.999*
NN1250-3672 (26 W)	*139*	*20 (14.4)*	*139*	*23 (16.5)*	*0.87 [0.50; 1.51]; 0.740*
Total					*0.93 [0.77; 1.13]; 0.469*
3579Ext[a] (104 W)	*519*	*215 (41.4)*	*151*	*65 (43.0)*	*0.96 [0.78; 1.19]; 0.779*

(continued)

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A) (continued)

Outcome category **Outcome** **Study**	**IDeg + metformin** **N**	**Patients with event n (%)**	**IGlar + metformin** **N**	**Patients with event n (%)**	**IDeg + metformin vs. IGlar + metformin** **RR [95% CI]; p-value**
Non-severe confirmed symptomatic nocturnal hypoglycaemic episodes (PG < 56 mg/dL) (additional information)					
NN1250-3579 (52 W)	*519*	*59 (11.4)*	*151*	*25 (16.6)*	*0.69 [0.45; 1.06]; 0.095*
NN1250-3587 (26 W)	*366*	*28 (7.7)*	*191*	*24 (12.6)*	*0.61 [0.36; 1.02]; 0.066*
NN1250-3672 (26 W)	*139*	*6 (4.3)*	*139*	*9 (6.5)*	*0.67 [0.24; 1.82]; 0.597*
Total					*0.65 [0.48; 0.895]; 0.008*
3579Ext[a] (104 W)	*519*	*93 (17.9)*	*151*	*35 (23.2)*	*0.77 [0.55; 1.09]; 0.159*
Severe hypoglycaemic episodes (SAEs)					
NN1250-3579 (52 W)	519	1 (0.2)	151	1 (0.7)	0.29 [0.02; 4.62]; 0.400
NN1250-3587 (26 W)	366	2 (0.5)	191	2 (1.0)	0.52 [0.07; 3.68]; 0.610
NN1250-3672 (26 W)	139	0 (0)	139	0 (0)	NC
Total					0.43 [0.09; 2.12]; 0.299
3579Ext[a] (104 W)	519	3 (0.6)	151	1 (0.7)	0.87 [0.09; 8.33]; > 0.999
Renal function disorder (SAE, SOC)					
NN1250-3579 (52 W)	518	1 (0.2)	151	1 (0.7)	0.29 [0.02; 4.63][c]; 0.474[b]
NN1250-3587 (26 W)	364	0 (0)	191	0 (0)	NC
NN1250-3672 (26 W)	139	0 (0)	139	1 (0.7)	0.33 [0.01; 8.11][c]; 0.409[b]
Total					0.24 [0.02; 2.60]; 0.238[f]
3579Ext[a] (104 W)	518	3 (0.6)	151	3 (2.0)	0.29 [0.06; 1.43][c]; 0.108[b]
Vomiting (AE, PT)					
NN1250-3579 (52 W)	518	15 (2.9)	151	9 (6.0)	0.49 [0.22; 1.09][c]; 0.108[b]
NN1250-3587 (26 W)	364	3 (0.8)	191	2 (1.0)	0.79 [0.13; 4.67][c]; 0.851[b]
NN1250-3672 (26 W)	139	4 (2.9)	139	3 (2.2)	1.33 [0.30; 5.85][c]; 0.793[b]
Total					0.66 [0.34; 1.25]; 0.201[d]
3579Ext[a] (104 W)	518	18 (3.5)	151	12 (7.9)	0.44 [0.22; 0.89][c]; 0.023[b]
Depression (AE, PT)					
NN1250-3579 (52 W)	518	6 (1.2)	151	0 (0)	3.81 [0.22; 67.20][c]; 0.189[b]
NN1250-3587 (26 W)	364	2 (0.5)	191	0 (0)	2.63 [0.13; 54.51][c]; 0.407[b]
NN1250-3672 (26 W)	139	0 (0)	139	1 (0.7)	0.33 [0.01; 8.11][c]; 0.409[b]
Total					1.76 [0.37; 8.39]; 0.475[d]
3579Ext[a] (104 W)	518	15 (2.9)	151	0 (0)	OR: 6.30 [1.35; ∞); 0.020[e]

(continued)

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A) (continued)

a: Extension study to study NN1250-3579.
b: Institute's calculation, p-value from unconditional exact test (CSZ method according to [8]).
c: Institute's calculation, in zero cells with continuity correction of 0.5 for all cells.
d: Institute's calculation, meta-analysis with fixed effect, Mantel-Haenszel method.
e: Institute's calculation, exact conditional logistic regression according to [9], one-sided p-value.
f: Institute's calculation, meta-analysis with fixed effect, beta-binomial model according to [10].
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; IDeg: insulin degludec; IGlar: insulin glargine; MACE: major adverse cardiovascular event; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculated; ND: no data; OR: odds ratio; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus; W: weeks

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A)

Outcome category Outcome Study	IDeg + metformin			IGlar + metformin			IDeg + metformin vs. IGlar + metformin
	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	MD [95% CI]; p-value
Morbidity							
Health status							
TRIM-D[c]							
Daily life							
NN1250-3579 (52 W)	519	77.79 (18.9)	3.57 (0.80)	151	76.14 (20.1)	2.70 (1.51)	0.87 [−2.49; 4.23]; 0.611
NN1250-3587 (26 W)	366	75.22 (17.8)	3.17 (0.84)	191	76.65 (16.1)	2.85 (1.19)	0.33 [−2.55; 3.20]; 0.824
NN1250-3672 (26 W)	139	76.08 (19.6)	3.50 (1.31)	139	77.78 (19.3)	3.81 (1.31)	−0.31 [−3.98; 3.35]; 0.867
Total							0.33 [−1.55; 2.21]; 0.730
3579Ext[d] (104 W)	Outcome not recorded						
Psychological health							
NN1250-3579 (52 W)	519	77.51 (17.3)	8.69 (0.69)	151	75.66 (18.5)	8.86 (1.30)	−0.17 [−3.06; 2.72]; 0.906
NN1250-3587 (26 W)	366	73.21 (19.2)	7.45 (0.79)	191	73.7 (18.6)	6.26 (1.12)	1.19 [−1.51; 3.89]; 0.388
NN1250-3672 (26 W)	139	76.01 (17.6)	8.87 (1.24)	139	77.95 (17.3)	5.76 (1.24)	3.11 [−0.36; 6.59]; 0.079
Total							1.18 [−0.54; 2.89]; 0.178
3579Ext[d] (104 W)	Outcome not recorded						
HbA1c (%) (additional information)							
NN1250-3579 (52 W)	*519*	*8.18 (0.8)*	*−1.16 (0.03)*	*151*	*8.31 (0.8)*	*−1.33 (0.06)*	*0.17 [0.03; 0.31]; 0.019*
NN1250-3587 (26 W)	*366*	*8.32 (0.83)*	*−1.25 (0.04)*	*191*	*8.28 (0.81)*	*−1.24 (0.06)*	*−0.01 [−0.16; 0.14]; 0.901*
NN1250-3672 (26 W)	*139*	*8.35 (0.99)*	*−1.25 (0.08)*	*139*	*8.33 (0.82)*	*−1.27 (0.08)*	*0.02 [−0.19; 0.23]; 0.877*
Total							*0.07 [−0.02; 0.17]; 0.117*
3579Ext[d] (104 W)	*519*	*8.14 (0.78)*	*−1.13 (0.04)*	*151*	*8.27 (0.79)*	*−1.26 (0.07)*	*0.12 [−0.03; 0.28]; 0.127*

(continued)

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A) (continued)

Outcome category Outcome Study	IDeg + metformin			IGlar + metformin			IDeg + metformin vs. IGlar + metformin
	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	MD [95% CI]; p-value
Morbidity							
Body weight (additional information)			*No results available for the relevant subpopulations*				
Health-related quality of life							
SF-36[e]							
Physical Component Summary (PCS)							
NN1250-3579 (52 W)	519	46.3 (8.7)	1.10 (0.32)	151	44.9 (9.22)	−0.78 (0.60)	1.88 [0.56; 3.21]; 0.006 Hedges' g: 0.31 [0.11; 0.52]
NN1250-3587 (26 W)	366	48.13 (7.62)	1.01 (0.33)	191	47.69 (7.39)	0.63 (0.46)	0.38 [−0.74; 1.50]; 0.503
NN1250-3672 (26 W)	139	44.62 (9.23)	1.84 (0.58)	139	45.91 (8.24)	1.42 (0.59)	0.42 [−1.21; 2.06]; 0.611
Total							0.88 [0.12; 1.64]; 0.023 Heterogeneity for Hedges' g: Q = 6.45, df = 2, p = 0.040, I^2 = 69.0%
3579Ext[d] (104 W)	519	46.78 (8.73)	−0.14 (0.38)	151	46.28 (9.13)	−2.02 (0.74)	1.88 [0.25; 3.52]; 0.024 Hedges' g: 0.26 [0.00; 0.51]
Mental Component Summary (MCS)							
NN1250-3579 (52 W)	519	48.76 (11.3)	1.05 (0.41)	151	48.33 (11.4)	1.46 (0.77)	−0.40 [−2.12; 1.32]; 0.645
NN1250-3587 (26 W)	366	47.38 (10.7)	0.92 (0.44)	191	47.82 (10.0)	0.74 (0.62)	0.19 [−1.31; 1.68]; 0.806
NN1250-3672 (26 W)	139	47.52 (11.7)	2.37 (0.77)	139	47.49 (10.7)	0.67 (0.78)	1.71 [−0.47; 3.88]; 0.125
Total							0.31 [−0.69; 1.31]; 0.541
3579Ext[d] (104 W)	519	50.06 (10.9)	0.70 (0.48)	151	50.26 (9.92)	0.05 (0.95)	0.65 [−1.43; 2.73]; 0.541
Individual domains of the SF-36			No results available for the relevant subpopulations				

(continued)

Table 13: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: insulin degludec + metformin vs. insulin glargine + metformin (research question A) (continued)

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at the start of the study may be based on other patient numbers.
b: Unless stated otherwise, MMRM analysis of the FAS population, with treatment, sex, antidiabetic therapy at baseline, and region as fixed effects, corresponding baseline value and age as covariates, as well as interaction between all fixed effects and study visit and between baseline value and study visit.
c: Higher values indicate improvement in health status with a positive difference indicating an advantage of the intervention; data on the individual domains were not available for the subpopulations.
d: Extension study to study NN1250-3579.
e: Higher values indicate better health-related quality of life; a positive difference indicates an advantage for the intervention.
CI: confidence interval; FAS: full analysis set; HbA1c: glycosylated haemoglobin A1c; IDeg: insulin degludec; IGlar: insulin glargine; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36: Short Form (36) Health Survey; TRIM-D: Treatment-Related Impact Measure for Diabetes; vs.: versus; W: weeks

As described in Section 2.3.2.2, the certainty of conclusions of the results based on the available data was assessed on the basis of the joint qualitative consideration of the results of the meta-analysis and the extension study at outcome level.

This deviates from the approach of the company, which derived at most proof on the basis of the results of the meta-analysis (studies NN1250-3579, NN1250-3587 and NN1250-3672). The company presented the results of the 3579Ext extension study as additional information, but did not consider them in the derivation of the added benefit.

In the following description of the results, all information on the meta-analysis refers to the meta-analysis of the studies NN1250-3579, NN1250-3587 and NN1250-3672, and all information on the extension study refers to study 3579Ext.

Mortality

All-cause mortality

Only few deaths occurred in both treatment arms of all studies. Neither the meta-analysis nor the extension study showed a statistically significant difference between insulin degludec + metformin and insulin glargine + metformin for the outcome “all-cause mortality”. This resulted in no hint of an added benefit of insulin degludec + metformin in comparison with insulin glargine + metformin; an added benefit is therefore not proven.

This concurs with the company’s assessment.

Morbidity

Cardiovascular events (MACE, including the components "cardiovascular death", "nonfatal stroke" and "acute coronary syndrome")

Neither the meta-analysis nor the extension study showed a statistically significant difference between the treatment arms for the composite outcome "cardiovascular events (MACE)" or the 2 components "cardiovascular death" and "nonfatal stroke". This resulted in no hint of an added benefit of insulin degludec + metformin in comparison with insulin glargine + metformin; an added benefit is therefore not proven.

The extension study showed a statistically significant effect to the disadvantage of insulin degludec + metformin for the outcome "acute coronary syndrome". In the meta-analysis, the effect was not statistically significant, but the direction of the effect was consistent. The joint consideration of the results showed that the events occurred mostly in the study with longer study duration (NN1250-3579 and its extension study). This resulted in a hint of lesser benefit of insulin degludec + metformin versus insulin glargine + metformin for this outcome.

The assessment regarding the outcome "cardiovascular events (MACE)" is consistent with that of the company. The company did not use the analyses of the individual components "cardiovascular death", "nonfatal stroke" and "acute coronary syndrome" for the derivation of the added benefit.

Health status (TRIM-D domains of daily life and psychological health)

The meta-analysis showed no statistically significant difference between the treatment arms for the outcome "health status", measured with the domains of daily life and psychological health of the TRIM-D questionnaire. The outcome was not recorded in the extension study. This resulted in no hint of an added benefit of insulin degludec + metformin in comparison with insulin glargine + metformin; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

SF-36 − Physical Component Summary (PCS) and Mental Component Summary (MCS)

The mean changes at the end of study versus baseline were considered for the SF-36 MCS and PCS

The meta-analysis and the extension study showed no statistically significant differences between the treatment arms for the MCS.

For the PCS, there was a statistically significant result for the change from baseline in the meta-analysis, with homogeneous data situation. No relevant effect could be derived from the standardized mean difference estimated with the Hedges' g effect measure. For the Hedges' g effect measure, there was heterogeneity between the studies of the meta-analysis ($p < 0.05$). The consideration of the results of the individual studies produced no effect in the same

direction. A statistically significant effect in favour of insulin degludec + metformin was only present in the NN1250-3579 study. This observed effect, assessed with Hedges' g, was not relevant, however. There was no statistically significant difference between the treatment groups in either of the studies NN1250-3587 and NN1250-3672. Hence, the effects were not in the same direction. The 3579Ext extension study showed a statistically significant difference in favour of insulin degludec + metformin for the PCS. The CI for Hedges' g was not fully outside the irrelevance range [−0.2; 0.2] also for the 3579Ext extension study. It can therefore not be inferred that the effect is relevant.

This resulted in no hint of an added benefit of insulin degludec + metformin in comparison with insulin glargine + metformin for the MCS or for the PCS; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

Serious adverse events

Neither the meta-analysis nor the extension study showed a statistically significant difference between the treatment arms for the outcome "SAEs".

This resulted in no hint of an added benefit of insulin degludec + metformin in comparison with insulin glargine + metformin for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to adverse events and renal function disorder (SAE, SOC)

Neither the meta-analysis nor the extension study showed statistically significant differences between the treatment groups for the outcomes "discontinuation due to AEs" and "renal function disorder". Hence, for these outcomes, there was no hint of greater or lesser harm from insulin degludec + metformin in comparison with insulin glargine + metformin; greater or lesser harm is therefore not proven.

For the outcome "discontinuation due to AEs", this is consistent with the company's assessment. The company did not use the outcome "renal function disorder (SAE)" in its assessment.

Hypoglycaemia

Non-severe hypoglycaemia

Neither the meta-analysis nor the extension study showed a statistically significant difference between the treatment arms for the outcome "non-severe confirmed symptomatic hypoglycaemic episodes in total (PG < 56 mg/dL)". In all studies, blood-glucose lowering in the insulin degludec arms was comparable to that in the insulin glargine arms (for HbA1c in

the course of the studies, see Figure 9 to Figure 12 in Appendix B.1 of the full dossier assessment).

Overall, there was no hint of greater or lesser harm from insulin degludec + metformin in comparison with insulin glargine + metformin for non-severe confirmed symptomatic hypoglycaemic episodes; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which derived proof of an added benefit for the outcome "non-severe confirmed symptomatic hypoglycaemic episodes in total" due to a statistically significant difference in the analysis of the rate ratio in the meta-analysis. As described above, the analyses of the RR were used for the present benefit assessment (for reasons, see Section 2.6.2.4.3.2 of the full dossier assessment). The results on the analyses of the rate ratio are presented as additional information in Appendix B.3 of the full dossier assessment. The effect was no more than marginal for non-severe confirmed hypoglycaemic episodes, so that no proof of lesser harm from insulin degludec would have resulted from consideration of the rate ratio either.

The company additionally used analyses separated by times of day for the added benefit and derived proof of an added benefit of insulin degludec for non-severe confirmed symptomatic nocturnal hypoglycaemic episodes. The separate analyses by times of day are presented as additional information in Table 42 of Appendix B.3 of the full dossier assessment (for reasons, see Section 2.6.2.4.3.2 of the full dossier assessment).

Severe hypoglycaemia

As an auxiliary measure, the company operationalized severe hypoglycaemic episodes as hypoglycaemic episodes documented as SAEs (for reasons, see Section 2.6.2.4.3.2 of the full dossier assessment). Neither the meta-analysis nor the extension study showed statistically significant differences between the treatment groups for the outcome "severe hypoglycaemic episodes (SAEs)". Hence, for this outcome, there was no hint of greater or lesser harm from insulin degludec + metformin in comparison with insulin glargine + metformin; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Specific adverse events

Vomiting (PT)

In the meta-analysis, there was no statistically significant effect between the treatment arms for the outcome "vomiting". In the extension study, however, there was a statistically significant difference in favour of insulin degludec + metformin for this outcome.

The joint consideration of the results showed that the events occurred mostly in the study with longer study duration (NN1250-3579) and continued to increase in the second year of the study (extension study) with the same direction of effect.

Due to the high risk of bias for this outcome in the extension study, there was overall a hint of lesser harm from insulin degludec + metformin versus insulin glargine + metformin.

The company did not use this outcome in its assessment.

Depression (PT)

In the meta-analysis, there was no statistically significant effect between the treatment arms for the outcome "depression (PT)". In the extension study, however, there was a statistically significant difference to the disadvantage of insulin degludec + metformin for this outcome.

The joint consideration of the results showed that the events occurred mostly in the study with longer study duration (NN1250-3579) and also in the second year of the study (extension study).

Due to the high risk of bias for the results on this outcome in the extension study, there was overall a hint of greater harm from insulin degludec + metformin versus insulin glargine + metformin.

The company did not use this outcome in its assessment.

2.3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present benefit assessment:

- age (< 65 years/≥ 65 years)
- sex (men/women)
- region (joint consideration of the characteristics "Europe/non-Europe" and "OECD country [yes/no]")

Subgroup analyses were only used if each subgroup comprised at least 10 people and, for binary data, if at least 10 events had occurred in one of the subgroups. Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. Moreover, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Altogether, no relevant effect modifications were observed for the considered subgroup characteristics. This concurs with the approach of the company, which also determined no relevant effect modifications on the basis of the subgroup characteristics considered by the company.

2.3.3 Probability and extent of added benefit

The derivation of probability and extent of the added benefit for research question A 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 [3].

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

2.3.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.3.2 (see Table 14). As described in Section 2.3.2.1, a joint qualitative consideration of the results of the meta-analysis and of the 3579Ext extension study was conducted.

Determination of the outcome category for symptoms and side effects

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were non-serious/non-severe or serious/severe. The classification of these outcomes is justified below.

Determination of the outcome category for the outcome "acute coronary syndrome"

Acute coronary syndrome was allocated to the outcome category of serious/severe symptoms/late complications as a comparison with the available listings in the study data on SAEs in the total population showed that almost all events were SAEs.

Determination of the outcome category for the outcomes on specific adverse events

The specific AEs "vomiting" and "depression" were allocated to the outcome category of non-serious/non-severe side effects as a comparison with the SAEs showed that the events were non-serious/non-severe.

Table 14: Extent of added benefit at outcome level: insulin degludec + metformin vs. insulin glargine + metformin (research question A)

Outcome category **Outcome**	**IDeg + metformin vs. IGlar + metformin** **Proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	Meta-analysis[c]: 0% vs. 0.5–0.7%[d] RR: 0.18 [0.03; 1.13]; p = 0.067 3579Ext extension study: 0.4% vs. 0.7% RR: 0.58 [0.05; 6.37]; p = 0.536	Lesser benefit/added benefit not proven
Morbidity		
Cardiovascular events (MACE)	Meta-analysis[c]: 0−2.2% vs. 0.7−1.4%[d] RR: 1.18 [0.35; 4.04]; p = 0.788 3579Ext extension study: 4.6% vs. 2.0% RR: 2.33 [0.71; 7.64]; p = 0.166	Lesser benefit/added benefit not proven
Cardiovascular death	Meta-analysis[c]: 0−0.2% vs. 0−0.7%[d] RR: 0.52 [0.06; 4.69]; p = 0.559 3579Ext extension study: 0.4% vs. 0.7% RR: 0.58 [0.05; 6.39]; p = 0.536	Lesser benefit/added benefit not proven
Nonfatal stroke	Meta-analysis[c]: 0−0.2% vs. 0.7−1.0%[d] RR: 0.20 [0.04; 1.11]; 0.066 3579Ext extension study: 1.2% vs. 1.3% RR: 0.87 [0.18; 4.29]; > 0.999	Lesser benefit/added benefit not proven
Acute coronary syndrome	Meta-analysis[c]: 0–2.2% vs. 0%[d] RR: 5.42 [0.70; 41.85]; p = 0.105 3579Ext extension study: 3.3% vs. 0% OR: 7.21 [1.54; ∞); p = 0.012[e] OR: 0.14 (0; 0.65][f] probability: “hint”	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk < 5% greater harm, extent: “considerable”

(continued)

Table 14: Extent of added benefit at outcome level: insulin degludec + metformin vs. insulin glargine + metformin (research question A) (continued)

Outcome category **Outcome**	**IDeg + metformin vs. IGlar + metformin** **Proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Morbidity		
Health status (TRIM-D)		
Daily life	Meta-analysis[c]: 3.17−3.57 vs. 2.70−3.81[d] MD: 0.33 [−1.55; 2.21]; p = 0.730 3579Ext extension study: outcome not recorded	Lesser benefit/added benefit not proven
Psychological health	Meta-analysis[c]: 7.45−8.87 vs. 5.76−8.86[d] MD: 1.18 [−0.54; 2.89]; p = 0.178 3579Ext extension study: outcome not recorded	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36		
Physical Component Summary (PCS)	Meta-analysis[c]: 0.32−0.58 vs. 0.46−0.60[d] MD: 0.88 [0.12; 1.64]; 0.023[g] 3579Ext extension study: −0.14 vs. −2.02 MD: 1.88 [0.25; 3.52]; p = 0.024 Hedges' g: 0.26 [0.00; 0.51][h]	Lesser benefit/added benefit not proven
Mental Component Summary (MCS)	Meta-analysis[c]: 0.92−2.37 vs. 0.67−1.46[d] MD: 0.31 [−0.69; 1.31]; 0.541 3579Ext extension study: 0.70 vs. 0.05 MD: 0.65 [−1.43; 2.73]; 0.541	Lesser benefit/added benefit not proven
Side effects		
SAEs	Meta-analysis[c]: 2.7−7.7% vs. 4.7−11.9%[d] RR: 0.72 [0.48; 1.08]; p = 0.114 3579Ext extension study: 15.4 vs. 16.6% RR: 0.93 [0.62; 1.40]; p = 0.705	Greater/lesser harm not proven

(continued)

Table 14: Extent of added benefit at outcome level: insulin degludec + metformin vs. insulin glargine + metformin (research question A) (continued)

Outcome category **Outcome**	**IDeg + metformin vs. IGlar + metformin** **Proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
Discontinuation due to AEs	Meta-analysis[c]: 0.5−2.7% vs. 1.0−1.4%[d] RR: 1.17 [0.43; 3.21]; p = 0.755 3579Ext extension study: 4.0% vs. 2.6% RR: 1.53 [0.53; 4.38]; p = 0.625	Greater/lesser harm not proven
Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 56 mg/dL), total	Meta-analysis[c]: 16.5−33.7% vs. 20.9−37.7%[d] RR: 0.89 [0.75; 1.06]; p = 0.182 3579Ext extension study: 45.7% vs. 47.0% RR: 0.97 [0.80; 1.18]; p = 0.781	Greater/lesser harm not proven
Severe hypoglycaemic episodes (SAEs)	Meta-analysis[c]: 0−0.5% vs. 0−1.0%[d] RR: 0.43 [0.09; 2.12]; p = 0.299 3579Ext extension study: 0.6% vs. 0.7% RR: 0.87 [0.09; 8.33]; > 0.999	Greater/lesser harm not proven
Renal function disorder (SAE, SOC)	Meta-analysis[c]: 0−0.2% vs. 00.7%[d] RR: 0.24 [0.02; 2.60]; p = 0.238 3579Ext extension study: 0.6% vs. 2.0% RR: 0.29 [0.06; 1.43]; 0.108	Greater/lesser harm not proven
Vomiting (PT)	Meta-analysis[c]: 0.8−2.9% vs. 1.0−6.0%[d] RR: 0.66 [0.34; 1.25]; p = 0.201 3579Ext extension study: 3.5% vs. 7.9% RR: 0.44 [0.22; 0.89]; p = 0.023 probability: “hint”	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ lesser harm, extent: “minor”

(continued)

Table 14: Extent of added benefit at outcome level: insulin degludec + metformin vs. insulin glargine + metformin (research question A) (continued)

Outcome category **Outcome**	**IDeg + metformin vs. IGlar + metformin** **Proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
Depression (PT)	Meta-analysis[c]: 0−1.2% vs. 0−0.7%[d] RR: 1.76 [0.37; 8.39]; p = 0.475 3579Ext extension study: 2.9% vs. 0% OR: 6.303 [1.353; ∞); p = 0.020[e] OR: 0.16 (0; 0.74][f] probability: “hint”	Outcome category: non-serious/non-severe side effects greater harm, extent: “considerable”

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Meta-analysis of the studies NN1250-3579, NN1250-3587 and NN3672.
d: Minimum and maximum proportions of events or mean changes in each treatment arm in the included studies.
e: Institute’s calculation, exact conditional logistic regression according to [9], one-sided p-value.
f: Institute’s calculation: reversed direction of effect to enable use of limits to derive the extent of the added benefit.
g: No common effect estimate provided due to heterogeneous data. Since the effects were not in the same direction, no added benefit was derived.
h: If the CI of Hedges’ g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; IDeg: insulin degludec; IGlar: insulin glargine; MACE: major adverse cardiovascular event; MD: mean difference; OR: odds ratio; PG: plasma glucose; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SAE: serious adverse event; SOC: System Organ Class; TRIM-D: Treatment-Related Impact Measure for Diabetes; vs.: versus

2.3.3.2 Overall conclusion on added benefit

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

Table 15: Positive and negative effects from the assessment of insulin degludec + metformin in comparison with insulin glargine + metformin (research question A)

Positive effects	Negative effects
–	Serious/severe symptoms/late complications acute coronary syndrome hint of greater harm – extent: “considerable”
Non-serious/non-severe side effects ▪ vomiting (PT) hint of lesser harm – extent: “minor”	Non-serious/non-severe side effects ▪ depression (PT) hint of greater harm – extent: “considerable”
PG: plasma glucose; PT: Preferred Term; SAE: serious adverse event	

The overall consideration of the data showed both positive and negative effects of insulin degludec + metformin versus insulin glargine + metformin. In summary, the negative effects, particularly the hint of greater harm regarding acute coronary syndrome (outcome category “serious/severe symptoms/late complications”) outweighed the positive effects, however. This resulted in a hint of lesser benefit of insulin degludec + metformin versus insulin glargine + metformin.

Due to the therapy targeted at a uniform FPG level between 90 and 125 mg/dL, the conclusions on added benefit or lesser benefit are limited to patients with the treatment goal of near-normal blood glucose levels with basal supported oral therapy. An added benefit or lesser benefit is not proven for patients without this treatment goal.

This assessment deviates from that of the company, which, based on the data presented, derived overall proof of a minor added benefit of insulin degludec for patients of research question A.

2.3.4 List of included studies

NN1250-3579

Novo Nordisk. Comparison of NN1250 versus insulin glargine in subjects with type 2 diabetes (BEGIN): study results [online]. In: ClinicalTrials.gov. 09.02.2017 [Accessed: 24.01.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00982644.

Novo Nordisk. A 52-week randomised, controlled, open label, multicentre, multinational treat-to-target trial comparing the efficacy and safety of NN1250 and insulin glargine, both injected daily in combination with oral anti-diabetic drugs (OADs), in subjects with type 2 diabetes mellitus currently treated with OADs and qualifying for more intensified treatment (BEGIN: Once Long); report synopsis [online]. In: EU Clinical Trials Register. 31.05.2011 [Accessed: 24.01.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/rest/download/result/attachment/2008-005776-27/1/6409.

Novo Nordisk. A 52-week randomised, controlled, open label, multicentre, multinational treat-to-target trial comparing the efficacy and safety of SIBA and insulin glargine, both injected once daily in combination with oral anti-diabetic drugs (OAD), in subjects with type 2 diabetes mellitus currently treated with OAD(s) and qualifying for more intensified treatment [online]. In: EU Clinical Trials Register. [Accessed: 24.01.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-005776-27.

Novo Nordisk. Comparison of NN1250 versus insulin glargine in subjects with type 2 diabetes (BEGIN): study details [online]. In: ClinicalTrials.gov. 09.02.2017 [Accessed: 24.01.2019]. URL: https://ClinicalTrials.gov/show/NCT00982644.

Novo Nordisk. A 52-week randomised, controlled, open label, multicentre, multinational treat-to-target trial comparing the efficacy and safety of NN1250 and insulin glargine, both injected daily in combination with oral anti-diabetic drugs (OADs), in subjects with type 2 diabetes mellitus currently treated with oads and qualifying for more intensified treatment (BEGIN: Once Long); study NN1250-3579; clinical trial report [unpublished]. 2011.

Novo Nordisk. A 52-week randomised, controlled, open label, multicentre, multinational treat-to-target trial comparing the efficacy and safety of SIBA and insulin glargine, both injected once daily in combination with oral anti-diabetic drugs (OAD), in subjects with type 2 diabetes mellitus currently treated with OAD(s) and qualifying for more intensified treatment: study NN1250-3579; statistical analysis plan [unpublished]. 2011.

Novo Nordisk. A 52-week randomised, controlled, open label, multicentre, multinational treat-to-target trial comparing the efficacy and safety of SIBA and insulin glargine, both injected once daily in combination with oral anti-diabetic drugs (OAD), in subjects with type 2 diabetes mellitus currently treated with OAD(s) and qualifying for more intensified treatment; study NN1250-3579; Zusatzanalysen [unpublished]. 2018.

Novo Nordisk. A 52-week randomised, controlled, open label, multicentre, multinational treat-to-target trial comparing the efficacy and safety of SIBA and insulin glargine, both injected once daily in combination with oral anti-diabetic drugs (OAD), in subjects with type 2 diabetes mellitus currently treated with OAD(s) and qualifying for more intensified treatment: study NN1250-3579; clinical study protocol; version 3.0 [unpublished]. 2009.

Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care 2012; 35(12): 2464-2471.

Study NN1250-3587

Mu YM, Guo LX, Li L, Li YM, Xu XJ, Li QM et al. The efficacy and safety of insulin degludec versus insulin glargine in insulin-naive subjects with type 2 diabetes: results of a Chinese cohort from a multinational randomized controlled trial [Chinese]. Zhonghua Nei Ke Za Zhi 2017; 56(9): 660-666.

Novo Nordisk. A trial comparing efficacy and safety of insulin degludec and insulin glargine in insulin naïve subjects with type 2 diabetes (BEGIN): study results [online]. In: ClinicalTrials.gov. 07.04.2017 [Accessed: 24.01.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01849289.

Novo Nordisk. A trial comparing efficacy and safety of insulin degludec and insulin glargine in insulin naïve subjects with type 2 diabetes (BEGIN): study details [online]. In: ClinicalTrials.gov. 07.04.2017 [Accessed: 24.01.2019]. URL: https://ClinicalTrials.gov/show/NCT01849289.

Novo Nordisk. BEGIN: ONCE; a trial comparing efficacy and safety of insulin degludec and insulin glargine in insulin naïve subjects with type 2 diabetes; a 26-week, multinational, randomised, open-label, two-arm, parallel-group, treat-to-target trial comparing efficacy and safety of insulin degludec once daily (OD) and insulin glargine OD both in combination with metformin in insulin-naïve subjects with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs (OADs); study NN1250-3587; clinical trial report [unpublished]. 2014.

Novo Nordisk. BEGIN: ONCE; a trial comparing efficacy and safety of insulin degludec and insulin glargine in insulin naïve subjects with type 2 diabetes; a 26-week, multinational, randomised, open-label, two-arm, parallel-group, treat-to-target trial comparing efficacy and safety of insulin degludec once daily (OD) and insulin glargine OD both in combination with metformin in insulin-naïve subjects with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs (OADs); study NN1250-3587; clinical study protocol; version 2.0 [unpublished]. 2010.

Novo Nordisk. BEGIN: ONCE; a trial comparing efficacy and safety of insulin degludec and insulin glargine in insulin naïve subjects with type 2 diabetes; a 26-week, multinational, randomised, open-label, two-arm, parallel-group, treat-to-target trial comparing efficacy and safety of insulin degludec once daily (OD) and insulin glargine OD both in combination with metformin in insulin-naïve subjects with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs (OADs); study NN1250-3587; statistical analysis plan [unpublished]. 2014.

Novo Nordisk. BEGIN: ONCE; a trial comparing efficacy and safety of insulin degludec and insulin glargine in insulin naïve subjects with type 2 diabetes: a 26-week, multinational, randomised, open-label, two-arm, parallel-group, treat-to-target trial comparing efficacy and safety of insulin degludec once daily (OD) and insulin glargine OD both in combination with metformin in insulin-naïve subjects with type 2 diabetes mellitus inadequately controlled on oral antidiabetic drugs (OADs); study NN1250-3587; Zusatzanalysen [unpublished]. 2018.

Pan C, Gross JL, Yang W, Lv X, Sun L, Hansen CT et al. A Multinational, randomized, open-label, treat-to-target trial comparing insulin degludec and insulin glargine in insulin-naive patients with type 2 diabetes mellitus. Drugs R D 2016; 16(2): 239-249.

Study NN1250-3643 (Extension study to study NN1250-3579)

Novo Nordisk. Comparison of NN1250 versus insulin glargine in subjects with type 2 diabetes (BEGIN): study results [online]. In: ClinicalTrials.gov. 09.02.2017 [Accessed: 24.01.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00982644.

Novo Nordisk. An extension trial to NN1250-3579 comparing safety and efficacy of NN1250 plus OAD(s) with insulin glargine plus OAD(s) in type 2 diabetes [BEGINTM: Once Long]: report synopsis [online]. In: EU Clinical Trials Register. 22.02.2013 [Accessed: 24.01.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/rest/download/result/attachment/2009-015754-38/1/6408.

Novo Nordisk. An extension trial to NN1250-3579 comparing safety and efficacy of NN1250 plus OAD(s) with insulin glargine plus OAD(s) in type 2 diabetes [online]. In: EU Clinical Trials Register. [Accessed: 24.01.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-015754-38.

Novo Nordisk. Comparison of NN1250 versus insulin glargine in subjects with type 2 diabetes (BEGIN): study details [online]. In: ClinicalTrials.gov. 09.02.2017 [Accessed: 24.01.2019]. URL: https://ClinicalTrials.gov/show/NCT00982644.

Novo Nordisk. An extension trial to NN1250-3579 comparing safety and efficacy of NN1250 plus OAD(s) with insulin glargine plus OAD(s) in type 2 diabetes (BEGIN: Once Long); study NN1250-3643; clinical study report [unpublished]. 2013.

Novo Nordisk. BEGIN: ONCE LONG; an extension trial to NN1250-3579 comparing safety and efficacy of NN1250 plus OAD(s) with insulin glargine plus OAD(s) in type 2 diabetes; study NN1250-3643; statistical analysis plan [unpublished]. 2013.

Novo Nordisk. BEGIN: ONCE LONG; an extension trial to NN1250-3579 comparing safety and efficacy of NN1250 plus OAD(s) with insulin glargine plus OAD(s) in type 2 diabetes; study NN1250-3643; Zusatzanalysen [unpublished]. 2018.

Novo Nordisk. BEGIN: ONCE LONG; an extension trial to NN1250-3579 comparing safety and efficacy of NN1250 plus OAD(s) with insulin glargine plus OAD(s) in type 2 diabetes; study NN1250-3643; clinical study protocol [unpublished]. 2009.

Rodbard HW, Cariou B, Zinman B, Handelsman Y, Philis-Tsimikas A, Skjoth TV et al. Comparison of insulin degludec with insulin glargine in insulin-naive subjects with Type 2 diabetes: a 2-year randomized, treat-to-target trial. Diabet Med 2013; 30(11): 1298-1304.

Rodbard HW, Cariou B, Zinman B, Handelsman Y, Wolden ML, Rana A et al. Health status and hypoglycaemia with insulin degludec versus insulin glargine: a 2-year trial in insulin-naive patients with type 2 diabetes. Diabetes Obes Metab 2014; 16(9): 869-872.

Study NN1250-3672

Gough SC, Bhargava A, Jain R, Mersebach H, Rasmussen S, Bergenstal RM. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naive patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: the BEGIN LOW VOLUME trial. Diabetes Care 2013; 36: 2536-2542.

Novo Nordisk. Comparison of NN1250 with insulin glargine in subjects with type 2 diabetes (BEGIN): study results [online]. In: ClinicalTrials.gov. 06.03.2017 [Accessed: 24.01.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01068665.

Novo Nordisk. Comparison of NN12501 with insulin glargine in subjects with type 2 diabetes (BEGIN): report synopsis [online]. In: EU Clinical Trials Register. 31.05.2011 [Accessed: 24.01.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/rest/download/result/attachment/2009-010662-28/1/6424.

Novo Nordisk. A trial comparing efficacy and safety of NN1250 and insulin glargine in subjects with type 2 diabetes [online]. In: EU Clinical Trials Register. [Accessed: 24.01.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-010662-28.

Novo Nordisk. Comparison of NN1250 with insulin glargine in subjects with type 2 diabetes (BEGIN): study details [online]. In: ClinicalTrials.gov. 06.03.2017 [Accessed: 24.01.2019]. URL: https://ClinicalTrials.gov/show/NCT01068665.

Novo Nordisk. BEGIN: LOW VOLUME; a trial comparing efficacy and safety of NN1250 and insulin glargine in subjects with type 2 diabetes; study NN1250-3672; clinical study protocol; version 3 [unpublished]. 2009.

Novo Nordisk. BEGIN: LOW VOLUME; a trial comparing efficacy and safety of NN1250 and insulin glargine in subjects with type 2 diabetes; study NN1250-3672; clinical trial report [unpublished]. 2011.

Novo Nordisk. BEGIN: LOW VOLUME; a trial comparing efficacy and safety of NN1250 and insulin glargine in subjects with type 2 diabetes; study NN1250-3672; statistical analysis plan [unpublished]. 2011.

Novo Nordisk. BEGIN: LOW VOLUME; a trial comparing efficacy and safety of NN1250 and insulin glargine in subjects with type 2 diabetes; study NN1250-3672; Zusatzanalysen [unpublished]. 2018.

Shestakova MV, Antciferov MB, Maiorov AY, Ruyatkina LA, Suplotova LA, Dogadin SA et al. Insulin degludec: a new basal insulin analogue with an ultra-long duration of action; safety and efficacy in Russian patients with diabetes. Diabetes mellitus 2015; 18(4): 130-141.

2.4 Research question B (patients pretreated with insulin)

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 (status: 5 September 2018)
- bibliographical literature search on insulin degludec (last search on 4 September 2018)
- search in trial registries for studies on insulin degludec (last search on 5 September 2018)

To check the completeness of the study pool:

- search in trial registries for studies on insulin degludec (last search on 17 December 2018)

No additional relevant studies were identified from the check.

The company identified 3 studies of direct comparisons from the steps of information retrieval mentioned: NN1250-3582 (including the NN1250-3667 extension study), NN1250-3668 and NN1250-3998. The NN1250-3582 study (including the NN1250-3667 extension study) investigated the comparison of insulin degludec + insulin aspart ± metformin versus insulin glargine + insulin aspart ± metformin. The 2 studies NN1250-3668 and NN1250-3998 compared insulin degludec ± metformin versus insulin glargine ± metformin.

Only the NN1250-3582 study and its extension study NN1250-3667 were relevant for the present research question.

The 2 studies NN1250-3668 [11] and NN1250-3998 [12], in contrast, were not relevant for the present benefit assessment. The G-BA defined optimization of the human insulin regimen as ACT for research question B. It further specified that continuation of an inadequate treatment regimen for type 2 diabetes mellitus did not concur with the ACT. The patients in both studies did not receive meaningful escalation of their ongoing insulin therapy, which was demonstrably inadequate. This is explained in detail below.

Study NN1250-3668

The NN1250-3668 study was an open-label, multicentre 3-arm RCT on the comparison of 2 different dosing regimens of insulin degludec (± OADs) and insulin glargine (± OADs). The study included adult patients with type 2 diabetes mellitus and inadequate glycaemic control (pretreatment with OADs [insulin-naive patients] or with basal insulin ± OADs). The company considered the subpopulation of patients pretreated with insulin for research question B. The explanations below only refer to the subpopulation considered by the company.

The patients in the study were randomly allocated to basal insulin treatment with insulin degludec or insulin glargine. For this purpose, the ongoing treatment with basal insulin in all

patients was discontinued before study start and switched to the insulin components of the study medication. The patients received either insulin degludec or insulin glargine once daily subcutaneously as study medication. Switching from the prior basal insulin to insulin degludec or insulin glargine corresponded to the prior basal insulin dose if this was applied once daily; otherwise, the basal insulin dose was reduced. In both study arms, the dose was uniformly titrated on the basis of the FPG to a target level of 5.0 to 7.0 mmol/L (90 to 125 mg/dL).

Hence, the therapeutic strategy was unchanged in both treatment arms of the NN1250-3668 study; only the dose of the basal insulin (insulin degludec or insulin glargine) was uniformly titrated on the basis of FPG levels to reach near-normal blood-glucose levels. The uniform continuation of the therapeutic strategy targeted at near-normal blood glucose levels, which was already in place before study inclusion, was inadequate in the present situation, however. Instead, in view of a demonstrably insufficient prior therapy, it would have been necessary to define individual targets and strategies for the patients with the option to change the strategy.

Changing the strategy is in line with treatment recommendations in CPGs [7,13], 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 [7]) 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 in the present treatment situation can consist in conventional insulin therapy (e.g. with mixed insulin) or intensified insulin therapy [7,13].

The study and intervention characteristics of the NN1250-3668 study are presented in Appendix C.1 of the full dossier assessment.

Study NN1250-3998

The NN1250-3998 study was an open-label, multicentre 2-arm RCT on the comparison of insulin degludec (± OADs) and insulin glargine (± OADs). The study included adult patients with type 2 diabetes mellitus and inadequate glycaemic control (HbA1c ≤ 9.5%) despite treatment with basal insulin ± OADs (metformin ± thiazolidinediones ± sulfonylureas ± glinides ± SGLT 2 inhibitors). In addition, patients had to have an increased risk of hypoglycaemia. This was operationalized as at least one severe hypoglycaemic episode within the previous year.

For its analyses, the company included the subpopulation of patients who had only received treatment with metformin (+ basal insulin).

The patients received either insulin degludec or insulin glargine once daily subcutaneously as study medication. Switching from the prior basal insulin to insulin degludec or insulin glargine corresponded to the prior basal insulin dose if this was applied once daily; otherwise, the basal insulin dose was reduced. In both study arms, the dose was uniformly titrated on the basis of the FPG to a target level of 4.0 to 5.0 mmol/L (71 to 90 mg/dL).

Hence, also in the NN1250-3998 study, the therapeutic strategy – continuation of basal insulin therapy – was unchanged in both treatment arms. Furthermore, it was notable in this study that the treatment goal in patients with increased risk of hypoglycaemia was a very low blood glucose level, using a therapeutic strategy that was demonstrably unsuitable for these patients.

The study and intervention characteristics of the NN1250-3998 study are presented in Appendix C.1 of the full dossier assessment.

2.4.1.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 16: Study pool – RCT, insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
NN1250-3582 (with the NN1250-3667 extension study)	Yes	Yes	No
a: Study sponsored by the company. RCT: randomized controlled trial; vs.: versus			

Section 2.5 contains a reference list for the studies included.

2.4.1.2 Study characteristics

Table 17 and Table 18 describe the studies used for the benefit assessment.

Table 17: Characteristics of the study included – RCT, direct comparison: insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
NN1250-3582 (with the NN1250-3667 extension study)	RCT, open-label, parallel, treat-to-target	Adults with type 2 diabetes mellitus for ≥ 6 months, without prior cardiovascular disease[b] Pretreatment with insulin ± OAD for at least 3 months HbA1c: 7.0–10%	IDeg + IAsp ± metformin ± pioglitazone (N = 755) IGlar + IAsp ± metformin ± pioglitazone (N = 251)	Screening: 1 week Treatment: 52 weeks, then Extension study (NN1250-3667): 26 weeks Follow-up: 1 week[c]	123 centres in Bulgaria, Germany, Hong Kong, Ireland, Italy, Romania, Russia, Slovakia, South Africa, Spain, Turkey, United States 9/2009–10/2010	Primary outcome: change in HbA1c after 52 weeks Secondary outcomes: all-cause mortality, hypoglycaemia, health-related quality of life, AEs

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
b: Within ≤ 6 months prior to the first study visit; defined as stroke, cardiac failure of NYHA class III or IV, myocardial infarction, unstable angina pectoris, coronary artery bypass or angioplasty.
c: For patients who have prematurely discontinued the main or the extension study or at the end of the main or the extension study.
AE: adverse event; HbA1c: glycosylated haemoglobin A1c; IAsp: insulin aspart; IDeg: insulin degludec; IGlar: insulin glargine; N: number of randomized patients; OAD: oral antidiabetic; RCT: randomized controlled trial; vs.: versus

Table 18: Characteristics of the interventions – RCT, direct comparison: insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B)

<table>
<tr><th>Study</th><th>Intervention</th><th>Comparison</th></tr>
<tr><td>NN1250-3582
(with the NN1250-3667 extension study)</td><td>Insulin degludec once/day, SC, with evening meal
+
insulin aspart, titrated to target, 3x/day, SC, prandial
±
metformin[a] ± pioglitazone[a]</td><td>Insulin glargine once/day, SC, at the same time of day
+
insulin aspart, titrated to target, 3x/day, SC, prandial
±</td></tr>
<tr><td></td><td colspan="2">Starting dose, titration, dose increase
<u>Starting dose:</u>
<u>Pretreatment with NPH or other basal insulin</u>
▪ prior basal insulin once/day: same number of units once/day
▪ prior basal insulin ≥ once/day: calculation of the total daily basal insulin dose, depending on the allocated study medication:
▫ insulin glargine arm: reduction by 20–30% recommended in accordance with approval
▫ insulin degludec arm: reduction at investigator’s choice recommended
<u>Pretreatment with bolus and basal insulin (mixed insulins or individual components)</u>
▪ calculation of the total basal insulin components
▪ prior mixed insulin once/day: same number of units once/day
▪ prior mixed insulin ≥ once/day: daily total insulin dose of the basal insulin components once/day, depending on the allocated study medication:
▫ insulin glargine arm: reduction by 20–30% recommended in accordance with approval
▫ insulin degludec arm: reduction at investigator’s choice recommended
<u>Pretreatment without prior basal insulin</u>
▪ insulin degludec or insulin glargine: starting dose 10 units/day
titration based on target value (first of basal insulin, then of bolus insulin)
Titration of the basal insulin on the basis of FPG according to the following regimen:
<table>
<tr><th colspan="2">Mean FPG
(before breakfast on 3 consecutive days, mean value)</th><th>Dose adjustment IDeg or IGlar
(units)</th></tr>
<tr><th>mmol/L</th><th>mg/dL</th><th></th></tr>
<tr><td>< 5.0</td><td>< 90</td><td>No adjustment</td></tr>
<tr><td>< 7.0</td><td>< 126</td><td>+2</td></tr>
<tr><td>< 8.0</td><td>< 144</td><td>+4</td></tr>
<tr><td>< 9.0</td><td>< 162</td><td>+6</td></tr>
<tr><td>≥ 9.0</td><td>≥ 162</td><td>+8</td></tr>
<tr><td>< 3.1 (without evident explanation)</td><td>< 56 (without evident explanation)</td><td>−4[b]</td></tr>
<tr><td>< 3.9 (without evident explanation)</td><td>< 70 (without evident explanation)</td><td>−2[c]</td></tr>
</table></td></tr>
</table>

(continued)

Table 18: Characteristics of the interventions – RCT, direct comparison: insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B) (continued)

<table>
<tr><th>Study</th><th>Intervention</th><th>Comparison</th></tr>
<tr><td></td><td colspan="2">Insulin aspart
Pretreatment with bolus insulin (individual components or as mixed insulin)
▪ prior human insulin or short-acting insulin analogues with meals: continuation of the same units
▪ prior mixed insulin (premixed or mixed manually): calculation of the total number of units of the bolus insulin components, divided by the number of meals; administered with meals
Pretreatment without prior bolus insulin
▪ starting with 4 units with each meal</td></tr>
<tr><td></td><td colspan="2">Titration of the bolus insulin according to the following regimen:
<table><tr><th colspan="2">Mean FPG (before meals)</th><th>Dose adjustment IAsp (units)</th></tr><tr><th>mmol/L</th><th>mg/dL</th><th></th></tr><tr><td>< 5.0</td><td>< 90</td><td>No adjustment</td></tr><tr><td>< 8.0</td><td>< 144</td><td>+2</td></tr><tr><td>< 10.0</td><td>< 180</td><td>+3</td></tr><tr><td>≥ 10.0</td><td>≥ 180</td><td>+4</td></tr></table></td></tr>
<tr><td></td><td colspan="2">Pretreatment and concomitant treatment:
Permitted pretreatment:
▪ basal and bolus insulin ± OAD ≥ 3 months before study start
▪ other OADs (except metformin and pioglitazone) had to be discontinued before randomization
Allowed concomitant treatment:
▪ inhaled corticosteroids
Non-permitted concomitant treatment:
▪ GLP-1 agonists (e.g. exenatide, liraglutide) and/or rosiglitazone ≤ 3 months before study start
▪ systemic corticosteroids, beta-blockers, monoamine oxidase inhibitors
▪ additional antidiabetic medications</td></tr>
<tr><td colspan="3">a: At a stable dosage from baseline.
b: For a prior dose of > 45 units, a 10% reduction is recommended.
c: For a prior dose of > 45 units, a 5% reduction is recommended.
GLP-1: glucagon-like peptide 1; IAsp: insulin aspart; IDeg: insulin degludec; IGlar: insulin glargine; NPH: neutral protamine Hagedorn; OAD: oral antidiabetic; SC: subcutaneous</td></tr>
</table>

Study characteristics

The NN1250-3582 study was a 2-arm, randomized, active-controlled, open-label phase 3 study with a treatment duration of 52 weeks. After a 1-week follow-up phase, the patients could participate in an extension study (NN1250-3667) for another 26 weeks, where they continued their study medication analogous to the NN1250-3582 study. The study had a treat-to-target design, in which fasting plasma glucose was titrated to a specified goal.

Adult patients with type 2 diabetes mellitus who had received insulin treatment with or without OADs for at least 3 months were included in the NN1250-3582 study. With the exception of metformin and pioglitazone, all other OADs were to be discontinued at the time point of randomization; administration of metformin and/or pioglitazone was to be continued without changes during the entire treatment phase. The patients had an HbA1c value of ≥ 7.0% and ≤ 10%.

The NN1250-3582 study investigated the comparison of a combination therapy of insulin degludec and insulin aspart with or without OADs versus a combination therapy of insulin glargine and insulin aspart with or without OADs. A total of 1006 patients were randomly allocated in a 3:1 ratio to the study arms of insulin degludec + insulin aspart (N = 755) and insulin glargine + insulin aspart (N = 251), each in combination with metformin and/or pioglitazone. Of these patients, 75.0% (N = 566) of the patients from the intervention arm and 76.1% (N = 191) of the patients from the control arm continued in the NN1250-3667 extension study without new randomization.

Primary outcome was the change in HbA1c from baseline to week 52. Patient-relevant secondary outcomes were all-cause mortality as well as outcomes on morbidity, health-related quality of life and AEs.

From the study, only a subpopulation of the patients was relevant. Patients receiving metformin only corresponded to the research question if they receive an approval-compliant dosage (1000 to 3000 mg/day). Patients receiving pioglitazone were not relevant for the present research question. The dossier contained no analyses for the relevant subpopulation, however. Since more than 80% of the patients included were relevant for the present research question, however, the data of the total population were used as an auxiliary measure (see Section 2.6.3.3.2 of the full dossier assessment).

Treatment with the study medication

Administration of insulin degludec, insulin glargine and insulin aspart in the NN1250-3582 study and in its extension study NN1250-3667 were in compliance with the respective SPC [5,6,14]. The basal insulin was injected at different time points, however: Insulin degludec was to be administered once daily with the evening meal, whereas insulin glargine was to be administered once daily at the same time of day.

Insulin aspart was administered 3 times daily with the meals. Hence, the treatment regimen administered in the study was consistent with an intensified insulin therapy (ICT) in both treatment arms.

At study start, the patients were switched to basal and bolus insulin doses depending on their pretreatments (see Table 7). During the study, both the doses of the basal insulin component (insulin degludec or insulin glargine) and of the bolus insulin component (insulin aspart) were titrated in the treatment arms; adjustments of the insulin dose were first to be conducted with

the respective basal insulin. The dose of the basal insulin component was based on the FPG values measured by the patient before breakfast on 3 consecutive days. Treatment goals were not specified for the individual patients, but treatment was targeted at a uniform value of 90 to 125 mg/dL. Titration of the dose of the bolus insulin component insulin aspart was also based on FPG values measured by the patient before the respective meals. Treatment goals for the bolus insulin component were also not specified for the individual patients, but treatment was targeted at a uniform value of 90 to 143 mg/dL.

The target values in the NN1250-3582 study for both basal and bolus insulin were below the range of 100 to 125 mg/dL recommended as reference values in the NVL on the treatment of type 2 diabetes mellitus [7].

Patient characteristics

Table 19 shows the characteristics of the patients in the studies included.

Table 19: Characteristics of the study population – RCT, direct comparison: insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B)

Study	**NN1250-3582 (with the NN1250-3667 extension study)**	
Characteristics **Category**	**IDeg + IAsp ± metformin**	**IGlar + IAsp ± metformin**
	N[a] = 744	**N[a] = 248**
Age [years], mean (SD)	59 (9)	58 (10)
Sex [F/M], %	46/54	46/54
BMI [kg/m²], mean (SD)	32.3 (4.7)	31.9 (4.5)
Body weight (kg), mean (SD)	92.6 (17.9)	92.2 (17.2)
Duration of diabetes [years], mean (SD)	13.6 (7.4)	13.4 (6.9)
HbA1c value [%], mean (SD)	8.3 (0.8)	8.4 (0.9)
HbA1c value, n (%)		
< 8%	301 (40.5)	92 (37.1)
≥ 8%	443 (59.5)	156 (62.9)
Antidiabetic therapy at screening, n (%)		
Basal insulin + bolus insulin ≥ 2x daily ± OAD	362 (48.7)	124 (50.0)
Basal insulin + bolus insulin < 2x daily ± OAD	19 (2.6)	3 (1.2)
Mixed insulin ± OAD	181 (24.3)	61 (24.6)
Basal insulin ± OAD	154 (20.7)	56 (22.6)
Bolus insulin ± OAD	28 (3.8)	4 (1.6)
Prior cardiovascular disease [yes/no][b]	ND	ND
Region, n (%)		
Europe	317 (42.6)	107 (43.1)
Non-Europe	427 (57.4)	141 (56.9)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)		
during study	137 (18.1)	40 (15.9)
during extension	27 (3.6)[c]	8 (3.2)[d]

a: Number of randomized patients of the FAS. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Patients with prior cardiovascular disease (defined as stroke, cardiac failure of NYHA class III or IV, myocardial infarction, unstable angina pectoris, coronary artery bypass or angioplasty) within the last 6 months prior to the first study visit were excluded from participation in the studies. There is no information on the number of included patients with prior cardiovascular disease within > 6 months before the first study visit.
c: 566 (75.0%) of the patients (FAS) enrolled in the extension study.
d: 191 (76.1%) of the patients (FAS) enrolled in the extension study.

BMI: body mass index; F: female; FAS: full analysis set; HbA1c: glycosylated haemoglobin A1c; IAsp: insulin aspart; IDeg: insulin degludec; IGlar: insulin glargine; M: male; n: number of patients in the category; N: number of patients of the FAS; ND: no data; NYHA: New York Heart Association; OAD: oral antidiabetic; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The demographic and clinical characteristics of the patients were largely balanced between the individual study arms.

The mean age of the patients in both study arms was about 59 years, and slightly more men than women were included. The mean HbA1c value at baseline was about 8.3% in both study arms. There was no information on treatment discontinuations. The number of patients who discontinued the study was approximately the same in both study arms (17.5%). In the NN1250-3667 extension study, an additional 3.6% and 3.2% of the patients discontinued the study.

Risk of bias across outcomes (study level)

Table 20 shows the risk of bias across outcomes (risk of bias at study level).

Table 20: Risk of bias across outcomes (study level) – RCT, direct comparison: insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
NN1250-3582	Yes	Yes	No	No	Yes	Yes	Low
NN1250-3667[a]	Yes	Yes	No	No	Yes	Yes	Low
a: Extension study to study NN1250-3582. RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low both for the main study NN1250-3582 and for its extension study NN1250-3667. This concurs with the company's assessment.

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

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.3.4.3.2 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity

- cardiovascular events (MACE)
  - cardiovascular death
  - nonfatal stroke
  - acute coronary syndrome
- health status (TRIM-D domains “daily life” and “psychological health”)

- Health-related quality of life
  - SF-36
- Side effects
  - SAEs
  - discontinuation due to AEs
  - non-severe symptomatic hypoglycaemic episodes in total (PG < 56 mg/dL)
  - severe hypoglycaemic episodes (SAEs)
  - renal function disorder (SAE)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 B), but did not consider renal function disorder as separate outcome. The results on non-severe confirmed symptomatic diurnal and nocturnal hypoglycaemic episodes (PG < 56 mg/dL), on the overall rate of AEs, and on changes in HbA1c and body weight are shown as additional information in the present assessment. A detailed explanation on the inclusion of outcomes can be found in Section 2.6.3.4.3.2 of the full dossier assessment.

The company presented analyses on the RRs and on the rate ratios for the outcomes on non-severe confirmed hypoglycaemic episodes (PG < 56 mg/dL) and on severe hypoglycaemic episodes. For the present assessment, the results for the effect measure RR were used for these outcomes. The results on the rate ratios are presented as additional information in Appendix C.3 of the full dossier assessment (for reasons, see Section 2.6.2.4.3.2 of the full dossier assessment).

Table 21 shows for which outcomes data were available in the studies included.

Table 21: Matrix of outcomes – RCT, direct comparison: insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B)

Study	Outcomes											
	All-cause mortality	Cardiovascular events (MACE)[a]	Cardiovascular death	Nonfatal stroke	Acute coronary syndrome	Health status (TRIM-D[b])	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Non-severe confirmed symptomatic hypoglycaemic episodes in total (PG < 56 mg/dL)	Severe hypoglycaemic episodes (SAEs)	Renal function disorder[c]
NN1250-3582	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
NN1250-3667[d]	Yes	Yes	Yes	Yes	Yes	No[e]	No[e]	Yes	Yes	Yes	Yes	Yes

a: Composite outcome: first occurrence of one of the events "cardiovascular death", "nonfatal stroke" or "acute coronary syndrome".
b: PCS and MCS are considered.
c: The following events (MedDRA coding) are considered: renal function disorder (SOC, SAE).
d: Extension study to study NN1250-3582.
e: Outcome not recorded in the extension study.

AE: adverse event; MACE: major adverse cardiovascular event; MCS: Mental Component Summary; MedDRA: Medical Dictionary for Regulatory Activities; PCS: Physical Component Summary; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; TRIM-D: Treatment-Related Impact Measure for Diabetes; vs.: versus

2.4.2.2 Risk of bias

Table 22 describes the risk of bias for the results of the relevant outcomes.

Table 22: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B)

Study	Study level	Outcomes											
		All-cause mortality	Cardiovascular events (MACE)[b]	Cardiovascular death	Nonfatal stroke	Acute coronary syndrome	Health status (TRIM-D)[c]	Health-related quality of life (SF-36v2)[d]	SAEs	Discontinuation due to AEs	Non-severe confirmed symptomatic hypoglycaemic episodes in total (PG < 56 mg/dL)	Severe hypoglycaemic episodes (SAEs)	Renal function disorder[e]
NN1250-3582	L	L	L	L	L	L	H[f, g]	H[f, g]	L	H[f]	H[f]	L	L
NN1250-3667[a]	L	H[h]	H[h]	H[h]	H[h]	H[h]	-[i]	-[i]	H[h]	H[f, h]	H[f, h]	H[h]	H[h]

a: Extension study to study NN1250-3582.
b: Composite outcome: first occurrence of one of the events "cardiovascular death", "nonfatal stroke" or "acute coronary syndrome".
c: The domains "daily life" and "psychological health" are considered.
d: PCS and MCS are considered.
e: The following events (MedDRA coding) are considered: renal function disorder (SOC, SAE).
f: Due to incomplete blinding in subjective recording of outcomes.
g: The results on Hedges' g are potentially highly biased because the estimation is unclear; proportions of missing values > 10% at end of study.
h: Possibly large proportion of patients with incomplete observation.
i: Outcome not recorded in the extension study.

AE: adverse event; H: high; L: low; MACE: major adverse cardiovascular event; MCS: Mental Component Summary; MedDRA: Medical Dictionary for Regulatory Activities; PCS: Physical Component Summary; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SOC: System Organ Class; TRIM-D: Treatment-Related Impact Measure for Diabetes; vs.: versus

For the NN1250-3582 study, the risk of bias was rated as low for the results on the outcomes "all-cause mortality", "cardiovascular events (MACE)" including the individual components "cardiovascular death", "nonfatal stroke" and "acute coronary syndrome", as well as on the side effect outcomes "SAEs" and "severe hypoglycaemia". This is consistent with the assessment of the company, which determined the risk of bias only for the results on the superordinate composite outcome "cardiovascular events (MACE)", but not for their individual components. The risk of bias for the result of the outcome "renal function disorder" was also rated as low. The company did not consider this outcome and hence did not rate the risk of bias.

Due to the lack of blinding in subjective recording of outcomes, the risk of bias was rated as high for the results on all other outcomes (health status measured with the instrument TRIM-D, health-related quality of life measured with the instrument SF-36, discontinuation due to AEs, non-severe symptomatic hypoglycaemic episodes in total [PG < 56 mg/dL]). The risk of bias for the results on the outcomes "health status (TRIM-D)" and "health-related quality of life (SF-36)" was high also because the results on Hedges' g were potentially highly biased due to the unclear estimation. In addition, the proportions of the missing values were > 10% at the end of study. This is largely consistent with the assessment of the company, which also rated the risk of bias as high for the results on these outcomes except non-severe confirmed hypoglycaemia.

For the NN1250-3667 extension study, the risk of bias was rated as high for all outcomes as there may have been a large proportion of patients with incomplete observation for the outcomes "all-cause mortality" and "cardiovascular events" (including the individual components) as well as all side effect outcomes.

This deviates from the assessment of the company, which rated the risk of bias as low for the outcomes "all-cause mortality", "cardiovascular events", "SAEs", "non-severe symptomatic hypoglycaemic episodes (PG < 56 mg/dL)" and "severe hypoglycaemic episodes" also for the extension study.

A detailed explanation on the risk of bias can be found in Section 2.6.3.4.2 of the full dossier assessment.

2.4.2.3 Results

Table 23 and Table 24 summarize the results on the comparison of insulin degludec with insulin glargine (each in combination with insulin aspart and possibly metformin) in patients pretreated with insulin. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The analyses of the rate ratios for the outcomes "non-severe confirmed symptomatic hypoglycaemic episodes (PG < 56 mg/dL)" and "severe hypoglycaemic episodes" are presented as additional information in Appendix C.3 of the full dossier assessment. Tables on common AEs can be found in Appendix C.4 of the full dossier assessment.

Table 23: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B)

Study **Outcome category** **Outcome** **Time point**	**IDeg + IAsp ± metformin** **N**	**IDeg + IAsp ± metformin** **Patients with event n (%)**	**IGlar + IAsp ± metformin** **N**	**IGlar + IAsp ± metformin** **Patients with event n (%)**	**IDeg + IAsp ± metformin vs. IGlar + IAsp ± metformin** **RR [95% CI]; p-value**
NN 1250-3582 (52 weeks) / NN1250-3667[a] (78 weeks)					
Mortality					
All-cause mortality					
52 weeks	744	8 (1.1)	248	2 (0.8)	1.33 [0.29; 6.24]; > 0.999
78 weeks	744	11 (1.5)	248	2 (0.8)	1.83 [0.41; 8.21]; 0.536
Morbidity					
Cardiovascular events (MACE)					
52 weeks	742	18 (2.4)	248	4 (1.6)	1.50 [0.51; 4.40]; 0.620
78 weeks	742	29 (3.9)	248	7 (2.8)	1.38 [0.61; 3.12]; 0.557
Cardiovascular death					
52 weeks	742	4 (0.5)	248	1 (0.4)	1.34 [0.15; 11.91]; > 0.999
78 weeks	742	5 (0.7)	248	1 (0.4)	1.67 [0.20; 14.24]; > 0.999
Nonfatal stroke					
52 weeks	742	3 (0.4)	248	0 (0)	ND; 0.577
78 weeks	742	7 (0.9)	248	0 (0)	ND; 0.202
Acute coronary syndrome					
52 weeks	742	11 (1.5)	248	3 (1.2)	1.23 [0.34; 4.36]; > 0.999
78 weeks	742	17 (2.3)	248	6 (2.4)	0.95 [0.38; 2.38]; > 0.999
Side effects					
AEs (additional information)					
52 weeks	*744*	*605 (81.3)*	*248*	*199 (80.2)*	-
78 weeks	*744*	*625 (84.0)*	*248*	*208 (83.9)*	-
SAEs					
52 weeks	744	111 (14.9)	248	40 (16.1)	0.93 [0.66; 1.29]; 0.683
78 weeks	744	138 (18.5)	248	53 (21.4)	0.87 [0.65; 1.15]; 0.353
Discontinuation due to AEs					
52 weeks	744	31 (4.2)	248	9 (3.6)	1.15 [0.55; 2.38]; 0.853
78 weeks	744	35 (4.7)	248	9 (3.6)	1.30 [0.63; 2.66]; 0.594

(continued)

Table 23: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B) (continued)

Study **Outcome category** **Outcome** **Time point**	**IDeg + IAsp ± metformin** **N**	**Patients with event n (%)**	**IGlar + IAsp ± metformin** **N**	**Patients with event n (%)**	**IDeg + IAsp ± metformin vs. IGlar + IAsp ± metformin** **RR [95% CI]; p-value**
Non-severe confirmed symptomatic hypoglycaemic episodes in total (PG < 56 mg/dL)					
52 weeks	744	556 (74.7)	248	188 (75.8)	0.99 [0.91; 1.07]; 0.800
78 weeks	744	581 (78.1)	248	192 (77.4)	1.01 [0.93 1.09]; 0.860
Non-severe confirmed symptomatic diurnal hypoglycaemic episodes (PG < 56 mg/dL) (additional information)					
52 weeks	*744*	*537 (72.2)*	*248*	*180 (72.6)*	*0.99 [0.91 1.09]; 0.935*
78 weeks	*744*	*563 (75.7)*	*248*	*185 (74.6)*	*1.01 [0.93 1.10]; 0.734*
Non-severe confirmed symptomatic nocturnal hypoglycaemic episodes (PG < 56 mg/dL) (additional information)					
52 weeks	*744*	*256 (34.4)*	*248*	*113 (45.6)*	*0.76 [0.64 0.89]; 0.002*
78 weeks	*744*	*278 (37.4)*	*248*	*127 (51.2)*	*0.73 [0.63; 0.85]; < 0.001*
Severe hypoglycaemic episodes (SAEs)					
52 weeks	744	19 (2.6)	248	3 (1.2)	2.11 [0.63 7.07]; 0.319
78 weeks	744	20 (2.7)	248	3 (1.2)	2.22 [0.67 7.41]; 0.228
Renal function disorder (SAE, SOC)					
52 weeks	753	2 (0.3)	251	2 (0.8)	0.33 [0.05; 2.35]; 0.257[b]
78 weeks	753	2 (0.3)	251	3 (1.2)	0.22 [0.04; 1.32]; 0.071[b]

a: Extension study to study NN1250-3582.
b: Institute's calculation, p-value from unconditional exact test (CSZ method according to [8]).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; IAsp: insulin aspart; IDeg: insulin degludec; IGlar: insulin glargine; MACE: major adverse cardiovascular event; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculated; ND: no data; PG: plasma glucose; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 24: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B)

Study **Outcome category** **Outcome** **Time point**	**IDeg + IAsp ± metformin** **N[a]**	**Values at baseline mean (SD)**	**Change at end of study mean (SE)**	**IGlar + IAsp ± metformin** **N[a]**	**Values at baseline mean (SD)**	**Change at end of study mean (SE)**	**IDeg + IAsp ± metformin vs. IGlar + IAsp ± metformin** **MD [95% CI]; p-value**
NN 1250-3582 (52 weeks) / NN1250-3667[b] (78 weeks)							
Morbidity							
Health status							
TRIM-D[c]							
Daily life							
52 weeks	744	72.05 (18.2)	3.02 (0.67)	248	72.43 (17.5)	2.88 (1.15)	0.14 [−2.48; 2.75]; 0.919
78 weeks	Outcome not recorded						
Psychological health							
52 weeks	744	75.87 (17.3)	5.14 (0.61)	248	73.67 (18.7)	5.26 (1.06)	−0.12 [−2.52 2.29]; 0.924
78 weeks	Outcome not recorded						
Health-related quality of life							
SF-36v2[c]							
PCS							
52 weeks	744	45.25 (9.25)	−0.35 (0.28)	248	44.53 (8.89)	−0.64 (0.48)	0.28 [−0.80 1.37]; 0.609
78 weeks	Outcome not recorded						
MCS							
52 weeks	744	47.89 (11.2)	1.21 (0.34)	248	48.72 (10.6)	0.29 (0.59)	0.92 [−0.42; 2.26]; 0.176
78 weeks	Outcome not recorded						
General health perception							
52 weeks	736	42.6 (9.6)	0.6 (0.5)[d]	243	41.7 (10.1)	0.1 (0.6)[d]	-
78 weeks	Outcome not recorded						
Physical functioning							
52 weeks	734	44.8 (10.5)	−1.1 (0.6)[d]	245	45.3 (10.0)	−1.0 (0.7)[d]	-
78 weeks	Outcome not recorded						
Physical role functioning							
52 weeks	732	45.3 (10.3)	−1.6 (0.6)[d]	244	45.9 (10.1)	−1.9 (0.7)[d]	-
78 weeks	Outcome not recorded						

(continued)

Table 24: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B) (continued)

Study **Outcome category** **Outcome** **Time point**	**IDeg + IAsp ± metformin**			**IGlar + IAsp ± metformin**			**IDeg + IAsp ± metformin vs. IGlar + IAsp ± metformin**
	N[a]	**Values at baseline mean (SD)**	**Change at end of study mean (SE)**	**N[a]**	**Values at baseline mean (SD)**	**Change at end of study mean (SE)**	**MD [95% CI]; p-value**
Bodily pain							
52 weeks	735	46.9 (11.0)	−0.7 (0.6)[d]	247	46.6 (10.9)	−2.2 (0.8)[d]	-
78 weeks	Outcome not recorded						
Emotional role functioning							
52 weeks	731	44.5 (12.0)	−1.1 (0.7)[d]	244	45.7 (11.3)	−1.7 (0.8)[d]	-
78 weeks	Outcome not recorded						
Mental wellbeing							
52 weeks	726	47.8 (11.1)	0.1 (0.6)[d]	244	48.1 (11.0)	−0.5 (0.7)[d]	-
78 weeks	Outcome not recorded						
Social functioning							
52 weeks	737	47.3 (10.3)	0.4 (0.6)[d]	248	47.2 (10.3)	−0.8 (0.8)[d]	-
78 weeks	Outcome not recorded						
Vitality							
52 weeks	726	49.1 (10.6)	−0.5 (0.6)[d]	244	49.0 (9.9)	−0.7 (0.7)[d]	-
78 weeks	Outcome not recorded						

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at the start of the study may be based on other patient numbers.
b: Extension study to study NN1250-3582.
c: Higher values indicate better health-related quality of life; a positive difference indicates an advantage for the intervention.
d: Least squares estimate from ANOVA; treatment, sex, region and antidiabetic therapy at screening as fixed effects, and age and baseline value as covariates.

ANOVA: analysis of variance; CI: confidence interval; IAsp: insulin aspart; IDeg: insulin degludec; IGlar: insulin glargine; MCS: Mental Component Summary; MD: mean difference; N: number of analysed patients; ND: no data; PCS: Physical Component Summary; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; TRIM-D: Treatment-Related Impact Measure for Diabetes; vs.: versus

Table 25: Results (supplementary outcomes: body weight and HbA1c) – RCT, direct comparison: insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B)

Study **Outcome category** **Outcome** **Time point**	**IDeg + IAsp ± metformin**			**IGlar + IAsp ± metformin**			**IDeg + IAsp ± metformin vs. IGlar + IAsp ± metformin**
	N[a]	**Values at baseline mean (SD)**	**Change at end of study mean (SE)**	**N[a]**	**Values at baseline mean (SD)**	**Change at end of study mean (SE)**	**MD [95% CI]; p-value**
NN 1250-3582 (52 weeks) / NN1250-3667[b] (78 weeks)							
Supplementary outcomes							
HbA1c (%)							
52 weeks	744	8.25 (0.79)	−1.28 (0.03)	248	8.34 (0.89)	−1.28 (0.05)	0.01 [−0.11 0.12]; 0.906
78 weeks	744	8.24 (0.79)	−1.01 (0.03)	248	8.32 (0.89)	−1.14 (0.05)	0.13 [0.00; 0.25]; 0.048
Body weight							
52 weeks	622	92.6 (17.9)	3.9 (5.0)	211	92.2 (17.2)	4.2 (4.8)	−0.31 [−0.98; 0.37]; ND
78 weeks	544	92.6 (17.9)	4.4 (5.1)	184	92.2 (17.2)	4.7 (4.9)	−0.34 [−1.05; 0.38]; ND

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at the start of the study may be based on other patient numbers.
b: Extension study to study NN1250-3582.

CI: confidence interval; IAsp: insulin aspart; IDeg: insulin degludec; HbA1c: glycosylated haemoglobin A1c; IGlar: insulin glargine; MD: mean difference; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

The data from the NN1250-3667 extension study (78 weeks) – if recorded – were primarily used in the benefit assessment. Since these data had a high risk of bias, at most hints could initially be derived. The corresponding results at the time point 52 weeks from the NN1250-3582 study were additionally considered. If these were consistent with the 78-week data and if the respective outcome had a low risk of bias at the time point 52 weeks, the certainty of results of the 78-week data was upgraded from “hint” to “indication”.

This deviates from the approach of the company, which derived at most proof on the basis of the results of a meta-analysis of the studies NN1250-3582, NN1250-3668 and NN1250-3998 for all outcomes except cardiovascular events (MACE) and severe hypoglycaemia. For the derivation of the added benefit on cardiovascular events (MACE) and severe hypoglycaemia, in contrast, the company considered the results of the individual studies NN1250-3582, NN1250-3668, NN1250-3998 and NN1250-3667.

In the following description of the results, all information provided by the company refers to its joint consideration of the studies NN1250-3582, NN1250-3668 and NN1250-3998.

Mortality

Only few deaths occurred in both treatment arms. After 78 weeks, the NN1250-3667 extension study showed no statistically significant difference between insulin degludec + insulin aspart ± metformin versus insulin glargine + insulin aspart ± metformin for the outcome "all-cause mortality". This resulted in no hint of an added benefit of insulin degludec + insulin aspart ± metformin in comparison with insulin glargine + insulin aspart ± metformin; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Cardiovascular events (MACE, including the components "cardiovascular death", "nonfatal stroke" and "acute coronary syndrome")

The NN1250-3667 extension study showed no statistically significant difference between the treatment arms for the outcome "cardiovascular events (MACE)" and its individual components "cardiovascular death", "nonfatal stroke" and "acute coronary syndrome". This resulted in no hint of an added benefit of insulin degludec + insulin aspart ± metformin in comparison with insulin glargine + insulin aspart ± metformin for these outcomes; an added benefit is therefore not proven.

The assessment regarding the outcome "cardiovascular events (MACE)" is consistent with that of the company. The company did not use the analyses of the individual components "cardiovascular death", "nonfatal stroke" and "acute coronary syndrome" for the derivation of the added benefit.

Health status (TRIM-D domains of daily life and psychological health)

The NN1250-3582 main study showed no statistically significant difference between the treatment arms for the outcome "health status", measured with the domains of daily life and psychological health of the TRIM-D questionnaire. This resulted in no hint of an added benefit of insulin degludec + insulin aspart ± metformin in comparison with insulin glargine + insulin aspart ± metformin; an added benefit is therefore not proven. The outcome was not recorded in the NN1250-3667 extension study.

The assessment concurs with that of the company.

Health-related quality of life

SF-36 − Physical Component Summary (PCS) and Mental Component Summary (MCS)

The mean changes at the end of study versus baseline were considered for the SF-36 MCS and PCS

There were no statistically significant differences between the treatment arms in the NN1250-3582 main study for the MCS or for the PCS. This resulted in no hint of an added benefit of insulin degludec + insulin aspart ± metformin in comparison with insulin glargine +

insulin aspart ± metformin; an added benefit is therefore not proven. The outcome was not recorded in the NN1250-3667 extension study.

This concurs with the company's assessment.

Side effects

Serious adverse events

Neither the NN1250-3582 main study nor the NN1250-3667 extension study showed a statistically significant difference between the treatment arms for the outcome "SAEs".

This resulted in no hint of greater or lesser harm from insulin degludec + insulin aspart ± metformin versus insulin glargine + insulin aspart ± metformin. Greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to adverse events and renal function disorder (SAE, SOC)

The NN1250-3667 extension study showed no statistically significant difference between the treatment groups for the outcomes "discontinuation due to AEs", "severe hypoglycaemic episodes (SAEs)" and "renal function disorder". Hence, for these outcomes, there was no hint of greater or lesser harm from insulin degludec + insulin aspart ± metformin in comparison with insulin glargine + insulin aspart ± metformin; greater or lesser harm is therefore not proven.

For the outcomes "discontinuation due to AEs" and "severe hypoglycaemic episodes (SAEs)", this is consistent with the company's assessment. The company did not use the outcome "renal function disorder (SAE)" in its assessment.

Hypoglycaemia

Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 56 mg/dL)

The NN1250-3667 extension study showed no statistically significant difference between the treatment arms for the outcome "non-severe confirmed symptomatic hypoglycaemic episodes in total (PG < 56 mg/dL)". Blood-glucose lowering in the intervention arm in the course of the study was comparable to that in the comparator arm (for HbA1c in the course of the study, see Figure 19 and Figure 20 in Appendix C.2 of the full dossier assessment).

Overall, there was no hint of greater or lesser harm from insulin degludec + insulin aspart ± metformin in comparison with insulin glargine + insulin aspart ± metformin for non-severe confirmed symptomatic hypoglycaemic episodes; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which derived proof of an added benefit for the outcome "non-severe confirmed symptomatic hypoglycaemic episodes in total" due to a statistically significant difference in the analysis of the rate ratio. The effect was no more than marginal for non-severe confirmed hypoglycaemic episodes, so that no proof of lesser harm

from insulin degludec would have resulted from consideration of the rate ratio either. As described above, the analyses of the relative risk were used for the present benefit assessment (see Section 2.6.2.4.3 of the full dossier assessment). The results on the analyses of the rate ratio for the outcome "non-severe confirmed symptomatic hypoglycaemic episodes" are presented as additional information in Appendix C.3 of the full dossier assessment.

Severe hypoglycaemia

As an auxiliary measure, the company operationalized severe hypoglycaemic episodes as hypoglycaemic episodes documented as SAEs (for reasons, see Section 2.6.2.4.3.2 of the full dossier assessment). The extension study showed no statistically significant difference between the treatment groups for the outcome "severe hypoglycaemic episodes (SAEs)". Hence, for this outcome, there was no hint of greater or lesser harm from insulin degludec + insulin aspart ± metformin in comparison with insulin glargine + insulin aspart ± metformin; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which derived an indication of an added benefit for the outcome "severe hypoglycaemia" due to a statistically significant difference in the NN1250-3998 study included by the company.

2.4.3 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present benefit assessment:

- age (< 65 years/≥ 65 years)
- sex (men/women)
- region (joint consideration of the characteristics "Europe/non-Europe" and "OECD country [yes/no]")
- insulin treatment regimen at screening (basal-bolus treatment regimen/mixed insulin ± OAD/basal insulin ± OAD/bolus insulin ± OAD)

Subgroup analyses were only used if each subgroup comprised at least 10 people and, for binary data, if at least 10 events had occurred in one of the subgroups. Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. Moreover, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 26 summarizes the subgroup results on the comparison of insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin.

Table 26: Subgroups (side effects, dichotomous) – RCT, direct comparison: insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B)

Study Outcome Characteristic Time point Subgroup	IDeg + IAsp ± metformin N	 Patients with event n (%)	IGlar + IAsp ± metformin N	 Patients with event n (%)	IDeg + IAsp ± metformin vs. IGlar + IAsp ± metformin RR [95% CI]	 p-value
NN 1250-3582 (52 weeks) / NN1250-3667[a] (78 weeks)						
SAEs (including hypoglycaemic episodes)						
Region						
52 weeks						
Europe	317	43 (13.6)	107	22 (20.6)	0.66 [0.41; 1.05]	0.089
Non-Europe	427	68 (15.9)	141	18 (12.8)	1.25 [0.77; 2.02]	0.418
					Interaction:	0.061
78 weeks						
Europe	317	49 (15.5)	107	28 (26.2)	0.59 [0.39; 0.89]	0.013[b]
Non-Europe	427	89 (20.8)	141	25 (17.7)	1.18 [0.79; 1.75]	0.555[b]
Total					Interaction	0.019[c]
OECD country[d]						
52 weeks						
Yes	576	90 (15.6)	189	30 (15.9)	0.98 [0.67; 1.44]	0.909
No	168	21 (12.5)	59	10 (16.9)	0.74 [0.37; 1.47]	0.386
					Interaction:	0.478
78 weeks						
Yes	576	116 (20.1)	189	40 (21.2)	0.95 [0.69; 1.31]	0.756
No	168	22 (13.1)	59	13 (22.0)	0.59 [0.32; 1.10]	0.141
Total					Interaction	0.196

a: Extension study to study NN1250-3582.
b: Institute's calculation, unconditional exact test (CSZ method according to [8]).
c: Institute's calculation, Cochran's Q test.
d: Additional presentation for the joint interpretation of the subgroup effects on the characteristic "region".
CI: confidence interval; CSZ: convexity, symmetry, z score; IAsp: insulin aspart; IDeg: insulin degludec; IGlar: insulin glargine; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculated; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

For the outcome "SAEs", an effect modification was shown for the NN1250-3667 extension study for the analysis by regions (Europe/non-Europe), but not for the analysis by OECD membership.

The stratum of Europe comprised the states of Bulgaria, Germany, Ireland, Italy, Romania, Russia, Slovak Republic, Spain and Turkey. Hence, heterogeneous health care situations within the stratum can be assumed. Presumably, there are important differences between the health care situations in Western European states such as Germany, Ireland, Italy and Spain compared

with those in Eastern or Southeastern states such as Bulgaria, Romania and Russia. Hence, an analysis only by the regions "Europe/non-Europe" constitutes only an inadequate representation of the differences in health care in the present constellation. The characteristic "OECD membership", however, comprises states with similar levels of economic development. A more similar health care situation can be assumed for OECD member states such as Germany, Ireland, Italy and Spain, for example. No differences between the treatment arms with missing effect modifications were shown for the treatment regions within the OECD.

Overall, no effect modification relevant for the present benefit assessment was assumed in the joint consideration of the analyses by region and OECD membership.

2.4.4 Probability and extent of added benefit

The derivation of probability and extent of the added benefit for research question B 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 [3].

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

2.4.4.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4.2 (see Table 27).

Table 27: Extent of added benefit at outcome level: insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**IDeg + metformin vs. IGlar + metformin** **Proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	1.5% vs. 0.8% RR: 1.83 [0.41; 8.21]; p = 0.536	Lesser benefit/added benefit not proven
Morbidity		
Cardiovascular events (MACE)	3.9% vs. 2.8% RR: 1.38 [0.61; 3.12]; p = 0.557	Lesser benefit/added benefit not proven
Cardiovascular death	0.7% vs. 0.4% RR: 1.67 [0.20; 14.24]; p > 0.999	Lesser benefit/added benefit not proven
Nonfatal stroke	0.9% vs. 0% RR: ND; p = 0.202	Lesser benefit/added benefit not proven
Acute coronary syndrome	2.3% vs. 2.4% RR: 0.95 [0.38; 2.38]; p > 0.999	Lesser benefit/added benefit not proven
Health status (TRIM-D)[c]		
Daily life	3.02 vs. 2.88 MD: 0.14 [−2.48; 2.75]; p = 0.919	Lesser benefit/added benefit not proven
Psychological health	5.14 vs. 5.26 MD: −0.12 [−2.52; 2.29]; p = 0.924	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36[c]		
Physical wellbeing	−0.35 vs. −0.64 MD: 0.28 [−0.80; 1.37]; p = 0.609	Lesser benefit/added benefit not proven
Mental wellbeing	1.21 vs. 0.29 MD: 0.92 [−0.42; 2.26]; p = 0.176	Lesser benefit/added benefit not proven
Side effects		
SAEs	18.5% vs. 21.4% RR: 0.87 [0.65; 1.15]; p = 0.353	Lesser benefit/added benefit not proven
Discontinuation due to AEs (including hypoglycaemic episodes)	4.7% vs. 3.6% RR: 1.30 [0.63; 2.66]; p = 0.594	Lesser benefit/added benefit not proven
Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 56 mg/dL), total	78.1% vs. 77.4% RR: 1.01 [0.93 1.09]; p = 0.860	Lesser benefit/added benefit not proven
Severe hypoglycaemic episodes (SAEs)	2.7% vs. 1.2% RR: 2.22 [0.67; 7.41]; p = 0.228	Lesser benefit/added benefit not proven
Renal function disorder (SAE, SOC)	0.3% vs. 1.2% RR: 0.22 [0.04; 1.32]; p = 0.071[d]	Lesser benefit/added benefit not proven

(continued)

Table 27: Extent of added benefit at outcome level: insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B) (continued)

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Only data from the NN1250-3582 study are available for this outcome.
d: Institute's calculation, p-value from unconditional exact test (CSZ method according to [8]).
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; IDeg: insulin degludec; IGlar: insulin glargine; MACE: major adverse cardiovascular event; MD: mean difference; PG: plasma glucose; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; SAE: serious adverse event; SOC: System Organ Class; TRIM-D: Treatment-Related Impact Measure for Diabetes; vs.: versus

2.4.4.2 Overall conclusion on added benefit

Table 28 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 28: Positive and negative effects from the assessment of insulin degludec + insulin aspart ± metformin vs. insulin glargine + insulin aspart ± metformin (research question B)

Positive effects	Negative effects
–	–

Based on the available and usable results, there are neither positive nor negative effects.

In summary, there is no hint of an added benefit of insulin degludec + insulin aspart ± metformin versus the ACT specified by the G-BA for adult patients with type 2 diabetes mellitus inadequately controlled by treatment with insulin with or without another blood-glucose lowering drug; an added benefit is therefore not proven.

The assessment described above deviates from that of the company, which claimed an indication of considerable added benefit for this research question.

2.4.5 List of included studies

Study NN1250-3582

Garber AJ, King AB, Del Prato S, Sreenan S, Balci MK, Munoz-Torres M et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012; 379(9825): 1498-1507.

Novo Nordisk. Comparison of NN1250 with insulin glargine plus insulin aspart with/without metformin and with/without pioglitazone in type 2 diabetes (BEGIN): study details [online]. In: ClinicalTrials.gov. 06.04.2017 [Accessed: 24.01.2019]. URL: https://ClinicalTrials.gov/show/NCT00972283.

Novo Nordisk. A 52-week randomised, controlled, open label,multicentre, multinational treat-to target trial comparing efficacy and safety of SIBA and insulin glargine both administered once daily in a basal-bolus regimen with insulin aspart as mealtime insulin ± treatment with metformin, ± pioglitazone in subjects with type 2 diabetes currently treated with insulin qualifying for intensified treatment [online]. In: EU Clinical Trials Register. [Accessed: 24.01.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-005777-35.

Novo Nordisk. Comparison of NN1250 with insulin glargine plus insulin aspart with/without metformin and with/without pioglitazone in type 2 diabetes (BEGIN): study results [online]. In: ClinicalTrials.gov. 06.04.2017 [Accessed: 24.01.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00972283.

Novo Nordisk. Comparison of NN1250 with insulin glargine plus insulin aspart with/without metformin and with/without pioglitazone in type 2 diabetes (BEGIN): report synopsis [online]. In: EU Clinical Trials Register. 31.05.2011 [Accessed: 12.02.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/rest/download/result/attachment/2008-005777-35/1/6410.

Novo Nordisk. A 52-week randomised, controlled, open label, multicentre, multinational treat-to-target trial comparing efficacy and safety of NN1250 and insulin glargine both administered once daily in a basal-bolus regimen with insulin aspart as mealtime insulin ±treatment with metformin, ± pioglitazone in subjects with type 2 diabetes currently treated with insulin qualifying for intensified treatment; study NN1250-3582; clinical study protocol; version 2.0 [unpublished]. 2009.

Novo Nordisk. A 52-week randomised, controlled, open label, multicentre, multinational treat-to-target trial comparing efficacy and safety of NN1250 and insulin glargine both administered once daily in a basal-bolus regimen with insulin aspart as mealtime insulin ±treatment with metformin, ± pioglitazone in subjects with type 2 diabetes currently treated with insulin qualifying for intensified treatment; study NN1250-3582; clinical trial report [unpublished]. 2011.

Novo Nordisk. A 52-week randomised, controlled, open label, multicentre, multinational treat-to-target trial comparing efficacy and safety of NN1250 and insulin glargine both administered once daily in a basal-bolus regimen with insulin aspart as mealtime insulin ±treatment with metformin, ± pioglitazone in subjects with type 2 diabetes currently treated with insulin qualifying for intensified treatment; study NN1250-3582; statistical analysis plan [unpublished]. 2011.

Novo Nordisk. A 52-week randomised, controlled, open label, multicentre, multinational treat-to-target trial comparing efficacy and safety of NN1250 and insulin glargine both administered once daily in a basal-bolus regimen with insulin aspart as mealtime insulin ±treatment with metformin, ± pioglitazone in subjects with type 2 diabetes currently treated with insulin qualifying for intensified treatment; study NN1250-3582; Zusatzanalysen [unpublished]. 2018.

Study NN1250-3667 (Extension study to NN1250-3582)

Hollander P, King AB, Del Prato S, Sreenan S, Balci MK, Munoz-Torres M et al. Insulin degludec improves long-term glycaemic control similarly to insulin glargine but with fewer hypoglycaemic episodes in patients with advanced type 2 diabetes on basal-bolus insulin therapy. Diabetes Obes Metab 2015; 17(2): 202-206.

Novo Nordisk. An extension trial comparing safety and efficacy of NN12501 with insulin glargine plus insulin aspart with/without metformin and with/without pioglitazone in type 2 diabetes (BEGIN): report synopsis [online]. In: EU Clinical Trials Register. 13.01.2012 [Accessed: 24.01.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/rest/download/result/attachment/2009-015816-17/1/6406.

Novo Nordisk. Comparison of NN1250 with insulin glargine plus insulin aspart with/without metformin and with/without pioglitazone in type 2 diabetes (BEGIN): study results [online]. In: ClinicalTrials.gov. 06.04.2017 [Accessed: 24.01.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00972283.

Novo Nordisk. Comparison of NN1250 with insulin glargine plus insulin aspart with/without metformin and with/without pioglitazone in type 2 diabetes (BEGIN): report synopsis [online]. In: EU Clinical Trials Register. 31.05.2011 [Accessed: 24.01.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/rest/download/result/attachment/2008-005777-35/1/6410.

Novo Nordisk. An extension trial to NN1250-3582 comparing safety and efficacy of NN1250 and insulin glargine, both with insulin aspart as meal-time insulin ± OADs in type 2 diabetes: report synopsis [online]. In: EU Clinical Trials Register. 13.01.2012 [Accessed: 12.02.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/rest/download/result/attachment/2009-015816-17/1/6406.

Novo Nordisk. BEGIN: BB; an extension trial to NN1250-3582 comparing safety and efficacy of NN1250 and insulin glargine, both with insulin aspart as meal-time insulin ± OADs in type 2 diabetes; study NN1250-3667; clinical study protocol [unpublished]. 2009.

Novo Nordisk. BEGIN: BB; an extension trial to NN1250-3582 comparing safety and efficacy of NN1250 and insulin glargine, both with insulin aspart as meal-time insulin ± OADs in type 2 diabetes; study NN1250-3667; clinical trial report [unpublished]. 2012.

Novo Nordisk. BEGIN: BB; an extension trial to NN1250-3582 comparing safety and efficacy of NN1250 and insulin glargine, both with insulin aspart as meal-time insulin ± OADs in type 2 diabetes; study NN1250-3667; statistical analysis plan [unpublished]. 2012.

Novo Nordisk. BEGIN: BB; an extension trial to NN1250-3582 comparing safety and efficacy of NN1250 and insulin glargine, both with insulin aspart as meal-time insulin ± OADs in type 2 diabetes; study NN1250-3667; Zusatzanalysen [unpublished]. 2018.

2.5 Probability and extent of added benefit – summary

Table 29: Insulin degludec – probability and extent of the added benefit in type 2 diabetes mellitus in adults

Research question[a]	Subindication	ACT[b]	Probability and extent of added benefit
A	Patients inadequately controlled by treatment with at least 2 blood-glucose lowering drugs (except insulin)[c]	Human insulin + metformin or human insulin + empagliflozin[d] or human insulin + liraglutide[d] or human insulin[e]	*Treatment goal near normal blood glucose levels:* hint of lesser benefit
			Other treatment goal: added benefit not proven
B	Patients inadequately controlled by treatment with insulin with or without another blood-glucose lowering drug[g]	Optimization of the human insulin regimen (possibly + metformin or empagliflozin[d] or liraglutide[d])	Added benefit not proven

a: Insulin degludec is approved for type 2 diabetes mellitus irrespective of pretreatment; hence, the research questions do not cover the complete approved therapeutic indication. According to the G-BA, therapeutic situations in which oral antidiabetic therapy would be the only option for the ACT are not considered as insulin is generally not indicated in these therapeutic situations.
b: Presentation of the respective ACT specified by the G-BA.
c: In the assessment referred to as "patients pretreated with at least 2 antidiabetics except insulin".
d: Empagliflozin or liraglutide, each in combination with other medication for the treatment of cardiovascular risk factors, in particular antihypertensive medications, anticoagulants and/or lipid-lowering drugs, and only for patients with manifest cardiovascular disease (for the operationalization, see study protocols of the respective outcome studies [1,2]).
e: If, according to the SPC, metformin and empagliflozin[d] and liraglutide[d] are not tolerated or contraindicated or are not sufficiently effective due to advanced type 2 diabetes mellitus.
f: At baseline.
g: In the assessment referred to as "patients pretreated with insulin".
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The assessment described above for research question A deviates from that of the company, which overall derived proof of a minor added benefit for insulin degludec + metformin in comparison with the ACT in patients pretreated with at least 2 antidiabetics, except insulin, on the basis of the presented data of the meta-analysis (studies NN1250-3579, NN1250-3587 and NN1250-3672), irrespective of the HbA1c value at baseline and of the treatment goal.

The assessment described above for research question B deviates from that of the company, which overall derived proof of a considerable added benefit for insulin degludec in comparison with the ACT in patients pretreated with insulin (with or without another blood-glucose lowering drug), on the basis of the studies NN1250-3582, NN1250-3668 and NN1250-3998.

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

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373(22): 2117-2128.

2. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375(4): 311-322.

3. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

4. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

5. Novo Nordisk. Tresiba: Fachinformation [online]. 11.2018 [Accessed: 23.01.2019]. URL: http://www.fachinfo.de.

6. Sanofi. Lantus Injektionslösung in einer Durchstechflasche/Patrone, Lantus SoloStar Injektionslösung in einem Fertigpen: Fachinformation [online]. 04.2018 [Accessed: 25.01.2019]. URL: http://www.fachinfo.de.

7. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Nationale VersorgungsLeitlinie: Therapie des Typ-2-Diabetes; Langfassung; Version 4 [online]. 11.2014 [Accessed: 25.01.2019]. URL: https://www.leitlinien.de/mdb/downloads/nvl/diabetes-mellitus/dm-therapie-1aufl-vers4-lang.pdf.

8. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

9. Hirji KF, Mehta CR, Patel NR. Computing distributions for exact logistic regression. J Am Stat Assoc 1987; 82(400): 1110-1117.

10. Kuss O. Statistical methods for meta-analyses including information from studies without any events: add nothing to nothing and succeed nevertheless. Stat Med 2015; 34(7): 1097-1116.

11. Meneghini L, Atkin SL, Gough SC, Raz I, Blonde L, Shestakova M et al. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. Diabetes Care 2013; 36(4): 858-864.

12. Wysham C, Bhargava A, Chaykin L, De la Rosa R, Handelsman Y, Troelsen LN et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. JAMA 2017; 318(1): 45-56.

13. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach; update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2015; 58(3): 429-442.

14. Novo Nordisk. NovoRapid: Fachinformation [online]. 04.2018 [Accessed: 11.09.2018]. URL: http://www.fachinfo.de.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-84-insulin-degludec-diabetes-mellitus-benefit-assessment-according-to-35a-social-code-book-v.11005.html.