Insulin icodec
(type 1 diabetes mellitus)

Benefit assessment according to §35a SGB V[1]

EXTRACT

Project: A24-90 Version: 1.0 Status: 28 Nov 2024 DOI: 10.60584/A24-90_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Insulin icodec (Diabetes mellitus Typ 1) – Nutzenbewertung gemäß § 35a SGB V*. 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.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Insulin icodec (type 1 diabetes mellitus) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

30 August 2024

Internal Project No.

A24-90

DOI-URL

https://doi.org/10.60584/A24-90_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Andreas Barthel, Germany

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

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Christof Dücker
- Dorothee Ehlert
- Ulrich Grouven
- Simone Heß
- Kirsten Janke
- Prateek Mishra
- Daniela Preukschat
- Min Ripoll

Keywords

Insulin Icodec, Diabetes Mellitus – Type 1, Benefit Assessment, NCT04848480

Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CGM	continuous glucose monitoring
CT	conventional insulin therapy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICT	intensified insulin therapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NYHA	New York Heart Association
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug insulin icodec. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 30 August 2024.

Research question

The aim of the present report is to assess the added benefit of insulin icodec in comparison with the appropriate comparator therapy (ACT) in adult patients with type 1 diabetes mellitus.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of insulin icodec[a]

Therapeutic indication	**ACT[b]**
Adult patients with type 1 diabetes mellitus	Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin degludec, insulin aspart, insulin glulisine, insulin lispro)[c]
a. In patients with type 1 diabetes mellitus, insulin icodec must be combined with bolus insulin in accordance with the SPC in order to cover the insulin requirement at mealtimes. b. Presentation of the ACT specified by the G-BA. c. The unchanged continuation of an inadequate therapy of type 1 diabetes mellitus, if there is still the option of optimizing insulin therapy, does not correspond to an ACT. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. In addition, the company states that insulin icodec must be administered in combination with bolus insulin in adults with type 1 diabetes mellitus. A distinction is made between 2 forms of combined insulin therapy, i.e. conventional insulin therapy (CT) and intensified conventional insulin therapy (ICT). The company considers ICT to be the relevant operationalization of the ACT for the population of the present research question. It justifies this by stating that ICT is the treatment standard for patients with type 1 diabetes mellitus in Germany.

According to the information in the S3 guideline on the treatment of type 1 diabetes mellitus and the requirements for structured treatment programmes for patients with type 1 diabetes mellitus, ICT is the standard treatment for the majority of patients; as described in the S3 guideline, CT with mandatory specification of both the insulin dose and the sequence and size of meals (fixed carbohydrate portions) is also considered as a secondary treatment option only in exceptional cases. Among others, this applies to patients who are unable to fulfil the requirements of an intensified therapy (e.g. due to cognitive impairment, disease or age) or

patients with significant adherence problems in long-term care, who are also covered by the therapeutic indication of insulin icodec.

In addition, according to the S3 guideline, the use of insulin pump therapy should be recommended or at least offered to patients who do not achieve their individual treatment goals despite ICT with the additional use of continuous glucose monitoring (CGM) or in the case of frequent hypoglycaemic episodes or recurrent severe hypoglycaemic episodes. As a long-acting insulin analogue, insulin icodec must not be used in insulin pumps, but the patient group eligible for pump therapy is also covered by the present therapeutic indication for insulin icodec. A comparison with insulin pump therapy with short-acting insulin or insulin analogues would also be conceivable for this group.

The company's restriction to ICT as a relevant operationalization of the ACT has no consequences for the present assessment insofar as no data are available for comparison with the other possible operationalizations (CT and insulin pump therapy) of the ACT (see also Table 3).

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 added benefit.

Study pool and study design

The benefit assessment of insulin icodec used the NN1436-4625 study (hereinafter referred to as ONWARDS 6).

ONWARDS 6 is a randomized, open-label, multicentre study comparing insulin icodec with insulin degludec, each in combination with insulin aspart, with a randomized treatment phase of 52 weeks. The study included adult patients diagnosed with type 1 diabetes mellitus who had to have been diagnosed at least 1 year before at the time of inclusion in the study. Patients also had to have been receiving therapy with multiple daily insulin injections (regimen with basal and bolus insulin analogues) for at least 1 year and have an HbA1c level of less than 10%. Patients who had experienced a myocardial infarction, stroke or hospitalization due to unstable angina pectoris or transient ischaemic attack within 180 days prior to study inclusion, or patients who had chronic heart failure (New York Heart Association [NYHA] class IV) at the time of study inclusion as well as patients with renal insufficiency (estimated glomerular filtration rate [eGFR] < 30 mL/min/1,73m^2) or impaired liver function were excluded from participation in the study. Patients with known hypoglycaemia perception disorder or with recurrent severe hypoglycaemic episodes in the past year were also excluded.

A total of 582 patients were included in the study and randomly assigned to insulin icodec + insulin aspart (N = 290) or insulin degludec + insulin aspart (N = 292). In the intervention and

the comparator arm of the ONWARDS 6 study, treatment with basal insulin was based on a fixed titration algorithm identical for all patients based on 3 consecutive fasting plasma glucose (PG) levels. Patients in the intervention and the comparator arm additionally received insulin aspart as bolus insulin. The bolus insulin dose at the start of the study was determined on the basis of the dose of the existing bolus insulin therapy at the time of study enrolment and had to be kept stable during the first 8 weeks of the study. After the first 8 weeks, adjustments could be made once a week depending on the self-monitoring blood glucose level according to a fixed titration algorithm and with the help of the investigator. According to the investigator's assessment, titration could alternatively be based on carbohydrate counting. Titration by carbohydrate counting should only be used in patients with experience in this method after appropriate training by the investigator. As part of this method, the investigator determined the insulin-to-carbohydrate ratio and the insulin sensitivity factor for each meal. In consultation with the investigator, patients were allowed to apply corrections to the bolus doses. The correction bolus doses were also determined by the investigator.

As part of the study, the insulin doses of basal and bolus insulin were titrated in both treatment arms using a target value corridor for fasting blood glucose, with a target range of 80 to 130 mg/dL being aimed at.

Treatment with insulin icodec in the intervention arm was largely in compliance with the specifications of the Summary of Product Characteristics (SPC). In the comparator arm of the study, treatment with insulin degludec was carried out in accordance with the SPC.

During the first 8 weeks of the study, treatment with insulin aspart deviated from the dosing specified in the SPC. According to the SPC, monitoring of blood glucose levels and adjustment of the insulin dose is recommended for the application. In the study, however, the dosage had to be kept stable for the first 8 weeks and could only be adjusted due to safety concerns.

During the study, patients were monitored using a CGM system (Dexcom G6). The data recorded via the system were only used to assess glycaemic control, e.g. by recording the time in the target range of 70 mg/dL to 180 mg/dL. In contrast, blood glucose levels measured by the patients themselves were used both for insulin dose adjustments according to the titration algorithm described above and for recording hypoglycaemic episodes. However, patients and investigators had access to the data from the CGM system and, according to the study design, patients were to perform a self-measurement in the event of hypoglycaemic episodes recorded by the CGM. If a PG level outside the target range (< 70 mg/dL) was confirmed, the hypoglycaemic episode was recorded as an event in the electronic diary, carbohydrates were administered and the doses of the blood glucose-lowering therapy were adjusted.

The primary outcome of the study was the change in HbA1c after 26 weeks. Secondary outcomes were outcomes of the categories “morbidity” and “adverse events (AEs).

Limitations of the ONWARDS 6 study

According to the guideline for the treatment of type 1 diabetes mellitus, blood glucose corrections and insulin dosing were carried out autonomously by the patient as part of ICT. In the study, however, adjustments were made for all patients according to a fixed titration algorithm. Adjustments to the bolus insulin dosage were also only possible after consultation with the investigator, including in the context of titration by means of carbohydrate counting. Based on the data presented by the company, it remains unclear in what proportion of patients in the study the specified titration algorithm was used for dose adjustments and in what proportion the method of titration by carbohydrate counting was used. In addition, the bolus insulin dosage had to be kept stable during the first 8 weeks of the study. This does not correspond to the specifications of the guideline or the approach in care. In Module 4 C of the dossier, the company also states that in practice, an individually adjusted titration algorithm is usually used in the context of treatment individualization for most patients with type 1 diabetes mellitus. Against the background of the titration requirements according to the study planning, however, it cannot be assumed that individualized dose adjustments were made in the study to the extent that would be expected in routine care.

Overall, it can therefore not be assumed that the procedure in the ONWARDS 6 study reflects the therapy envisaged in the guideline or used in routine care. For this reason, it remains unclear whether the results of the ONWARDS 6 study are fully transferable to patients in the German health care context. This uncertainty has been taken into account in the assessment of the certainty of conclusions.

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes was rated as low for the ONWARDS 6 study. The risk of bias for the results on the outcomes of all-cause mortality, HbA1c level, acute coronary syndrome, cerebrovascular events and heart failure was considered to be low. In the side effects category, the bias of the results on the outcomes of serious AEs (SAEs), severe hypoglycaemic episodes and serious hypoglycaemic episodes was rated as low, while the bias of the outcomes of discontinuation due to AEs, non-severe confirmed symptomatic hypoglycaemia (< 54 mg/dL) and diabetic ketoacidosis was rated as high due to lack of blinding for subjective decision to discontinue treatment and lack of blinding for subjective recording of outcomes.

As described above, it remains unclear whether the results of the ONWARDS 6 study can be transferred without restriction to the target population in the German health care context. Overall, this reduces the certainty of conclusions of the study results for the present research question. Based on the ONWARDS 6 study, at most hints, e.g. of an added benefit, can be derived for all presented outcomes.

Results

Mortality

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome "all-cause mortality". This resulted in no hint of an added benefit of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart for this outcome; an added benefit is therefore not proven.

Morbidity

HbA1c level as sufficiently valid surrogate for microvascular late complications

For the outcome “HbA1c level”, a statistically significant difference between the treatment arms to the disadvantage of insulin icodec + insulin aspart compared to insulin degludec + insulin aspart is shown based on the mean differences (for the change in the HbA1c level from baseline). The European Medicines Agency (EMA) uses a threshold value of 0.3 percentage points for the HbA1c level to assess the non-inferiority; however, current documents of the US Food and Drug Administration (FDA) provide the general information that the magnitude of changes in the HbA1c level must be weighed against the risks, and that statistically significant but minor reductions in the HbA1c level may possibly not outweigh serious adverse drug reactions. Irrespective of this, the effect observed in the present data situation is not considered relevant simply because the 95% confidence interval of the effect with the lower limit of 0.02% is close to the zero effect. Given this data situation, a relevant effect cannot be assumed with sufficient certainty. This resulted in no hint of an added benefit of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart for this outcome; an added benefit is therefore not proven.

Based on the threshold of 0.3 percentage points used by the EMA, the non-inferiority at Week 52 is not proven.

Acute coronary syndrome, cerebrovascular events, heart failure

There was no statistically significant difference between the treatment arms for either of the outcomes “acute coronary syndrome”, “cerebrovascular events” and “heart failure”. This resulted in no hint of an added benefit of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart for these outcomes; an added benefit is therefore not proven.

End-stage renal disease

No suitable data are available for the outcome of end-stage renal disease. This resulted in no hint of an added benefit of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart for this outcome; an added benefit is therefore not proven.

Diabetic retinopathies

No suitable data are available for the outcome of diabetic retinopathies. This resulted in no hint of an added benefit of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart for this outcome; an added benefit is therefore not proven.

Health-related quality of life

In the ONWARDS 6 study, health-related quality of life was not recorded. There is no hint of an added benefit of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs

There was no statistically significant difference between the treatment arms for either of the outcomes of SAEs and discontinuation due to AEs. For these outcomes, there was no hint of greater or lesser harm from insulin icodec + insulin aspart versus insulin degludec + insulin aspart; greater or lesser harm is therefore not proven.

Non-severe confirmed symptomatic hypoglycaemic episodes

No statistically significant difference between the treatment arms was shown for the outcome of non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL). For this outcome, there was no hint of greater or lesser harm from insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart; greater or lesser harm is therefore not proven.

No data are available for the outcome of non-severe confirmed symptomatic hypoglycaemia (PG < 70 mg/dL). For this outcome, there was no hint of greater or lesser harm from insulin icodec + insulin aspart versus insulin degludec + insulin aspart; greater or lesser harm is therefore not proven.

Severe hypoglycaemic episodes

There is no statistically significant difference between treatment arms for the outcome of severe hypoglycaemic episodes. For the outcome of severe hypoglycaemic episodes, there was no hint of greater or lesser harm from insulin icodec + insulin aspart versus insulin degludec + insulin aspart; greater or lesser harm is therefore not proven.

Serious hypoglycaemic episodes (SAEs)

For the outcome of serious hypoglycaemic episodes, there was a statistically significant difference to the disadvantage of insulin icodec + insulin aspart compared to insulin degludec + insulin aspart. For this outcome, there is hint of greater harm from insulin icodec + insulin aspart compared to insulin degludec + insulin aspart.

Diabetic ketoacidosis

There was no statistically significant difference between the treatment arms for the outcome of diabetic ketoacidosis. For the outcome of diabetic ketoacidosis, there was no hint of greater or lesser harm from insulin icodec + insulin aspart versus insulin degludec + insulin aspart; 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 icodec in comparison with the ACT are assessed as follows:

Overall, there is a negative effect for serious hypoglycaemic episodes. Although this is not offset by any positive effects, the negative effect with the extent “minor” is not shown in the operationalization of severe hypoglycaemic episodes, but only for serious hypoglycaemic episodes. Although the proportion of patients with severe hypoglycaemic episodes is slightly higher than for serious hypoglycaemic episodes - particularly in the comparator arm - it is also in the low single-digit percentage range. Overall, the derivation of lesser benefit does not appear justified in the present data situation.

In summary, there is no hint of an added benefit of insulin icodec over the ACT for adult patients with type 1 diabetes mellitus.

The result of the assessment of the added benefit of insulin icodec in comparison with the ACT is summarized in Table 3.

[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 [1,2].

Table 3: Insulin icodec[a] – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
Adult patients with type 1 diabetes mellitus[c]	Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin degludec, insulin aspart, insulin glulisine, insulin lispro)[d]	Added benefit not proven

a. In patients with type 1 diabetes mellitus, insulin icodec must be combined with bolus insulin in accordance with the SPC in order to cover the insulin requirement at mealtimes.
b. Presentation of the ACT specified by the G-BA.
c. The ONWARDS 6 study only included patients who had been diagnosed with type 1 diabetes mellitus for at least 1 year and were receiving intensified conventional insulin therapy (ICT). It remains unclear whether the observed results can be transferred to patients with newly diagnosed type 1 diabetes mellitus and to patients for whom conventional therapy (CT) or an insulin pump is an option. In the ONWARDS 6 study, insulin icodec was also only used in combination with insulin aspart, not with other bolus insulins. It remains unclear whether the observed results can be transferred to an application in combination with other bolus insulins.
d. The unchanged continuation of an inadequate therapy of type 1 diabetes mellitus, if there is still the option of optimizing insulin therapy, does not correspond to an ACT.

ACT: appropriate comparator therapy; CT: conventional therapy; G-BA: Federal Joint Committee; ICT: intensified conventional insulin therapy

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

I 1 Research question

The aim of the present report is to assess the added benefit of insulin icodec in comparison with the ACT in adult patients with type 1 diabetes mellitus.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of insulin icodec[a]

Therapeutic indication	**ACT[b]**
Adult patients with type 1 diabetes mellitus	Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin degludec, insulin aspart, insulin glulisine, insulin lispro)[c]
a. According to the SPC [3] , insulin icodec must be combined with bolus insulin in patients with type 1 diabetes mellitus in order to cover the insulin requirement at mealtimes. b. Presentation of the ACT specified by the G-BA. c. The unchanged continuation of an inadequate therapy of type 1 diabetes mellitus, if there is still the option of optimizing insulin therapy, does not correspond to an ACT. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT. In addition, the company states that insulin icodec must be administered in combination with bolus insulin in adults with type 1 diabetes mellitus. A distinction is made between 2 forms of combined insulin therapy, i.e. CT and ICT. The company considers ICT to be the relevant operationalization of the ACT for the population of the present research question. It justifies this by stating that ICT is the treatment standard for patients with type 1 diabetes mellitus in Germany.

According to the information in the S3 guideline on the treatment of type 1 diabetes mellitus [4] and the requirements for structured treatment programmes for patients with type 1 diabetes mellitus [5], ICT is the standard treatment for the majority of patients; as described in the S3 guideline, CT with mandatory specification of both the insulin dose and the sequence and size of meals (fixed carbohydrate portions) is also considered as a secondary treatment option only in exceptional cases. Among others, this applies to patients who are unable to fulfil the requirements of an intensified therapy (e.g. due to cognitive impairment, disease or age) or patients with significant adherence problems in long-term care [4], who are also covered by the therapeutic indication of insulin icodec.

In addition, according to the S3 guideline, the use of insulin pump therapy should be recommended or at least offered to patients who do not achieve their individual treatment goals despite ICT with the additional use of CGM or in the case of frequent hypoglycaemic episodes or recurrent severe hypoglycaemic episodes [4]. As a long-acting insulin analogue, insulin icodec must not be used in insulin pumps [3], but the patient group eligible for pump therapy is also covered by the present therapeutic indication for insulin icodec. A comparison

with insulin pump therapy with short-acting insulin or insulin analogues would also be conceivable for this group.

The company's restriction to ICT as a relevant operationalization of the ACT has no consequences for the present assessment insofar as no data are available for comparison with the other possible operationalizations (CT and insulin pump therapy) of the ACT (see also Table 17).

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 added benefit. This concurs with the company’s inclusion criteria.

I 2 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 icodec (status: 20 July 2024)
- bibliographical literature search on insulin icodec (last search on 02 June 2024)
- search in trial registries/trial results databases for studies on insulin icodec (last search on 26 July 2024)
- search on the G-BA website for insulin icodec (last search on 20 July 2024)

To check the completeness of the study pool:

- search in trial registries for studies on insulin icodec (last search on 12 September 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 2.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: insulin icodec + insulin aspart vs. insulin degludec + insulin aspart

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
NN1436-4625 (ONWARDS 6[d])	Yes	Yes	No	Yes [6]	Yes [7,8]	Yes [9,10]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The ONWARDS 6 study was used for the benefit assessment. The study pool is consistent with the study pool of the company. The study is described in the following section.

I 2.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: insulin icodec + insulin aspart vs. insulin degludec + insulin aspart

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ONWARDS 6	RCT, open-label, parallel	Adults (≥ 18 years of age) with type 1 diabetes mellitus ▪ diagnosis of diabetes mellitus type 1 ≥ 1 year ▪ HbA1c level < 10% at screening ▪ pretreatment with basal insulin + bolus insulin ≥ 1 year	Insulin icodec (N = 290) insulin degludec (N = 292) each in combination with insulin aspart	Screening: 2 weeks treatment: 52 weeks[b] follow-up: 5 weeks	97 study centres in Austria, Canada, Germany, India, Italy, Japan, Netherlands, Russia, Spain, Turkey, United Kingdom, USA 04/2021–12/2022	Primary: change in HbA1c at Week 26 secondary: morbidity, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes for this benefit assessment.
b. Consisting of a 26-week main phase and a 26-week extension phase (according to the study design, all study participants should enter the extension phase).

AE: adverse event; HbA1c: glycosylated haemoglobin A1c; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: insulin icodec + insulin aspart vs. insulin degludec + insulin aspart (multipage table)

<table>
<tr><th>Study</th><th>Intervention</th><th>Comparison</th></tr>
<tr><td>ONWARDS 6</td><td>Insulin icodec 700 U/mL once a week, SC
+
insulin aspart 100 U/mL 2-4 × daily, SC</td><td>Insulin degludec 100 U/mL once daily, SC.
+
insulin aspart 100 U/mL 2-4 × daily, SC</td></tr>
<tr><td></td><td>Starting dose, titration, dose increase for insulin icodec:
▪ starting dose: determined individually for each patient[a]
▪ dose adjustments according to the following table[b]:
<table><tr><th colspan="3">3 consecutive fasting plasma glucose levels</th><th>Dose adjustment</th></tr><tr><td></td><td>mmol/L</td><td>mg/dL</td><td>E</td></tr><tr><td rowspan="3">lowest SMPG level</td><td>< 4.4</td><td>< 80</td><td>-20</td></tr><tr><td>4.4–7.2</td><td>80–130</td><td>0</td></tr><tr><td>> 7.2</td><td>> 130</td><td>+20</td></tr></table></td><td>Starting dose, titration, dose increase for insulin degludec:
▪ starting dose: according to the local Summary of Product Characteristics
▪ dose adjustments according to the following table[b]:
<table><tr><th colspan="3">3 consecutive fasting plasma glucose levels</th><th>Dose adjustment</th></tr><tr><td></td><td>mmol/L</td><td>mg/dL</td><td>E</td></tr><tr><td rowspan="3">lowest SMPG level</td><td>< 4.4</td><td>< 80</td><td>-3</td></tr><tr><td>4.4–7.2</td><td>80–130</td><td>0</td></tr><tr><td>> 7.2</td><td>> 130</td><td>+3</td></tr></table></td></tr>
<tr><td></td><td colspan="2">Insulin aspart[c]
▪ starting dose: individualized, according to the existing meal-dependent bolus insulin dose, change from other short-acting insulin analogue 1:1 by units
▪ adjustment of the dose based on carbohydrate counting[d] or according to the following table[e]:
<table><tr><th colspan="2">Lowest SMPG level (pre-meal or bedtime level)</th><th>Dose adjustment</th></tr><tr><td>mmol/L</td><td>mg/dL</td><td>E</td></tr><tr><td>< 4.4</td><td>< 80</td><td>-1</td></tr><tr><td>4.4–7.2</td><td>80–130</td><td>0</td></tr><tr><td>> 7.2</td><td>> 130</td><td>+1</td></tr></table>
Allowed pretreatment
▪ multiple daily insulin injections (basal and bolus insulin analogues) ≥ 1 year before screening
disallowed prior and concomitant treatment
▪ any drug for the indications of diabetes or obesity that is not listed under permitted pre-treatment, within 90 days prior to screening
▪ commencing a new or changing the existing concomitant treatment for > 14 consecutive days if it is known to have an effect on weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones or corticosteroids).</td></tr>
</table>

Table 7: Characteristics of the intervention – RCT, direct comparison: insulin icodec + insulin aspart vs. insulin degludec + insulin aspart (multipage table)

Study	Intervention	Comparison
a. Patients who had received insulin glargine 300 U/mL or basal insulin (twice daily) before randomization (regardless of the HbA1c level at screening) or patients with an HbA1c level of < 8% (64 mmol/mol) at screening received an insulin icodec starting dose corresponding to their total basal insulin dose before randomization × 7 + 50% of their total basal insulin dose before randomization as a single insulin icodec loading dose. Patients with an HbA1c level of ≥ 8% (64 mmol/mol) at screening received an insulin icodec starting dose corresponding to their total basal insulin dose before randomization × 7 + 100% of their total basal insulin dose before randomization as a single insulin icodec loading dose. b. During the treatment phase, the individual dose was titrated weekly (implementation of the treat-to-target approach to optimize blood glucose control) based on 3 consecutive fasting plasma glucose values. There was no maximum or minimum insulin dose. c. Insulin aspart was to be injected 2 to 4 times a day with the main meals. d. A dose adjustment based on carbohydrate counting could be carried out by patients with experience in this method. As part of the study, the investigator then determined the insulin-to-carbohydrate ratio and the insulin sensitivity factor for each meal. e. During the first 8 weeks, dose adjustments were only allowed to be made for safety reasons. Thereafter, dose adjustments could be made once a week with the help of the investigator. Titration was performed once a week based on the lowest pre-meal or bedtime fasting plasma glucose value of the previous week. Deviations from the titration algorithm were only permitted due to safety concerns. In such cases, the investigator had to document the reasons for the deviation. HbA1c: glycosylated haemoglobin A1c; RCT: randomized controlled trial; SC: subcutaneous; SMPG: self-monitoring blood glucose; U: units		

Study design

ONWARDS 6 is a randomized, open-label, multicentre study comparing insulin icodec with insulin degludec, each in combination with insulin aspart. The study comprised a randomized treatment phase of 52 weeks in total, consisting of a 26-week main phase and a 26-week extension phase. According to the study planning, all study participants were to enter the extension phase.

The study included adult patients diagnosed with type 1 diabetes mellitus who had to have been diagnosed at least 1 year before at the time of inclusion in the study. Patients also had to have been receiving therapy with multiple daily insulin injections (regimen with basal and bolus insulin analogues) for at least 1 year and have an HbA1c level of less than 10%. Patients who had experienced a myocardial infarction, stroke or hospitalization due to unstable angina pectoris or transient ischaemic attack within 180 days prior to study inclusion, or patients who had chronic heart failure (NYHA class IV) at the time of study inclusion as well as patients with renal insufficiency (eGFR < 30 mL/min/1,73m^2) or impaired liver function were excluded from participation in the study. Patients with known hypoglycaemia perception disorder or with recurrent severe hypoglycaemic episodes in the past year were also excluded.

A total of 582 patients were included in the study and randomly assigned to insulin icodec + insulin aspart (N = 290) or insulin degludec + insulin aspart (N = 292). Randomization was

stratified by basal insulin treatment prior to study entry (administration twice daily or treatment with insulin glargine 300 U/mL versus administration once daily) and HbA1c level at screening < 8% or ≥ 8%). Patients in each stratum were randomly assigned to treatment with insulin icodec (once weekly) or insulin degludec (once daily) as basal insulin, in each case in combination with insulin aspart as bolus insulin.

In the intervention and the comparator arm of the ONWARDS 6 study, treatment with basal insulin was based on a fixed titration algorithm identical for all patients based on 3 consecutive fasting PG levels (see Table 7). Patients in the intervention and the comparator arm additionally received insulin aspart as bolus insulin. The bolus insulin dose at the start of the study was determined on the basis of the dose of the existing bolus insulin therapy at the time of study enrolment and had to be kept stable during the first 8 weeks of the study. During this period, adjustments were only permitted for safety reasons. After the first 8 weeks, adjustments could be made once a week depending on the self-monitoring blood glucose level according to a fixed titration algorithm and with the help of the investigator. According to the investigator's assessment, titration could alternatively be based on carbohydrate counting. Titration by carbohydrate counting should only be used in patients with experience in this method after appropriate training by the investigator. As part of this method, the investigator determined the insulin-to-carbohydrate ratio and the insulin sensitivity factor for each meal. In consultation with the investigator, patients were allowed to apply corrections to the bolus doses. The correction bolus doses were also determined by the investigator (see also the text section on treatment with the study medication).

As part of the study, the insulin doses of basal and bolus insulin were titrated in both treatment arms using a target value corridor for fasting blood glucose, with a target range of 80 to 130 mg/dL being aimed at. Deviations from the titration algorithm were only permitted due to safety concerns. In such cases, the investigator had to document the reasons for the deviation.

Treatment with insulin icodec in the intervention arm was largely in compliance with the specifications of the SPC [3]. Patients with an HbA1c level ≥ 8% who had not received insulin glargine 300 U/mL or twice-daily injections of basal insulin as part of their previous therapy received an additional single injection of 100% of the insulin icodec dose. This is not in line with the SPC for insulin icodec, which provides for a one-off loading dose of an additional 50% of the insulin icodec dose for type 1 diabetes mellitus. In the further course, treatment was then compliant with the SPC, whereby the titration algorithm used is not part of the SPC[3]. In the present data situation, the increased loading dose has no consequences for some of the patients. This is due to the fact that only some of the patients included had received the increased dosage over a short period of time at the start of the study. In addition, the available data on the time course of the serious hypoglycaemic episodes (PT; SAEs) do not suggest that

the events occurred more frequently at the start of the study (for explanation see Section I 4.1).

In the comparator arm of the study, treatment with insulin degludec was carried out in accordance with the SPC [11]. However, the titration algorithm used in the study is also not described in the SPC for insulin degludec.

During the first 8 weeks of the study, treatment with insulin aspart deviated from the dosing specified in the SPC [12]. According to the SPC, monitoring of blood glucose levels and adjustment of the insulin dose is recommended for the application. In the study, however, the dosage had to be kept stable for the first 8 weeks and could only be adjusted due to safety concerns. For a detailed explanation and the consequences for the present assessment, see text section on the treatment with the study medication.

During the study, patients were monitored using a CGM system (Dexcom G6). The data recorded via the system were only used to assess glycaemic control, e.g. by recording the time in the target range of 70 mg/dL to 180 mg/dL. In contrast, blood glucose levels measured by the patients themselves were used both for insulin dose adjustments according to the titration algorithm described above and for recording hypoglycaemic episodes. However, patients and investigators had access to the data from the CGM system and, according to the study design, patients were to perform a self-measurement in the event of hypoglycaemic episodes recorded by the CGM. If a plasma glucose (PG) level outside the target range (< 70 mg/dL) was confirmed, the hypoglycaemic episode was recorded as an event in the electronic diary, carbohydrates were administered and the doses of the blood glucose-lowering therapy were adjusted.

The primary outcome of the study was the change in HbA1c after 26 weeks. The primary objective of the study was to show the non-inferiority compared to insulin degludec with regard to the change in HbA1c at Week 26. Secondary outcomes were outcomes of the categories “morbidity” and “AEs”.

Study conduct (protocol deviations)

The study documents show that important protocol deviations occurred on a large scale (see Table 18 in I Appendix B) with clearly more important protocol deviations being recorded in the intervention arm than in the comparator arm (146 vs. 84). In the documents, the important protocol deviations are referred to as subject-level important protocol deviations. It remains unclear whether this is to be understood as the number of patients with an important protocol deviation or whether the data refer to the events. A clear difference for individual categories of important protocol deviations between the study arms can be seen in the administration of the study medication (48 vs. 19). However, it remains unclear to what extent the treatment deviated from the planned study design. In addition, it remains unclear

whether the difference may result from the fact that there were more deviations overall and not from the fact that a different number of patients had important protocol deviations. Other important protocol deviations did not occur to any great extent, and there were no pronounced differences between the study arms. Overall, the differences between the arms with regard to important protocol deviations do not have any consequences for the present assessment.

Limitations of the ONWARDS 6 study

Treatment with the study medication

According to the guideline for the treatment of type 1 diabetes mellitus [4], blood glucose corrections and insulin dosing were carried out autonomously by the patient as part of ICT. In the study, however, adjustments were made for all patients according to a fixed titration algorithm. Adjustments to the bolus insulin dosage were also only possible after consultation with the investigator, including in the context of titration by means of carbohydrate counting. Based on the data presented by the company, it remains unclear in what proportion of patients in the study the specified titration algorithm was used for dose adjustments and in what proportion the method of titration by carbohydrate counting was used. In addition, the bolus insulin dosage had to be kept stable during the first 8 weeks of the study. This does not correspond to the specifications of the guideline or the approach in care. In Module 4 C of the dossier, the company also states that an individually adjusted titration algorithm is normally used in practice for most patients with type 1 diabetes mellitus as part of treatment individualization. Against the background of the titration requirements according to the study planning, however, it cannot be assumed that individualized dose adjustments were made in the study to the extent that would be expected in routine care.

Overall, it can therefore not be assumed that the procedure in the ONWARDS 6 study reflects the therapy envisaged in the guideline or used in routine care. For this reason, it remains unclear whether the results of the ONWARDS 6 study are fully transferable to patients in the German health care context. This uncertainty is taken into account in the assessment of the certainty of conclusions (see Section I 4.2).

Characteristics of the study population

Table 8 shows the patient characteristics of the included study.

Table 8: Characteristics of the study population as well as discontinuation of the study/therapy – RCT, direct comparison: insulin icodec + insulin aspart vs. insulin degludec + insulin aspart

Study characteristic category	**Insulin icodec + insulin aspart N = 290**	**Insulin degludec + insulin aspart N = 292**
ONWARDS 6		
Age [years], mean (SD)	44 (14.1)	44 (14.1)
Sex [F/M], %	43/57	41/59
Family origin, n (%)		
African	9 (3)	2 (1)
Asian	51 (18)	72 (25)
Caucasian	230 (79)	218 (75)
Geographical region, n (%)		
Asia	48 (17)	68 (23)
Europe	136 (47)	139 (48)
North America	106 (37)	85 (29)
Duration of diabetes [years], mean (SD)	20.1 (13.2)	19.0 (12.9)
HbA1c level in % upon randomization, mean (SD)	7.6 (1.0)	7.6 (0.9)
HbA1c level in % upon randomization, n (%)		
≤ 8.5	235 (81)	242 (83)
> 8.5	55 (19)	50 (17)
Fasting plasma glucose [mg/dL], median [min; max]	169.4 (43.3; 441.5)	156.8 (39.6; 499.2)
Body weight [kg], mean (SD)	78.7 (17.6)	77.1 (16.8)
BMI [kg/m^2], mean (SD)	26.8 (5.0)	26.2 (4.5)
Treatment discontinuation[a], n (%)	28 (10[b])	14 (5[b])
Study discontinuation[c], n (%)	16 (6[b])	11 (4[b])

a. Common reasons for treatment discontinuation in the intervention vs. the control arm were: other (16 vs. 7) and withdrawal of consent (5 vs. 4).
b. Institute's calculation.
c. The most common reason for study discontinuation in the intervention vs. the control arm was withdrawal of consent (13 versus 9).

BMI: body mass index; f: female; HbA1c: glycosylated haemoglobin A1c; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the patients are largely balanced between the two treatment arms of the ONWARDS 6 study. The mean age of the patients was 44 years; the majority of them were male (57% or 59%) and were predominantly included in the study in Europe (47% or 48%). The mean time since diabetes diagnosis was 20 or 19 years, and the mean HbA1c level at the time of randomization was 7.6%. Treatment was discontinued more frequently in the intervention arm than in the comparator arm (10% or 5%). The most common reason for treatment

discontinuation was the category "other" at 6% and 2% respectively. The reasons for which treatment was discontinued in this category cannot be learned from the dossier. However, the publication on the study [9] shows that in the intervention arm, 9 patients in this category discontinued treatment for reasons related to the control of blood glucose levels (e.g. due to frequent occurrence of low levels or high variability of levels). In contrast, there were no such discontinuations in the category “Other “ in any patient in the comparator arm. A comparable, low proportion of patients in the intervention and the comparator arm discontinued the study (6% and 4% respectively).

Table 9 shows the antidiabetic medication that patients in the ONWARDS 6 study were receiving at the time of inclusion in the study.

Table 9: Information on the antidiabetic therapy at the time point of screening – RCT, direct comparison: insulin icodec + insulin aspart vs. insulin degludec + insulin aspart

Characteristic category	Patients in ONWARDS 6 antidiabetic therapy at study inclusion n (%[a])	
	insulin icodec + insulin aspart N = 290	insulin degludec + insulin aspart N = 292
Basal bolus therapy	290 (100)	292 (100)
Basal insulin once daily + bolus insulin three times a day	227 (78)	234 (80)
Basal insulin twice daily + bolus insulin 3 times a day	33 (11)	34 (12)
Basal insulin once daily + bolus insulin twice daily	10 (3)	7 (2)
Basal insulin once daily + bolus insulin deviating[b]	9 (3)	8 (3)
Basal insulin twice daily + bolus insulin 4 times a day	2 (< 1)	3 (1)
Basal insulin once daily + bolus insulin four times a day	4 (1)	1 (< 1)
Basal insulin once daily + bolus insulin > 4 times a day	1 (< 1)	3 (1)
Basal insulin twice daily + bolus insulin > 4 times a day	2 (< 1)	0 (0)
Basal insulin twice daily + bolus insulin deviating[b]	1 (< 1)	1 (< 1)
Basal insulin twice daily + bolus insulin 2 twice daily	1 (< 1)	0 (0)
Basal insulin once daily + bolus insulin once daily	0 (0)	1 (< 1)
Basal insulin once daily		
Insulin degludec	117 (40)	111 (38)
Insulin detemir	9 (3)	9 (3)
Insulin glargine 100 U/mL	80 (28)	78 (27)
Insulin glargine 300 U/mL	45 (16)	55 (19)
Insulin isophane	0 (0)	1 (< 1)
Basal insulin twice daily		
Insulin degludec	3 (1)	2 (< 1)
Insulin degludec + insulin glargine 100 U/mL	0 (0)	1 (< 1)
Insulin detemir	11 (4)	20 (7)
Insulin glargine 100 U/mL	17 (6)	13 (4)
Insulin glargine 100 U/mL + insulin degludec	1 (< 1)	0 (0)
Insulin glargine 300 U/mL	5 (2)	2 (< 1)
Insulin isophane	2 (< 1)	0 (0)

a. Institute's calculation.
b. Deviating frequency, includes patients with carbohydrate counting.

n: number of patients in the category; N: number of randomized patients; U: units

The antidiabetic therapy administered to the patients at the time point of study inclusion was largely balanced between the two treatment arms of the ONWARDS 6 study. The patients mainly received basal insulin once daily and bolus insulin three times a day (78% and 80%

respectively). A large proportion of patients in the comparator arm were already receiving insulin degludec as a once-daily basal insulin at the time of inclusion in the study. Information on the bolus insulin administered is not available, so it is not possible to assess how many patients were already receiving insulin aspart at the time point of screening. However, adjustments to the insulin dose according to the titration algorithm provided in the study should be made independently of the therapy at the time of screening, so that it can be assumed that the therapy was optimized within the framework of the study if this was necessary. Even for patients in the comparator arm who were already receiving insulin degludec or a combination of insulin degludec and insulin aspart at the time point of screening, it is therefore not assumed that an inadequate therapy before the start of the study was continued within the framework the study.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: insulin icodec + insulin aspart vs. insulin degludec + insulin aspart

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			
ONWARDS 6	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the ONWARDS 6 study.

Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

On the one hand, the company states that a large proportion of patients in the study population of ONWARDS 6 came from Europe and America (approx. 83% in the intervention arm and approx. 77% in the comparator arm), that approx. three quarters of the patients were of Caucasian origin and that a great proportion of patients were recruited in German study centres. Overall, from the company's perspective, the study population thus corresponds to a type 1 diabetes mellitus population in Germany and the company considers the analysed results of the study population to be transferable to the German health care context.

However, in the discussion of the results of the ONWARDS 6 study, the company points out that, in contrast to the approach in the study, an individually adjusted titration algorithm is usually used in practice as part of treatment individualization in most patients with type 1 diabetes mellitus with the aid of a CGM device. It also states that smaller titration steps (10 units instead of 20 units per week), longer titration intervals (titration every 4 weeks instead of every week) in order to wait until a steady state is reached, or an adjustment of the bolus insulin in everyday clinical practice could reduce the occurrence of hypoglycaemic episodes.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also Section I 3.2.

I 3 Results on added benefit

I 3.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - HbA1c level as sufficiently valid surrogate for microvascular late complications
  - acute coronary syndrome
  - cerebrovascular events
  - cardiac failure
  - end-stage renal disease
  - diabetic retinopathies
- Health-related quality of life
- Side effects
  - serious AEs (SAEs)
  - discontinuation due to AEs
  - non-severe confirmed symptomatic hypoglycaemic episodes
    - PG < 54 mg/dL
    - PG < 70 mg/dL
  - severe hypoglycaemic episodes
  - serious hypoglycaemic episodes (Preferred Term [PT], SAE)
  - diabetic ketoacidosis (PT, AE)
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used additional outcomes in its dossier (Module 4 C). In the present benefit assessment, the outcome of body weight is presented as supplementary information.

Table 11 shows the outcomes for which data are available in the included study.

Table 11: Matrix of outcomes – RCT, direct comparison: insulin icodec + insulin aspart vs. insulin degludec + insulin aspart

Study	Outcomes															
	All-cause mortality[a]	HbA1c	Acute coronary syndrome[b]	Cerebrovascular events[c]	Heart failure[d]	End-stage renal disease	Diabetic retinopathies	Health-related quality of life	SAEs	Discontinuation due to AEs	Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL)	Non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL)	Severe hypoglycaemic episodes[e]	Serious hypoglycaemic episodes (PT, SAE)	Diabetic ketoacidosis (PT, AE)	Other specific AEs
ONWARDS 6	Yes	Yes	Yes	Yes	Yes	No[f]	No[g]	No[h]	Yes	Yes	Yes	No[i]	Yes	Yes	Yes	No[j]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Includes the following adjudicated events: all types of acute myocardial infarction and unstable angina pectoris requiring hospitalization.
c. Includes strokes following adjudication of the following events: Stroke or transient ischaemic attack (episode of focal or global neurological dysfunction caused by brain, spinal cord or retinal vascular injury as a result of haemorrhage or ischaemia, with or without infarction).
d. Described by the company in Module 4 C of the dossier as heart failure or myocardial infarction; the study documents indicate that the outcome includes the following adjudicated events: new episode or worsening of existing heart failure that led to urgent, unscheduled hospitalization or a visit to a clinic/practice/emergency room.
e. Defined by the following criteria: required the assistance of healthcare professionals for treatment with glucagon or glucose IV; were life-threatening; resulted in hospitalization or were characterized by severe neuroglycopenic symptoms.
f. The study did not include a dedicated recording of end-stage renal disease; see the following text section for an explanation.
g. The study did not include a dedicated recording of diabetic retinopathies; see the following text section for an explanation
h. Outcome not recorded.
i. In the study, hypoglycaemic episodes were recorded using the PG threshold values of 70 mg/dL and 54 mg/dL. In Module 4 C of the dossier, the company presents analyses on non-severe confirmed symptomatic hypoglycaemic episodes exclusively for the threshold value of 54 mg/dL.
j. No further specific AEs were identified based on the AEs that had occurred in the study presented by the company.

AE: adverse event; HbA1c: glycosylated haemoglobin A1c; IV: intravenous; n: no; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; y: yes

Morbidity

HbA1c

In patients with type 1 diabetes mellitus, the HbA1c level is a sufficiently valid surrogate for microvascular complications (e.g. diabetic retinopathy, neuropathy) [13-16]. The company presents mean differences in the change in the HbA1c level compared to baseline. This operationalization was pre-specified in the study and is used for the present benefit assessment.

Composite outcome on cardiovascular events

In Module 4 C of the dossier, the company presents analyses on a composite outcome comprising cardiovascular events that were recorded in the ONWARDS 6 study via the AE recording and assessed by an external blinded committee (EAC). In doing so, the company presented analyses on cardiovascular AEs regardless of severity as well as analyses on severe cardiovascular AEs or serious cardiovascular AEs. In Section 4.2.5.2.2.3 in Module 4 C of the dossier, the company states that these analyses considered the following events: acute coronary syndrome, cerebrovascular events or myocardial infarction. However, it can be learned from the study documents that the component of acute coronary syndrome would also include acute myocardial infarction and the third component is listed as heart failure instead of myocardial infarction. In Appendix 4-G in Module 4 C of the dossier, the company also refers to the third component as heart failure. Against this background, it is assumed that the summarizing analysis refers to the 3 components acute coronary syndrome, cerebrovascular event and heart failure. However, as there is no direct allocation in Appendix 4-G in Module 4 C, the individual components were used for the present benefit assessment. In the ONWARDS 6 study, both in the individual components and in the combined analysis of the 3 components, events only occurred in individual patients in both study arms, so that this produces no consequence for the present assessment.

End-stage renal disease

The study does not include a dedicated recording of end-stage renal disease. The company also did not present any data based on AE analyses that are suitable for mapping the outcome. For example, results on a composite outcome based on an eGFR < 15 mL/min/1.73 m², on a renal transplant or on the start of chronic dialysis would be suitable [17]. As the company did not present any analyses on a suitable operationalization, no data are available on the outcome "end-stage renal disease” for the present assessment.

Diabetic retinopathies

The study does not include a dedicated recording of diabetic retinopathies. The company also did not present any data based on AE analyses that are suitable for mapping the outcome. As

the company did not present any analyses on a suitable operationalization, no data are available on the outcome "diabetic retinopathies" for the present assessment.

Side effects

Overall rate of AEs and SAEs

In Module 4 C of the dossier, the company presents analyses for the overall rates of AEs and SAEs, both taking into account all events and without taking into account non-severe, symptomatic or serious hypoglycaemic episodes. As in the present therapeutic indication hypoglycaemia is an AE that is considered both separately as a specific AE and as part of the overall rates for the benefit assessment, analyses considering all events were used and presented as supplementary information for this benefit assessment. In the present data situation, regardless of the operationalization of the overall rates, no statistically significant differences were found between the treatment groups, so that the company's approach has no consequences for the present benefit assessment.

Hypoglycaemic episodes

In Module 4 C of the dossier, the company presents various analyses on hypoglycaemic episodes, some of which were conducted post hoc for the dossier.

- Firstly, the company presented post hoc analyses of the number of patients with at least one non-severe hypoglycaemia, which was confirmed by a PG value < 54 mg/dL and was also accompanied by hypoglycaemic symptoms.
- In addition, the company presented post hoc analyses on the number of patients with at least one severe hypoglycaemic episode, which were defined by the following criteria: They required the assistance of healthcare professionals for treatment with glucagon or glucose IV, were life-threatening, resulted in hospitalization or were characterized by severe neuroglycopenic symptoms.
- The company also presented analyses on the number of patients with at least one serious hypoglycaemic episode that was recorded in the study as an SAE via the PT "hypoglycaemic episodes" according to MedDRA.
- In addition, the company presented a post hoc analysis based on SAEs, which includes a collection of PTs that the company classified as being associated with hypoglycaemia. SAEs of the following PTs were considered: glycopenia, hypoglycaemia, hypoglycaemic seizure, unconsciousness caused by hypoglycaemia, hypoglycaemic encephalopathy, hypoglycaemic coma, hypoglycaemic shock, hypoglycaemia not perceived, neuroglycopenia and postprandial hypoglycaemia.

In contrast, the recording of

- hypoglycaemic episodes with PG values between 54 mg/dL and 70 mg/dL (regardless of the occurrence of symptoms),
- of hypoglycaemic episodes with PG values below 54 mg/dL as clinically significant hypoglycaemic episodes (independent of the occurrence of symptoms) and of
- severe hypoglycaemic episodes was planned in the study. According to the study design, severe hypoglycaemic episodes were not characterized by a specific PG value, but by severe cognitive impairment with the need for help from another person. Help from another person could include the administration of carbohydrates, glucagon or other actions to correct the hypoglycaemia.
- The study report also contains analyses on the previously described PT collection based on SAEs that were classified as being associated with hypoglycaemic episodes. In Module 4 C of the dossier, the company justifies the performance of these post hoc analyses by stating that the fact that statistically significantly more patients with at least one serious hypoglycaemic episode occurred in the intervention arm than in the comparator arm led to a more detailed investigation, in the context of which the additional post hoc analysis was performed using the PT collection.

Only the post hoc analyses of non-severe symptomatic hypoglycaemic episodes (PG value < 54 mg/dL), of severe hypoglycaemic episodes as well as the analyses of serious hypoglycaemic episodes that were recorded as SAEs were used for the present assessment. For its assessment, the company also considered the analysis of the post hoc collection of PTs based on SAEs that were classified by the company as "associated with hypoglycaemia". However, this analysis is not suitable for the present assessment, as the PTs were selected post hoc and therefore it cannot be ruled out that the compilation was results-driven.

Analyses of non-severe, confirmed symptomatic hypoglycaemic episodes for the PG threshold value of 70 md/dL are also relevant for the present assessment. However, the company did not present any analyses of events associated with symptoms for this threshold value, although it would have been able to do so on the basis of the recordings performed as part of the study, analogous to the analyses for the 54 mg/dL threshold value.

Overall, it is notable that in the study the proportion of patients with non-severe, confirmed symptomatic hypoglycaemic episodes (< 54 mg/dL) based on the post hoc analysis presented by the company for the dossier is very small compared to the patients with clinically significant hypoglycaemic episodes recorded in the study, which were recorded exclusively on the basis of the PG value without the presence of symptoms (see Table 19 in I Appendix C for the results on the operationalizations according to the study design). One possible explanation for the fact that the majority of patients did not develop any symptoms could be that continuous monitoring by means of CGM took place in the study. Adjustments to the therapy were already

planned for hypoglycaemic alarm signals, which were recorded via the threshold value of 70 mg/dL in the study.

Comments on hypoglycaemic episodes in the SPC or from the approval procedure

In the context of the approval procedure, the European Medicines Agency (EMA) discussed not only the proportions of patients with events but also the events that occurred (i.e. analyses of first and subsequent events) [10]. For the events that were recorded for the operationalizations according to the study design, see Table 19 in I Appendix C. Based on the summary of the results on hypoglycaemic episodes according to the operationalization as planned in the ONWARDS 6 study, the EMA included a warning in the SPC that there was an increased risk of hypoglycaemia in patients with type 1 diabetes treated with insulin icodec compared to insulin degludec. According to the SPC, patients with type 1 diabetes should therefore only be treated with insulin icodec if a clear benefit is expected from once-weekly dosing [3,10]. Neither the SPC nor the EMA assessment report provide clear criteria for assessing this.

In connection with the higher event rates observed for hypoglycaemic episodes, the increased loading dose of 100% in Week 1 for some of the patients in the ONWARDS 6 study was also discussed in the EMA assessment report and not included in the SPC for safety reasons (for an explanation of the loading dose, see also Section I 3.2). However, this had no consequence for the present assessment, as the available data on the time course of serious hypoglycaemic episodes (PT; SAEs) do not suggest that the events occurred more frequently at the start of the study. Only in one patient in the intervention arm did the first event occur early in the study, after 17 days of receiving the loading dose. In all other patients with at least one event in the intervention arm, this occurred 99 days after receiving the loading dose at the earliest. The other events in the patient with the 1st event on Day 17 also occurred at significantly later time points (100, 108 and 219 days after the loading dose). For the post hoc analyses of non-severe symptomatic hypoglycaemic episodes (PG value < 54 mg/dL) and severe hypoglycaemic episodes, no information is available on the time points at which events occurred during the course of the study.

I 3.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: insulin icodec + insulin aspart vs. insulin degludec + insulin aspart

Study	Study level	Outcomes															
		All-cause mortality[a]	HbA1c	acute coronary syndrome[b]	Cerebrovascular events[c]	Heart failure[d]	End-stage renal disease	Diabetic retinopathies	Health-related quality of life	SAEs	Discontinuation due to AEs	Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL)	Non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL)	Severe hypoglycaemic episodes[e]	Serious hypoglycaemic episodes (PT, SAE)	Diabetic ketoacidosis (PT, AE)	Other specific AEs
ONWARDS 6	L	L	L	L	L	L	–[f]	–[g]	–[h]	L	H[i]	H[j]	–[k]	L	L	H[j]	–[l]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Includes the following adjudicated events: all types of acute myocardial infarction and unstable angina pectoris requiring hospitalization.
c. Includes strokes following adjudication of the following events: Stroke or transient ischaemic attack (episode of focal or global neurological dysfunction caused by brain, spinal cord or retinal vascular injury as a result of haemorrhage or ischaemia, with or without infarction).
d. Described by the company in Module 4 C of the dossier as heart failure or myocardial infarction; the study documents indicate that the outcome includes the following adjudicated events: new episode or worsening of existing heart failure that led to urgent, unscheduled hospitalization or a visit to a clinic/practice/emergency room.
e. Defined by the following criteria: required the assistance of healthcare professionals for treatment with glucagon or glucose IV; were life-threatening; resulted in hospitalization or were characterized by severe neuroglycopenic symptoms.
f. The study did not include a dedicated recording of end-stage renal disease; see Section I 4.1 for an explanation.
g. The study did not include a dedicated recording of diabetic retinopathies; see Section I 4.1 for an explanation.
h. Outcome not recorded.
i. Lack of blinding in subjective decision for treatment discontinuation.
j. Lack of blinding in subjective recording of outcomes.
k. In the study, hypoglycaemic episodes were recorded using the PG threshold values of 70 mg/dL and 54 mg/dL. In Module 4 C of the dossier, the company presents analyses on non-severe confirmed symptomatic hypoglycaemic episodes exclusively for the threshold value of 54 mg/dL.
l. No further specific AEs were identified based on the AEs that had occurred in the study presented by the company.

AE: adverse event; H: high; IV: intravenous; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event

The risk of bias for the results on the outcomes of all-cause mortality, HbA1c level, acute coronary syndrome, cerebrovascular events and heart failure was considered to be low. In the side effects category, the bias of the results on the outcomes of SAEs, severe hypoglycaemic episodes and serious hypoglycaemic episodes was rated as low, while the bias of the outcomes of discontinuation due to AEs, non-severe confirmed symptomatic hypoglycaemic episodes (< 54 mg/dL) and diabetic ketoacidosis was rated as high due to lack of blinding in subjective decision to discontinue treatment and lack of blinding in subjective recording of outcomes.

Summary assessment of the certainty of conclusions

It remains unclear whether the results of the ONWARDS 6 study can be transferred without restriction to the target population in the German health care context. This is due to the fact that against the background of the fixed specifications on the titration algorithm according to the study design, it cannot be assumed that the procedure in the ONWARDS 6 study reflects the therapy intended according to the guideline or used in everyday care with individualized adjustments. For this reason, it remains unclear whether the results of the ONWARDS 6 study are fully transferable to the German health care context. Overall, this reduces the certainty of conclusions of the study results for the present research question. Based on the ONWARDS 6 study, at most hints, e.g. of an added benefit, can be derived for all presented outcomes.

I 3.3 Results

Table 13 and Table 14 summarize the results on the comparison of insulin icodec + insulin aspart with insulin degludec + insulin aspart in adult patients with type 1 diabetes mellitus at the end of the study (Week 52 and Week 57). Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: insulin icodec + insulin aspart vs. insulin degludec + insulin aspart (multipage table)

Study outcome category outcome	Insulin icodec + insulin aspart		Insulin degludec + insulin aspart		Insulin icodec + insulin aspart vs. insulin degludec + insulin aspart
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
ONWARDS 6					
Mortality					
All-cause mortality[b]	290	1 (0.3)	292	0 (0)	3.02 [0.12; 73.84]; 0.370
Morbidity					
Acute coronary syndrome[c]	290	1 (0.3)	292	2 (0.7)	0.50 [0.05; 5.52]; 0.683
Cerebrovascular events[d]	290	2 (0.7)	292	1 (0.3)	2.01 [0.18; 22.09]; 0.602
Cardiac failure[e]	290	1 (0.3)	292	0 (0)	3.02 [0.12; 73.94]; 0.370
End-stage renal disease	No suitable data[f]				
Diabetic retinopathies	No suitable data[g]				
Health-related quality of life	Outcome not recorded				
Side effects					
AEs (supplementary information)	290	240 (82.8)	292	236 (80.8)	–
SAEs	290	24 (8.3)	292	21 (7.2)	1.15 [0.66; 2.02]; 0.683
Discontinuation due to AEs	290	2 (0.7)	292	1 (0.3)	2.01 [0.18; 22.09]; 0.602
Non-severe confirmed symptomatic hypoglycaemic episodes					
PG < 54 mg/dL	290	3 (1.0)	292	5 (1.7)	0.60 [0.15; 2.50]; 0.533
PG < 70 mg/dL	No suitable data				
Severe hypoglycaemia[h]	290	11 (3.8)	292	6 (2.1)	1.85 [0.69; 4.93]; 0.248
Serious hypoglycaemia (PT, SAE)	290	8 (2.8)	292	1 (0.3)	8.06 [1.01; 64.00]; 0.018
Diabetic ketoacidosis (PT, AE)	290	1 (0.3)	292	0 (0)	3.02 [0.12; 73.84][i]; 0.370

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: insulin icodec + insulin aspart vs. insulin degludec + insulin aspart (multipage table)

Study outcome category outcome	Insulin icodec + insulin aspart		Insulin degludec + insulin aspart		Insulin icodec + insulin aspart vs. insulin degludec + insulin aspart
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]

a. Institute's calculation (unconditional exact test [CSZ method according to [18]]).
b. The results on all-cause mortality are based on the data on fatal AEs.
c. Includes the following adjudicated events: all types of acute myocardial infarction and unstable angina pectoris requiring hospitalization.
d. Includes strokes following adjudication of the following events: stroke or transient ischaemic attack (episode of focal or global neurological dysfunction caused by brain, spinal cord or retinal vascular injury as a result of haemorrhage or ischaemia, with or without infarction).
e. Described by the company in Module 4 C of the dossier as heart failure or myocardial infarction; the study documents indicate that the outcome includes the following adjudicated events: new episode or worsening of existing heart failure that led to urgent, unscheduled hospitalization or a visit to a clinic/practice/emergency room.
f. The study did not include a dedicated recording of end-stage renal disease; see Section I 4.1 for an explanation.
g. The study did not include a dedicated recording of diabetic retinopathies; see Section I 4.1 for an explanation.
h. Defined by the following criteria: required the assistance of healthcare professionals for treatment with glucagon or glucose IV; were life-threatening; resulted in hospitalization or were characterized by severe neuroglycopenic symptoms.
e. Institute's calculation of RR [95% CI] (asymptotic).

CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 14: Results (morbidity) – RCT, direct comparison: insulin icodec + insulin aspart vs. insulin degludec + insulin aspart

Study outcome category outcome	Insulin icodec + insulin aspart			Insulin degludec + insulin aspart			Insulin icodec + insulin aspart vs. insulin degludec + insulin aspart
	N[a]	values at baseline mean (SD)	change by Week 52 mean (SE)[b]	N[a]	values at baseline mean (SD)	change by Week 52 mean (SE)[b]	MD [95% CI]; p-value[b]
ONWARDS 6							
Morbidity							
HbA1c (%)[c]	270	7.59 (0.96)	-0.37 (0.05)	278	7.63 (0.93)	-0.54 (0.05)	0.17 [0.02; 0.31]; 0.021
Body weight (kg) (supplementary information)	273	78.65 (17.62)	1.25 (0.27)	279	77.10 (16.78)	1.67 (0.29)	-0.42 [-1.20; 0.37]; 0.296

a. Number of patients taken into account in the effect estimation; baseline values (and values at Week 52) may rest on different patient numbers.
b. ANCOVA model, adjusted for treatment, HbA1c value at screening < 8% (yes/no), basal insulin treatment twice daily or treatment with insulin glargine 300 U/mL before study entry (yes/no), and geographical region as fixed factors and the baseline value as covariate; missing values imputed by multiple imputation.
c. Sufficiently valid surrogate for microvascular late complications.

CI: confidence interval; HbA1c: glycosylated haemoglobin A1c; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error

As explained in Section I 4.2, no more than hints, e.g. of an added benefit, can therefore be determined for all outcomes on the basis of the available information.

Mortality

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome "all-cause mortality". This resulted in no hint of an added benefit of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart for this outcome; an added benefit is therefore not proven.

Morbidity

HbA1c level as sufficiently valid surrogate for microvascular late complications

For the outcome “HbA1c level”, a statistically significant difference between the treatment arms to the disadvantage of insulin icodec + insulin aspart compared to insulin degludec + insulin aspart is shown based on the mean differences (for the change in the HbA1c level from baseline). The EMA uses a threshold value of 0.3 percentage points for the HbA1c level to assess the non-inferiority [19]; however, current documents of the US FDA provide the general information that the magnitude of changes in the HbA1c level must be weighed against the

risks, and that statistically significant but minor reductions in the HbA1c level may possibly not outweigh serious adverse drug reactions [20]. Irrespective of this, the effect observed in the present data situation is not considered relevant simply because the 95% confidence interval of the effect with the lower limit of 0.02% is close to the zero effect. Given this data situation, a relevant effect cannot be assumed with sufficient certainty. This resulted in no hint of an added benefit of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart for this outcome; an added benefit is therefore not proven.

Based on the threshold of 0.3 percentage points used by the EMA, the non-inferiority at Week 52 is not proven.

Acute coronary syndrome

There was no statistically significant difference between the treatment arms for the outcome of acute coronary syndrome. This resulted in no hint of an added benefit of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart for this outcome; an added benefit is therefore not proven.

Cerebrovascular events

No statistically significant difference between treatment arms was shown for the outcome of cerebrovascular events. This resulted in no hint of an added benefit of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart for this outcome; an added benefit is therefore not proven.

Cardiac failure

No statistically significant difference between treatment arms was shown for the outcome of heart failure. This resulted in no hint of an added benefit of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart for this outcome; an added benefit is therefore not proven.

End-stage renal disease

No suitable data are available for the outcome of end-stage renal disease. This resulted in no hint of an added benefit of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart for this outcome; an added benefit is therefore not proven.

Diabetic retinopathies

No suitable data are available for the outcome of diabetic retinopathies. This resulted in no hint of an added benefit of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart for this outcome; an added benefit is therefore not proven.

Health-related quality of life

In the ONWARDS 6 study, health-related quality of life was not recorded. There is no hint of an added benefit of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart; an added benefit is therefore not proven.

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome of SAEs. For the outcome of SAEs, there was no hint of greater or lesser harm from insulin icodec + insulin aspart versus insulin degludec + insulin aspart; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome "discontinuation due to AEs". For the outcome of discontinuations due to AEs, there was no hint of greater or lesser harm from insulin icodec + insulin aspart versus insulin degludec + insulin aspart; greater or lesser harm is therefore not proven.

Non-severe confirmed symptomatic hypoglycaemic episodes

No statistically significant difference between the treatment arms was shown for the outcome of non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL). For this outcome, there was no hint of greater or lesser harm from insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart; greater or lesser harm is therefore not proven.

No data are available for the outcome of non-severe confirmed symptomatic hypoglycaemia (PG < 70 mg/dL). For this outcome, there was no hint of greater or lesser harm from insulin icodec + insulin aspart versus insulin degludec + insulin aspart; greater or lesser harm is therefore not proven.

Severe hypoglycaemia

There is no statistically significant difference between treatment arms for the outcome of severe hypoglycaemic episodes. For the outcome of severe hypoglycaemic episodes, there was no hint of greater or lesser harm from insulin icodec + insulin aspart versus insulin degludec + insulin aspart; greater or lesser harm is therefore not proven.

Serious hypoglycaemic episodes (SAEs)

For the outcome of serious hypoglycaemic episodes, there was a statistically significant difference to the disadvantage of insulin icodec + insulin aspart compared to insulin degludec

+ insulin aspart. For this outcome, there is hint of greater harm from insulin icodec + insulin aspart compared to insulin degludec + insulin aspart.

Diabetic ketoacidosis

There was no statistically significant difference between the treatment arms for the outcome of diabetic ketoacidosis. For the outcome of diabetic ketoacidosis, there was no hint of greater or lesser harm from insulin icodec + insulin aspart versus insulin degludec + insulin aspart; greater or lesser harm is therefore not proven.

I 3.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for the present benefit assessment:

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

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Applying the methods described above, there were no effect modifications for the characteristics of age and sex.

I 4 Probability and extent of added benefit

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

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

I 4.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 15).

Table 15: Extent of added benefit at outcome level: insulin icodec + insulin aspart vs. insulin degludec + insulin aspart (multipage table)

Outcome category **outcome**	**Insulin icodec + insulin aspart vs. insulin degludec + insulin aspart** **proportion of events (%) or mean change** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0.3% vs. 0% RR: 3.02 [0.12; 73.84]; p = 0.370	Lesser/added benefit not proven
Morbidity		
Hba1c level[c]	-0.37 vs. -0.54 MD: 0.17 [0.02; 0.31]; p = 0.021	Lesser/added benefit not proven
Acute coronary syndrome	0.3% vs. 0.7% RR: 0.50 [0.05; 5.52]; p = 0.683	Lesser/added benefit not proven
Cerebrovascular events	0.7% vs. 0.3% RR: 2.01 [0.18; 22.09]; p = 0.602	Lesser/added benefit not proven
Cardiac failure	0.3% vs. 0% RR: 3.02 [0.12; 73.94]; p = 0.370	Lesser/added benefit not proven
End-stage renal disease	No suitable data	Lesser/added benefit not proven
Diabetic retinopathies	No suitable data	Lesser/added benefit not proven

Table 15: Extent of added benefit at outcome level: insulin icodec + insulin aspart vs. insulin degludec + insulin aspart (multipage table)

Outcome category **outcome**	**Insulin icodec + insulin aspart vs. insulin degludec + insulin aspart** **proportion of events (%) or mean change** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
–	Outcome not recorded	Lesser/added benefit not proven
Side effects		
SAEs	8.3% vs. 7.2% RR: 1.15 [0.66; 2.02]; p = 0.683	Greater/lesser harm not proven
Discontinuation due to AEs	0.7% vs. 0.3% RR: 2.01 [0.18; 22.09]; p = 0.602	Greater/lesser harm not proven
Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL)	1.0% vs. 1.7% RR: 0.60 [0.15; 2.50]; p = 0.533	Greater/lesser harm not proven
Non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL)	No suitable data	Greater/lesser harm not proven
Severe hypoglycaemic episodes	3.8% vs. 2.1% RR: 1.85 [0.69; 4.93]; p = 0.248	Greater/lesser harm not proven
Serious hypoglycaemia (PT, SAE)	2.8% vs. 0.3% RR: 8.06 [1.01; 64.00]; RR: 0.12 [0.02; 0.99][d]; p = 0.018 probability: “hint”	Outcome category: severe/serious side effects $0.90 \leq CI_u \leq 1.00$ greater harm, extent: “minor”
Diabetic ketoacidosis (PT, AE)	0.3% vs. 0% 3.02 [0.12; 73.84]; p = 0.370	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category and the scale of the outcome, effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_l).
c. Sufficiently valid surrogate for microvascular late complications.
d. Institute’s calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.

AE: adverse event; CI: confidence interval; CI_l: lower limit of confidence interval; CI_u: upper limit of confidence interval; HbA1c: glycosylated haemoglobin A1c; MD: mean difference; PG: plasma glucose; PT: Preferred Term; RR: relative risk; SAE: serious adverse event

I 4.2 Overall conclusion on added benefit

Table 16 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of insulin icodec + insulin aspart in comparison with insulin degludec + insulin aspart

Positive effects	**Negative effects**
–	Serious/severe side effects ▪ serious hypoglycaemic episodes: hint of greater harm – extent: “minor”
No data are available for the outcomes of end-stage renal disease, diabetic retinopathies, health-related quality of life and non-severe confirmed symptomatic hypoglycaemic episodes (PG < 70 mg/dL).	
PG: Plasma glucose	

Overall, there is a negative effect for serious hypoglycaemic episodes. Although this is not offset by any positive effects, the negative effect with the extent “minor” is not shown in the operationalization of severe hypoglycaemic episodes, but only for serious hypoglycaemic episodes. Although the proportion of patients with severe hypoglycaemic episodes is slightly higher than for serious hypoglycaemic episodes - particularly in the comparator arm - it is also in the low single-digit percentage range. Overall, the derivation of lesser benefit does not appear justified in the present data situation.

In summary, there is no hint of an added benefit of insulin icodec over the ACT for adult patients with type 1 diabetes mellitus.

The result of the assessment of the added benefit of insulin icodec in comparison with the ACT is summarized in Table 17.

Table 17: Insulin icodeca – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
Adult patients with type 1 diabetes mellitus[c]	Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin degludec, insulin aspart, insulin glulisine, insulin lispro)[d]	Added benefit not proven

a. According to the SPC [3] , insulin icodec must be combined with bolus insulin in patients with type 1 diabetes mellitus in order to cover the insulin requirement at mealtimes.
b. Presentation of the ACT specified by the G-BA.
c. The ONWARDS 6 study only included patients who had been diagnosed with type 1 diabetes mellitus for at least 1 year and were receiving intensified conventional insulin therapy (ICT). It remains unclear whether the observed effects can be transferred to patients with newly diagnosed type 1 diabetes mellitus and to patients for whom conventional therapy (CT) or an insulin pump is an option. In the ONWARDS 6 study, insulin icodec was also only used in combination with insulin aspart, not with other bolus insulins. It remains unclear whether the observed results can be transferred to an application in combination with other bolus insulins.
d. The unchanged continuation of an inadequate therapy of type 1 diabetes mellitus, if there is still the option of optimizing insulin therapy, does not correspond to an ACT.

ACT: appropriate comparator therapy; CT: conventional therapy; G-BA: Federal Joint Committee; ICT: intensified conventional insulin therapy

The assessment described above concurs with that of the company.

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

I 5 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. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Novo Nordisk. Awiqli 700 Einheiten/ml Injektionslösung im Fertigpen [online]. 2024 [Accessed: 02.09.2024]. URL: https://www.fachinfo.de.

4. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Therapie des Typ-1-Diabetes [online]. 2023 [Accessed: 02.09.2024]. URL: https://register.awmf.org/de/leitlinien/detail/057-013.

5. Gemeinsamer Bundesausschuss. Richtlinie zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme [online]. 2024. URL: https://www.g-ba.de/richtlinien/83/.

6. Novo Nordisk. Efficacy and Safety of Once Weekly Insulin Icodec Compared to Once Daily Insulin Degludec 100 units/mL, Both in Combination With Insulin Aspart, in Adults With Type 1 Diabetes; A 26-week, randomised, multicentre, open-label, active-controlled, parallel group, two armed, treat-to-target trial investigating the effect on glycaemic control and safety of treatment with once weekly insulin icodec compared to once daily insulin degludec, both in combination with insulin aspart in adults with type 1 diabetes, with a 26-week extension investigating long term safety; study NN1436-4625; ONWARDS 6; Results from the complete trial; Trial Phase: 3a; clinical trial report [unpublished]. 2023.

7. Novo Nordisk. Efficacy and safety of once weekly insulin icodec compared to once daily insulin degludec 100 units/ml, both in combination with insulin aspart, in adults with type 1 diabetes [online]. [Accessed: 15.10.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-002374-27.

8. Novo Nordisk. A Research Study to Compare a New Weekly Insulin, Insulin Icodec, and an Available Daily Insulin, Insulin Degludec, Both in Combination With Mealtime Insulin in People With Type 1 Diabetes (ONWARDS 6) [online]. 2023 [Accessed: 15.10.2024]. URL: https://clinicaltrials.gov/study/NCT04848480.

9. Russell-Jones D, Babazono T, Cailleteau R et al. Once-weekly insulin icodec versus once-daily insulin degludec as part of a basal-bolus regimen in individuals with type 1 diabetes (ONWARDS 6): a phase 3a, randomised, open-label, treat-to-target trial. Lancet 2023; 402(10413): 1636-1647. https://doi.org/10.1016/s0140-6736(23)02179-7.

10. European Medicines Agency. Awiqli; Assessment report [online]. 2024 [Accessed: 02.09.2024]. URL: https://www.ema.europa.eu/en/documents/assessment-report/awiqli-epar-public-assessment-report_en.pdf.

11. Novo Nordisk. Tresiba [online]. 2024 [Accessed: 02.09.2024]. URL: https://www.fachinfo.de.

12. Novo Nordisk. NovoRapid [online]. 2024 [Accessed: 02.09.2024]. URL: https://www.fachinfo.de/.

13. Nathan DM, Genuth S, Lachin J et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329(14): 977-986. https://doi.org/10.1056/NEJM199309303291401.

14. Jeffcoate SL. Diabetes control and complications: the role of glycated haemoglobin, 25 years on. Diabet Med 2004; 21(7): 657-665. https://doi.org/10.1046/j.1464-5491.2003.01065.x.

15. Oduneye F. Insulin pumps, conventional and instensive multiple injection insulin therapy for type 1 diabetes mellitus. STEER 2002; 2(4): 1-8.

16. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Langwirksame Insulinanaloga zur Behandlung des Diabetes mellitus Typ 1; Abschlussbericht [online]. 2019 [Accessed: 14.11.2024]. URL: http://www.iqwig.de/download/A05-01_Abschlussbericht_Langwirksame_Insulinanaloga_bei_Diabetes_mellitus_Typ_1.pdf.

17. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Tirzepatid (Diabetes mellitus Typ 2); Addendum zum Projekt A23-112 (Dossierbewertung) [online]. 2023 [Accessed: 14.11.2024]. URL: https://www.iqwig.de/download/a24-32_tirzepatid_addendum-zum-projekt-a23-112_v1-0.pdf.

18. 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. https://doi.org/10.1016/0167-9473(94)90148-1.

19. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus [online]. 2023 [Accessed: 22.10.2024]. URL: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-or-prevention-diabetes-mellitus-revision-2_en.pdf.

20. Federal Drug Administration. Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products; Guidance for Industry [online]. 2023 [Accessed: 14.11.2024]. URL: https://www.fda.gov/media/168475/download.

The full report (German version) is published under https://www.iqwig.de/en/projects/a24-90.html.