Insulin icodec
(type 2 diabetes mellitus)

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

EXTRACT

Project: A24-91 Version: 1.0 Status: 28 Nov 2024 DOI: 10.60584/A24-91_en

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Insulin icotec (Diabetes mellitus Typ 2) – 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 2 diabetes mellitus) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

30 August 2024

Internal Project No.

A24-91

DOI-URL

https://doi.org/10.60584/A24-91_en

Address of publisher

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Recommended citation

Institute for Quality and Efficiency in Health Care. Insulin icodec (type 2 diabetes mellitus); Benefit assessment according to §35a SGB V; Extract [online]. 2024 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A24-91_en.

Keywords

Insulin Icodec, Diabetes Mellitus – Type 2, Benefit Assessment, NCT04460885, NCT04880850, Benefit Assessment

Medical and scientific advice

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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.

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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
CT	conventional therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycosylated haemoglobin
ICT	Intensified insulin therapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NVL	National Disease Management Guideline
NYHA	New York Heart Association
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

I 1 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 2 diabetes mellitus.

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of insulin icodec

Research question	Therapeutic indication[a]	ACT[b]
1	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin + metformin
2	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin + metformin + empagliflozin or ▪ human insulin + metformin + dapagliflozin or ▪ human insulin + metformin + liraglutide
3	Insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy CT, possibly + metformin or dulaglutide or ICT
4	Insulin-experienced adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy: CT or ICT, in each case in combination with metformin and empagliflozin or dapagliflozin or liraglutide

a. Subdivision of the therapeutic indication according to the G-BA.
- For the treatment of comorbidities in adults with type 2 diabetes mellitus (hypertension, dyslipoproteinaemia, coronary artery disease, renal disorders etc.), especially in patients with manifest cardiovascular disease who receive additional drugs for treating cardiovascular risk factors, individualized treatment of the respective comorbidities in accordance with current medical knowledge is assumed to be administered, with said treatment particularly including antihypertensives, anticoagulants, and/or lipid-lowering drugs, taking into account the particular characteristics of the present disease.
- Patients on insulin should undergo regular examinations to determine whether insulin therapy remains indicated or whether de-escalation of the insulin therapy might be possible and indicated.
- Continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus does not correspond to the ACT.
- The specific ACT options in patient groups a2, b1 and b2 (i.e. research questions 2, 3 and 4) are each equally appropriate treatment alternatives.

b. Presentation of the respective ACT specified by the G-BA.

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

In this benefit assessment, the subpopulations a1, a2, b1 and b2 named by the G-BA and the company, are referred to as research questions 1 to 4 in accordance with the research questions in Table 2.

Two aspects should be emphasized in the context of this assessment:

1) The description of the population for research question 1 ("who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and who are indicated for insulin therapy") reflects the fact that (unlike in type 1 diabetes mellitus) insulin therapy is the last treatment option in type 2 diabetes mellitus and is only used if all other prior drug (and non-drug) treatment options have failed.
2) The wording "Adults... who have not achieved adequate glycaemic control with their present therapy/regimen" makes clear that this describes patient groups for whom therapy intensification is necessary due to inadequate glycaemic control. Consequently, this means that, according to the G-BA's specification of the ACT, treatment escalation is required in each case. A switch of the insulin therapy to insulin icodec (e.g. from insulin glargine or other daily administered basal insulins) for reasons other than inadequate glycaemic control is therefore not part of the research questions addressed in this assessment. Similarly, there are no further research questions that reflect the use of insulin icodec in patients whose therapy has already been escalated to the maximum.

The company followed the G-BA's specification of the ACT. For research questions 3 and 4, the company stated that, in contrast to the G-BA, it only considered intensified insulin therapy (ICT) to be a relevant escalation of insulin therapy. For research question 3, the company also stated that it considered further treatment with non-insulin antidiabetics (including metformin, dulaglutide, empagliflozin, dapagliflozin and liraglutide) to be regularly indicated in addition to ICT in insulin-experienced adults without manifest cardiovascular disease. However, in accordance with the ACT specified by the G-BA, it exclusively considered patients who did not receive concomitant treatment with non-insulin antidiabetics for the data it submitted on research question 3. For all 4 research questions, the company also described that although the G-BA did not name insulin analogues as an ACT, insulin glargine is considered a suitable comparator by the G-BA. In doing so, the company refers to a consultation with the G-BA on 16 August 2022. Although the company does not comment on further insulin analogues in the dossier, it also considered studies for its assessment in which insulin aspart was used, while it excluded studies in which insulin degludec was used, on the grounds that neither human insulin nor insulin glargine, but insulin degludec, was used as a comparator.

These deviations described above are of no consequence for the present assessment, as the company did not present suitable data on the comparison of insulin icodec with the ACT for either of the research questions.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for deriving any added benefit.

Research question 1: Insulin-naive adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated (without manifest cardiovascular disease)

Results

The check for completeness of the study pool revealed no relevant study for the comparison of insulin icodec versus the ACT. In contrast, the company first identified the 3 potentially suitable studies NN1436-4383, NN1436-4477 (hereinafter ONWARDS 1) and NN1436 4481 (hereinafter ONWARDS 5), each of which examined insulin-naive adults with type 2 diabetes mellitus. Since various concomitant medications that did not correspond to the ACT were permitted in these studies, the company first examined the potentially suitable studies to determine whether a relevant subpopulation for research question 1 (referred to as research question a1 by the company in the dossier) could be delimited in each case. Based on the information available for the potentially suitable studies identified by it, the company attempts to delimit a subpopulation of patients for research question 1 who are treated exclusively in combination with metformin in addition to the respective insulin administration and who are also pretreated with at least 2 blood glucose-lowering drugs. According to the company's information in Module 4 A of the dossier, a subpopulation comprising sufficient patients for a benefit assessment can only be formed for the ONWARDS 1 study for research question 1, which is why the company only uses results on a subpopulation of this study for its assessment in Module 4 A of the dossier for research question 1. However, the data presented by the company on the subpopulation of the ONWARDS 1 study are not suitable for the benefit assessment of insulin icodec versus the ACT.

This is mainly due to the fact that the documents submitted do not provide information on whether the non-drug and drug treatment options with non-insulin antidiabetics were exhausted in the subpopulation presented by the company and that there was therefore an indication for insulin therapy. The reasoning is provided below.

Evidence presented by the company – ONWARDS 1 study

ONWARDS 1 is an open-label, randomized, active-controlled study on the comparison of insulin icodec with insulin glargine, each in combination with non-insulin antidiabetics with a treatment duration of 78 weeks. Insulin-naive adults with type 2 diabetes mellitus and with glycosylated haemoglobin (HbA1c) levels between ≥ 7.0% and ≤ 11.0% at study inclusion were included. Patients were excluded from participation in the study if they had suffered a myocardial infarction, stroke or hospitalization due to unstable angina pectoris or due to transient ischaemic attack within 180 days prior to the day of screening or if they had chronic heart failure (New York Heart Association [NYHA] class IV) at the time of screening. Patients for whom a change in lifestyle with an impact on glycaemic control was to be expected were also excluded.

In the ONWARDS 1 study, insulin icodec was compared with insulin glargine, each in combination with the present non-insulin antidiabetics. According to the inclusion criteria, monotherapy or combination therapies with metformin, sulphonylureas, glinides, DPP-4 inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, thiazolidinediones, alpha-glucosidase inhibitors, oral or injectable glucagon-like peptide-1 [GLP-1] receptor agonists were permitted. The concomitant therapy was to be administered at a stable dose for at least 90 days prior to study inclusion and had to be continued during the study. Only sulphonylureas and glinides had to be discontinued at the time of randomization.

Treatment with insulin icodec in the intervention arm was largely in accordance with the specifications of the Summary of Product Characteristics (SPC), as was the administration of insulin glargine in the comparator arm. Patients in both study arms had to titrate their fasting blood glucose to a value between 80 and 130 mg/dL.

In the study, a total of 984 patients were randomly assigned in a 1:1 ratio to the two study arms of insulin icodec (N = 492) and insulin glargine (N = 492), each in combination with the present therapy with non-insulin antidiabetics. Stratification was not performed here. The company presents data of a subpopulation of the ONWARDS 1 study: patients without cardiovascular disease who received only metformin in addition to insulin icodec or insulin glargine during the study and who were already being treated with at least 2 blood glucose-lowering drugs. In addition, the company only considered patients without a history of cardiovascular disease. This subpopulation comprises 37 patients in the intervention arm and 28 patients in the comparator arm.

Primary outcome of the study was the change in HbA1c after 52 weeks compared with baseline. Secondary outcomes were outcomes of the categories “morbidity” and “adverse events (AEs).

ONWARDS 1 study unsuitable for the benefit assessment

No indication for insulin therapy for the subpopulation of the ONWARDS 1 study formed by the company

According to the subdivision of the therapeutic indication based on the ACT defined by the G-BA, insulin therapy was to be indicated for patients in the present research question 1. However, indication for insulin therapy was not an explicit inclusion criterion in the ONWARDS 1 study. According to the National Disease Management Guideline (NVL) on type 2 diabetes mellitus, insulin therapy is only recommended if the individual therapy goal is not achieved despite exhaustion of non-drug measures and drug therapy. Insulin therapy is also used in the case of metabolic derailment, administration of diabetogenic drugs (e.g. glucocorticoids), and in the case of severely impaired renal function. However, it is not clear from the documents submitted that the non-drug and drug treatment options with non-insulin antidiabetic drugs

were exhausted in the subpopulation presented by the company, nor that one of the other (alternative) reasons for the commencement of insulin therapy was given.

The study documents do not indicate that non-drug measures were used in the study. Patients for whom a change in lifestyle with an impact on glycaemic control was to be expected were also excluded from participation in the study. Furthermore, the inclusion criteria of the study do not specify that patients must have received certain prior therapies in the past, nor do they provide information on the previous therapies administered to the patients included in the study. The information in the case report form (CRF) also does not indicate that corresponding data on prior therapies were recorded in the ONWARDS 1 study, but only information on concomitant medication during screening, which was continued stably during the study, with the exception of sulphonylureas and glinides, which had to be discontinued at the start of the study. Therefore, for the formation of the subpopulation regarding pre-treatment with at least 2 blood glucose-lowering drugs and regarding the necessary pre-treatments resulting from the indication for insulin therapy, the company can only rely on specifications or information on present concomitant medications at the time of study inclusion.

Concomitant treatment with metformin, which - according to the G-BA's ACT - is required as concomitant treatment for the patient group in research question 1, could also only be continued as present concomitant medication at the time of screening. A change in the concomitant medication (e.g. from treatment with at least 2 non-insulin antidiabetics) to insulin administration in combination with metformin was not planned according to the study design. Thus, the subpopulation of patients whose present drug therapy consisted of at least 2 blood glucose-lowering drugs and for whom the company considers the ACT to be implemented can only be delimited by the fact that patients with a concomitant therapy consisting of metformin + sulfonylureas and/or glinides were considered for screening. It is not clear from the available data that these patients had already received other drug therapies in the past. However, in the case of prior therapy exclusively with metformin + sulphonylureas and/or glinides, it cannot be assumed that all other drug treatment options have already been exhausted, so that there is an indication for insulin therapy. According to the NVL treatment algorithm, the selection of an additional or alternative antidiabetic drug would be indicated as an intensification of treatment before the start of insulin administration for patients in the subpopulation presented who are receiving an antidiabetic therapy consisting of metformin + sulphonylureas/glinides at the time of screening. Accordingly, pursuant to the justification on the G-BA decision on the benefit assessment of tirzepatide (in the indication of type 2 diabetes mellitus), an insulin-free combination consisting of metformin and two other drugs (empagliflozin and liraglutide or empagliflozin and sitagliptin) should be used first. Where the dual combination is escalated to the triple combination, it should be examined whether doing so can achieve an adequate blood glucose-lowering effect or whether the initiation of insulin therapy should ultimately be contemplated. In contrast to

type 1 diabetes mellitus, insulin therapy is therefore the last treatment option for type 2 diabetes mellitus and is only used if all other prior drug (and non-drug) treatment options have failed.

Data for the entire study population of the ONWARDS 1 study on treatment at the time of screening show that therapy with a combination of several oral antidiabetic drugs or, for example, the use of SGLT2 inhibitors, DPP-4 inhibitors or GLP-1-receptor agonists was quite common before these patients then received additional insulin during the study. An indication for insulin might be conceivable for these patients. However, since the ACT (which consists of human insulin + metformin for research question 1) has not been implemented for them due to the continuation of their present antidiabetic therapy (e.g. with SGLT2 inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists), these patients cannot be included in the benefit assessment either.

Overall, it is assumed for the patients in the subpopulation presented by the company on the basis of the available data that they were not (yet) indicated for insulin therapy. For this reason, the Onwards 1 study is not suitable for the benefit assessment.

Irrespective of the question of the suitability of the ONWARDS 1 study, no meaningful data on benefit outcomes (mortality, morbidity, health-related quality of life) are available for the subpopulation presented by the company. Firstly, health-related quality of life was not recorded in the study, and secondly, due to the short study duration, no events occurred for other patient-relevant morbidity outcomes (as well as for mortality).

Results on added benefit

Since no suitable data are available for the present research question, there is no hint of added benefit of insulin icodec in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: Insulin-naive adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated (with manifest cardiovascular disease)

Results

The check for completeness of the study pool revealed no relevant study for the comparison of insulin icodec versus the ACT. In contrast, the company first identified the 3 potentially suitable studies NN1436-4383, ONWARDS 1 and ONWARDS 5. For these studies, in each of which insulin-naive adults with type 2 diabetes mellitus were examined, the company investigated, analogous to its approach for research question 1, whether a relevant subpopulation for research question 2 (referred to by the company in the dossier as research question a2) can be delimited. However, according to the company, a population for the direct

derivation of the added benefit cannot be delimited for this research question for any of the studies, so that the company did not present any data for research question 2.

Results on added benefit

Since no data are available for the present research question, there is no hint of added benefit of insulin icodec in comparison with the ACT; an added benefit is therefore not proven.

Research question 3: Insulin-experienced adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise (without manifest cardiovascular disease)

Results

The check for completeness of the study pool revealed no relevant study for the comparison of insulin icodec versus the ACT. The company, in contrast, identified the study NN1436-4480 (hereinafter ONWARDS 4), which examined insulin-experienced adults with type 2 diabetes mellitus. For this study, the company concluded after appropriate investigation that a relevant subpopulation can be delimited for research question 3 (referred to as research question b1 by the company in the dossier) that fulfils the requirements regarding cardiovascular diseases and concomitant therapies according to the ACT specified by the G-BA, and uses this population for its assessment. However, the analyses on the ONWARDS 4 study presented by the company are unsuitable for the present benefit assessment. This is mainly due to the fact that the available information fails to show that the ACT of an escalation of the insulin therapy as specified by the G-BA was implemented with the insulin therapy administered in the comparator arm of the study. The reasoning is provided below.

Evidence presented by the company – ONWARDS 4 study

ONWARDS 4 is an open-label, randomized, active-controlled study on the comparison of insulin icodec with insulin glargine, each in combination with insulin aspart with a treatment duration of 26 weeks. In addition, potential present therapies with non-insulin antidiabetics were continued in both arms. Insulin-experienced adults with type 2 diabetes mellitus and with HbA1c levels between ≥ 7.0% and ≤ 10.0% at study inclusion were included. Patients were excluded from participation in the study if they had experienced a myocardial infarction, stroke or hospitalization due to unstable angina pectoris or due to transient ischaemic attack within 180 days prior to the day of screening or if they had chronic heart failure (NYHA class IV) at the time of screening. Patients for whom a change in lifestyle with an impact on glycaemic control was to be expected were also excluded.

In the ONWARDS 4 study, insulin icodec was compared with insulin glargine, each in combination with the bolus insulin insulin aspart as well as with the present non-insulin antidiabetics as required. According to the inclusion criteria, patients had to have been receiving treatment with basal insulin once daily and a bolus insulin analogue 2 to 4 times a

day for at least 90 days prior to inclusion in the study. Moreover, concomitant treatment with non-insulin antidiabetics was permitted in accordance with the inclusion criteria, provided it had been administered at a stable dose for at least 90 days prior to study inclusion. These therapies had to be continued stably as concomitant medication during the study, with the exception of sulphonylureas and glinides, which had to be discontinued at the time point of randomization.

Treatment with insulin icodec in the intervention arm was largely in accordance with the specifications of the SPC, as was the administration of insulin glargine in the comparator arm. The individual insulin dose was adjusted weekly based on 3 consecutive fasting plasma glucose values according to a predetermined titration scheme. Patients in the intervention and the comparator arm of the ONWARDS 4 study additionally received insulin aspart as bolus insulin. The bolus insulin dose at baseline was determined on the basis of the dose of the present 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. This does not correspond to the SPC for insulin icodec, which refers to the need to adjust the dose and time of the administration of bolus insulin preparations when switching to insulin icodec, nor to the SPC for insulin aspart, which recommends monitoring the blood glucose level and adjusting the insulin dose for use. After the first 8 weeks, adjustments could be made twice a week depending on the self-measured plasma glucose level according to a fixed titration algorithm. Patients in both study arms had to titrate their fasting blood glucose to a value between 80 and 130 mg/dL.

In the study, a total of 582 patients were randomly assigned in a 1:1 ratio to the two study arms of insulin icodec (N = 291) and insulin glargine (N = 291), each in combination with insulin aspart ± non-insulin antidiabetics. Stratification was not performed here. The company presented data from a subpopulation of the ONWARDS 4 study, which it formed on the basis of the non-insulin antidiabetics received at the time of study inclusion. In order to correspond to the ACT, it only takes into account patients who were receiving ICT without non-insulin antidiabetics or with sulphonylureas and/or glinides at this time, as the latter had to be discontinued at the start of the study. In addition, the company only considered patients without a history of cardiovascular disease for the subpopulation. This subpopulation comprised 57 patients in the intervention arm and 52 patients in the comparator arm.

Primary outcome of the study was the change in HbA1c after 26 weeks compared with baseline. Secondary outcomes comprised outcomes of the categories “morbidity” and “adverse events”.

ONWARDS 4 study unsuitable for the benefit assessment

No implementation of the ACT in the ONWARDS 4 study

According to the subdivision of the therapeutic indication by the ACT specified by the G-BA, patients in this research question 3 who have not achieved adequate glycaemic control with their present insulin regime in addition to diet and exercise must have their insulin therapy escalated (see also the comments on the research questions described in Table 2). In contrast to type 1 diabetes mellitus, insulin therapy is therefore the last treatment option for type 2 diabetes mellitus and is only used if all other prior treatment options have failed. However, even for insulin-experienced patients, the ACT requires treatment escalation. Beyond ICT, no further options for treatment escalation are described in the NVL for type 2 diabetes mellitus. In contrast to their use in type 1 diabetes mellitus, insulin pumps are only rarely indicated in the treatment of type 2 diabetes mellitus.

The ONWARDS 4 study included patients who had already been receiving treatment with basal insulin once daily and bolus insulin 2 to 4 times daily for at least 90 days at that time. This means that the included patient population had already received a treatment consisting of basal and bolus insulin before the start of the study, so that no further escalation steps of insulin therapy were possible according to the NVL. Accordingly, it was no longer possible to escalate insulin therapy to CT or ICT, as provided for in the ACT for research question 3. This means that the ACT that requires an escalation of insulin therapy in the comparator arm is not implemented in the ONWARDS 4 study. For this reason, the Onwards 4 study is not suitable for the benefit assessment.

Irrespective of the question of the suitability of the ONWARDS 4 study, no meaningful data on benefit outcomes (mortality, morbidity, health-related quality of life) are available for the subpopulation presented by the company. Firstly, health-related quality of life was not recorded in the study, and secondly, due to the short study duration, no events occurred for other patient-relevant morbidity outcomes and only one event occurred for mortality.

Results on added benefit

Since no suitable data are available for the present research question, there is no hint of added benefit of insulin icodec in comparison with the ACT; an added benefit is therefore not proven.

Research question 4: Insulin-experienced adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise (with manifest cardiovascular disease)

Results

The check for completeness of the study pool revealed no relevant study for the comparison of insulin icodec versus the ACT. The company, in contrast, identified the ONWARDS 4 study. For this study, which examined insulin-experienced adults with type 2 diabetes mellitus, the

company investigated, analogous to its approach for research question 3, whether a relevant subpopulation can be delimited for research question 4 (referred to by the company in the dossier as research question b2). However, according to the company, a population for the direct derivation of the added benefit cannot be delimited for this research question, so that the company did not present any data for research question 4.

Results on added benefit

Since no data are available for the present research question, there is no hint of added benefit of insulin icodec in comparison with the ACT; an added benefit is therefore not proven.

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

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

[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 – probability and extent of added benefit

Research question	Therapeutic indication[a]	ACT[b]	Probability and extent of added benefit
1	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin + metformin	Added benefit not proven
2	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin + metformin + empagliflozin or ▪ human insulin + metformin + dapagliflozin or ▪ human insulin + metformin + liraglutide	Added benefit not proven
3	Insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy (conventional therapy [CT], possibly + metformin or dulaglutide or ICT)	Added benefit not proven
4	Insulin-experienced adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy: conventional therapy (CT) or ICT, in each case in combination with metformin and empagliflozin or dapagliflozin or liraglutide	Added benefit not proven

a. Subdivision of the therapeutic indication according to the G-BA.
- For the treatment of comorbidities in adults with type 2 diabetes mellitus (hypertension, dyslipoproteinaemia, coronary artery disease, renal disorders etc.), especially in patients with manifest cardiovascular disease who receive additional drugs for treating cardiovascular risk factors, individualized treatment of the respective comorbidities in accordance with current medical knowledge is assumed to be performed, with said treatment particularly including antihypertensives, anticoagulants, and/or lipid-lowering drugs, taking into account the particular characteristics of the present disease.
- Patients on insulin should undergo regular examinations to determine whether insulin therapy remains indicated or whether de-escalation of the insulin therapy might be possible and indicated.
- Continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus does not correspond to the ACT.
- The specific ACT options in patient groups a2, b1 and b2 (i.e. research questions 2, 3 and 4) are each equally appropriate treatment alternatives.

b. Presentation of the respective ACT specified by the G-BA.

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

The G-BA decides on the added benefit.

I 2 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 2 diabetes mellitus.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of insulin icodec

Research question	Therapeutic indication[a]	ACT[b]
1	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin + metformin
2	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin + metformin + empagliflozin or ▪ human insulin + metformin + dapagliflozin or ▪ human insulin + metformin + liraglutide
3	Insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy (CT, possibly + metformin or dulaglutide or ICT)
4	Insulin-experienced adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy: CT or ICT, in each case in combination with metformin and empagliflozin or dapagliflozin or liraglutide

a. Subdivision of the therapeutic indication according to the G-BA.
- For the treatment of comorbidities in adults with type 2 diabetes mellitus (hypertension, dyslipoproteinaemia, coronary artery disease, renal disorders etc.), especially in patients with manifest cardiovascular disease who receive additional drugs for treating cardiovascular risk factors, individualized treatment of the respective comorbidities in accordance with current medical knowledge is assumed to be administered, with said treatment particularly including antihypertensives, anticoagulants, and/or lipid-lowering drugs, taking into account the particular disease characteristics of the present disease.
- Patients on insulin should undergo regular examinations to determine whether insulin therapy remains indicated or whether de-escalation of the insulin therapy might be possible and indicated.
- Continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus does not correspond to the ACT.
- The specific ACT options in patient groups a2, b1 and b2 (i.e. research questions 2, 3 and 4) are each equally appropriate treatment alternatives.

b. Presentation of the respective ACT specified by the G-BA.

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

Notes on the research questions

In this benefit assessment, the subpopulations a1, a2, b1 and b2 named by the G-BA and the company, are referred to as research questions 1 to 4 in accordance with the research questions in Table 4.

To derive the ACT and the resulting research questions, the G-BA refers to the recommendations of the NVL on type 2 diabetes mellitus (as of 15 May 2023) [3] and to the results of cardiovascular outcome studies in the justification on the decision on the benefit assessment of tirzepatide (in the indication of type 2 diabetes mellitus) [4].

Two aspects should be emphasized in the context of this assessment:

3) The description of the population for research question 1 ("who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and who are indicated for insulin therapy") reflects the fact that (unlike in type 1 diabetes mellitus) insulin therapy is the last treatment option in type 2 diabetes mellitus and is only used if all other prior drug (and non-drug) treatment options have failed.

   The sequence of the required prior drug escalation steps for patients without manifest cardiovascular disease is reflected in the G-BA's research questions for the benefit assessment of tirzepatide [4] as follows, whereby - unlike in the present assessment - patient groups for whom insulin therapy is not yet indicated are also included:

   a) after exhaustion of all non-drug therapies, start of drug therapy with a blood glucose-lowering drug in addition to the non-drug therapies (according to NVL: metformin monotherapy)
   b) intensification of treatment with an additional drug while metformin is continued (dual combination)
   c) insulin-free multiple combination consisting of metformin and two other drugs (triple combination)
   d) administration of insulin in combination with metformin

4) The wording "Adults... who have not achieved adequate glycaemic control with their present therapy/regimen", which is found in each of the four research questions, makes clear that this describes patient groups for whom treatment intensification is necessary due to inadequate glycaemic control. According to the NVL, a change of therapy is only recommended if the individual treatment goal was not achieved with the previously received therapy and is accompanied by an escalation, usually with the addition of further antidiabetic therapies. Consequently, this means that, according to the G-BA's specification of the ACT, treatment escalation is required in each case and the sole continuation of an inadequate treatment (regimen) does not correspond to the ACT. A switch of the insulin therapy to insulin icodec (e.g. from insulin glargine or other daily administered basal insulins) for reasons other than inadequate glycaemic control is therefore not part of the research questions addressed in this assessment. Similarly, there are no further research questions that reflect the use of insulin icodec in patients whose therapy has already been escalated to the maximum.

Deviation of the company from G-BA's ACT

The company followed the G-BA's specification of the ACT. For research questions 3 and 4, the company stated that, in contrast to the G-BA, it only considered ICT to be a relevant escalation of insulin therapy. For research question 3, the company also stated that it considered further treatment with non-insulin antidiabetics (including metformin, dulaglutide, empagliflozin, dapagliflozin and liraglutide) to be regularly indicated in addition to ICT in insulin-experienced adults without manifest cardiovascular disease. However, in accordance with the ACT specified by the G-BA, it exclusively considered patients who did not receive concomitant treatment with non-insulin antidiabetics for the data it submitted on research question 3. For all 4 research questions, the company also described that although the G-BA did not name insulin analogues as an ACT, insulin glargine is considered a suitable comparator by the G-BA. For this purpose, the company refers to a consultation with the G-BA of 16 August 2022 [5]. Although the company does not comment on further insulin analogues in the dossier, it also considered studies for its assessment in which insulin aspart was used, while it excluded studies in which insulin degludec was used, on the grounds that neither human insulin nor insulin glargine, but insulin degludec, was used as a comparator.

The deviations described above are of no consequence for the present assessment, as the company did not present suitable data on the comparison of insulin icodec with the ACT for either of the research questions (for explanation see Chapters I 3 to I 6).

Outcomes, study type and minimum duration

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 deriving any added benefit. This concurs with the company's inclusion criteria.

I 3 Research question 1: Insulin-naive adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated (without manifest cardiovascular disease)

I 3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on insulin icodec (status: 26 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 for completeness of the study pool revealed no relevant study for the comparison of insulin icodec versus the ACT.

In contrast, the company first identified the 3 potentially suitable studies NN1436-4383 [6,7], NN1436-4477 (hereinafter ONWARDS 1) [8-11] and NN1436-4481 (hereinafter ONWARDS 5) [12,13], in each of which insulin-naive adults with type 2 diabetes mellitus were investigated. Since various concomitant medications that did not correspond to the ACT were permitted in these studies, the company first examined the potentially suitable studies to determine whether a relevant subpopulation for research question 1 (referred to as research question a1 by the company in the dossier) could be delimited in each case.

According to the company's information in Module 4 A of the dossier, a subpopulation comprising sufficient patients for a benefit assessment can only be formed for the ONWARDS 1 study for research question 1, which is why the company only uses results on a subpopulation of this study for its assessment in Module 4 A of the dossier for research question 1. However, the data presented by the company on the subpopulation of the ONWARDS 1 study are not suitable for the benefit assessment of insulin icodec versus the ACT.

In the following, the company's procedure for the formation of the subpopulation for the potentially suitable studies for the present research question is first addressed. The ONWARDS 1 study is then described and it is explained why the results presented by the company on a subpopulation of this study are not suitable for the benefit assessment.

Evidence provided by the company

For its information retrieval, the company first identified the 3 potentially suitable studies NN1436-4383, ONWARDS 1 and ONWARDS 5, each of which examined insulin-naive adults with type 2 diabetes mellitus. In each of these studies, the study design did not specify that the patients had to have received certain prior therapies in the past. Instead, the inclusion criteria only contain specifications on present concomitant medications at the time of study inclusion, including various drugs that do not correspond to the ACT. Concomitant treatment with metformin, which - according to the G-BA's ACT - is required as concomitant treatment for the patient group in research question 1, could also only be continued in the studies as present medication at the time of screening. A change in the concomitant medication (e.g. from treatment with at least 2 non-insulin antidiabetics) to insulin administration in combination with metformin was not planned according to the study design.

Based on the information available for the potentially suitable studies identified by it, the company attempts to delimit a subpopulation of patients for research question 1 who are treated exclusively in combination with metformin in addition to the respective insulin administration and who are also pretreated with at least 2 blood glucose-lowering drugs. Below, the formation of the subpopulations by the company is explained in more detail for the individual studies.

Procedure of the company for the formation of the subpopulations

Study NN1436-4383 investigated the comparison of insulin icodec with insulin glargine, each in combination with metformin ± DPP-4 inhibitors. Neither metformin nor DPP-4 inhibitors were administered as study medication, but the present concomitant therapy at the time of study inclusion was continued.

For study NN1436-4383, the company described that it was not possible to delimit a subpopulation. It justified this by stating that the study included patients who had been treated with metformin ± DPP-4 inhibitor before the study and continued this treatment during the study. According to the company, patients without treatment with a DPP-4 inhibitor did not fulfil the inclusion criterion for the population, as they had not been pre-treated with at least 2 blood glucose-lowering drugs. According to the company, patients treated with a DPP-4 inhibitor fulfil the inclusion criterion for the population, but not the criterion for the comparator therapy, as they continued to receive DPP-4 inhibitor treatment during the study.

The company's approach to exclude study NN1436-4383 on the basis of the available information results exclusively from the available information on concomitant medication at study inclusion, which was continued in the study. In Module 4 A of the dossier, the company does not discuss information on patients' prior therapies that were discontinued before the time of study inclusion. The study documents in Module 5 of the dossier also contain no information on prior therapies of the patients included in the study. Furthermore, the case report form (CRF) does not provide information on whether data on prior therapies that had been discontinued before the time of study inclusion was recorded at all as part of the study. Accordingly, the dossier includes no information on prior therapies that can be used to form a subpopulation for the study, so that only information on concomitant medication at the time of study inclusion is available to delimit a subpopulation. Against the background of the available data, it is comprehensible that the company was unable to form a subpopulation from study NN1436-4383 that fulfils the criteria for research question 1. In addition, due to the lack of information on prior therapies, it is unclear which or whether patients in study NN1436-4383 have an indication for insulin therapy.

A similar data situation exists for the ONWARDS 5 study that compares insulin icodec with various insulin analogues (insulin glargine 100 units [U]/mL, insulin glargine 300 U/mL or insulin degludec). The ONWARDS 5 study included patients for whom, at the discretion of the treating investigator, an intensification of insulin therapy was indicated in order to achieve the glycaemic target value (80 to 130 mg/dL). In addition, potential present therapies with non-insulin antidiabetics were continued in both arms of this study. In addition, an automatic DoseGuide system was used exclusively in the intervention arm to support the therapy with the intervention. For this study, too, the study documents in Module 5 of the dossier do not contain any information on prior therapies that had already been discontinued before the time of study inclusion, but only information on concomitant therapy at the time of study inclusion. In this study, however, the concomitant therapy could be adjusted from the time of randomization in consultation with the investigator, whereby the discontinuation of concomitant therapies was also permitted. Accordingly, it is possible to form a subpopulation of patients who received only metformin as concomitant medication in the study, but who were treated with at least 2 blood glucose-lowering drugs as part of the concomitant medication at the time of study inclusion.

Since information on pretreatment is lacking, the company could also only consider the data on concomitant medication with non-insulin antidiabetics at study inclusion to form the subpopulation for the ONWARDS 5 study. In addition, the company only considered patients from this study who were assigned to treatment with insulin glargine at the time of study inclusion. However, patients who were assigned to treatment with insulin degludec were excluded from the formation of the subpopulation. According to the company, the resulting subpopulation ultimately comprised only 7 patients in each of the two study arms for

ONWARDS 5. As the resulting population did not include at least 10 patients or 5% of the study population, the company refrained from presenting this study. A flow chart on the formation of the subpopulation by the company for this study can be found in Figure 2 in I Appendix B.1.

Irrespective of whether the company's approach for forming the subpopulation of ONWARDS 5 is adequate, the study is not suitable for the benefit assessment because the automated DoseGuide system was only used in the intervention arm, but not in the comparator arm. A fair comparison of intervention and comparator therapy is therefore not possible on the basis of the study, as only in the intervention arm the therapy was additionally optimized through the use of the system and therefore the effects of the intervention can potentially be overestimated.

In the ONWARDS 1 study comparing insulin icodec with insulin glargine, each in combination with non-insulin antidiabetics, the concomitant medication was continued stably during the study at the time of study inclusion - similar to study NN1436-4383. Exceptions to this were sulphonylureas and glinides, which had to be discontinued at the start of the study. For this study, too, the study documents in Module 5 of the dossier do not contain any information on prior therapies that had already been discontinued before the time of study inclusion, but only information on concomitant therapy at the time of study inclusion. Since information on pretreatment is lacking, the company could accordingly also only consider the data on concomitant medication with non-insulin antidiabetics at study inclusion to form the subpopulation for this study. On the basis of this information, however, a subpopulation can only be delimited regarding the fact that treatment with metformin in combination with sulphonylureas and/or glinides was in place at the time of screening (i.e. continuation of metformin alone and pretreatment with at least 2 blood glucose-lowering drugs is fulfilled for these patients). In addition, the company only considered patients without a history of cardiovascular disease for the subpopulation for research question 1. The subpopulation that the company formed for the ONWARDS 1 study and used for its assessment ultimately comprised 37 patients in the intervention arm and 28 patients in the comparator arm. A flow chart on the formation of the subpopulation by the company for this study can be found in Figure 1 in I Appendix B.1.

In addition to the studies identified by the company as potentially suitable, the company's study programme on insulin icodec also includes study NN1436-4479 (hereinafter ONWARDS 3) [14,15], which also investigated insulin-naive adults with type 2 diabetes mellitus. However, the company excluded this study on the grounds that insulin degludec was used as a comparator and not human insulin or insulin glargine. Irrespective of whether the exclusion of the study for this reason is appropriate, the study is not suitable for the benefit assessment, as in this case, too, no information is available on the fact that prior therapies had been recorded, but only data on the concomitant therapy at the time of study inclusion. In this

study, as in study NN1436-4383, all concomitant therapies were continued, so it was not possible to use these therapies to delimit a population that received only 1 concomitant therapy (i.e. metformin) but had already been treated with at least 2 blood-glucose lowering drugs.

Overall, from the point of view of the company, a subpopulation for research question 1 could only be delimited for the ONWARDS 1 study. Accordingly, the company used results on this subpopulation for its assessment. However, the data presented by the company on the subpopulation of the ONWARDS 1 study are not suitable for the benefit assessment of insulin icodec versus the ACT. This is further explained below.

Design of the ONWARDS 1 study

ONWARDS 1 is an open-label, randomized, active-controlled study on the comparison of insulin icodec with insulin glargine, each in combination with non-insulin antidiabetics with a treatment duration of 78 weeks, consisting of a 52-week main phase and a 26-week extension phase. In doing so, all study participants were to enter the extension phase. Insulin-naive adults with type 2 diabetes mellitus and with HbA1c levels between ≥ 7.0% and ≤ 11.0% at study inclusion were included. Furthermore, patients had to have a body mass index of ≤ 40 kg/m^2. Patients were excluded from participation in the study if they had suffered a myocardial infarction, stroke or hospitalization due to unstable angina pectoris or due to transient ischaemic attack within 180 days prior to the day of screening or if they had chronic heart failure (NYHA class IV) at the time of screening. Patients for whom a change in lifestyle with an impact on glycaemic control was to be expected were also excluded.

In the ONWARDS 1 study, insulin icodec was compared with insulin glargine, each in combination with the present non-insulin antidiabetics. According to the inclusion criteria, monotherapy or combination therapies with metformin, sulphonylureas, glinides, DPP-4 inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, thiazolidinediones, alpha-glucosidase inhibitors, oral or injectable glucagon-like peptide-1 [GLP-1] receptor agonists were permitted. The concomitant therapy was to be administered at a stable dose for at least 90 days prior to study inclusion and had to be continued during the study. Only sulphonylureas and glinides had to be discontinued at the time of randomization.

In the ONWARDS 1 study, treatment with insulin icodec in the intervention arm was largely in compliance with the specifications of the SPC [16]. In the ONWARDS 1 study, it was planned to adjust the individual dose of insulin icodec every 1 to 2 weeks. This only partially corresponds to the specifications of the SPC [16], which specifies for a weekly dose adjustment of insulin icodec. In addition, the study planning allowed a certain flexibility in the administration of insulin icodec (weekly administration of insulin icodec flexible ± 3 days): The study report shows that a large proportion of the total study population (n = 362, 73.6%) made

use of the flexibility and deviated on average by ± 1.4 days from the planned days of administration. Information about the subpopulation presented by the company is not available. However, the European Medicines Agency (EMA) describes that the safety of this flexibilization of the dosage should have been investigated, but such investigation was not carried out during the approval procedure, which is why bringing the dose forward is not recommended [17]. Accordingly, this option is not foreseen in the SPC [16]. The administration of insulin glargine in the comparator arm was in line with the SPC [18].

Patients in both study arms had to titrate their fasting blood glucose to a value between 80 and 130 mg/dL. The individual insulin dose was adjusted every 1 to 2 weeks based on 3 consecutive fasting plasma glucose values according to a predetermined titration scheme.

Patients were also monitored using a continuous glucose monitoring (CGM) system during certain periods of the study (Weeks 0 to 4, Weeks 22 to 26, Weeks 48 to 52,Weeks 74 to 78 as well as during the 5-week follow-up). 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 for both insulin dose adjustments according to the titration algorithm described above and the recording of hypoglycaemic episodes. Moreover, the data from the CGM system were blinded for patients and investigators.

In the study, a total of 984 patients were randomly assigned in a 1:1 ratio to the two study arms of insulin icodec (N = 492) and insulin glargine (N = 492), each in combination with the present therapy with non-insulin antidiabetics. Stratification was not performed here. The company presents data of a subpopulation of the ONWARDS 1 study: patients without cardiovascular disease who received only metformin in addition to insulin icodec or insulin glargine during the study and who were already being treated with at least 2 blood glucose-lowering drugs (for reasons see also the text section “Approach of the company for the formation of the subpopulations”). As described before, this subpopulation comprised 37 patients in the intervention arm and 28 patients in the comparator arm.

Primary outcome of the study was the change in HbA1c after 52 weeks compared with baseline. Secondary outcomes were outcomes of the categories “morbidity” and “adverse events (AEs).

Further information on the characteristics of the ONWARDS 1 study, on the interventions used, on the patients in the subpopulation presented by the company and on the antidiabetic treatment upon screening for the study population can be found in I Appendix C.1.

No indication for insulin therapy for the subpopulation of the ONWARDS 1 study formed by the company

According to the subdivision of the therapeutic indication based on the ACT defined by the G-BA, insulin therapy was to be indicated for patients in the present research question 1. However, indication for insulin therapy was not an explicit inclusion criterion in the ONWARDS 1 study. According to the NVL [3], insulin therapy is only recommended if the individual treatment goal is not achieved despite exhaustion of non-drug measures and drug therapy. Insulin therapy is also used in the case of metabolic derailment, administration of diabetogenic drugs (e.g. glucocorticoids), and in the case of severely impaired renal function. However, it is not clear from the documents submitted that the non-drug and drug treatment options with non-insulin antidiabetic drugs were exhausted in the subpopulation presented by the company, nor that one of the other (alternative) reasons for the commencement of insulin therapy was given.

The study documents do not indicate that non-drug measures were used in the study. Patients for whom a change in lifestyle with an impact on glycaemic control was to be expected were also excluded from participation in the study.

As already described above, the inclusion criteria also do not specify that patients must have received certain prior therapies in the past. The study documents do not suggest that information on prior therapies was recorded in the ONWARDS 1 study, but only information on concomitant medication during screening, which was continued stably during the study, with the exception of sulphonylureas and glinides, which had to be discontinued at the start of the study. Information on the concomitant therapies administered in the ONWARDS 1 study at the time of screening is presented for the total study population in Table 9 and Table 10 in I Appendix C.1. For the subpopulation presented by it, the company did not provide any information on concomitant medication during the screening.

According to the ACT, concomitant treatment with metformin alone is planned for the population in research question 1. As already described above, the subpopulation of patients whose present drug therapy consisted of at least 2 blood glucose-lowering drugs and for whom the company considers the ACT to be implemented can thus only be delimited by the fact that patients with a concomitant therapy consisting of metformin + sulfonylureas and/or glinides were considered for screening. It is not clear from the available data that these patients had already received other drug therapies in the past. However, in the case of prior therapy exclusively with metformin + sulphonylureas and/or glinides, it cannot be assumed that all other drug treatment options have already been exhausted, so that there is an indication for insulin therapy. According to the NVL treatment algorithm, the selection of an additional or alternative antidiabetic drug would have been be indicated as an intensification of treatment before the start of insulin administration for patients in the subpopulation

presented who were receiving an antidiabetic therapy consisting of metformin + sulphonylureas/glinides at the time of screening [3]. Accordingly, pursuant to the justification on the G-BA decision on the benefit assessment of tirzepatide, an insulin-free multiple combination consisting of metformin and two other drugs (empagliflozin and liraglutide or empagliflozin and sitagliptin) [4] should have been used first. Where the dual combination is escalated to the triple combination, it should be examined whether doing so can achieve an adequate blood glucose-lowering effect or whether the initiation of insulin therapy should ultimately be contemplated. In contrast to type 1 diabetes mellitus, insulin therapy is therefore the last treatment option for type 2 diabetes mellitus and is only used if all other prior drug (and non-drug) treatment options have failed.

Data for the entire study population (N=984) of ONWARDS 1 on the treatment at the time of screening (see Table 9 and Table 10 in I Appendix C.1) show that treatment with a combination of several oral antidiabetics or, for example, the use of SGLT2 inhibitors, DPP-4 inhibitors or GLP-1 receptor agonists had been quite common before these patients then additionally received insulin during the study. An indication for insulin might be conceivable for these patients. However, since the ACT (which consists of human insulin + metformin for research question 1) has not been implemented for them due to the continuation of their present antidiabetic therapy (e.g. with SGLT2 inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists), these patients cannot be included in the benefit assessment either.

Overall, it is assumed for the patients in the subpopulation presented by the company on the basis of the available data that they were not (yet) indicated for insulin therapy. For this reason, the Onwards 1 study is not suitable for the benefit assessment.

Further points of criticism

Irrespective of the fact that the data of the ONWARDS 1 study submitted by the company are not suitable for the benefit assessment for the reason described above, there are the following further points of criticism on the data submitted by the company:

- It is unclear whether cardiovascular diseases were adequately taken into account when forming the subpopulation of ONWARDS 1
  - When forming the subpopulation, the company excluded patients with pre-existing conditions upon study inclusion in the last step, defined by the preferred terms (PTs) of cerebral ischaemia, cerebrovascular accident, vascular encephalopathy, myocardial infarction, myocardial ischaemia and cerebral infarction according to the Medical Dictionary for Drug Regulatory Activities (MedDRA). However, as the company did not provide any information on pre-existing conditions at study inclusion for the subpopulation with concomitant treatment according to the ACT formed by it, it cannot be verified whether all relevant illnesses were considered. It

therefore remains unclear whether the criterion that no manifest cardiovascular disease was present was fulfilled for all patients and in the subpopulation presented by the company.

- No definition of individualized treatment goals
  - The HbA1c value reflects the average blood glucose level of the last 8 to 12 weeks and is an important target value in the treatment of type 2 diabetes mellitus. For example, it can be used to assess the success of the therapy and help to discover whether an intensification of the therapy is indicated. The German National Care Guideline for type 2 diabetes mellitus [3] specifies an HbA1c target corridor between 6.5% and 8.5%, but individualized treatment targets for the HbA1c value should be agreed as part of the treatment of type 2 diabetes mellitus (recommendation grade A), as patients benefit from different target values. The individualized HbA1c target ranges are influenced by various factors, such as age, physical condition, comorbidities, time since diabetes diagnosis, treatment adherence, treatment level and risk of hypoglycaemia and other adverse events [3]. Treatment goals must therefore be agreed together with the patients and tailored to their individual needs and everyday life. Furthermore, it is necessary to repeatedly review the treatment goals during the course of treatment, as these can shift due to changes in the patient's life situation [3].

    In the ONWARDS 1 study, however, no individualized HbA1c target values were agreed either at the start of the study or during its course. This approach is not appropriate and does not comply with the previously described recommendations of the German National Care Guideline [3] for setting individualized HbA1c target values. In ONWARDS 1, patients had to titrate their fasting blood glucose values to a fixed target range between 80 to 130 mg/dL by adjusting the insulin dose instead.

Conclusion

Overall, the ONWARDS 1 study is unsuitable for the assessment of the added benefit of insulin icodec over the ACT in insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated. This is mainly due to the fact that the documents submitted do not provide information on whether the non-drug and drug treatment options with non-insulin antidiabetics were exhausted in the subpopulation presented by the company and that there was therefore an indication for insulin therapy.

The ONWARDS 1 study is presented for information in I Appendix C. However, conclusions on the added benefit of insulin icodec versus the ACT cannot be derived on the basis of the ONWARDS 1 study.

Irrespective of the question of the suitability of the ONWARDS 1 study, no meaningful data on benefit outcomes (mortality, morbidity, health-related quality of life) are available for the subpopulation presented by the company. Firstly, health-related quality of life was not recorded in the study, and secondly, due to the short study duration, no events occurred for other patient-relevant morbidity outcomes (as well as for mortality).

I 3.2 Results on added benefit

No data are available for the assessment of the added benefit of insulin icodec in comparison with the ACT in insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is indicated. There is no hint of an added benefit of insulin icodec in comparison with the ACT; an added benefit is therefore not proven.

I 3.3 Probability and extent of added benefit

As the company presented no suitable data for the assessment of the added benefit of insulin icodec in comparison with the ACT in insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is indicated, an added benefit is not proven for these patients.

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit for this patient group. Although the company initially stated that there were no statistically significant differences in the patient-relevant mortality, morbidity or safety outcomes presented by it, it ultimately nevertheless derived a hint of a non-quantifiable added benefit. It justifies this assessment with the medical advantages of insulin icodec, primarily the reduced injection frequency due to the once-weekly administration.

I 4 Research question 2: Insulin-naive adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated (with manifest cardiovascular disease)

I 4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on insulin icodec (status: 26 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 for completeness of the study pool revealed no relevant study for the comparison of insulin icodec versus the ACT.

In contrast, the company first identified the 3 potentially suitable studies NN1436-4383, ONWARDS 1 and ONWARDS 5. For these studies, in each of which insulin-naive adults with type 2 diabetes mellitus were examined, the company investigated, analogous to its approach for research question 1, whether a relevant subpopulation for research question 2 (referred to by the company in the dossier as research question a2) can be delimited. For a detailed explanation of the company's approach for the formation of the subpopulation, see Section I 3.1. A flow chart on the formation of the subpopulations by the company for the studies ONWARDS 1 and ONWARDS 5 can be found in Figure 3 and Figure 4 in I Appendix B.2.

For the present research question, the company applied a similar approach to the existing studies, whereby, in contrast to its approach for research question 1, it considered patients for research question 2 who received concomitant treatment with metformin in combination with empagliflozin or dapagliflozin or liraglutide and who had cardiovascular diseases. Such a subpopulation is not available for study NN1436-4383, as the drugs empagliflozin, dapagliflozin and liraglutide were not permitted as concomitant treatment in the study. For the ONWARDS 5 study, the company was unable to identify any patients for whom the above criteria were met. For the ONWARDS 1 study, the company was only able to identify 2 patients

in the intervention arm and 1 patient in the comparator arm. Therefore, according to the company, the studies ONWARDS 1 and ONWARDS 5 could not be used for the direct derivation of the added benefit for research question 2.

As already described for research question 1 (see Section I 3.1), it remains unclear whether the company adequately considered patients with manifest cardiovascular disease when forming the subpopulation of the ONWARDS 1 study. The subpopulation includes patients who had the PTs of cerebral ischaemia, cerebrovascular accident, vascular encephalopathy, myocardial infarction, myocardial ischaemia and cerebral infarction according to MedDRA as a pre-existing condition at the time of study inclusion. However, as the company did not provide any information on pre-existing conditions at study inclusion for the subpopulation with concomitant treatment according to the ACT formed by it, it cannot be verified whether all relevant illnesses were considered. However, this is of no consequence for the present assessment, as the company did not present any data on the comparison of insulin icodec with the ACT for research question 2.

I 4.2 Results on added benefit

No data are available for the assessment of the added benefit of insulin icodec in comparison with the ACT in insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is indicated. There is no hint of an added benefit of insulin icodec in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

As the company presented no data for the assessment of the added benefit of insulin icodec in comparison with the ACT in insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is indicated, an added benefit is not proven for these patients.

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit for this patient group. The company justified this assessment by stating that, due to similarities in the underlying disease, it can be assumed that the subpopulation for research question 2 will benefit from the same advantages as the subpopulation for research question 1. In the company's view, this allows a joint conclusion on the added benefit of insulin icodec for research questions 1 and 2.

I 5 Research question 3: Insulin-experienced adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise (without manifest cardiovascular disease)

I 5.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on insulin icodec (status: 02 June 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 for completeness of the study pool revealed no relevant study for the comparison of insulin icodec versus the ACT.

In contrast, the company identified the study NN1436-4480 (hereinafter ONWARDS 4) [19-22], which examined insulin-experienced adults with type 2 diabetes mellitus. For this study, the company concluded after appropriate investigation that a relevant subpopulation can be delimited for research question 3 (referred to as research question b1 by the company in the dossier) that fulfils the requirements regarding cardiovascular diseases and concomitant therapies according to the ACT specified by the G-BA, and uses this population for its assessment.

The data on ONWARDS 4 submitted by the company are unsuitable for the present benefit assessment because it cannot be learned from the available information that an escalation of the insulin therapy (specified as ACT by the G-BA) was implemented in the comparator arm with the insulin therapy administered.

In addition to the study identified as relevant by the company, the company's study programme on insulin icodec also includes study NN1436-4478 (hereinafter ONWARDS 2) [23,24], which also investigated insulin-experienced adults with type 2 diabetes mellitus. However, the company excluded this study on the grounds that insulin degludec was used as a comparator and not human insulin or insulin glargine. Irrespective of whether the exclusion

of the study for this reason is appropriate, this has no consequences for the present assessment, as it is not clear from the available data for the ONWARDS 2 study that the ACT of an escalation of insulin therapy specified by the G-BA was implemented in the comparator arm of the study with the insulin therapy administered. In this study, the patients included were already receiving insulin therapy exclusively with basal insulin at the time of inclusion in the study. As part of the study, the insulin therapy was also done with basal insulin alone, with a switch to another drug as required, if insulin degludec had not already been used before. The study is therefore not suitable for the benefit assessment of insulin icodec, regardless of whether an insulin analogue other than insulin glargine was used, as the ACT of an escalation of insulin therapy specified by the G-BA was not implemented in the comparator arm, just as in the ONWARDS 4 study.

Evidence provided by the company

For its benefit assessment, the company used results on a subpopulation of the ONWARDS 4 study on the comparison of insulin icodec with insulin glargine, each in combination with insulin aspart. However, the data submitted by the company are unsuitable for the present benefit assessment because it cannot be learned from the available information that an escalation of the insulin therapy (specified as ACT by the G-BA) was implemented in the comparator arm with the insulin therapy administered. This is explained below.

Design of the ONWARDS 4 study

ONWARDS 4 is an open-label, randomized, active-controlled study on the comparison of insulin icodec with insulin glargine, each in combination with insulin aspart with a treatment duration of 26 weeks. In addition, potential present therapies with non-insulin antidiabetics were continued in both arms. Insulin-experienced adults with type 2 diabetes mellitus and with HbA1c levels between ≥ 7.0% and ≤ 10.0% at study inclusion were included. Furthermore, patients had to have a body mass index of ≤ 40 kg/m^2. Patients were excluded from participation in the study if they had experienced a myocardial infarction, stroke or hospitalization due to unstable angina pectoris or due to transient ischaemic attack within 180 days prior to the day of screening or if they had chronic heart failure (NYHA class IV) at the time of screening. Patients were also excluded if they had been diagnosed with hypoglycaemia perception disorder, recurrent severe hypoglycaemic episodes in the last year or diabetic ketoacidosis in the 90 days prior to the day of screening, as well as patients who were expected to have a change in lifestyle affecting glycaemic control.

In the ONWARDS 4 study, insulin icodec was compared with insulin glargine, each in combination with the bolus insulin insulin aspart as well as with the present non-insulin antidiabetics as required. According to the inclusion criteria, patients had to have already been receiving treatment with basal insulin once daily (neutral protamine Hagedorn [NPH] insulin, insulin degludec, insulin detemir, insulin glargine 100 U/mL or insulin glargine 300 U/mL) and

a bolus insulin analogue (insulin aspart, rapid-acting insulin aspart, insulin lispro, rapid-acting insulin lispro, insulin glulisine) administered 2 to 4 times a day, for at least 90 days prior to study inclusion. Moreover, concomitant treatment with non-insulin antidiabetics was permitted in accordance with the inclusion criteria, provided it had been administered at a stable dose for at least 90 days prior to study inclusion. Mono therapies or combination therapies with metformin, sulphonylureas, glinides, DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones, alpha-glucosidase inhibitors, oral or injectable GLP-1 receptor agonists were possible. These therapies had to be continued stably as concomitant medication during the study, with the exception of sulphonylureas and glinides, which had to be discontinued at the time point of randomization.

In the ONWARDS 4 study, treatment with insulin icodec in the intervention arm was largely in compliance with the specifications of the SPC [16]. In the study, the patients received insulin icodec at the previously administered daily dosage of basal insulin multiplied by 7. In addition, all patients received a loading dose of 50% of this dosage in Week 1. However, according to the SPC, the use of a loading dose is only recommended in cases where the aim is to achieve glycaemic control more quickly. Based on the available data, it remains unclear whether this was necessary for all patients in the study. In addition, the study planning allowed a certain flexibility in the administration of insulin icodec (weekly administration of insulin icodec flexible ± 3 days): The study report shows that about half of the total study population (n = 143, 49.1%) made use of the flexibility and deviated on average by ± 1.5 days from the planned days of administration. Information about the subpopulation presented by the company is not available. However, the EMA describes that the safety of this flexibilization of the dosage should have been investigated, but such investigation had not been carried out during the approval procedure, which is why bringing the dose forward is not recommended [17]. Accordingly, this option is not foreseen in the SPC [16]. The administration of insulin glargine in the comparator arm was in line with the SPC [18]. The individual insulin dose of the basal insulin was adjusted weekly based on 3 consecutive fasting plasma glucose values according to a predetermined titration scheme.

Patients in the intervention and the comparator arm of the ONWARDS 4 study additionally received insulin aspart as bolus insulin. The bolus insulin dose at baseline was determined on the basis of the dose of the present 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. This does not correspond to the SPC for insulin icodec [16], which refers to the need to adjust the dose and time of the administration of bolus insulin preparations when switching to insulin icodec, nor to the SPC for insulin aspart[25], which recommends monitoring the blood glucose level and adjusting the insulin dose for use. After the first 8 weeks, adjustments could be made twice a week depending on the self-measured plasma glucose level according to a fixed titration algorithm (see Table 15 of the full dossier

assessment). However, in the ONWARDS 4 study, it was not possible to adjust the dose of insulin aspart based on the carbohydrate counting method. In addition, the concomitant treatment with non-insulin antidiabetics existing at the time of study inclusion had to be continued at a stable dosage.

Patients in both arms of the ONWARDS 4 study had to titrate their fasting blood glucose to a value between 80 and 130 mg/dL.

Patients were also monitored using a continuous glucose monitoring (CGM system) (Dexcom G6) during certain periods of the study (Weeks 0 to 4 and Weeks 22 to 26 as well as during the 5-week follow-up). 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 for both insulin dose adjustments according to the titration algorithm described above and the recording of hypoglycaemic episodes. Moreover, the data from the CGM system were blinded for patients and investigators.

In the study, a total of 582 patients were randomly assigned in a 1:1 ratio to the two study arms of insulin icodec (N = 291) and insulin glargine (N = 291), each in combination with insulin aspart ± non-insulin antidiabetics. Stratification was not performed here. The company presents data from a subpopulation of the ONWARDS 4 study. As for the potentially suitable studies identified by the company for research question 1 (see Section I 3.1), only information on the concomitant therapy at the time of study inclusion is available for the ONWARDS 4 study. The company formed the subpopulation for this study on the basis of the non-insulin antidiabetics received at the time of study inclusion. In order to correspond to the ACT, it only takes into account patients who were receiving ICT without non-insulin antidiabetics or with sulphonylureas and/or glinides at this time, as the latter had to be discontinued at the start of the study. In addition, the company only considered patients without a history of cardiovascular disease for the subpopulation for research question 3. The subpopulation that the company formed for the ONWARDS 4 study and used for its assessment comprised 57 patients in the intervention arm and 52 patients in the comparator arm. A flow chart on the formation of the subpopulation by the company for this study can be found in Figure 5 in I Appendix B.3.

Primary outcome of the study was the change in HbA1c after 26 weeks compared with baseline. Secondary outcomes comprised outcomes of the categories “morbidity” and “AEs”.

Further information on the characteristics of the ONWARDS 4 study, on the interventions used, on the patients in the subpopulation presented by the company and on the antidiabetic treatment upon screening for the study population can be found in I Appendix D.1.

No implementation of the ACT in the ONWARDS 4 study

According to the subdivision of the therapeutic indication by the ACT specified by the G-BA, patients in this research question 3 who have not achieved adequate glycaemic control with their present insulin regime in addition to diet and exercise must have their insulin therapy escalated (see also the comments on the research questions in Chapter I 2). In contrast to type 1 diabetes mellitus, insulin therapy is therefore the last treatment option for type 2 diabetes mellitus and is only used if all other prior treatment options have failed. However, even for insulin-experienced patients, the ACT requires treatment escalation. Beyond ICT, no further options for treatment escalation are described in the NVL for type 2 diabetes mellitus. In contrast to their use in type 1 diabetes mellitus, insulin pumps are only rarely indicated in the treatment of type 2 diabetes mellitus [3,26,27].

The ONWARDS 4 study included patients who had already been receiving treatment with basal insulin once daily and bolus insulin 2 to 4 times daily for at least 90 days at that time. This means that the included patient population had already received ICT consisting of basal and bolus insulin before the start of the study, so that no further escalation steps of insulin therapy were possible according to the NVL. Accordingly, it was no longer possible to escalate insulin therapy to CT or ICT for the patients included, as provided for in the ACT for research question 3.

Optimization of prior therapy in the ONWARDS 4 study only possible to a limited extent

Information on the insulin therapies administered in the ONWARDS 4 study at the time of screening is presented for the total study population in Table 17 in I Appendix D.1. These data show that 68.4% of the study population in the comparator arm were already receiving insulin glargine as basal insulin and 50.2% were receiving insulin aspart as bolus insulin at the time of screening. This means that insulin therapy at the start of the study was continued in these patients within the framework of the study. For the subpopulation presented by it, the company did not provide any information on insulin therapies administered at the time point of screening. However, it can be assumed that the majority of the subpopulation also continued insulin glargine as basal insulin or insulin aspart as bolus insulin. In the other patients, the present treatment regimen was continued by switching to another insulin analogue, which also did not represent an escalation of the insulin therapy.

The titration algorithm used in the study enabled at best dose adjustments to be made during the study, so that the present insulin regimen could be optimized. However, optimization was also only possible to a limited extent within the scope of the study. Thus, the bolus insulin dose had to be kept stable during the first 8 weeks of the ONWARDS 4 study, unless an adjustment was necessary for safety reasons, so that it was not possible to optimize the therapy regimen using bolus insulin during this period. Data on the mean change in insulin dose over the course of the study for the subpopulation presented by the company also indicate that the insulin dose in the comparator arm was not increased in the majority of

patients (see Figure 7 in I Appendix D). Irrespective of this, optimizing the insulin dose does not represent an intensification in the sense of treatment escalation, but is part of an ICT anyway. In the context of the ICT, the insulin dose is flexibly adjusted anyway based on the plasma glucose values or the carbohydrate supply [3]. For the necessity of treatment escalation, see notes on the research questions in Chapter I 2.

Overall, this means that the ACT that requires an escalation of insulin therapy in the comparator arm is not implemented in the ONWARDS 4 study. For this reason, the Onwards 4 study is not suitable for the benefit assessment.

Further points of criticism

Irrespective of the fact that the data of the ONWARDS 4 study submitted by the company are not suitable for the benefit assessment for the reason described above, there are the following further points of criticism on the data submitted by the company:

- It is unclear whether cardiovascular diseases were adequately taken into account when forming the subpopulation of ONWARDS 4
  - When forming the subpopulation, the company excluded patients with pre-existing conditions upon study inclusion in the last step, defined by the PTs of cerebral ischaemia, cerebrovascular accident, vascular encephalopathy, myocardial infarction, myocardial ischaemia and cerebral infarction according to MedDRA. However, as the company did not provide any information on pre-existing conditions at study inclusion for the subpopulation with concomitant treatment according to the ACT formed by it, it cannot be verified whether all relevant illnesses were considered. It therefore remains unclear whether the criterion that no manifest cardiovascular disease was present was fulfilled for all patients and in the subpopulation presented by the company.
- No definition of individualized treatment goals
  - Analogous to the ONWARDS 1 study, which the company used for research question 1 of the benefit assessment, it is also not clear from the dossier for the ONWARDS 4 study that patient-specific HbA1c target values had been agreed at the start of the study or in its further course (for detailed explanation, see Section I 3.1). In ONWARDS 4, patients had to titrate their fasting blood glucose values to a fixed target range between 80 to 130 mg/dL by adjusting the insulin dose instead.

Conclusion

Overall, the ONWARDS 4 study is not suitable for assessing the added benefit of insulin icodec compared with the ACT in insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their

present insulin regimen in addition to diet and exercise. This is mainly due to the fact that the G-BA's ACT, which requires an escalation of insulin therapy in the comparator arm, was not implemented in the study.

The ONWARDS 4 study is presented for information in I Appendix D. However, conclusions on the added benefit of insulin icodec versus the ACT cannot be derived on the basis of the ONWARDS 4 study.

Irrespective of the question of the suitability of the ONWARDS 4 study, no meaningful data on benefit outcomes (mortality, morbidity, health-related quality of life) are available for the subpopulation presented by the company. Firstly, health-related quality of life was not recorded in the study, and secondly, due to the short study duration, no events occurred for other patient-relevant morbidity outcomes and only one event occurred for mortality.

I 5.2 Results on added benefit

No suitable data are available for the assessment of the added benefit of insulin icodec in comparison with the ACT in insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise. There is no hint of an added benefit of insulin icodec in comparison with the ACT; an added benefit is therefore not proven.

I 5.3 Probability and extent of added benefit

As the company presented no suitable data for the assessment of the added benefit of insulin icodec in comparison with the ACT in insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise, an added benefit is not proven for these patients.

The assessment described above deviates from that of the company, which nevertheless derived a hint of non-quantifiable added benefit for this patient group, irrespective of the fact that the results it presented on a subpopulation of the ONWARDS 4 study do not show any statistically significant differences between the treatment groups. It justifies this assessment with the medical advantages of insulin icodec, primarily the reduced injection frequency due to the once-weekly administration.

I 6 Research question 4: Insulin-experienced adults with type 2 diabetes mellitus who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise (with manifest cardiovascular disease)

I 6.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on insulin icodec (status: 02 June 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 for completeness of the study pool revealed no relevant study for the comparison of insulin icodec versus the ACT.

The company, in contrast, identified the ONWARDS 4 study. For this study, which examined insulin-experienced adults with type 2 diabetes mellitus, the company investigated, analogous to its approach for research question 3, whether a relevant subpopulation can be delimited for research question 4 (referred to by the company in the dossier as research question b2). For a detailed explanation of the company's approach for the formation of the subpopulation, see Section I 5.1. A flow chart on the formation of the subpopulation by the company for this study can be found in Figure 6 in I Appendix B.4.

For the present research question, the company applied a similar approach to the study, whereby, in contrast to its approach for research question 3, it considered patients for research question 4 who received concomitant treatment with metformin in combination with empagliflozin or dapagliflozin or liraglutide and who had cardiovascular diseases. For the ONWARDS 4 study, the company was only able to identify 1 patient in the intervention arm and 4 patients in the comparator arm who met these criteria. Therefore, according to the company, the ONWARDS 4 study could not be used for the direct derivation of the added benefit for research question 4.

As already described for research question 3, it remains unclear whether the company adequately considered patients with manifest cardiovascular disease when forming the subpopulation of the ONWARDS 4 study (see Section I 5.1). The subpopulation includes patients who had the PTs of cerebral ischaemia, cerebrovascular accident, vascular encephalopathy, myocardial infarction, myocardial ischaemia and cerebral infarction according to MedDRA as a pre-existing condition at the time of study inclusion. However, as the company did not provide any information on pre-existing conditions at study inclusion for the subpopulation with concomitant treatment according to the ACT formed by it, it cannot be verified whether all relevant illnesses were considered. However, this is of no consequence for the present assessment, as the company did not present any data on the comparison of insulin icodec with the ACT for research question 4.

I 6.2 Results on added benefit

No data are available for the assessment of the added benefit of insulin icodec in comparison with the ACT in insulin-experienced adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise. There is no hint of an added benefit of insulin icodec in comparison with the ACT; an added benefit is therefore not proven.

I 6.3 Probability and extent of added benefit

As the company presented no data for the assessment of the added benefit of insulin icodec in comparison with the ACT in insulin-experienced adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise, an added benefit is not proven for these patients.

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit for this patient group. The company justified this assessment by stating that, due to similarities in the underlying disease, it can be assumed that the subpopulation for research question 4 will benefit from the same advantages as the subpopulation for research question 3. In the company's view, this allows a joint conclusion on the added benefit of insulin icodec for research questions 3 and 4.

I 7 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of insulin icodec in comparison with the ACT is summarized in Table 5.

Table 5: Insulin icodec – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication[a]	ACT[b]	Probability and extent of added benefit
1	Insulin-naive adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin + metformin	Added benefit not proven
2	Insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their present drug therapy consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise and for whom insulin therapy is indicated	▪ Human insulin + metformin + empagliflozin or ▪ human insulin + metformin + dapagliflozin or ▪ human insulin + metformin + liraglutide	Added benefit not proven
3	Insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy (CT, possibly + metformin or dulaglutide or ICT)	Added benefit not proven
4	Insulin-experienced adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their present insulin regimen in addition to diet and exercise	▪ Escalation of insulin therapy: CT or ICT, in each case in combination with metformin and empagliflozin or dapagliflozin or liraglutide	Added benefit not proven

a. Subdivision of the therapeutic indication according to the G-BA.
- For the treatment of comorbidities in adults with type 2 diabetes mellitus (hypertension, dyslipoproteinaemia, coronary artery disease, renal disorders etc.), especially in patients with manifest cardiovascular disease who receive additional drugs for treating cardiovascular risk factors, individualized treatment of the respective comorbidities in accordance with current medical knowledge is assumed to be administered, with said treatment particularly including antihypertensives, anticoagulants, and/or lipid-lowering drugs, taking into account the particular disease characteristics of the present disease.
- Patients on insulin should undergo regular examinations to determine whether insulin therapy remains indicated or whether de-escalation of the insulin therapy might be possible and indicated.
- Continuation of an inadequate treatment (regimen) for type 2 diabetes mellitus does not correspond to the ACT.
- The specific ACT options in patient groups a2, b1 and b2 (i.e. research questions 2, 3 and 4) are each equally appropriate treatment alternatives.

b. Presentation of the respective ACT specified by the G-BA.

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

The G-BA decides on the added benefit.

I 8 References for English extract

Please see full dossier assessment for full reference list.

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