Insulin Icodec
Treatment to Improve Glycemic Control in Adults with Diabetes Mellitus
BLA 761326

Briefing Document

Endocrinologic and Metabolic Drugs Advisory Committee

May 24, 2024

Advisory Committee Briefing Materials: Available for Public Release

1 Executive Summary

Novo Nordisk is seeking approval for insulin icodec, a basal insulin for once-weekly subcutaneous administration. Insulin icodec is a once-weekly long-acting human insulin analogue which was developed to provide glycemic control in adults with diabetes (BLA 761326).

The purpose of the EMDAC meeting is to discuss the benefit-risk of insulin icodec for the treatment of people with type 1 diabetes (T1D). Therefore, this document will focus on T1D based on the single randomized, controlled pivotal study known as ONWARDS 6. In addition, this document also includes data from five randomized, controlled studies (ONWARDS 1 to 5) supporting a positive benefit-risk in patients with type 2 diabetes, since those data inform the overall benefits and safe use of insulin icodec.

1.1 Diabetes overview and unmet medical need (Section 2)

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both. Diabetes mellitus is generally classified according to etiological factors, where type 1 diabetes (T1D) and type 2 diabetes (T2D) constitute the vast majority of cases. The number of people living with diabetes worldwide is predicted to increase to 783 million by 2045. In the United States, 37.3 million people (11.3% of the population) are affected by diabetes which represents a significant medical, social and economic burden.[1, 2]

The chronic hyperglycemia of diabetes mellitus is associated with clinically significant long-term complications that entail macrovascular and microvascular complications and may greatly affect people's quality of life. The microvascular disorders associated with diabetes are typically retinopathy, nephropathy, and neuropathy. Maintaining tight glycemic control (70–180 mg/dL) reduces the risk of long-term complications associated with diabetes.[3]

Given its progressive nature, the current treatment cascade for T2D follows a stepwise approach comprising lifestyle changes in combination with pharmacological intervention that may eventually lead to more intensive therapies, including basal insulins. Since T1D is characterized by absolute insulin deficiency, the current gold standard of care is insulin therapy involving multiple daily injections of bolus and basal insulin or continuous subcutaneous insulin infusion [4,5, 6].

Insulin is highly effective in lowering blood glucose, and different insulin formulations are currently approved for the treatment of T2D and T1D. Hypoglycemia is an inherent risk of all insulins and the choice of insulin should be balanced against the benefits for each individual person. In addition, the complicated treatment requirements are considered by both people living with diabetes and physicians to be a barrier to insulin therapy initiation and adherence, as insulin therapy may require frequent injections to maintain glycemic control.[7, 8] Importantly, the degree of adherence to insulin treatment has been shown to be a significant predictor of reductions in HbA_{1c}[9, 10] and decreased adherence is associated with the development of microvascular disorders.

In current practice, clinicians and people living with diabetes can choose from a range of insulins that can be employed in various regimens to suit an individual's needs, based on the pathology, individual requirements, lifestyle, and personal preferences.[11] Insulin icodec, as a once-weekly basal insulin, would represent an alternative option for people with T2D or T1D, conferring the additional benefit of a simplified and more convenient basal insulin treatment.

1.2 Product description and molecular mechanism (Section 4)

Insulin icodec is a novel long-acting human insulin analogue, which has been designed to retain the same, well-established biological/metabolic effects of human insulin while extending the half-life to cover the basal insulin requirements for a full week allowing for a once-weekly subcutaneous injection.

The insulin icodec molecule consists of a modified insulin peptide backbone and a fatty acid-containing sidechain. The addition of the C20 fatty-diacid-containing chain imparts a strong but reversible binding to albumin which leads to the formation of a depot of essentially inactive insulin icodec, from which insulin icodec is slowly and continuously released. In addition, three amino acid substitutions in the peptide backbone of insulin icodec provide molecular stability and contribute to attenuating insulin receptor binding and clearance, resulting in a considerably extended half-life (Figure 4-1).

1.3 Clinical pharmacology (Section 6)

Pharmacokinetic assessments demonstrated that steady state for insulin icodec was reached after 2-4 weeks of once-weekly administration. At steady state, the concentration-time profile showed that insulin icodec exposure covered the one-week dosing interval (Figure 6-1). The terminal half-life of insulin icodec at steady state was approximately 1 week. Total exposure and maximum concentration increased proportionally with increasing dose. The within-subject variability in insulin icodec exposure from week to week at steady state was found to be low (Section 6.2).

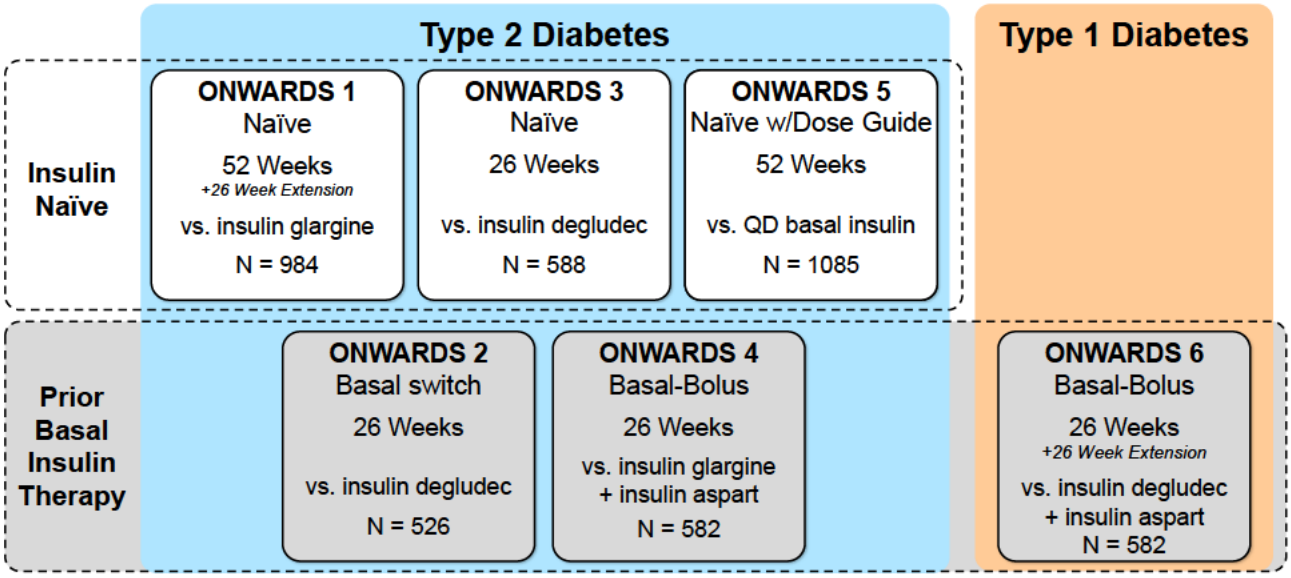
Pharmacodynamic assessments demonstrated that, at steady state, the glucose-lowering effect of insulin icodec covered the full weekly dosing interval both in T2D and T1D, with the greatest glucose lowering- effect occurring on Days 2-4 after the weekly administration (Figure 6-2 and Figure 6-3). The day-to-day differences in glucose-lowering effect over the weekly dosing interval were larger in T1D than in T2D, similar to what has been shown over the daily dosing interval for daily basal insulin products (Section 6.3).

Population pharmacokinetic analysis showed that insulin icodec exposure was comparable across age, sex, race (White, Black, Japanese, Chinese, Other Asian), ethnicity, anti-insulin icodec antibody level, albumin level, and diabetes population (T2D versus T1D) (Figure 6-4). Increased body weight was associated with reduced insulin icodec exposure, which was expected because clearance and volume of distribution generally scale with body size. In practice, this effect of body weight is mitigated by individual dose titration. The pharmacokinetic properties of insulin icodec were not affected to any clinically meaningful extent by renal or hepatic impairment (Section 6.4).

1.4 Overview of phase 3 program (Section 8)

The clinical development program of insulin icodec consisted of 18 clinical trials in total (six phase 3a, three phase 2, and nine clinical pharmacology trials), including trials in both T1D and T2D populations. Phase 3a trials were referred to as ‘ONWARDS’ trials and their key features are summarized in Figure 1-1.

Figure 1-1 Schematic overview of ONWARDS trials



Abbreviations: N= number of participants; QD = quaque die (once daily); vs = versus

ONWARDS 3 was double-blind while all other trials were open-label. See Section 8 for further details on trial design.

The eligibility criteria for the trials were set to ensure that the enrolled participants represented the intended target population for insulin icodec. Most inclusion and exclusion criteria were common for ONWARDS 1-4 and 6, while less restrictive criteria were applied for ONWARDS 5 (Table 8-1 and Table 8-2). ONWARDS 1 and ONWARDS 6 had a main phase for efficacy and safety evaluation and an extension for long-term safety evaluation.

Results from each clinical trial in the ONWARDS program have been published.[12,13,14,15,16,17]

1.5 Endpoints and assessments (Section 8)

The primary objective for all ONWARDS trials was to demonstrate the effect of once-weekly insulin icodec on glycemic control. In all ONWARDS trials, the primary endpoint was the change in HbA_{1c} from baseline to the landmark visit (week 26 for ONWARDS 2, 3, 4 and 6 or week 52 for ONWARDS 1 and 5). The primary hypothesis was that the change in HbA_{1c} with insulin icodec was non-inferior to daily basal insulin, with a non-inferiority margin pre-specified at 0.3%. Satisfying this margin would demonstrate imputed superiority of insulin icodec versus placebo. In ONWARDS 1, 2, 3 and 5, additional confirmatory hypotheses were tested (Figure 8-2).

Efficacy assessments are listed in Table 8-3.

All ONWARDS trials included prespecified safety evaluations, including the frequency and severity of hypoglycemic events. Safety assessments are listed in Section 8.2.

Hypoglycemia is a known risk for all insulins and was carefully analyzed in the insulin icodec development program. Hypoglycemic episodes were classified by severity in accordance with international guidelines (Figure 1-2). Hypoglycemia data are reported as the percentage of participants who experienced one or more episodes, as well as the event rate which reflects the total number of episodes per exposure time. Thus, the event rate reflects the total hypoglycemia event

burden. However, the overall event rate may not be reflective of the experience of individual participants, as some individuals experience a large number of episodes.

Figure 1-2 Classification of hypoglycemia

Level	Glycemic criteria	Description
Hypoglycemia alert value (level 1)	< 3.9 mmol/L (70 mg/dL) and ≥ 3.0 mmol/L (54 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycemia (level 2)	< 3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

Notes: The Novo Nordisk terms are adapted from IHSG[18], ADA[19], ISPAD[20], type 1 diabetes outcomes program[21], ATTD[22]. Severe hypoglycemia as defined by Seaquist[23] and ISPAD[20]

Continuous glucose monitoring (CGM) was utilized at pre-specified time periods in selected ONWARDS trials. As a post-hoc analysis, hypoglycemia has also been evaluated using CGM-based data. CGM-based hypoglycemia detection and reporting is well established in current clinical guidelines[24] and regulatory guidance[25, 26]. The method is based on extensive data with 5-minute interval glucose values and, contrary to the self-measured blood glucose (SMBG)-based approach, is not dependent on the frequency of measuring and manual reporting by the patient, thereby giving a more unbiased assessment of hypoglycemia. The analysis of hypoglycemia based on CGM data is intended to be complementary to SMBG-based analysis, in order to provide the most accurate evaluation of hypoglycemia.

Mirroring the parameters defining hypoglycemic levels based on SMBG, CGM-based hypoglycemic episodes are classified as “clinically significant” or “level 2”, when interstitial glucose (IG) was <54 mg/dL for at least 15 consecutive minutes at any time during the episode. The episodes are considered resolved when IG is maintained ≥70 mg/dL for at least 15 consecutive minutes.

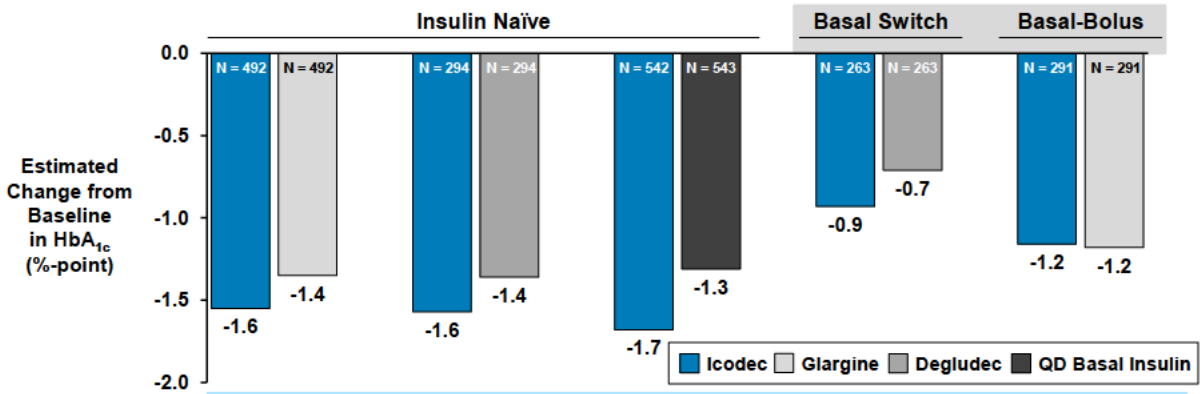
It should be noted that severe (level 3) hypoglycemic episodes are defined as episodes associated with severe cognitive impairment requiring external assistance for recovery, and not by a specific threshold of glycemia. Therefore, severe (level 3) hypoglycemic episodes are not defined based on CGM data or SMBG data, but on symptoms and management only.

1.6 Clinical results in participants with T2D (Section 9)

1.6.1 Efficacy in participants with T2D (Section 9.2)

In all T2D populations (ONWARDS 1 to 5), insulin icodec was demonstrated to be non-inferior to daily basal insulin in terms of change from baseline in HbA_{1c}. In addition, in T2D insulin naïve participants and in participants on basal only prior to trial, once-weekly injection with insulin icodec provided statistically superior reductions in HbA_{1c} compared to daily basal insulin, in a secondary pre-specified multiplicity adjusted analysis (Figure 1-3). Although statistical superiority was achieved, the clinical relevance of the difference between treatments has not been established.

Figure 1-3 T2D – Change from baseline in HbA_{1c}



T2D Studies	ONWARDS 1	ONWARDS 3	ONWARDS 5	ONWARDS 2	ONWARDS 4
Baseline HbA_{1c} (%)	8.47	8.52	8.92	8.13	8.30
Difference [95% CI]	**-0.19** [-0.36, -0.03]	**-0.21** [-0.34, -0.08]	**-0.38** [-0.66, -0.09]	**-0.22** [-0.37, -0.08]	**0.02** [-0.11, 0.15]
p-value Non-Inferiority	**< 0.0001**	**< 0.0001**	**< 0.0001**	**< 0.0001**	**< 0.0001**
p-value Superiority	0.0210	0.0016	0.0092	0.0028	NA

Abbreviations: CI = confidence interval; ETD = estimated treatment difference; NA = Not assessed
Note: ONWARDS 1 data were only from the main phase of the trial

In all T2D-ONWARDS trials, HbA_{1c} levels decreased from baseline to week 26 (landmark visit for ONWARDS 2, 3 and 4), and remained stable until week 52 (landmark visit for ONWARDS 5 and ONWARDS 1).

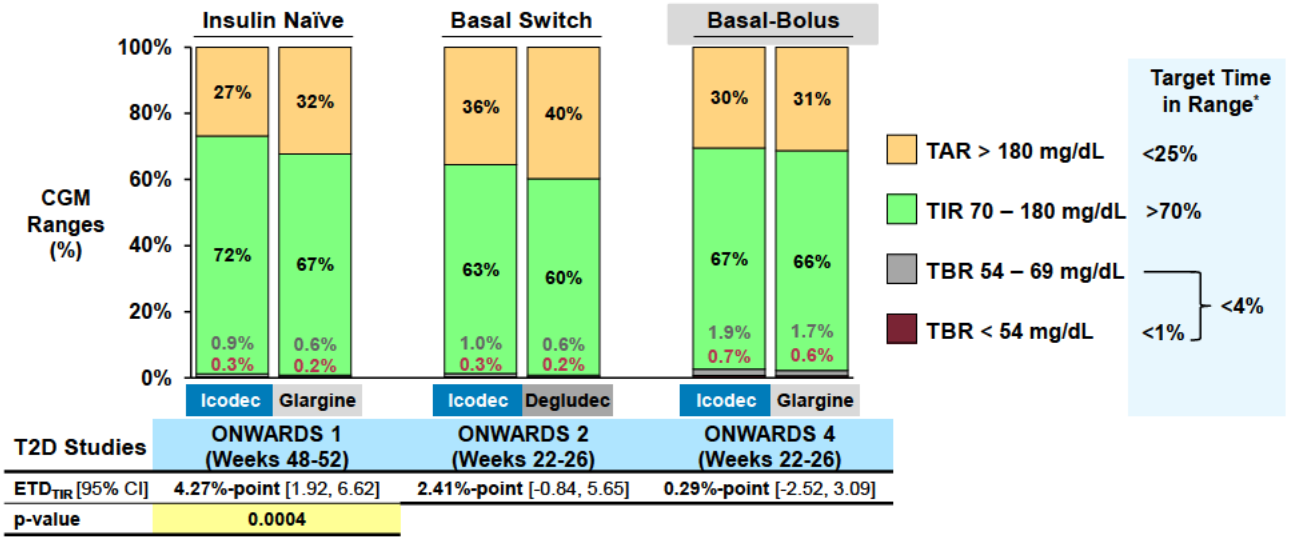
The time course of glycemic improvement in the insulin icodec-treated participants was similar to that in daily basal insulin-treated participants, as measured by HbA_{1c} levels (Figure 9-2) and SMBG measurements (Figure 9-5).

CGM data were collected in the T2D insulin naïve population (ONWARDS 1), and in T2D populations previously on basal only (ONWARDS 2) or on basal-bolus regimen (ONWARDS 4) during the last 4 weeks of treatment. Time in range (TIR) is defined as the percentage of time when interstitial glucose is between 70 and 180 mg/dL. TIR was a pre-specified confirmatory endpoint to assess insulin icodec efficacy in ONWARDS 1, where insulin icodec was statistically superior to insulin glargine for this parameter. In ONWARDS 1, time above and below range (TAR and TBR) were not statistically different between the 2 treatment arms.

In ONWARDS 2 (T2D previously on basal only) and ONWARDS 4 (previously on basal-bolus), TIR, TAR and TBR were not statistically different between the 2 treatment arms.

In all T2D trials where CGM was evaluated, TIR, TAR and TBR in the insulin icodec arm were within the window recommended by the international guidelines (Figure 1-4).

Figure 1-4 T2D – CGM – percentage time above, below, and in range



Abbreviations: CGM = continuous glucose monitoring; ETD = estimated treatment difference; CI = confidence interval; T2D = type 2 diabetes; TAR = time spent above range; TIR = time spent in range; TBR = time spent below range

Notes: observed data; Time spent is defined as 100 times the number of recorded measurements in a given range, divided by the total number of recorded measurements; ONWARDS 1 data were only from the main phase of the trial; * [24]

1.6.2 Hypoglycemia in participants with T2D (Section 9.3)

A high proportion (85.9–90.2%) of the participants with T2D treated with insulin icodec who were insulin naïve or on basal insulin only prior to trial, did not experience any clinically significant or severe (level 2 or level 3) hypoglycemic episode during the trials. In line with what is expected in participants with T2D on a basal-bolus regimen, the proportion of participants on basal-bolus therapy who did not experience a clinically significant or severe (level 2 or level 3) hypoglycemic episode was lower than in the other T2D trials, but similar between treatment arms (48.5% vs. 44.3% in insulin icodec vs. daily basal insulin). Overall, the proportion of participants experiencing a level 2 or level 3 hypoglycemic episode was similar between treatment arms across all T2D-ONWARDS trials (Table 1-1).

Across all T2D populations, the risk of severe (level 3) hypoglycemia was similar between treatment arms, and ranging between 0.002 to 0.04 per patient year in the insulin icodec arm and between 0.006 and 0.02 per patient year in the daily basal insulin arm. In total, 4 episodes of level 3 hypoglycemia in 3 participants with T2D were nocturnal, and none occurred in the insulin icodec treatment arm. The level 3 episodes were of similar duration between treatment arms, and were managed and resolved using the same means (Table 1-1).

The number of episodes that were reported as SAEs were similar in the 2 treatment arms (3 in insulin icodec arm and 4 in daily basal insulin). Importantly, in insulin icodec-treated participants all SAEs associated with hypoglycemia were resolved and none led to permanent treatment discontinuation.

Table 1-1 T2D – Level 2 and level 3 hypoglycemic episodes

		Insulin icodec (N = 1880)			Daily basal insulin (N = 1878)		
Trial	**Classification**	**%**	**E**	**R**	**%**	**E**	**R**
Insulin naïve							
ONWARDS 1	**Level 2**	9.8	143	0.29	10.0	75	0.15
	Level 3	0.2	1	0.002	0.6	3	0.006
ONWARDS 3	**Level 2**	8.9	53	0.31	5.8	23	0.13
	Level 3	0	0		0.7	2	0.01
ONWARDS 5	**Level 2**	11.8	104	0.19	7.8	76	0.14
	Level 3	0	0		0.7	5	0.009
Basal switch							
ONWARDS 2	**Level 2**	14.1	113	0.73	7.2	41	0.27
	Level 3	0	0		0.4	1	0.007
Basal-bolus							
ONWARDS 4	**Level 2**	50.9	937	5.60	55.0	935	5.60
	Level 3	1.4	7	0.04	0.7	3	0.02

Abbreviations: % = percentage of participants with one or more episodes; E = number of episodes; N = number of participants; R = Rate (number of events per 1 PYE); PYE = Patient years of exposure (1 PYE = 365.25 days); T2D = type 2 diabetes

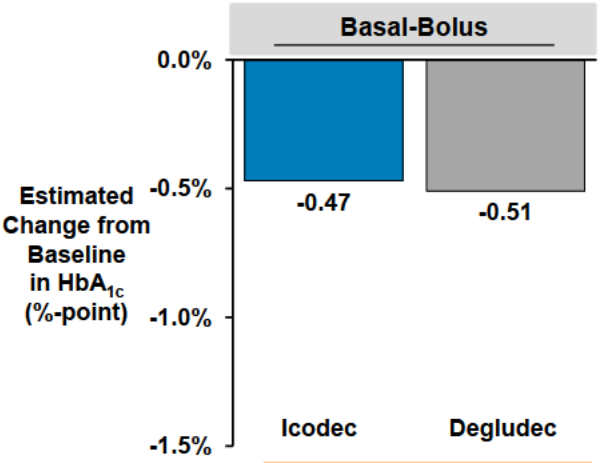
According to international recommendations, the achievement of HbA_{1c} levels below 7.0% and preferably below 6.5% are considered clinically meaningful, as they are associated with reduced risks of diabetes complications.[27] Combining the achievement of these glycemic targets with the absence of clinically significant or severe hypoglycemic episodes (level 2 or level 3) enables a meaningful evaluation of the balance between HbA_{1c} reduction and risk of hypoglycemia. In T2D populations, the proportion of participants that reached HbA_{1c} levels <7.0% or ≤6.5% at landmark visit without hypoglycemic episodes (level 2 or level 3) in the prior 12 weeks was higher in the insulin icodec arm than in the daily basal insulin arm in both insulin naïve participants and participants previously on basal only therapy, while similar between treatment arms for participants on prior basal-bolus therapy. Thus, insulin icodec achieved target glycemic control without unacceptable increases in hypoglycemia when compared with daily insulin therapy.

1.7 Clinical results in participants with T1D (Section 10)

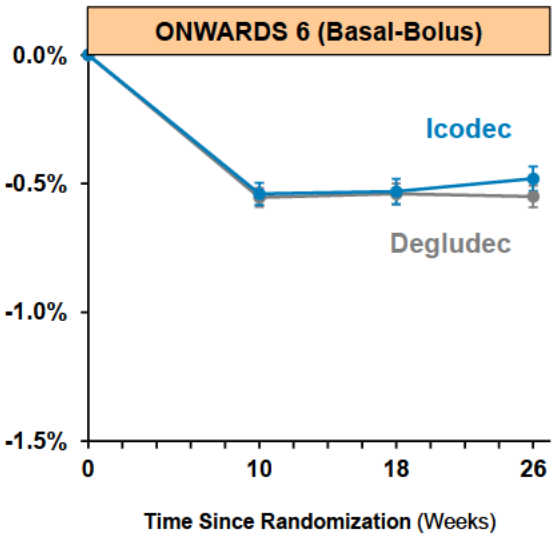
1.7.1 Efficacy in participants with T1D (Section 10.2)

In the T1D population (ONWARDS 6), insulin icodec was demonstrated to be non-inferior to daily basal insulin in terms of change in HbA_{1c} (Figure 1-5 left).

Figure 1-5 T1D – Change of HbA_{1c} from baseline to week 26



T1D Study	ONWARDS 6
Baseline HbA_{1c} (%)	7.6
Difference [95% CI]	0.05 [-0.13, 0.23]
p-value Non-Inferiority	0.0065

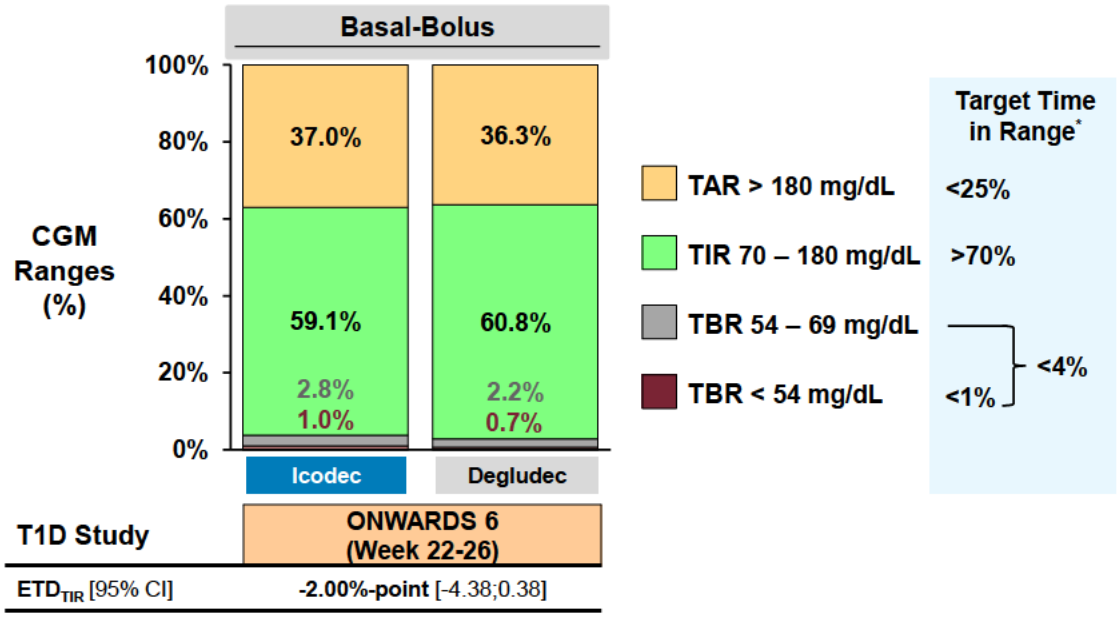


Abbreviations: CI = confidence interval; ETD = estimated treatment difference; HbA_{1c} = glycosylated hemoglobin; T1D = type 1 diabetes
Note: data were only from the main phase of the trial.

In the T1D population, HbA_{1c} decreased rapidly from baseline to week 10 and then remained stable until week 26 (Figure 1-5 right). The time course of glycemic improvement in insulin icodec-treated participants was similar to that in daily basal insulin-treated participants, as measured by HbA_{1c} levels (Figure 1-5 right) and SMBG measurements (Figure 10-5).

CGM measurements, defining the percentage of time spent above, below or in range (TAR, TBR and TIR, respectively) were evaluated in the T1D population. In ONWARDS 6, TAR, TIR and TBR were comparable between the 2 treatment arms. In the insulin icodec arm, time spent below 70 mg/dL was within the recommended window, while time spent below 54 mg/dL was 1% which corresponds to the threshold recommended by international consensus guidelines (Figure 1-6).

Figure 1-6 T1D – CGM ranges at landmark visit



Abbreviations: CGM = continuous glucose monitoring; CI = confidence interval; ETD = estimated treatment difference; T1D = type 1 diabetes; TAR = time spent above range; TIR = time spent in range; TBR = time spent below range

Notes: observed data; Time spent is defined as 100 times the number of recorded measurements in a given range, divided by the total number of recorded measurements; * [24]

1.7.2 Hypoglycemia in participants with T1D (Section 10.3)

In the T1D population, a higher risk of clinically significant (level 2) or severe (level 3) hypoglycemic episodes was observed in the insulin icodec treatment arm compared to insulin degludec. Therefore, it is central to assess the risk of hypoglycemia in participants with T1D, how the data from the clinical trial will translate in real clinical practice, and how hypoglycemic episodes will be managed by people with T1D treated with insulin icodec. To this purpose, extensive pre-specified as well as post-hoc analyses have been conducted in order to identify the root cause of higher rates of hypoglycemia for insulin icodec and how to mitigate them.

In T1D, the proportion of participants reporting one or more episodes of severe (level 3) hypoglycemia was 3.1% in both treatment arms. In the insulin icodec arm, one patient accounted for 33 out of the 47 severe hypoglycemic episodes (70%). Despite the many level 3 episodes, the investigator considered it safe and beneficial to keep this participant in the trial. Furthermore, the participant completed the trial and did not discontinue treatment. In the insulin degludec arm, one patient accounted for 7 out of the 17 severe (level 3) hypoglycemic episodes (41%). The clinical presentation of severe (level 3) hypoglycemic episodes in participants with T1D was similar between treatment arms in terms of duration, management, and recovery. In the insulin icodec arm, 80.9% of the level 3 hypoglycemic episodes did not require medical assistance and 83.0% were resolved with oral carbohydrates only. In all insulin icodec cases, participants recovered after treatment.

Hypoglycemia in the participant with 33 severe (level 3) episodes has been carefully analyzed and is presented in more details in Section 10.3.3.1.

Severe (level 3) nocturnal hypoglycemia occurred in 2 participants (0.7%) in the insulin icodec arm and 3 participants (1.0%) in the insulin degludec arm.

Both the proportion of participants experiencing a clinically significant or severe hypoglycemic episode (level 2 or level 3) and the rates of these episodes were higher in the insulin icodec arm compared to insulin degludec. Analysis of combined level 2 or level 3 hypoglycemia was a pre-specified safety endpoint, however, the higher rates and proportion of participants were driven by level 2 episodes (Table 1-2).

Table 1-2 T1D – Level 2 and level 3 hypoglycemic episodes

		Insulin icodec			Insulin degludec		
Trial	**Classification**	**%**	**E**	**R**	**%**	**E**	**R**
ONWARDS 6	**Level 2**	84.8	2789	19.60	76.4	1478	10.26
	Level 3	3.1	47	0.33	3.1	17	0.12

Abbreviations: % = Percentage of participants with one or more events; E = number of events; R = Rate (number of events per 1 PYE); PYE = Patient years of exposure (1 PYE = 365.25 days); T1D = type 1 diabetes

The characterization of the distribution of the risk of hypoglycemia across the week showed that the risk of experiencing a level 2 hypoglycemia episode was higher on Days 2-4 after the weekly injection, when plasma icodec exposure and pharmacodynamic effects are greatest, as per the PD profile.

Similarly to level 3 episodes, the duration of level 2 episodes was comparable between treatment arms, indicating that the clinical presentation of hypoglycemia does not differ between insulins.

The risk of level 2 and level 3 hypoglycemic episodes did not increase over time in the 2 treatment arms. The number of hypoglycemic episodes reported as SAEs was higher in insulin icodec (7 events) than in the insulin degludec arm (1 event). All SAEs in insulin icodec-treated participants reported in relation to hypoglycemia were resolved and did not lead to treatment discontinuation.

In order to identify potential factors associated with a higher risk of hypoglycemia for insulin icodec, several baseline and demographic characteristics of participants experiencing level 2 or level 3 hypoglycemic episodes have been analyzed. No unique risk factor was identified for insulin icodec. Rather, in both treatment arms the same characteristics were found associated with a higher risk of hypoglycemia, and were consistent with what is reported in the literature for other basal insulins. To gain more insights on how these risk factors may impact the efficacy and safety profile of insulin icodec, an in-depth analysis has been conducted on subgroups of people with T1D having glycemic variability above or below 36%. Glycemic variability is a well-established risk factor for hypoglycemia and a clear cut off of ≤36% has been identified as associated with a lower risk of hypoglycemia.[24, 27,28] As expected, a lower risk of level 2 and level 3 hypoglycemia was observed in both treatment arms for people with CV≤36% compared to total population, while efficacy parameters were similar to those of the total population. This finding indicates that these

characteristics can be used by the healthcare practitioners to assess hypoglycemia risk at the individual level, similarly to what they already do in clinical practice for daily basal insulins.

1.8 General clinical safety (Section 11)

The secondary objective of all ONWARDS trials was to evaluate the safety of insulin icodec in comparison with a daily basal insulin. In the ONWARDS trials the safety profile of insulin icodec has been evaluated in 2170 participants with T1D or T2D, with a total exposure of 2119 patient-years. The ONWARDS program demonstrated that insulin icodec had a safety profile similar to the well-established profile of daily basal insulin, and no unexpected findings or unacceptable risks were identified.

1.9 Benefit-risk assessment (Section 12)

Novo Nordisk considers the overall benefit-risk profile of insulin icodec to be favorable in people living with diabetes mellitus.

Once-weekly insulin icodec represents a valuable option for people with diabetes who need basal insulin as part of their therapy and can benefit by a reduced treatment burden. With the once-weekly dosing regimen, insulin icodec has the potential to reduce time to insulin initiation and improve treatment adherence. It is well established that on time and sustained glycemic control leads to greatest reduction in long term micro- and macrovascular complications. [29,30,31,32,33,9, 10]

For people with T2D the absolute risk of hypoglycemia (level 2 or level 3) was low and within the same range as reported for other marketed basal insulins. With an overall similar safety profile, a comparable reduction of HbA_{1c}, a higher proportion of patients reaching relevant HbA_{1c} targets without hypoglycemia, and a greater TIR compared to daily basal insulins, the benefit-risk profile of insulin icodec is favorable.

For people with T1D, Novo Nordisk acknowledges that the higher risk of hypoglycemia needs to be balanced in an individualized manner while considering other potential benefits of a weekly insulin.

Insulin icodec demonstrated non-inferiority to insulin degludec in terms of improvement in glycemic control from baseline in participants with T1D, as assessed by HbA_{1c} reduction.

The safety profile was similar between treatment arms except for hypoglycemia, where a higher risk was identified for insulin icodec compared to insulin degludec. Hypoglycemia is the main risk for all insulins and extensive analyses have been performed to characterize the nature and root cause of the excess risk of hypoglycemia in participants with T1D. Severe hypoglycemic episodes (level 3) occurred in similar proportion of participants between the two treatment arms and the higher rates in the insulin icodec arm are mostly due to 1 participant experiencing 70% of the episodes. In both treatment arms the severe hypoglycemia episodes were of similar duration and managed and resolved in the same way. Clinically significant (level 2) episodes were more frequent among participants treated with insulin icodec compared to insulin degludec. Several baseline and demographic characteristics were analyzed and no factor associated with a higher risk of hypoglycemia has been identified as unique for insulin icodec. In fact, the risk factors identified were the same for both insulin icodec and insulin degludec and consistent with those described in literature for daily basal insulins. Taken together, these analyses indicate that healthcare

practitioners can use the same risk factors as for daily basal insulins to evaluate the risks and balance them against the benefit that a once-weekly posology can infer. Similarly, people living with T1D can use the same means to manage hypoglycemic episodes as for other daily basal insulins with which they are already familiar. In summary, while the risk of hypoglycemia can be effectively managed by guidance provided from physicians considering the individual clinical situation, the availability of a weekly insulin could provide an important and unique alternative treatment option for some people living with T1D.

List of abbreviations

ADA	American diabetes association
AE	Adverse event
AGP	Ambulatory glucose profile
ANCOVA	Analysis of covariance
AUC	Area under the curve
BLA	Biologic License Application
BMI	Body mass index
CGM	Continuous glucose monitoring
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CSII	Continuous subcutaneous insulin infusion
CV	Cardiovascular
DKA	Diabetic ketoacidosis
DPP-4i	Dipeptidyl peptidase-4 inhibitor
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EAC	Event adjudication committee
ECG	Electrocardiogram
EMA	European Medicines Agency
EMDAC	Endocrinologic and Metabolic Drugs Advisory Committee
ERR	Estimated rate ratio
ETD	Estimated treatment difference
ETR	Estimated treatment ratio
EU	European Union
FAS	Full analysis set
FDA	Food and drug administration
FPG	Fasting plasma glucose
eGFR	Estimated glomerular filtration rate
GIR	Glucose infusion rate
GLP-1	Glucagon-like peptide 1

HR	Hazard-ratio
ICH	International council for harmonisation
IG	Interstitial glucose
IND	Investigational New Drug
IV	Intravenously
MACE	Major adverse cardiovascular event
MDI	Multiple daily injections
NPH	Neutral protamine Hagedorn
OAD	Oral antidiabetic drug
PD	Pharmacodynamics
PG	Plasma glucose
PRO	Patient reported outcome
PT	Preferred term
PK	Pharmacokinetics
PYE	Patient years of exposure
QD	Quaque die
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SGLT-2i	Sodium-glucose cotransporter-2 inhibitor
SMBG	Self-measured blood glucose
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
TAR	Time above range
TBR	Time below range
TIR	Time in range
US	United States
WHO	World Health Organization

Table of contents

Page

Table of figures

Page

Table of tables

Page

2 Diabetes overview

Summary

- Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, insulin action or both
- The number of people with diabetes is predicted to be 783 million by 2045 (as estimated by "The International Diabetes Federation's Diabetes Atlas" in 2021)
- In advanced T2D and in T1D, insulin treatment is required to manage glucose control, in a spectrum of regimens, requiring one or multiple daily injections
- Daily and multiple daily insulin injections are frequently barriers to the initiation of insulin therapy and can negatively affect adherence to therapy
- The choice of insulin is based on individual needs, including pathology characteristics, lifestyle and personal preferences

2.1 Disease background

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, insulin action or both. Diabetes mellitus is generally classified according to etiological factors, where type 1 diabetes (T1D) and type 2 diabetes (T2D) constitute the vast majority of cases. In the latest edition of the International Diabetes Federation's Diabetes Atlas (2021), the estimated worldwide diabetes prevalence was 537 million, with a prediction that the number of people with diabetes will increase to 783 million by 2045. In the United States, 37.3 million people (11.3% of the population) are affected by diabetes (28.7 million people diagnosed and 8.5 million undiagnosed - based on FPG and HbA_{1c} levels among people self-reporting no diabetes), representing a significant medical, social, and economic burden.[1,2]

T1D is a heterogeneous disorder characterized by T cell-mediated autoimmune destruction of insulin-producing beta cells in the pancreas, eventually resulting in a complete deficiency of insulin secretion.[34] T1D is the major type of diabetes in youth, and people with T1D require lifelong administration of exogenous insulin. T1D is a heritable polygenic disease, although how the disease is triggered and how the haplotypes interact and alter the risk is not completely clear.[35]

T2D, which accounts for more than 90% of diabetes cases, is a progressive disorder characterized by a combination of insulin resistance and defective insulin secretion that is insufficient to compensate for that resistance.[36] The pathogenesis of T2D is not fully understood but seems to be heterogeneous, involving environmental, lifestyle, and genetic factors.[37]

The chronic hyperglycemia of diabetes mellitus (both T2D and T1D) is associated with clinically significant long-term complications that entail macrovascular and microvascular disorders and may greatly affect people's quality of life. On the basis of cohort studies from developed countries, the relative risk of macrovascular and microvascular disorders among people with diabetes mellitus was estimated to be at least 2–4 times higher and 10–20 times higher, respectively, than in people without diabetes mellitus.[38] Macrovascular complications include cardiovascular disease (e.g. stroke and coronary heart disease) which is the major cause of death in diabetes, accounting in most populations for >50% of all diabetes fatalities, and much disability. The microvascular disorders associated with diabetes are typically retinopathy, nephropathy, and neuropathy. In particular,

diabetic neuropathy results in significant morbidity and mortality[39, 40] and is the leading cause for non-traumatic amputations secondary to foot ulceration.[41] Especially in people with T1D, insulin deficiency can cause hyperglycemia and metabolic acidosis leading to the development of diabetic ketoacidosis (DKA), an acute and potentially life-threatening complication.[34]

2.2 Current therapies

Type 1 diabetes

Since T1D is characterized by absolute insulin deficiency, insulin therapy is a life-saving treatment. In the U.S., approximately 1.7 million people live with T1D and use insulin.[2] The current gold standard of care is based on intensive insulin therapy with multiple daily injections of bolus and basal insulin or continuous subcutaneous insulin infusion via an insulin pump. [42] Based on individual needs, several treatment regimens exist using either human insulin or insulin-analog products. These include:

- Continuous subcutaneous insulin infusion (CSII) via pump with a rapid acting insulin analog, whereby a fixed or variable basal rate is infused 24 hours a day and bolus doses are delivered at mealtimes by insulin pump. Approximately 1 million people with T1D in the US are treated with CSII regimen. [2,43]
- Basal-bolus therapy – also referred to as MDI (multiple daily injections), in which basal (intermediate- or long-acting) insulin is injected once or twice daily to cover the basal insulin requirements, and bolus (short-acting) insulin is administered at meals to cover postprandial glucose excursions. Approximately 350,000-700,000 people with T1D in the US are treated with MDI regimen. [2,43]
- Administration of mixed insulin products, which contain both intermediate or long-acting insulin and short-acting insulin to cover both basal and meal-related requirements with a reduced number of injections.

For many people, insulin delivery by infusion pump has radically improved the clinical management of their diabetes. Nonetheless, more than a third of people living with T1D in the US (across races and ethnicities) still require multiple injections of insulin and use a basal insulin as the foundation of their therapy. [43,44]

Hypoglycemia with daily basal insulins

All insulins carry an inherent risk of hypoglycemia, including long-acting insulins which are commonly used by people living with T1D. The risk of clinically significant (level 2) hypoglycemia reported for the most recently approved long-acting insulins (insulin glargine U300 and insulin degludec) in people with T1D was approximately 18 to 43 episodes per patient year of exposure (PYE) in the phase 3a pre-approval clinical trials, and 22 to 30 episodes per PYE in post-approval clinical trials. [45,46,47,48] It is important to note that these trials were conducted with both glucose targets and definitions of “clinically significant hypoglycemia” that were slightly different from what has been used in the clinical development program of insulin icodec. Therefore, comparisons should be made with caution.

Type 2 diabetes

For T2D, the current treatment cascade follows a stepwise approach. In asymptomatic individuals, the first line of treatment is always lifestyle modifications, such as healthier eating patterns and increased physical activity with the aim of reducing weight and improving insulin sensitivity[5, 49], which may also have a beneficial effect on lipids and blood pressure.

When lifestyle changes become insufficient to control glycemia, glucose-lowering agent monotherapy is generally recommended as the initial pharmacology therapy. As the disease progresses, single agent therapy is followed by a combination therapy with other oral antidiabetic drugs (OADs),[50] glucagon-like peptide 1 (GLP-1) receptor agonists[51, 52] and eventually insulin, based on basal insulins and even basal-bolus insulin therapies in the most advanced cases.[53] Currently, in the U.S. approximately one third of people living with T2D are treated with insulin, corresponding to about 7.4 million people.[54,55,2]

2.3 Unmet need

The recognized core objective of diabetes treatment is to prevent or forestall the complications associated with hyperglycemia, both short term (diabetic ketoacidosis, hyperosmolar coma) and long-term (micro- and macro-vascular). It has been shown that maintaining tight glycemic control with HbA1c<7% reduces the risk of long-term complications. However, in real-world practice approximately almost a half of people with diabetes do not reach this target, indicating that optimizing glycemic control remains a challenge for many.[3,56,2]

Insulin therapy is highly effective in lowering blood glucose and different insulin formulations are currently approved for the treatment of T2D and T1D. As presented in the section above, currently in US more than 30% of people living with diabetes are on insulin therapy.[55]

Insulin therapy is associated with a significant treatment burden, since it requires at least one or more daily injections for people with T2D on a basal-only therapy and typically four injections (at least one basal and at least three bolus) for people with T2D on basal-bolus treatment and people with T1D not using an insulin pump. The burden of multiple daily injections is considered by both patients and physicians to be a barrier to insulin therapy initiation and adherence.[7, 8] This is also highlighted by a high rate of non-adherence in both people with T2D and T1D, spanning from 33-88%.[57,8,58] Delay in insulin therapy initiation and low adherence contribute to triggering a spiral of negative consequences such as poor clinical outcomes, comorbidities, increased hospitalization, and mortality.[8,59, 60,61] Therefore, an unmet medical need remains for an efficacious and simpler insulin treatment of diabetes mellitus. Due to the intrinsic needs of a clinical trial design, treatment adherence cannot be measured in a clinical trial setting. However, real-world evidence demonstrated that once-weekly GLP-1 receptor agonists (GLP-1 RA) have higher therapy persistence and adherence, compared to once-daily GLP1-RA.[62,63] Similar results showing that reduced treatment frequency improves adherence were published from across a range of therapeutic areas including growth hormone deficiency, multiple sclerosis, and osteoporosis. [64,65,66,67, 68] Therefore, based on experience with other medications, it can be reasonably expected that once-weekly insulin icodec will improve adherence to insulin therapy in select individuals with diabetes.

In current practice, clinicians and patients can choose from a range of insulins that can be employed in various regimens to suit an individual's needs, based on the pathophysiology, individual requirements, lifestyle, and personal preferences.[11,69] Once-weekly insulin icodec would represent

an alternative basal insulin option for people living with T2D or T1D, with the additional benefit of a simplified and more convenient treatment regimen.

Type 2 diabetes

In real world practice, glucose control is inadequate among insulin-treated patients, in part attributable to insulin omission/non-adherence and lack of dose adjustment. [8] Indeed, almost a half of people leaving with diabetes is not reaching target HbA_{1c} as defined per guidelines [2], whereas 33-88% is reporting non adherence. [57,8,58] This highlights that improved adherence has the potential to achieve better glycemic control. It is well established that early and sustained glycemic control leads to greater reductions in microvascular and macrovascular complications and mortality.

In patient and physician studies, 93% of people on insulin would like to have good blood sugar control without daily injections and 59% of physicians identified the number of daily injections as a difficulty for people living with T2D.[8,70, 71] A comprehensive systematic literature review identified real-world factors affecting adherence to insulin therapy in people with diabetes, where 'real-world' refers to factors encountered by the average person using insulin outside a controlled clinical setting such as a clinical trial. One of the barriers identified by patients is a concern regarding injections and the need to fit them into their daily life.[8, 72] A once-weekly dosing regimen would reduce the number of basal insulin injections from at least 365 per year to approximately 52 leading to a simplified and more convenient insulin treatment, especially for people with T2D who are on basal-only insulin therapy. Beside the impact on their everyday life, this would have the potential to translate to better persistence and adherence to therapy. This in turn could lead to better glycemic control and reduced long-term diabetes-related complications, such as microvascular diseases, hospitalization rates, and mortality.[73, 74]

Type 1 diabetes

Due to the complete absence of endogenous insulin, exogenous insulin is indispensable for people living with T1D. Therefore, all people with T1D need to follow a therapeutic regimen based on utilization of insulin, for which there is a limited number of options. When adding a new basal insulin option, it is reasonable to consider the types of patients who might use the new treatment in clinical practice. While a weekly basal insulin may not be the preferred approach for all people with T1D, it has the potential to be helpful for some. Those who might prefer or benefit from weekly basal insulin could include individuals who struggle to use daily basal insulin consistently (due for example to work schedules or forgetfulness), those who rely on caregivers, those with recurrent DKA due to erratic insulin use, or those who simply want to take fewer injections. Some of these hypothetical situations, which were not explicitly called out in the clinical trials, are discussed below.

Despite insulin treatment, only a third of patients with T1D reach clinically meaningful targets of HbA_{1c}.[75] Consequently, many people with T1D on a basal-bolus therapy do not have optimal glycemic control, resulting in a higher risk of developing microvascular or macrovascular complications. This seems to be at least partially due to lack of consistency with daily basal insulin administration and suggests that alternative insulin options may be beneficial to reduce treatment burden and improve adherence. Based on real-world data, it has been estimated that the probability of missing at least one basal insulin dose over any given 14-day period was 22%, and that lack of adherence to basal insulin is associated with a decreased glycemic control as evaluated by time-in-

range measured by CGM, and is in alignment with other findings reported in the literature.[76,77] Missed injections of basal insulin could be potentially compensated by adjusting the bolus dose, but this requires careful monitoring by the individual and would only be possible during daytime.

Lack of consistency with daily basal insulin administration is also linked to increased rates of diabetic ketoacidosis (DKA) in people with T1D who have recurrent DKA, including young adults (18-25 years old).[78] These patients, who were not specifically studied in ONWARDS 6, could also benefit from a once-weekly basal insulin option, reducing the risk of DKA linked to a missed basal insulin dose and preventing DKA-related hospitalization. [78]

A simplified treatment could therefore lead to better glycemic control and better clinical outcomes, especially for patients with T1D who struggle to adhere to therapy.

3 Regulatory history

The insulin icodec IND was submitted to the FDA on August 6, 2018 and cleared on September 5, 2018. A Type C Guidance meeting on May 18, 2020 and a Type B End-of-Phase 2 (EOP2) meeting on December 11, 2020 were held with the Agency to discuss the clinical phase 3 programs in participants with type 2 diabetes and participants with type 1 diabetes, respectively. During these meetings the FDA provided feedback on the overall clinical program proposed by Novo Nordisk to support the insulin icodec BLA submission for the indication of treatment of diabetes mellitus.

During the conduct of the clinical phase 3, two Type C meeting Written Responses were received from the Agency where FDA agreed with the Novo Nordisk proposed pooling strategy for clinical safety data, the presentation of safety and efficacy data in the BLA and the proposed strategy for assessing neutralizing effect of anti-insulin icodec antibodies in the phase 3 trials.

The Type B pre-BLA meeting was held on November 29, 2022 where the Agency agreed to the overall content and format of the BLA submission.

At the time of the finalization of this document, insulin icodec has been submitted for regulatory approval in several countries worldwide in addition to US. These included, but are not limited to, EU, Canada, Switzerland, Australia, Brazil, Japan and China.

At this time, insulin icodec has been approved in Canada and Switzerland, and the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion to EMA with the recommendation of approval of insulin icodec in Europe for the treatment of diabetes mellitus in adults.

4 Product background, mode of action and mechanism of protraction

Summary

- Insulin icodec is intended for the treatment of adults with type 2 and type 1 diabetes mellitus
- Insulin icodec was engineered to:
  - retain the same, well-established biological/metabolic effects of human insulin
  - have a very strong but reversible binding to albumin leading to the formation of an inactive depot, from which insulin icodec is slowly and continuously released
  - be more stable and have a low affinity for the insulin receptor, leading to reduced clearance and an extended half-life
- Insulin icodec was designed to simplify insulin therapy, leading to improved initiation and adherence

Insulin icodec is a novel long-acting human insulin analogue, designed to retain the same well-established biological/metabolic effects as human insulin while extending the half-life to cover the basal insulin requirements for a full week with a once-weekly subcutaneous (s.c.) injection.[79]

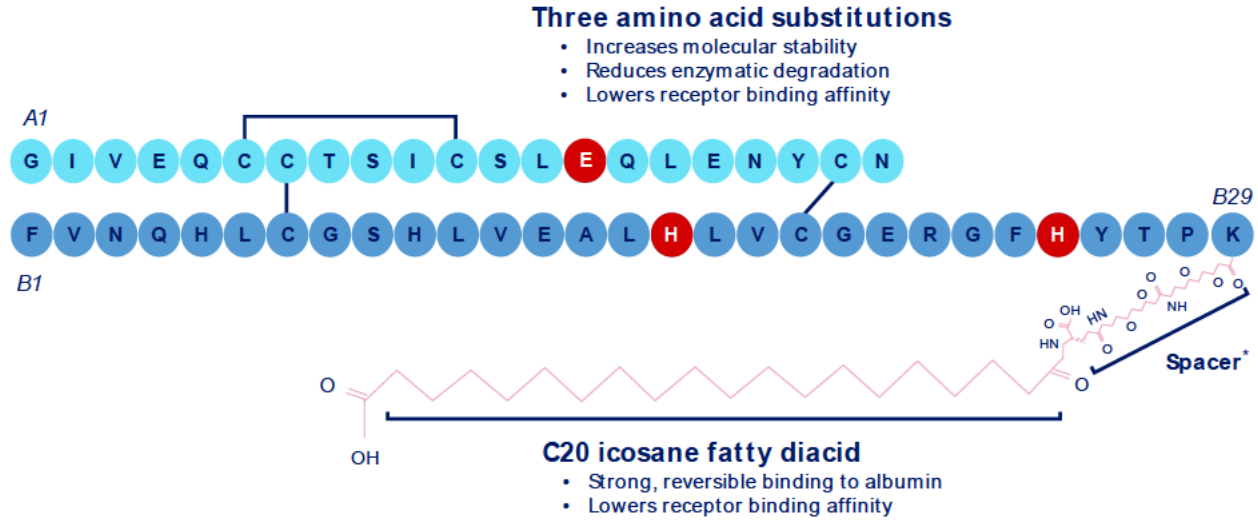
The proposed indication of insulin icodec is to achieve glycemic control in adults with T2D or T1D with once weekly injection of basal insulin.

The molecule consists of a modified human insulin backbone and a fatty acid-containing sidechain (see Figure 4-1). Insulin icodec was engineered not only to have a very long half-life, but also to ensure that there is effective glucose-lowering throughout the week. These characteristics were achieved by designing an insulin with high affinity to albumin, improved stability, low binding affinity to the insulin receptor, and high solubility.[79] The addition of the C20 fatty-diacid-containing sidechain imparts a strong but reversible binding to albumin which leads to the formation of a depot of essentially inactive insulin icodec in the interstitial compartment and throughout the circulation. From these sites, insulin icodec is slowly and continuously released as unbound insulin icodec, free to activate insulin receptors and subsequently cleared. In addition, three amino acid substitutions (shown in red in Figure 4-1) in the peptide backbone provide molecular stability and contribute to attenuating insulin receptor binding. As insulin is primarily cleared by internalization only after binding and activating its receptors, a reduction in the insulin receptor binding affinity does not give rise to a reduced metabolic effect since every molecule dosed will eventually activate the receptor, triggering a response before being cleared. In this way, insulin icodec, with its very low insulin receptor binding affinity has the same glucose lowering potency as native human insulin, but the effect occurs over a much longer time period, due to insulin icodec's slow clearance. Overall, the slow and steady glucose-lowering effect of insulin icodec is driven by reversible albumin binding, increased molecular stability as well as reduced insulin receptor binding and receptor-mediated clearance from the circulating insulin icodec depot. Despite the introduction of these modifications that confer insulin icodec with a very long half-life, it has been demonstrated that icodec maintains the same biological and metabolic actions as human insulin.[79]

The molecular modifications described also lead to increased solubility. This allows for a 7-fold more concentrated formulation of insulin icodec (U700).[80,80] The net result is a per dose injection volume that is the same as for once-daily basal insulins.

The insulin icodec 700 U/mL formulation, which contains 4200 nmol/mL of insulin icodec, has been used for all clinical trials and is intended for the market.

Figure 4-1 Molecular structure of insulin icodec



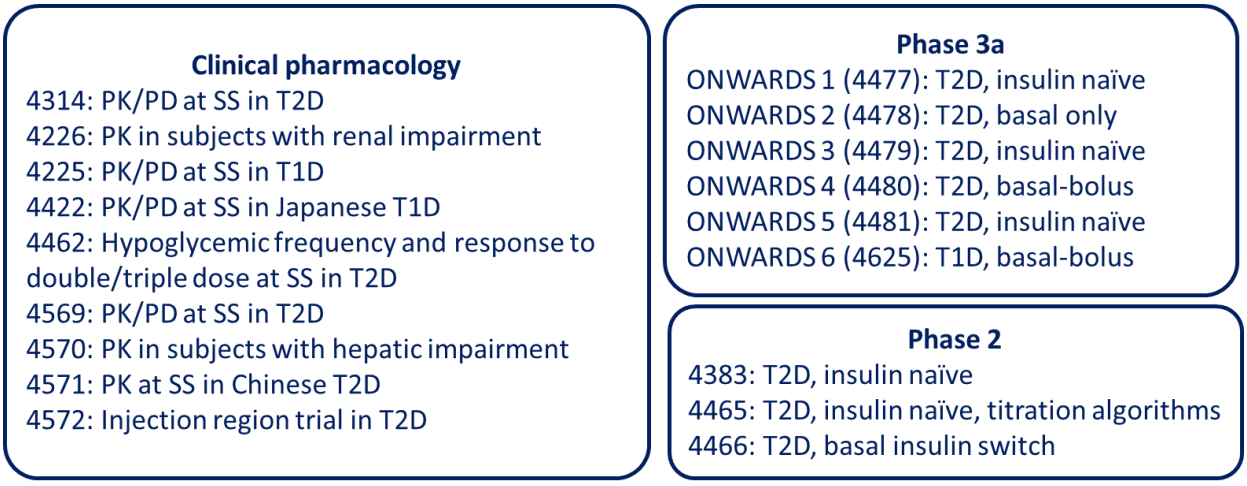
Note: The human insulin molecule is shown in light blue (A-chain) and dark blue (insulin B-chain), with the 3 amino acids substituted in insulin icodec shown in red. The spacer and fatty diacid side chain are attached to the lysine (B29) on the C-terminus of the insulin B-chain (B1).

5 Overview of clinical development program

The development program supporting the efficacy and safety of insulin icodec consisted of a total of 18 clinical trials in T1D and T2D populations. the insulin icodec clinical development program is summarized in Figure 5-1 and includes:

- 9 clinical pharmacology trials
- 3 phase 2 exploratory trials
- 6 phase 3 confirmatory efficacy and safety trials

Figure 5-1 Overview of insulin icodec clinical development



Clinical pharmacology trials are summarized in Section 6.

Phase 3a trials were referred to as ONWARDS and represent the main source of data for the evaluation of insulin icodec efficacy and safety in T1D and T2D populations. The ONWARDS development program was designed to evaluate insulin icodec for the treatment of adult patients with diabetes mellitus. Details of ONWARDS trial design are provided in Section 8.

6 Clinical pharmacology

Summary

- Steady state for insulin icodec was reached after 2-4 weeks of once-weekly administration
- The terminal half-life of insulin icodec at steady state was approximately 1 week
- Total exposure and maximum concentration of insulin icodec increased proportionally with increasing dose within the therapeutic dose range
- The within-subject variability in insulin icodec exposure from week to week at steady state was found to be low (CV% for total exposure: 5.9%)
- The duration of glucose-lowering effect of insulin icodec covered the one-week dosing interval both in T2D and T1D
  - The glucose-lowering effect was greatest on Days 2-4 after administration
  - As expected, the differences in glucose-lowering effect between separate days were larger in T1D than in T2D
- Total exposure of insulin icodec was comparable across age, sex, race and ethnicity, anti-insulin icodec antibodies, albumin level and diabetes population (T2D vs T1D)
- As expected, total exposure of insulin icodec decreased with increasing body weight
- The pharmacokinetic properties of insulin icodec were not affected to any clinically meaningful extent by renal or hepatic impairment
- Double or triple doses of insulin icodec were shown not to lead to an increased risk of hypoglycemia compared to double or triple doses of insulin glargine, and the management of the recovery from hypoglycemia induced by double or triple doses was shown to be similar between treatments

The clinical pharmacology program consisted of a total of 9 dedicated trials providing a detailed evaluation of the pharmacokinetic and pharmacodynamic properties of insulin icodec in people with T2D and T1D. In addition, one exploratory phase 2 trial (Trial 4383) and four confirmatory phase 3 trials (ONWARDS 2, 3, 4 and 6) were included in a population pharmacokinetic analysis to evaluate the effect of intrinsic factors on the pharmacokinetic properties of insulin icodec. All trials used the same formulation of insulin icodec and were conducted in accordance with ICH Good Clinical Practice.[81]

6.1 Methodology

The concentration of insulin icodec in serum was analyzed using a validated immunoassay. Insulin icodec binds reversibly to serum albumin and the assay measures the total amount of insulin icodec (both albumin-bound and free).

The glucose-lowering effect of insulin icodec was evaluated in multiple-dose trials where participants received optimized, individualized and clinically relevant doses of insulin icodec. The glucose-lowering effect was assessed using euglycemic clamps. Since it would be too burdensome for the participants if the dosing interval of one week for insulin icodec was covered fully with glucose clamps, partial glucose clamps were conducted and the full weekly pharmacodynamic

effect was assessed using pharmacokinetic-pharmacodynamic modelling based on the observed pharmacokinetic data and clamp data.

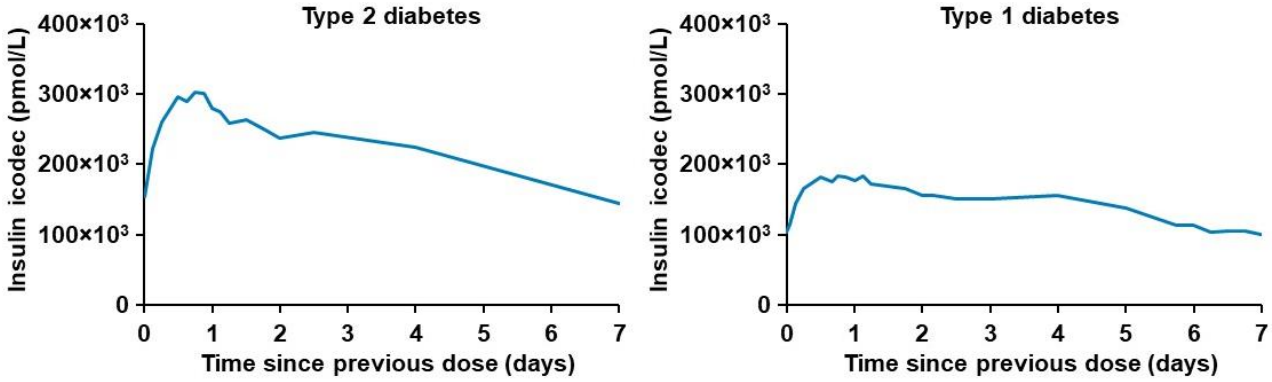
The pharmacokinetic and pharmacodynamic properties of insulin icodec were investigated in relevant populations including participants with T2D or T1D, and both men and women were included in all the trials. Standardized inclusion and exclusion criteria were applied to facilitate comparisons across trials. As people with diabetes often suffer from renal and/or hepatic impairment,[82, 83] two trials were designed to include participants without diabetes and with various degrees of renal or hepatic impairment. The control groups in these trials were healthy participants.

6.2 Pharmacokinetic properties

6.2.1 Absorption and dose-concentration relationship

The steady-state concentration-time profiles for insulin icodec showed that insulin icodec exposure covered the one-week dosing interval both in participants with T2D and T1D (Figure 6-1). The median time to maximum concentration was comparable across all clinical pharmacology trials and was generally between 15 and 18 hours after dosing at steady state.

Figure 6-1 T2D and T1D – Mean insulin icodec concentration-time profiles across one week at steady state



Abbreviations: N = number of individuals; T1D = type 1 diabetes; T2D = type 2 diabetes; U = units

Notes: T2D (Trial 4569): One-week pharmacokinetic profile at steady state after minimum 8 weeks of insulin icodec treatment at an individualized dose (1.5–5.64 U/kg body weight) (N=42). T1D (Trial 4225): One-week pharmacokinetic profile at steady state after 8 weeks of insulin icodec treatment at an individualized dose (1.09–3.33 U/kg body weight) (N=65).

The total exposure and maximum concentration of insulin icodec increased proportionally with increasing dose both in T2D and T1D.

6.2.2 Distribution and elimination

The fatty acid moiety of insulin icodec allows it to bind strongly but reversibly to albumin in the bloodstream corresponding to a plasma protein binding of >99%. As a result, distribution of insulin icodec is likely limited to tissues where albumin distributes, i.e. the vascular and extravascular space. Volume of distribution (V_d) for insulin icodec is small and around V_d for albumin (0.1 L/kg).

As for all other insulin products, elimination of insulin icodec is primarily mediated by the insulin receptor with non-specific degradation as a minor pathway. The initial peptide cleavage of insulin

icodec is the same as seen for human insulin. Results in participants with and without renal impairment demonstrated negligible renal clearance of intact insulin icodec.

6.2.3 Terminal half-life

The terminal half-life of insulin icodec at steady state was approximately 1 week, independent of dose, supporting once-weekly dosing in both T2D and T1D populations.

6.2.4 Time to steady state

Based on Trial 4569 in participants with T2D, clinical steady state – defined as 90% of the final plateau exposure level [84] – was reached after 3-4 weeks when the administered insulin icodec starting dose was equal to 7 times the daily basal insulin dose prior to the trial, i.e. when initiating insulin icodec without a one-time additional dose. When adding a one-time additional dose of 50% with the first insulin icodec dose (i.e. when the first dose of insulin icodec was 10.5 times the usual daily basal insulin dose), the time to steady state was shortened to 2-3 weeks.

Based on Trial 4225 in participants with T1D, clinical steady state was reached after 2-3 weeks without a one-time additional dose, and 1 week faster when adding a one-time additional dose of 50% with the first insulin icodec dose.

For details about the starting dose, please refer to Section 7.

6.2.5 Within-individual variability

Within-individual variability in insulin icodec exposure from week to week was evaluated in Trial 4569 in individuals with T2D based on observed serum icodec concentrations during three consecutive weeks at steady state. The within-individual variability in total exposure and maximum concentration at steady state (measured as CV%) was found to be low (5.9% and 8.3%, respectively).

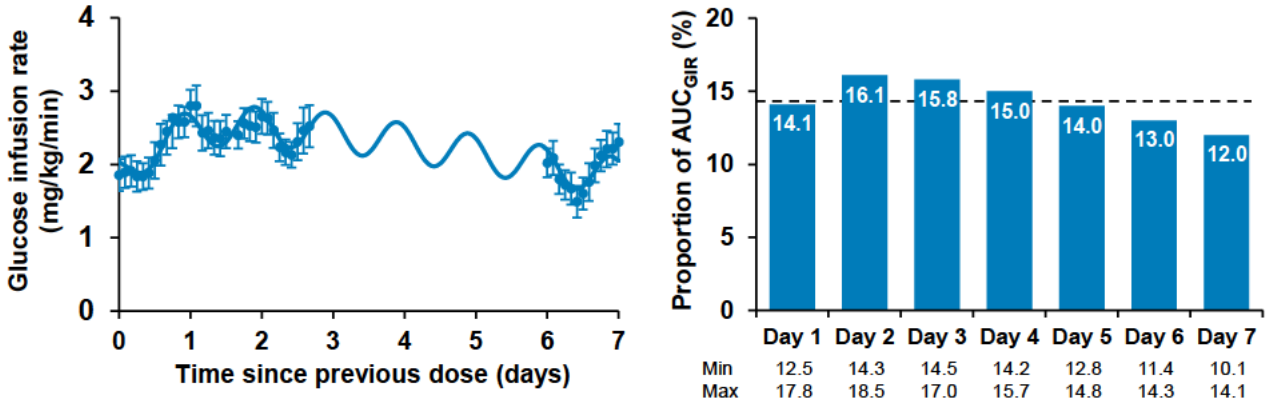
6.3 Pharmacodynamic properties

Part of the protraction of insulin icodec occurs at the insulin receptor level (Section 4). The action of insulin icodec may therefore be better reflected by its pharmacodynamic rather than by its pharmacokinetic properties. This is particularly so in situations of increased or decreased insulin icodec absorption, where the depot of albumin-bound insulin icodec can serve as a buffer.

6.3.1 Glucose-lowering effect at steady state in individuals with T2D

At steady state, the glucose-lowering effect of insulin icodec in individuals with T2D was close to evenly distributed across the one-week dosing interval, and the duration of glucose-lowering effect covered one week at clinically relevant doses (Figure 6-2). The mean daily proportions of glucose-lowering effect during the one-week dosing interval ranged from 12.0% (on Day 7) to 16.1% (on Day 2) of the total weekly effect (Figure 6-2).

Figure 6-2 T2D – Glucose-lowering effect profile and distribution of model-predicted glucose-lowering effect across one week at steady state



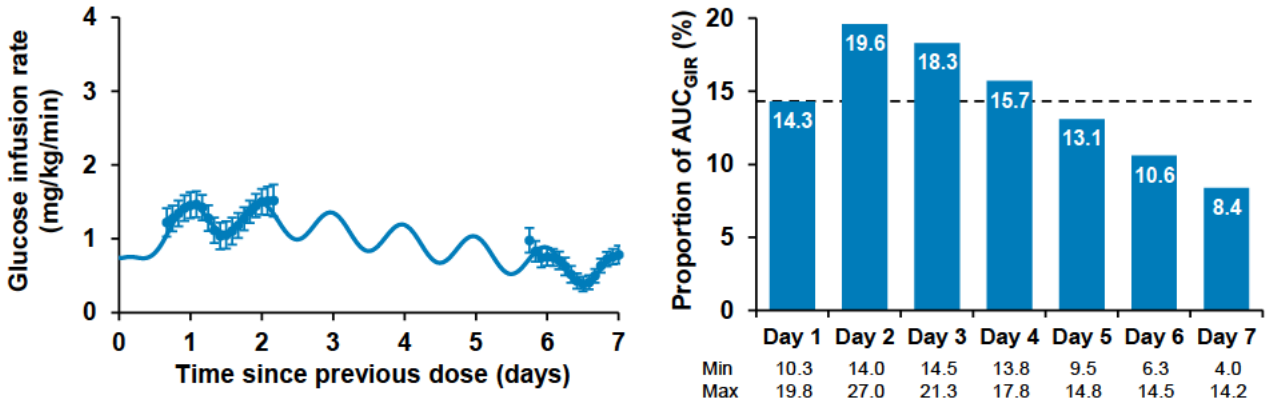
Abbreviations: AUC = area under the curve; GIR = glucose infusion rate; Max = maximum; Min = minimum; N = number of individuals; U = units

Notes: Left: Observed and model-predicted glucose-lowering effect at steady state after minimum 6 weeks of insulin icodec treatment at an individualized dose (1.53-5.64 U/kg body weight) (Trial 4569; N=42). Dots show observed clamp data with standard error of the mean from glucose clamps during three consecutive weeks, respectively (0-36 hours, 40-64 hours and 144-168 hours after dosing). Continuous line shows model-predicted data.
Right: Distribution of model-predicted glucose-lowering effect across one week at steady state. Dotted line shows equal distribution of glucose-lowering effect per day across the week. Numbers on and below each bar show the mean and range.

6.3.2 Glucose-lowering effect at steady state in individuals with T1D

The glucose-lowering effect profile of insulin icodec in individuals with T1D across the one-week dosing interval at steady state is shown in Figure 6-3. The duration of glucose-lowering effect covered one week at clinically relevant doses. The mean daily proportions of glucose-lowering effect during the one-week dosing interval ranged from 8.4% (on Day 7) to 19.6% (on Day 2) of the total weekly effect, and the greatest glucose-lowering effect was observed on Days 2-4 (Figure 6-3). Thus, the differences in glucose-lowering effect between separate days were larger in T1D than observed for T2D. The same has previously been shown over the daily dosing interval for daily basal insulin products[83, 85, 86] and is considered to originate mainly from the greater insulin sensitivity in T1D versus T2D and the residual beta-cell function in T2D.

Figure 6-3 T1D – Glucose-lowering effect profile and distribution of model-predicted glucose-lowering effect across one week at steady state



Abbreviations: AUC = area under the curve; GIR = glucose infusion rate; Max = maximum; Min = minimum; N = number of individuals; U = units

Notes: Left: Observed and model-predicted glucose-lowering effect at steady state after 8 weeks of insulin icodec treatment at an individualized dose (1.21-3.33 U/kg body weight) (Trial 4225; N=49). Dots show observed clamp data with standard error of the mean from glucose clamps 16-52 hours and 138-168 hours after the last dose. Continuous line shows model-predicted data. Right: Distribution of model-predicted glucose-lowering effect across one week at steady state. Dashed dotted line shows equal distribution of glucose-lowering effect per day across the week. Numbers on and below each bar show the mean and range.

6.3.3 Molar dose ratio

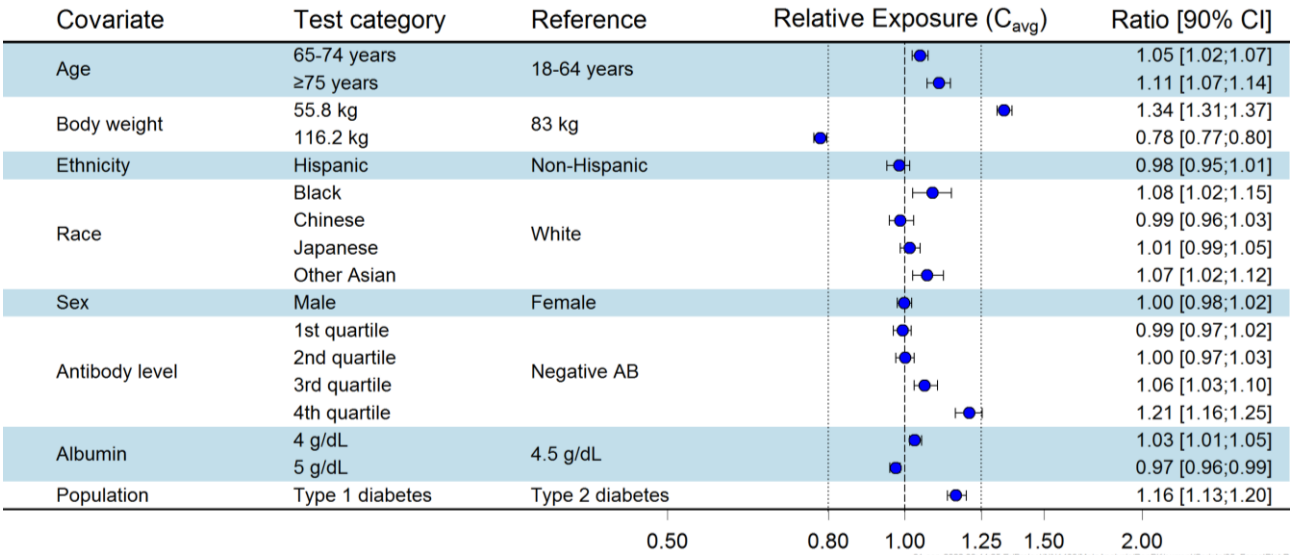
The molar dose ratio for insulin icodec was estimated versus once-daily insulin degludec in individuals with T2D in Trial 4314 and versus once-daily insulin glargine U100 in individuals with T1D in Trial 4225. For insulin icodec, the full one-week glucose-lowering effect was derived by pharmacokinetic-pharmacodynamic modelling based on the observed pharmacokinetic data and partial glucose-lowering effect assessed in glucose clamps. For once-daily insulin, the 24-hour glucose-lowering effect was fully assessed in a glucose clamp. The molar dose ratio was calculated based on the one-week glucose-lowering effect for each insulin assuming that identical molar doses were administered per week.

In T2D, the estimated molar dose ratio for insulin icodec versus insulin degludec was 1.03, 95% CI: [0.74; 1.44]. In T1D, the estimated molar dose ratio for insulin icodec versus insulin glargine U100 was 1.19, 95% CI: [1.00; 1.43]. Thus, insulin icodec is considered equipotent to insulin degludec and insulin glargine U100 (i.e. 1 U of insulin icodec can be compared to 1 U of daily basal insulin), and by extrapolation also to insulin detemir and NPH insulin.

6.4 Intrinsic factors

Overall, the population pharmacokinetic analysis based on phase 2 Trial 4383 and phase 3 trials ONWARDS 2, 3, 4 and 6 showed that insulin icodec exposure was comparable across age, sex, race (White, Black, Japanese, Chinese, Other Asian), ethnicity, anti-insulin icodec antibody level, albumin level, and diabetes population (T2D versus T1D) (Figure 6-4). Insulin icodec exposure decreased with increasing body weight, an effect that was expected because clearance and volume of distribution generally scale with body size. Note that as insulin icodec dose is individually titrated, small differences in exposure are unlikely to be clinically relevant.

Figure 6-4 Forest plot of covariates included in the population pharmacokinetic analysis and their effect on dose-normalized insulin icodec exposure at steady state



Abbreviations: C_{avg} = dose-normalized average exposure; CI = confidence interval; N = number of individuals

Notes: The population pharmacokinetic analysis included phase 2 Trial 4383 and phase 3 trials ONWARDS 2, 3, 4 and 6 (N=1244). Each covariate is presented with test categories compared to a reference category. Body weight and albumin test categories represent the 5th and 95th percentiles in the data. The exposure ratio for each test category relative to the reference category is plotted as blue dots with 90% CI (and also listed to the right). Vertical lines corresponding to equal exposure (dashed line) and the typical pharmacokinetic equivalence interval from 0.8 to 1.25 (dotted lines) are included for comparison.

A large fraction of insulin icodec in the circulation is present as an essentially inactive form bound to albumin. In the circulation on average, albumin is roughly 2000 times more abundant than insulin icodec, which occupies less than 0.05% of the total albumin pool. Thus, it is unlikely that low levels of serum albumin could have an impact on insulin icodec effect or mode of action. This was confirmed in Trials 4226 and 4570, conducted to evaluate the pharmacokinetic properties of insulin icodec in participants with different degrees of renal or hepatic impairment, respectively, representing a range of serum albumin levels between 2.7 g/dL and 5.1 g/dL. There was no clinically meaningful impact of renal or hepatic impairment on the exposure of insulin icodec. Furthermore, results from both trials did not indicate any association between observed baseline albumin concentration and total exposure of insulin icodec (Appendix A, Figure 14-1).

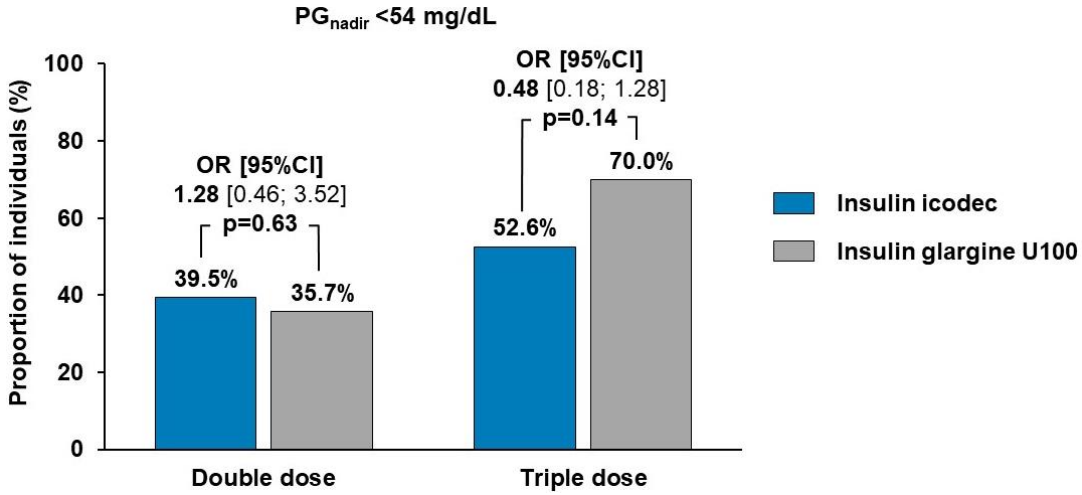
6.5 Hypoglycemia frequency and physiological response to double or triple doses of insulin icodec

Given the unique pharmacokinetic and pharmacodynamic properties of insulin icodec, attention to potential hypoglycemic risk was a focus throughout development. As part of this focus, a clinical pharmacology trial investigated the physiological response to double or triple doses of insulin icodec compared to double or triple doses of insulin glargine U100 in a controlled, clinical setting in participants with T2D. Individuals in the trial were also monitored by CGM following the intentional insulin over-exposure. Results are summarized below and have been published in detail[87].

In a crossover design, participants were treated with once-weekly insulin icodec (for 6 weeks) and once-daily insulin glargine U100 (for 11 days) at equimolar total weekly doses based on each participants' usual basal insulin dose. At steady state, double and triple doses of insulin icodec and insulin glargine U100 were administered followed by hypoglycemia induction starting at the expected time of maximum glucose-lowering effect for each insulin product. During the hypoglycemia induction experiments, plasma glucose was allowed to decrease to no less than 45 mg/dL (PG_{nadir}). Thereafter, euglycemia was restored by constant IV glucose infusion (5.5 mg/kg/min) and maintained by variable glucose infusion.

Following the double and triple insulin doses, comparable proportions of participants experienced clinically significant hypoglycemia (level 2, PG_{nadir}<54 mg/dL) during the hypoglycemia induction experiments for insulin icodec versus insulin glargine U100 (Figure 6-5).

Figure 6-5 Proportion of individuals with T2D with clinically significant hypoglycemia after double and triple dose



Abbreviations: CI = confidence interval; N = number of individuals; OR = odds ratio; PG = plasma glucose.

Note: Trial 4462: Crossover trial in individuals with T2D receiving double and triple doses of insulin icodec and insulin glargine U100 during insulin icodec treatment (for 6 weeks) and insulin glargine U100 treatment (for 11 days) at equimolar total weekly doses based on each participants' usual basal insulin dose. Double dose: N=43 for insulin icodec and N=42 for insulin glargine U100; Triple dose: N=38 for insulin icodec and N=40 for insulin glargine U100.

Full recovery from level 2 hypoglycemia (<54 mg/dL) to a plasma glucose level of 100 mg/dL was achieved within 30 minutes for both insulin icodec and insulin glargine U100 when a constant IV glucose infusion of 5.5 mg/kg/min was applied. The amount of glucose needed to restore and maintain euglycemia was similar for insulin icodec and insulin glargine U100 (Appendix A, Figure 14-2).

Overall, these data suggest that a double or triple dose of insulin icodec did not lead to an increased risk of hypoglycemia compared to a double or triple dose of insulin glargine U100, and that the management of the immediate recovery from hypoglycemia was similar between treatments.

CGM data showed that mean percentage time spent below range from the end of the hypoglycemia induction until 14 days after the double insulin icodec dose and until 7 days after the triple insulin icodec dose was well below the consensus guidance clinical targets for CGM data.[28] Importantly, for participants who experienced a clinically significant (level 2) hypoglycemic episode during the

hypoglycemia induction experiment, the percentage of time spent below range was within the recommended threshold. As the next dose of insulin after the double or triple dose was skipped in this trial, it reflects the clinical situation when administration of a higher-than-normal dose is discovered and mitigated prior to the next planned dose. Importantly, no severe (level 3) hypoglycemic episodes were observed for either of the two treatments.

Based on this trial, the physiological response to hypoglycemia induced by insulin icodec was considered appropriate. Concentrations of the counterregulatory hormones adrenaline, noradrenaline, glucagon, cortisol, and growth hormone increased during hypoglycemia induction for both insulin icodec and insulin glargine U100 following double and triple doses. During hypoglycemia induced by double or triple insulin doses, comparable symptomatic and moderately greater endocrine responses were elicited by insulin icodec versus insulin glargine U100. No differences in subjective clinical responses to the hypoglycemia were noted between treatments.

7 Starting dose and titration

Summary

- The dosing algorithm used in ONWARDS trials was based on insulin icodec's long half-life, PK data and PD modelling
- Insulin naïve participants with T2D received a 70 U starting dose, allowing a rapid achievement of glycemic targets (similar to the 10 U starting dose used with daily basal insulin)
- Participants with T1D or T2D on daily basal insulin received a higher single starting dose, allowing a smooth transition to insulin icodec and a rapid achievement of glycemic targets
- Insulin icodec was titrated once weekly based on SMBG measurements, allowing a sustained glycemic improvement, designed to minimize the risk of hypoglycemia
- The investigator could overrule the titration algorithm based on relevant clinical information

The dosing and titration of insulin icodec used in the ONWARDS trials are described in this section.

The starting dose and the titration of insulin icodec were based on the results from the clinical pharmacology trials and PD modelling. In addition, two phase 2 clinical trials in T2D population were conducted to define the starting dose and the final titration algorithm, based on safety and efficacy outcomes.

Starting dose in insulin naïve participants

For insulin naïve participants with T2D, the starting weekly dose of insulin icodec was 70 U, which corresponds to the recommended starting dose when initiating a marketed daily basal insulin (insulin glargine U100 or insulin degludec), multiplied by 7. As is common for other marketed insulins the same starting dose is recommended for all naïve participants with T2D, regardless of their baseline characteristics.

Starting dose in participants prior on basal insulin

For all participants with T1D or T2D previously on daily basal insulin (basal only or basal-bolus), transition to insulin icodec dose began with a single starting dose that was higher than their daily basal insulin dose prior trial multiplied by 7, in order to avoid a glycemic slip during the first week of treatment. The dose initiation algorithm is summarized in Table 7-1.

Table 7-1 Dose initiation algorithm

	1st dose	2nd dose
T2D		
Insulin naïve	70 U	(follow titration algorithm)
Basal only	1.5 x daily basal x 7	Daily basal x 7
Basal-bolus		
T1D		
HbA_{1c} <8%	1.5 x daily basal x 7	Daily basal x 7
Insulin glargine U300		
Twice daily basal insulin		
HbA_{1c} ≥8%	2 x daily basal x 7	Daily basal x 7

Abbreviations: HbA_{1c} = glycosylated hemoglobin; T1D = type 1 diabetes; T2D = type 2 diabetes; U = units

In all cases with a higher single starting dose, it was received one time only and as a single injection.

It is important to note that, due to insulin icodec's molecular properties, the higher first dose did not lead to an increased risk of hypoglycemia. This is shown by the fact that across all trials hypoglycemia rates in the insulin icodec arm are not higher during the first month of treatment compared to subsequent months (Figure 10-11) for participants with T1D, not shown for participants with T2D). This was expected since the vast majority of the injected insulin icodec becomes bound to albumin forming an inactive depot, as described in Section 4.

Titration

The subsequent doses (second dose for insulin naïve participants and third dose for participants previously on basal insulin) were calculated based on the self-monitored blood glucose (SMBG). Titration followed a "treat-to-target" approach with the aim of maintaining fasting glucose levels between 80 and 130 mg/dL. The doses of insulin icodec were adjusted once weekly by the investigator in connection with the scheduled visit or phone contacts.

In the clinical trials, the dose adjustment was based on the three pre-breakfast SMBG values measured on the day of titration and on the two preceding days. For both insulin icodec and daily basal insulins used as comparators, the same algorithms were used by the investigators, except for ONWARDS 5 for which insulin icodec dose recommendations were integrated into a dose guidance application (DoseGuide System). Insulin icodec was adjusted by increments of +/- 20 units, while the daily basal insulin by increments of +/- 3 units.

For participants with T2D, the following algorithm was applied:

- if the lowest of the three SMBG values was below 80 mg/dL insulin would be down-titrated, regardless of the mean value.
- if all three SMBG values were above 80 mg/dL, the mean of all three measurement was calculated:
    - if the mean was between 80 and 130 mg/dL, no dose adjustment would be required,
    - if above 130 mg/dL insulin would be up-titrated.

For participants with T1D, the algorithm was based on the lowest SMBG value only, regardless of the mean. If the lowest of the three SMBG values was below 80 mg/dL insulin would be down-titrated, if between 80 and 130 mg/dL no dose adjustment would be required, and if above 130 mg/dL insulin would be up-titrated.

In the ONWARDS trials, for both populations the titration guideline in the protocol emphasized that information such as symptoms of hypoglycemia, hyperglycemia, previous response to dose adjustments, additional glucose measurements and other indicators of the patient's level of glycemic control, were to be taken into consideration when decisions on dosing were made. Thus, the investigator could overrule the titration algorithm based on relevant clinical situations. This is in line with normal clinical practice and aligned with the recommendation to individualize treatment with insulin.[88]

8 Overview of phase 3 program

Summary

- The icodec clinical program was global and included participants from all major regions of the world in order to represent participants across various race and ethnic groups
  - The primary objective for all ONWARDS trials was to demonstrate the effect of glycemic control of once-weekly insulin icodec in both T2D and T1D patient populations
- In all ONWARDS trials, the primary endpoint was the change in HbA_{1c} from baseline to the planned end of trial.
- All phase 3 (ONWARDS) trials were randomized, parallel-group, multicenter, multinational trials comparing the efficacy and safety of insulin icodec versus an active control, and included:
  - People living with T2D:
    - ONWARDS 1 (insulin naïve)
    - ONWARDS 2 (prior basal only)
    - ONWARDS 3 (insulin naïve; double blind)
    - ONWARDS 4 (prior basal - bolus)
    - ONWARDS 5 (insulin naïve)
  - People living with T1D
    - ONWARDS 6 (prior basal - bolus)
  - ONWARDS 5 had pragmatic elements implemented into the study design that were less restrictive as compared to the other trials
  - In all ONWARDS trials, the secondary objective was to evaluate parameters of safety with once weekly insulin icodec versus a daily basal insulin

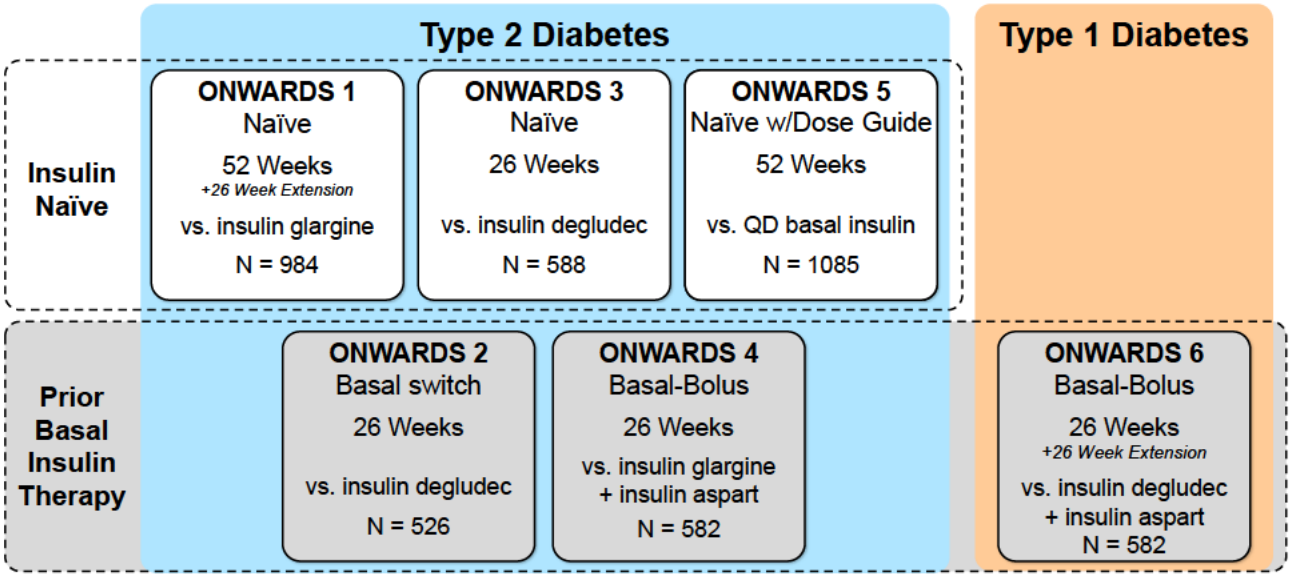
The six phase 3 trials, which were referred to as ONWARDS trials and numbered from 1 to 6, provided the primary evidence for evaluating the efficacy and safety of insulin icodec, as they investigated insulin icodec in the intended target population and contribute to the majority of the total exposure to insulin icodec.

Results from each clinical trial in the ONWARDS program have been published.[12,13,14,15,16,17]

The populations studied comprised participants with T2D insulin-naïve, on a basal only insulin regimen, and participants with T2D and T1D on a basal-bolus insulin regimen prior to trial.

Key trial design characteristics of the ONWARDS trials main features are given in Figure 8-1.

Figure 8-1 Key features of ONWARDS trials



Note: QD basal insulins in ONWARDS 5 included insulin degludec and insulin glargine (U100 or U300).

Abbreviation: QD=quaque die; in ONWARDS 5 participants in the comparator arms were assigned to different daily basal insulins (insulin glargine U100, insulin glargine U300 or insulin degludec), at the discretion of the investigator.

All ONWARDS trials were randomized 1:1, parallel-arm, multicenter and multinational trials comparing the efficacy and safety of insulin icodec versus an active control. Insulin glargine (U100 or U300) and insulin degludec represent the standard of care treatment options for individuals with diabetes.

The ONWARDS trials had a duration spanning from 26 weeks to 78 weeks. ONWARDS 1 and ONWARDS 6 trials had a main phase (of 52 weeks and 26 weeks, respectively) and an extension phase (of 26 weeks in each trial) to evaluate long-term safety, leading to a total duration of 78 weeks for ONWARDS 1 (T2D, insulin naïve) and 52 weeks for ONWARDS 6 (T1D). The ONWARDS 1 and ONWARDS 6 results presented in this document are based primarily on data from main phase, as this was where the primary objective was evaluated. In addition, extension data are presented for the most relevant efficacy assessments, safety assessment and hypoglycemia.

Safety evaluation, including general safety and hypoglycemia, included a follow-up period of 5 weeks after last dosing interval (except for ONWARDS 1 and ONWARDS 6 when presented at the end of main phase). Efficacy endpoints were evaluated at the end of the last dosing interval (one week after last administration for insulin icodec and last day of daily basal insulin administration).

After the end of treatment, participants were transferred to a marketed product at the discretion of the investigator.

As in the standard design of clinical trial for insulins, all ONWARDS trials were open label except ONWARDS 3 which incorporated a double-dummy, double-blind design. The rationale for having open label insulin icodec clinical trials was based on keeping the burden for the participants as low as possible, given the high number of injections required in a double-blind, double-dummy trial. Importantly, the efficacy and safety profiles of insulin icodec from ONWARDS 3 were consistent

with the results obtained in the other ONWARDS trials, suggesting that the open-label approach did not affect the outcomes.

8.1 Eligibility criteria

The eligibility criteria for the trials were set to ensure that the enrolled participants represented the intended target population for insulin icodec.

Both male and female participants were enrolled to obtain information on efficacy and safety of insulin icodec treatment in both sexes, and there was no upper age limit, so that efficacy and safety in elderly participants could be evaluated.

The exclusion criteria precluded enrolment of participants with concomitant conditions which could jeopardize the safety of the participants or compliance with the protocol. This was to safeguard participants, and to avoid compromising trial validity and confounding of trial results.

Most inclusion and exclusion criteria were common for ONWARDS 1-4 and 6, while a more minimal set applied to ONWARDS 5 allowing for a broader T2D population. Inclusion and exclusion criteria are presented in Table 8-1 and Table 8-2.

Table 8-1 Inclusion criteria

	T2D					T1D
	OW1	OW2	OW3	OW4	OW5	OW6
General						
Informed consent obtained before any trial-related activities	X	X	X	X	X	X
Male or female of at least 18 years of age[a]	X	X	X	X	X	X
HbA_{1c} limits						
7.0–10.0% (53–85.8 mmol/mol)		X		X		
7.0–11.0% (53−96.7 mmol/mol)	X		X			
Above 7.0% (53 mmol/mol)					X	
Below 10% (85.8 mmol/mol)						X
Diabetes history at screening						
Diagnosed with T1D ≥ 1 year						X
Diagnosed with T2D ≥ 180 days	X	X	X	X	X	
Intensification with insulin is indicated to achieve glycemic target (4.4-7.2 mmol/L [80-130 mg/dL]) at the discretion of the treating investigator					X	
Anti-diabetic treatment at screening						
Insulin naïve	X		X		X	
Once or twice daily basal insulin ≥ 90 days		X				
Basal[b]-bolus insulin regimen				X[c]		X[d]
Stable dose(s) for ≥ 90 days of OAD monotherapy, OAD combination therapy, or injectable GLP-1 RA	X	X[e]	X	X[e]	X	
Body mass index (BMI)						
BMI ≤ 40.0 kg/m^2	X	X	X	X		

Abbreviations: GLP-1 = glucagon like peptide-1; HbA_{1c} = glycated hemoglobin; OAD = oral anti-diabetic drug; OW = ONWARDS; RA = receptor agonist; T1D = type 1 diabetes; T2D = type 2 diabetes

Notes: [a] Japanese subjects (in ONWARDS 1, 2, 4 and 6) had to be ≥20 years at the time of signing informed consent. [b] basal insulin analogues or neutral protamine hagedorn insulin in ONWARDS 4, in ONWARDS 6 only basal insulin analogues. [c] For ≥90 days prior to screening, [d] For ≥1 year prior to screening, [e] Only for subjects on non-insulin.

anti-diabetic treatment (which they were to continue during the trial), subjects were not required to be on non-insulin anti-diabetic treatment to be in the trial.

Table 8-2 Exclusion criteria

	T2D					T1D
	OW1	OW2	OW3	OW4	OW5	OW6
Known or suspected hypersensitivity to trial product(s) or related products.	X	X	X	X	X	X
Previous participation in the trial. Participation is defined as signed informed consent.	X	X	X	X	X	X
Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice).	X	X	X	X	X	X
Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening.[a]	X	X	X	X	X	X
Any disorder, except for conditions associated with type 2 diabetes mellitus[b], which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.[c]	X	X	X	X	X	X
Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening.	X	X	X	X		X
Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening.	X	X	X	X		X
Planned coronary, carotid or peripheral artery revascularisation.	X	X	X	X		X
Renal impairment with estimated glomerular filtration rate (eGFR) value of eGFR < 30 ml/min/1.73m^2 at screening by central laboratory analysis.	X	X	X	X		X
Impaired liver function, defined as alanine aminotransferase (ALT) ≥ 2.5 times or bilirubin >1.5 times upper normal limit at screening by central laboratory analysis.	X	X	X	X		X
Inadequately treated blood pressure defined as systolic ≥180 mmHg or diastolic ≥110 mmHg at screening.	X	X	X	X		X
Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days prior to the day of screening.	X	X	X	X		X
Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids).	X	X	X	X		X
Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening or in the period between screening and randomization. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.	X	X	X	X		X
Presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, in-situ carcinomas of the cervix, or in situ prostate cancer) within 5 years prior to the day of screening.	X	X	X	X		X

	T2D					T1D
	OW1	OW2	OW3	OW4	OW5	OW6
Any episodes of diabetic ketoacidosis according to medical records within 90 days prior to screening	X	X	X	X		
Anticipated change in lifestyle affecting glucose control	X	X	X	X		
Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question		X		X		X
Recurrent severe hypoglycemic episodes within the last year as judged by the investigator		X		X		X

Abbreviations: eGFR = estimated glomerular filtration rate; OW = ONWARDS; T1D = type 1 diabetes; T2D = type 2 diabetes

Notes: [a] Simultaneous participation in a trial with the primary objective of evaluating an approved or non-approved IMP for prevention or treatment of COVID-19 disease or postinfectious conditions was allowed if the last IMP dose was received more than 30 days before screening. [b] For ONWARDS 6: type 1 diabetes mellitus. [c] In ONWARDS 5 the criterion was: "Any disorder which in the investigator's opinion might jeopardize subject's safety".

Stratification was conducted in 2 trials:

- In ONWARDS 3, randomization was stratified by region (Asia, North America, South America, Europe) and treatment with sulfonylureas or glinides (yes/no).
- In ONWARDS 6, randomization was stratified by pre-trial basal insulin regimen (either twice daily/insulin glargine U300 or once daily) and HbA_{1c} at screening (either <8% or ≥8%).

To minimize the risk of hypoglycemia, treatment with glinides or sulfonylureas was to be discontinued (ONWARDS 1, 2 and 4) or reduced by approximately 50% (ONWARDS 3 and 5) at randomization, in line with clinical practice.

8.2 Endpoints and assessments

For trials with an extension phase (ONWARD 1 and ONWARDS 6), please note that:

- efficacy and hypoglycemia were evaluated considering main phase only, as per trial design. However, results for the main efficacy and hypoglycemia-related endpoints (change in HbA_{1c}, CGM-metrics and rate of hypoglycemia) considering the complete trial (main+extension) are also included.
- safety evaluation of all parameters, is presented for main+extension phase data, since the main purpose of extension phases was to assess safety after a longer period of insulin icodec treatment.

The primary objective of the phase 3 program was to demonstrate the effect on glycemic control of once weekly insulin icodec. The secondary objective of all ONWARDS trials was to compare the safety of insulin icodec with daily basal insulin.

8.2.1 Efficacy evaluation

In all ONWARDS trials, the primary endpoint was the change in HbA_{1c} from baseline to the landmark visit. To further evaluate glycemic control, time in range was a pre-specified confirmatory primary endpoint in ONWARDS 1.

Efficacy assessments are presented in Table 8-3 and described below.

Table 8-3 Efficacy assessments

	T2D					T1D
	Insulin naïve			Basal switch	Basal-bolus	Basal-bolus
	OW1	OW3	OW5	OW2	OW4	OW6
Primary objective – efficacy parameters						
Primary endpoint						
Change in HbA_{1c}	X	X	X	X	X	X
Confirmatory secondary endpoint						
Time spent in range (70-180 mg/dL)[a]	X					
Supportive secondary endpoints						
Change in FPG	X	X		X	X	X
CGM metrics[a]	X	X		X	X	X
Patient reported outcome			X	X		X
Mean weekly insulin dose[b]	X	X		X	X	X

Abbreviations: CGM = continuous glucose monitoring; FPG = fasting plasma glucose; HbA_{1c} = glycosylated hemoglobin; OW = ONWARDS; T1D = type 1 diabetes; T2D = type 2 diabetes

Notes: [a] in the last 4 weeks of treatment; [b] in the last 2 weeks of treatment.

Achievement of HbA_{1c} targets without hypoglycemia – prespecified analysis

According to international recommendations, a clinical meaningful target achievement is reached when HbA_{1c} is below 7.0% for T2D and T1D, and below 6.5% for some T2D, as these levels are associated with reduced risks of diabetes complications. Combining the achievement of these glycemic targets with not having experienced any clinically significant or severe hypoglycemic episodes (level 2 or level 3) enables a meaningful evaluation of the balance between HbA_{1c} reduction and risk of hypoglycemia, which is a key consideration in clinical practice. Classification of hypoglycemia is provided in Table 8-5.

CGM metrics - prespecified analyses

Key CGM measurements comprise the percentage of readings within a target glucose range (TIR), below target glucose range (TBR) and above target glucose range (TAR). The primary goal for effective and safe glucose control is to increase the TIR while reducing the TBR. The target range is defined when interstitial glucose is between 70 and 180 mg/dL. Additional targets and clinical recommendation to achieve optimal glycemic control are provided in Table 8-4.

Dexcom G6® CGM system has been used consistently across all trials.

Table 8-4 Guidance on CGM targets for assessment of glycemic control for adults with T1D or T2D

TBR		TIR		TAR	
% of readings	**Below target range**	**% of readings**	**Target range**	**% of readings**	**Above target range**
<4	<70 mg/dL	>70	70-180 mg/dL	<25	>180 mg/dL
<1	<54 mg/dL				

Abbreviation: CGM = continuous glucose monitoring; TBR = target below range; TIR = target in range; TAR = target above range; T1D = type 1 diabetes; T2D = type 2 diabetes

Note: Adapted from [24].

8.2.2 Safety evaluation

A general evaluation of safety, incorporating knowledge of the therapeutic area and interactions with the Agency, included, but were not limited to, the following assessments:

- Number and nature of adverse events
- Safety focus areas, including
  - Cardiovascular disorders
  - Injection site reactions
  - Immunogenicity

Pre-specified secondary safety endpoints for all ONWARDS trials were:

- Number of severe (level 3) hypoglycemic episodes
- Number of clinically significant (level 2) hypoglycemic episodes, confirmed by SMBG
- Number of severe (level 3) or clinically significant (level 2) hypoglycemic episodes confirmed by SMBG
- Change in body weight

In addition to the above, post-hoc analyses of hypoglycemic episodes have been performed based on CGM data. Details about how hypoglycemia was analyzed are provided below.

8.2.2.1 Analysis of hypoglycemia

Hypoglycemia is a known risk associated with all insulins. Hypoglycemic episodes have been carefully analyzed as part of the overall safety evaluation in the insulin icodec development program.

Hypoglycemia data are reported as the percentage of participants who experienced one or more episodes, as well as the event rate which reflects the total number of episodes per exposure time. Thus, the event rate reflects the total hypoglycemia event burden. However, the overall event rate may not be reflective of the experience of individual participants, as some individuals experience a large number of episodes.

In the ONWARDS trials, participants were asked to measure their pre-breakfast SMBG daily and as needed (i.e. in case of symptoms of hypoglycemia), from week 0 to end of trial. Based on the

SMBG value and/or on the management of the symptoms, the hypoglycemic episode was registered as level 1, 2 or 3, according to the international guidelines (Table 8-5).

Please note that level 2 episodes (clinically significant) are defined by the level of SMBG (<54 mg/dL), regardless of the symptoms or the management for recovery. Symptoms of a level 2 hypoglycemic episode can be very broad, ranging from no symptoms to various levels of discomfort, but that do not require external assistance.

Table 8-5 Classification of hypoglycemia

Level	Glycemic criteria	Description
Hypoglycemia alert value (level 1)	<3.9 mmol/L (70 mg/dL) and ≥3.0 mmol/L (54 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycemia (level 2)	<3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

Notes: The Novo Nordisk terms are adapted from IHSG[18], ADA[19], ISPAD[20], type 1 diabetes outcomes program[21], ATTD[22]. Severe hypoglycemia as defined by Seaquist[23] and ISPAD[20].

At the discretion of the investigator, a hypoglycemic episode could also be reported as an AE. If reported as an AE, any hypoglycemic episode, irrespective of the classification, could be reported as an SAE if it fulfilled the following criteria (as for any other AE):

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/defect
- Important medical event

Please note that there is no direct correlation between a level 3 (severe) or level 2 (clinically significant) hypoglycemic episode and an SAE (serious adverse event). As a consequence, a level 3 hypoglycemic episode is not necessarily classified as an SAE, as it may not fulfil any of the above conditions.

CGM-based hypoglycemia

As a post-hoc analysis, hypoglycemia has also been evaluated using continuous glucose monitoring (CGM)-based data. CGM-based hypoglycemia detection and reporting is well established in current clinical guidelines[24] and regulatory guidance[25, 26]. The method is based on extensive data with 5-minute interval glucose values and, contrary to the self-measured blood glucose (SMBG)-based approach, is not impacted by the frequency of measuring and manual reporting by the patient, thereby giving a more objective assessment of hypoglycemia. CGM-based hypoglycemia detection has been shown to capture hypoglycemic episodes to a significantly larger extent than traditional SMBG-based hypoglycemia [24,48] and – as stated in the FDA 2023 draft guidance[26] on efficacy endpoints in diabetes clinical trials – CGM-based hypoglycemia collection has certain advantages

over SMBG-based hypoglycemia measurements. Since CGM-based hypoglycemia is independent on the participant measuring and reporting hypoglycemia, it is particularly relevant for the evaluation of nocturnal hypoglycemia. As a result of the different methodologies, the hypoglycemia rates may differ between CGM-based and SMBG-based hypoglycemia reporting.

CGM-based hypoglycemic episodes are defined as an interstitial glucose (IG) <70 mg/dL for at least 15 consecutive minutes and are considered resolved when IG has been ≥70 mg/dL for at least 15 consecutive minutes.[22,24] Mirroring the parameters defining hypoglycemic level based on SMBG, CGM-based hypoglycemic episodes are classified as follows:

- Clinically significant (level 2) hypoglycemic episode: IG <54 mg/dL for at least 15 consecutive minutes at any time during the episode
- Hypoglycemia alert value (level 1) episode: all other CGM-based hypoglycemic episodes not meeting the criterion for being a level 2 hypoglycemic episode.

It should be noted that severe (level 3) hypoglycemic episodes are defined as occurring when associated with severe cognitive impairment requiring external assistance for recovery, and not by a specific threshold of glycemia, therefore, severe (level 3) hypoglycemic episodes cannot be defined based on CGM data or SMBG data, but on symptoms and management only.

8.3 Statistical considerations

8.3.1 Statistical methods

The sample size for each clinical trial provided adequate power with respect to the primary hypothesis for the primary endpoint of testing non-inferiority for HbA_{1c}. ONWARDS 1 was also powered with respect to confirming statistical superiority of icodec in terms of Time in Range and change in HbA_{1c}.

The statistical evaluations were based on pre-specified analyses for each trial individually, using common statistical principles and analysis methods across the phase 3a program. In addition, a meta-analysis of cardiovascular safety was prospectively planned. The pre-specified primary statistical evaluation of efficacy was based on the full analysis set (FAS) adhering to the intention-to-treat principle. [24] Safety evaluations were presented descriptively based on the safety analysis set (SAS) with statistical analyses being based on the FAS.

8.3.2 Estimand

In all trials, the treatment policy estimand was assessed. As such, the estimand was defined as the treatment difference between insulin icodec and once daily basal insulin comparator of the change in HbA_{1c} from baseline to the landmark visit (week 26 for ONWARDS 2, 3, 4 and 6 or week 52 for ONWARDS 1 and 5) for all randomized participants, irrespective of adherence to randomized treatment and changes to anti-diabetic background medication. Hence, the treatment policy strategy was applied to the following intercurrent events:

- treatment discontinuation or
- initiation of bolus treatment lasting for more than 2 weeks in bolus-naïve participants (ONWARDS 1, 3, and 5).

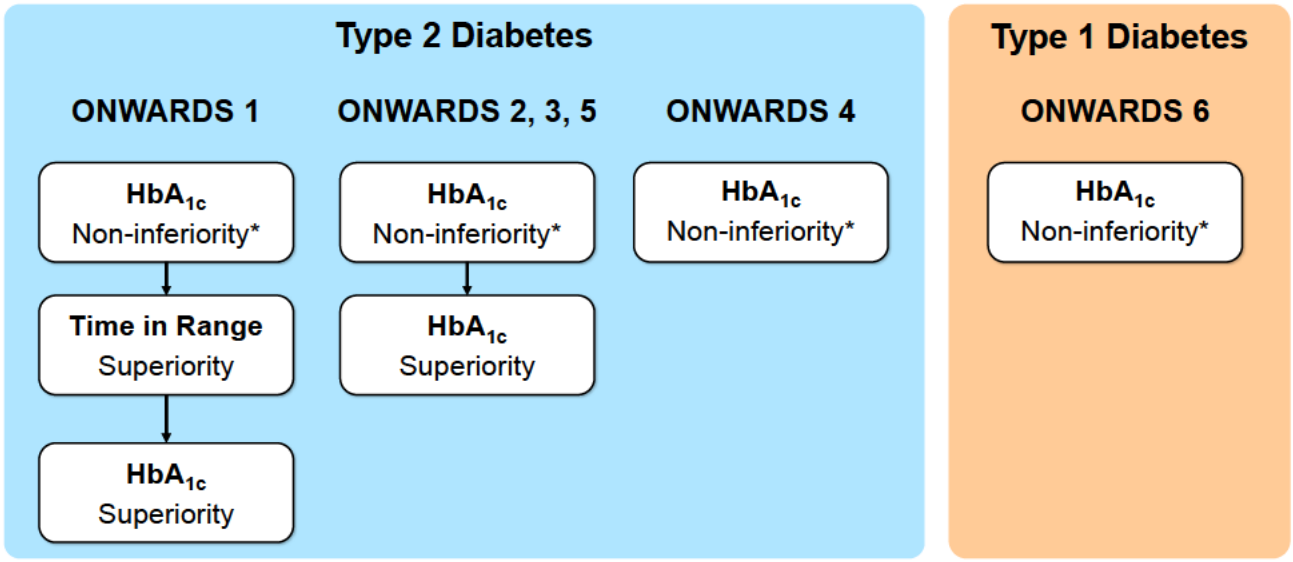
This estimand intends to give an estimation of the population-level treatment effect, i.e., an 'intention-to-treat' analysis.

8.3.3 Primary and confirmatory statistical testing strategy

The primary hypothesis was that insulin icodec was non-inferior to daily insulin comparator in terms of change from baseline to the landmark visit. The non-inferiority margin was pre-specified at 0.3%-point based on the recommendation in the US Food and Drug Administration guidance for industry on developing drugs for treatment of diabetes [89] as well as what was considered to preserve sufficient effect of the comparators effect over placebo.

In ONWARDS 1, 2, 3 and 5, additional clinically-relevant confirmatory hypotheses were tested to assess additional benefits of once weekly insulin icodec treatment. Evaluations of these confirmatory hypotheses were adjusted for multiplicity via a hierarchical testing approach. Operationally the hypotheses were evaluated by a 2-sided test with a 5% significance level. However, conclusions of non-inferiority or superiority respectively were only made in case the point estimate was in the appropriate 1-sided direction. An overview of the hierarchical confirmatory statistical testing set-up is illustrated in Figure 8-2.

Figure 8-2 Overview of hierarchical confirmatory statistical set-up



Note: * Prespecified non-inferiority margin of 0.3%

8.3.4 Missing data

Missing values for the primary endpoint, confirmatory secondary endpoints and body weight were imputed by multiple imputation from trial participants experiencing an intercurrent event and having a measurement at the landmark visit. In case the amount of data for the imputation model was insufficient for meaningful imputation, the imputation model was either simplified or replaced by a return-to-baseline imputation approach.

Missing values for other continuous assessments were imputed by a return-to-baseline multiple imputation approach if there was planned data collection at baseline. Otherwise, the imputation was

based on trial participants in the comparator arm who had completed the trial and had a measurement at the landmark visit.

Missing data for the achievement of HbA_{1c} targets were imputed by applying the threshold to the imputed HbA_{1c} values. Participants who discontinued randomized treatment prematurely had the dichotomous outcome also evaluating hypoglycemia set to 'no'.

For participants who discontinued their randomized treatment, the number of SMBG-based hypoglycemic episodes in the missing period was imputed using a multiple imputation technique assuming the event rate during the missing period followed that of the once daily insulin comparator.

Further details on missing data imputation can be found in Appendix B, Section 15.1.

8.3.5 Statistical considerations

Continuous endpoints (including the primary endpoint of change in HbA_{1c}) except time below glycemic range (TBR) were analyzed using a standard analysis of covariance (ANCOVA) including treatment, stratification factor (ONWARDS 3 and 6), personal CGM device use (y/n) (ONWARDS 2 and 4) and region as fixed effects and the baseline value of the response as covariate (where relevant). Log-transformation was applied for analyses of mean insulin dose during the last two weeks of treatment. Binary assessments were analyzed using a logistic regression model. TBR and number of hypoglycemic episodes were analyzed using a negative binomial regression model with a log-link function, and the logarithm of the observation period as offset. The observation period used as offset for TBR and CGM-based hypoglycemia was the CGM wear period. Both models included the same fixed factors as specified for the ANCOVA model. The logistic regression model also included baseline as covariate (when applicable).

Post-hoc analyses to evaluate treatment effect in subgroups were done by applying similar models as in the full study evaluation but with the addition of subgroup and treatment by subgroup interaction as fixed effects. Missing data was imputed the same way as in the full study evaluation of the respective assessments.

Data were pooled for the purpose of evaluating adverse events. To minimize the potential risk of confounding by trial (Simpson's Paradox) caused by any differences in trial population, adjustments were made for the proportion of participants with events and the event rates for the phase 3a and the T2D pool respectively by using Cochran-Mantel-Haenszel weights.[90]

While safety assessments were generally pooled across studies, certain safety parameters, like e.g. hypoglycemia, body weight and immunogenicity, are expected to be quite different between trial populations of insulin naïve, previous insulin users, T1D and T2D. Hence, by-trial evaluation has been made for these assessments.

For details on statistical considerations for other assessments see Appendix B, Section 15.

9 Clinical results in T2D

Summary

Trial population

- A total of 3765 people with T2D were randomized 1:1 in the T2D-ONWARDS trials
- In the T2D pool, more than 94% of enrolled participants completed the trial, with similar proportions in both treatment arms and across trials

Efficacy

In all T2D-ONWARDS trials, once-weekly insulin icodec met the primary endpoint, demonstrating non-inferiority to daily basal insulin for change in HbA_{1c}

To further support insulin icodec efficacy on glycemic control in participants with T2D, it was demonstrated that:

- Glucose time in range was comparable to insulin degludec
- Time course of glycemic improvement was similar to daily basal insulin
- HbA_{1c} reduction was sustained until the end of the trials (up to 52 weeks)
- Insulin icodec provided a statistically superior reduction of HbA_{1c} in insulin naïve patients and in patients with T2D previously on a daily basal insulin only (no bolus)

Hypoglycemia

In all T2D-ONWARDS trials, hypoglycemic episodes were manageable and were resolved using the same methods as daily basal insulins

- 85.9-93.9% of insulin naïve participants or those on daily basal prior to trial did not experience any severe (level 3) or clinically significant (level 2) hypoglycemic episodes
- Overall, the numbers of severe (level 3) hypoglycemic episodes were similar between treatment arms
- Clinically significant (level 2) hypoglycemia in the insulin icodec arm were reported by a few patients accounting for many episodes
- The duration of level 2 hypoglycemic episodes was similar between treatment arms

The proportion of patients in the insulin icodec arm achieving clinically meaningful HbA_{1c} targets without hypoglycemia was higher than or comparable to the daily basal insulin arm.

Conclusion

The T2D-ONWARDS program demonstrated that insulin icodec can be used safely and effectively for glycemic control by people with T2D.

9.1 Trial population in T2D

The participants enrolled in the T2D-ONWARDS program represent a global population from 33 countries. The populations in the T2D clinical trials are considered representative of the intended

T2D treatment population. Overall, a broad, diverse population of participants with varying degrees of T2D has been studied in the clinical development program.

9.1.1 Baseline and demographic characteristics

Key baseline and demographic characteristics of the participants enrolled in the insulin icodec arms in T2D trials (ONWARDS 1 to 5) are presented by trial, since they are dependent on specific trial design and can affect the efficacy results (Table 9-1 and Table 9-2).

The overall disease-related baseline characteristics of the trial populations were representative of a broad T2D population as seen in clinical practice in terms of treatment regimen, BMI, renal impairment, diabetes duration, HbA_{1c} and FPG levels. The overall demographic characteristics were also representative of typical T2D population with regards to age, race, ethnicity and country of origin.

Please note that demographic and baseline characteristics were similar between participants in the insulin icodec and daily basal insulin arms within each trial.

Table 9-1 T2D – Key demographic characteristics – by trial

	T2D (N=3765)				
	Insulin Naïve (N=2657)			Basal Switch	Basal-bolus
	ONWARDS 1	ONWARDS 3	ONWARDS 5	ONWARDS 2	ONWARDS 4
	N=984	N=588	N=1085	N=526	N=582
Sex, N (%)					
Male	558 (56.7)	369 (62.8)	622 (57.3)	302 (57.4)	304 (52.2)
Female	426 (43.3)	219 (37.2)	463 (42.7)	224 (42.6)	278 (47.8)
Age (years)					
Mean (SD)	59.0 (9.9)	58.1 (10.0)	59.3 (10.5)	62.5 (9.1)	59.8 (10.0)
Age group, N (%)					
≥18 - <65 years	665 (67.6)	411 (69.9)	722 (66.5)	294 (55.9)	373 (64.1)
≥65 - <75 years	278 (28.3)	158 (26.9)	304 (28.0)	198 (37.6)	188 (32.3)
≥65 years	319 (32.4)	177 (30.1)	363 (33.5)	232 (44.1)	209 (35.9)
≥75 years	41 (4.2)	19 (3.2)	59 (5.4)	34 (6.5)	21 (3.6)
Race, N (%)					
White	650 (66.1)	354 (60.2)	971 (89.5)	298 (56.7)	370 (63.6)
Black or African American	27 (2.7)	15 (2.6)	52 (4.8)	23 (4.4)	21 (3.6)
Asian	274 (27.8)	165 (28.1)	47 (4.3)	196 (37.3)	188 (32.3)
Other	33 (3.4)	23 (3.9)	14 (1.3)	9 (1.7)	2 (0.3)
Missing	0	31 (5.3)	1 (0.1)	0	1 (0.2)
Ethnicity, N (%)					
Not Hispanic or Latino	878 (89.2)	393 (66.8)	989 (91.2)	494 (93.9)	476 (81.8)
Hispanic or Latino	106 (10.8)	164 (27.9)	95 (8.8)	32 (6.1)	105 (18.0)
Missing	0	31 (5.3)	1 (0.1)	0	1 (0.2)
Region					
Europe	471 (47.9)	142 (24.1)	557 (51.3)	167 (31.7)	205 (35.2)
North America	220 (22.4)	149 (25.3)	528 (48.7)	1393 (26.4)	133 (22.9)
South America	41 (4.2)	152 (25.9)	0	0	66 (11.3)
Africa	0	0	0	50 (9.5)	0
Asia	252 (25.6)	145 (24.7)	0	170 (32.3)	178 (30.6)

Abbreviations: % = Percentage of participants, BMI = Body mass index; N = Number of participants; SD = standard deviation; T2D = type 2 diabetes

Notes: "Other race" includes American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander. Participants from France did not report race and ethnicity and are included in the row 'Missing'.

Table 9-2 T2D – Key baseline diabetes characteristics – by trial

	T2D (N=3765)				
	Insulin Naïve (N=2657)			Basal Switch	Basal-bolus
	ONWARDS 1	ONWARDS 3	ONWARDS 5	ONWARDS 2	ONWARDS 4
	N=984	N=588	N=1085	N=526	N=582
BMI (kg/m^2)					
Mean (SD)	30.1 (4.9)	29.6 (5.1)	32.8 (7.0)	29.3 (5.0)	30.3 (5.0)
Renal function (eGFR, mL/min/1.73m^2)					
Normal (≥90)	446 (45.3)	358 (60.9)	618 (57.0)	203 (38.6)	250 (43.0)
Mild impairment (≥60 -<90)	436 (44.3)	185 (31.5)	345 (31.8)	243 (46.2)	241 (41.4)
Moderate impairment (≥30 - <60)	101 (10.3)	44 (7.5)	113 (10.4)	80 (15.2)	91 (15.6)
Severe impairment (<30)	1 (0.1)	0	8 (0.7)	0	0
Missing	0	1 (0.2)	1 (0.1)	0	0
Duration of diabetes					
<10 years	441 (44.8)	274 (46.6)	471 (43.4)	102 (19.4)	117 (20.1)
≥10 years	543 (55.2)	314 (53.4)	614 (56.6)	424 (80.6)	465 (79.9)
HbA_{1c} (%)					
Mean (SD)	8.5 (1.0)	8.5 (1.1)	8.9 (1.6)	8.1 (0.8)	8.3 (0.9)
<8%, N	358 (36.4)	217 (36.9)	346 (31.9)	251 (47.7)	237 (40.7)
≥8%, N	626 (63.6)	371 (63.1)	738 (68.0)	275 (52.3)	345 (59.3)
FPG (mg/dL)					
Mean (SD)	185.5 (50.3)	181.4 (50.4)	N/A	151.5 (44.3)	169.8 (59.0)
History of cardiovascular disease					
Yes, N (%)	232 (23.6)	140 (23.9)	261 (24.2)	183 (34.9)	188 (32.3)
No, N (%)	752 (76.4)	447 (76.1)	819 (75.8)	342 (65.1)	394 (67.7)

Abbreviations: % = Percentage of participants; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; N = number of participants; BMI = body mass index; SD = standard deviation; T2D = type 2 diabetes

Notes: FPG was not collected in ONWARDS 5. Data from ONWARDS 1-5, only main phase of ONWARDS 1. Baseline refers to week 0 except for renal function, which was evaluated at screening. Renal function categories are based on eGFR derived using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.

Most participants in the T2D-ONWARDS trials were from Europe, Asia and North America, and most were White. In total, 174 participants ≥75 years were included in the T2D-ONWARDS trials. The percentage of participants from North America was between 24% and 51% across trials, with a good representation across race and ethnicity that aligns with US demographics, including 138 (3.7%) Black or African American participants.

Trial populations across ONWARDS 1 to 5 included people with T2D in need of insulin initiation (ONWARDS 1, 3 and 5, with mean diabetes duration of 11-12 years) and people with T2D previously on a basal only insulin regimen (ONWARDS 2 with a mean diabetes duration 16.7 years) or on basal-bolus regimen (ONWARDS 4 with a mean diabetes duration of 16.9 years).

The mean baseline HbA_{1c} ranged from 8.1% to 8.9% and mean FPG from 151.5 to 185.5 mg/dL. Fasting plasma glucose was not measured as part of the clinical laboratory assessments in ONWARDS 5 to mimic a clinical practice setting and optimize patient retention by not including fasting visits.

All T2D trials included participants with various degrees of renal impairment; across trials, 7.5% to 15.6% of participants had moderate renal impairment. In ONWARDS 5, 8 participants with severe renal impairment were included, as specific eGFR values were not an exclusion criterion for this trial.

The anti-diabetic background medication that participants were receiving at screening (and continued during the ONWARDS T2D trials, with pre-specified dose adjustments) covered a range of non-insulin, anti-diabetic treatments, reflecting the wide range of treatments employed in T2D (Table 9-3).

Table 9-3 T2D – Anti-diabetic non-insulin background medication at screening

	Insulin naïve			Basal Switch	Basal-bolus
	ONWARDS 1	ONWARDS 3	ONWARDS 5	ONWARDS 2	ONWARDS 4
N (%)	**N=984**	**N=588**	**N=1085**	**N=526**	**N=582**
Metformin	885 (89.9)	530 (90.1)	998 (92.0)	440 (83.7)	385 (66.2)
SGLT-2i	359 (36.5)	214 (36.4)	474 (43.7)	173 (32.9)	168 (28.9)
GLP-1 RA	175 (17.8)	112 (19.0)	306 (28.2)	137 (26.0)	71 (12.2)
DPP-4i	347 (35.3)	156 (26.5)	306 (28.2)	128 (24.3)	83 (14.3)
SU	446 (45.3)	260 (44.2)	439 (40.5)	114 (21.7)	44 (7.6)
Alpha-glucosidase inhibitor	45 (4.6)	38 (6.5)	6 (0.6)	28 (5.3)	18 (3.1)
Thiazolidinediones	49 (5.0)	45 (7.7)	45 (4.1)	21 (4.0)	18 (3.1)
Glinides	26 (2.6)	11 (1.9)	13 (1.2)	19 (3.6)	2 (0.3)

Abbreviations: % = percentage of participants; DPP-4i = dipeptidyl peptidase-4 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; N = number of subjects; SU = sulfonylureas; SGLT-2i = sodium-glucose cotransporter 2 inhibitor; T2D = type 2 diabetes

9.1.2 Participant disposition

Participant disposition was similar between treatment arms for the main phase (Table 9-4). Corresponding tables including data from extension phase of ONWARDS 1 are presented in Appendix A, Table 14-1. Across the T2D-ONWARDS trials and across treatment arms, the proportions of participants completing the scheduled end-of-treatment visit at the end of main phase were high (ranging from 91.3% to 98.7%). Hence, retention rates were adequate to preserve trial integrity with limited need for endpoint imputation. As expected, the lowest proportion of completers was in ONWARDS 5, where a sparse visit schedule more consistent with clinical practice led to lower retention in both treatment arms. The proportion of participants completing the scheduled end-of-treatment visit without discontinuation of insulin icodec treatment was also high, ranging from 89.1% in ONWARDS 5 to 97.3% in ONWARDS 2. The proportion of participants who discontinued the trial product was comparable between treatment arms across the trials.

Table 9-4 T2D pool (ONWARDS 1 to 5) - Participant disposition

	Insulin icodec		Daily basal insulin	
	N	%	N	%
Randomized	1882	100.0	1883	100
Exposed	1880	99.9	1878	99.7
Permanent treatment discontinuation of trial product	113	6.0	105	5.6
Adverse event	29	1.5	23	1.2
Hypoglycemic episode	3	0.2	1	0.1
Protocol deviation	3	0.2	3	0.2
Lack of efficacy [a]	1	0.1	0	
Intensification to a basal bolus regime or continuous use of bolus insulin [b]	2	0.1	0	
Lost to follow up	14	0.7	21	1.1
Withdrawal of consent	30	1.6	35	1.9
Pregnancy	1	0.1	0	
Site closure	1	0.1	0	
Other	29	1.5	22	1.2
Withdrawn from trial	80	4.3	88	4.7
Patient's withdrawal consent	40	2.1	42	2.2
Lost to follow up	19	1.0	26	1.4
Investigator decision	8	0.4	8	0.4
Death	11	0.6	12	0.6
Site closure	2	0.1	0	0
Completed trial	1804	95.9	1798	95.5
Without permanent discontinuation of trial product	1796	94.0	1777	94.4
After permanent discontinuation of trial product	35	1.9	21	1.1

Abbreviations: N = number of participants; % percentage of participants; T2D = type 2 diabetes

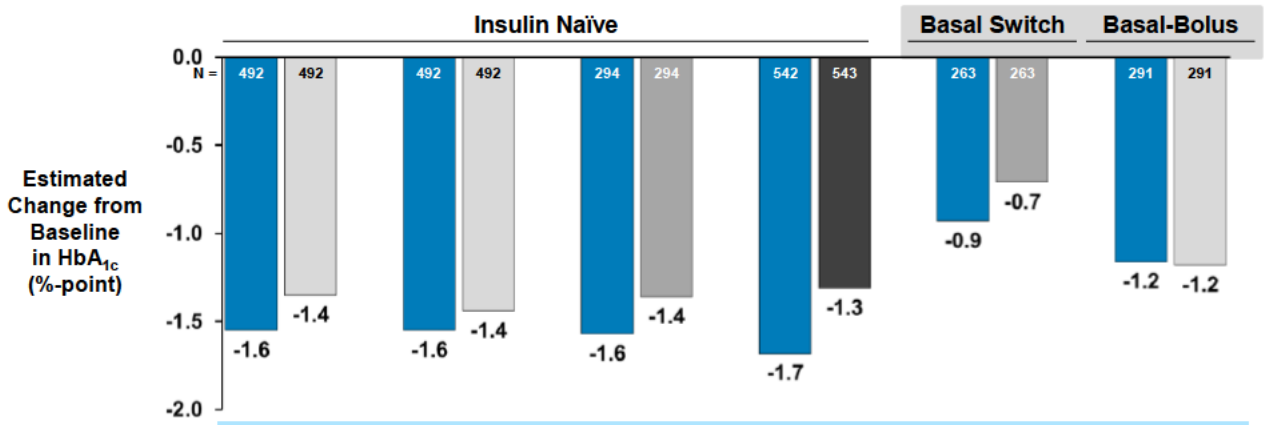
Note: [a] Lack of efficacy criterion applies to all trials except ONWARDS 5; [b]: intensification to a basal bolus regime or continuous use of bolus insulin only applies to ONWARDS 5

9.2 Efficacy in people with T2D

9.2.1 Change in HbA_{1c}

In all T2D ONWARDS trials, insulin icodec was demonstrated to be non-inferior to daily basal insulin in terms of change of HbA_{1c}. Furthermore, in T2D insulin-naïve participants (ONWARDS 1, 3, and 5) in participants with T2D previously on basal-only regimen (ONWARDS 2) insulin icodec was confirmed to be statistically superior to the daily basal insulins in reducing HbA_{1c} from baseline to planned end of treatment. Although statistical superiority was achieved, the clinical relevance of the difference between treatments has not been established. Change from baseline and statistical analysis results are presented in Figure 9-1.

Figure 9-1 T2D – Change from baseline in HbA_{1c}



T2D Studies	ONWARDS 1	ONWARDS 1 Ext	ONWARDS 3	ONWARDS 5	ONWARDS 2	ONWARDS 4
Baseline HbA_{1c} (%)	8.47	8.47	8.52	8.92	8.13	8.30
Difference [95% CI]	**-0.19** [-0.36, -0.03]	**-0.11** [-0.22, 0.00]	**-0.21** [-0.34, -0.08]	**-0.38** [-0.66, -0.09]	**-0.22** [-0.37, -0.08]	**0.02** [-0.11, 0.15]
p-value Non-Inferiority	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
p-value No treatment diff	0.0210	0.0506	0.0016	0.0092	0.0028	NA

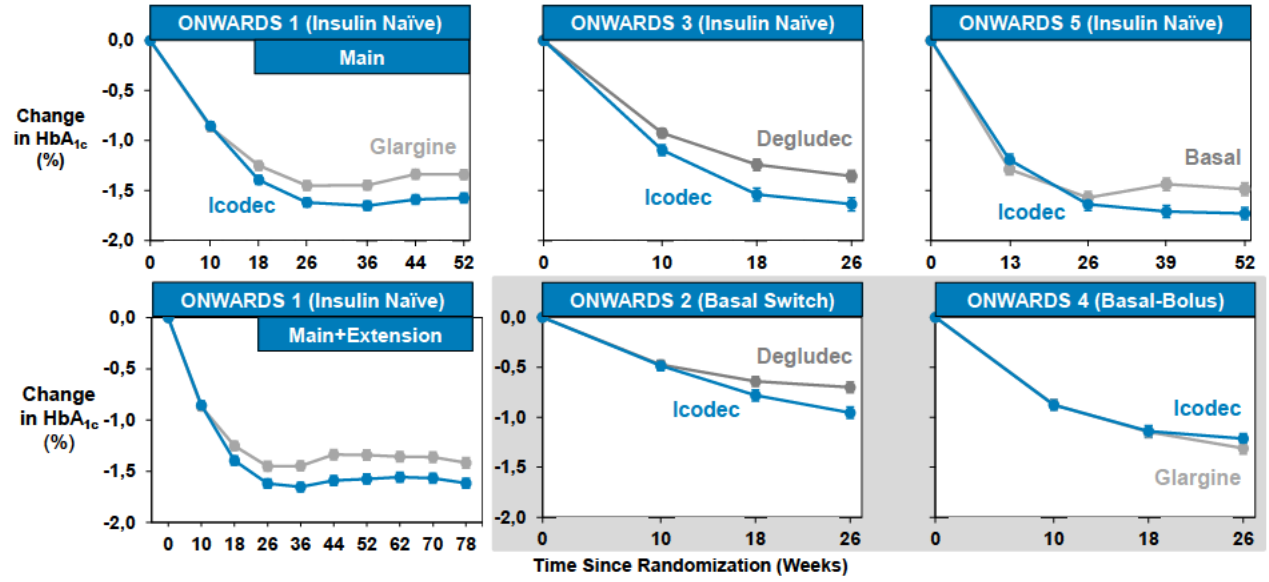
Notes: ONWARDS 5 participants receiving insulin icodec used an electronic dosing guide to optimize therapy. In the other trials, the dose of insulin icodec was adjusted once weekly by the investigator in connection with the scheduled visit or phone contacts.

Superiority testing was pre-specified as part of a hierarchical testing strategy after confirmation of non-inferiority in ONWARDS 1, 2, 3 and 5.

Abbreviations: CI = confidence interval; Difference = estimated treatment difference; Ext = extension phase; NA = Not assessed

In all T2D populations, HbA_{1c} decrease by week followed comparable curves between treatment arms, suggesting a similar time course to achieve glycemic benefit, as measured by HbA_{1c} (Figure 9-2).

Figure 9-2 T2D – Mean HbA_{1c} by treatment week – Change from baseline



Abbreviations: HbA_{1c} = glycosylated hemoglobin; T2D = type 2 diabetes

Notes: Observed data including data obtained after premature discontinuation.

Change in HbA_{1c} from baseline to the end of ONWARDS 1 complete trial (including the 26-week extension) confirmed the results at the end of the main phase, demonstrating that glycemic benefit was sustained for up to 78 weeks.

9.2.2 CGM metrics

CGM metrics were evaluated during the first 4 weeks and the last 4 weeks in 3 T2D trials: ONWARDS 1 (insulin naïve), ONWARDS 2 (previously on daily basal insulin as the only insulin therapy) and ONWARDS 4 (on a basal-bolus insulin regimen) (Figure 9-3). Both participants and investigators were blinded to the measurements. CGM data were not collected before randomization.

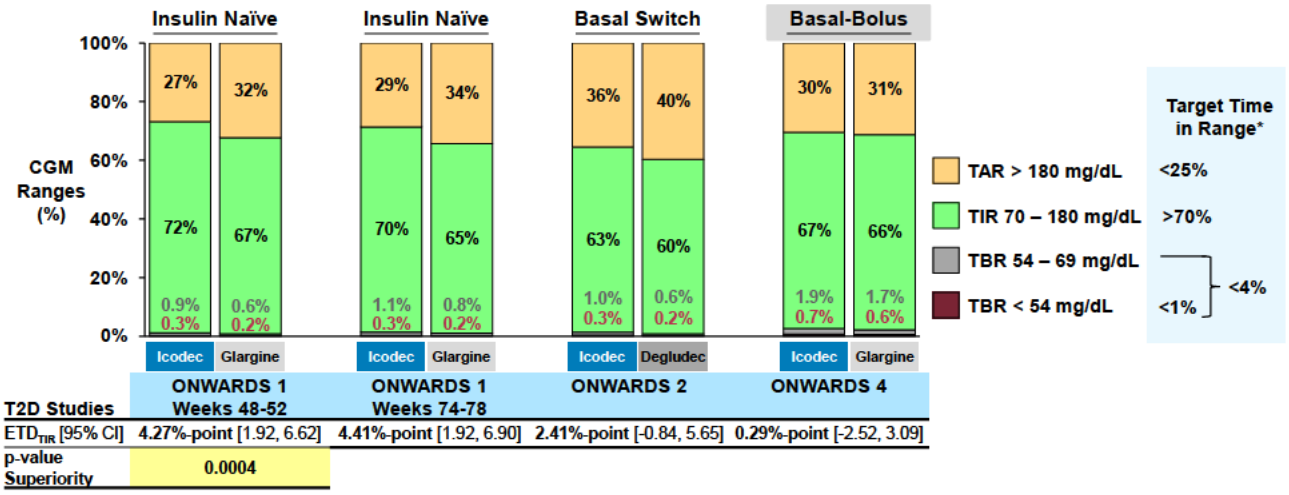
In ONWARDS 1 (insulin naïve population), time in range was a pre-specified confirmatory endpoint to assess the efficacy of insulin icodec and was tested in a hierarchical approach for superiority (see Figure 8-2). Percentage time in range for insulin icodec was statistically superior to insulin glargine, further confirming the efficacy of insulin icodec on glycemic control. Importantly, the estimated treatment difference for time in range between insulin icodec and insulin glargine arm can be considered clinically meaningful, as it was above the threshold of 3% defined by international guidelines.[24] In this population, time above range was lower in the insulin icodec arm compared to insulin glargine, while time below range was similar between the 2 treatment arms.

In ONWARDS 2 and ONWARDS 4, the average percentage of time spent in range, below or above range showed a similar pattern between the 2 treatment arms.

In all T2D populations where CGM was evaluated, the average percentage of time spent below range is well within the recommended window (Table 8-4), indicating that insulin icodec met the international consensus guidelines and did not lead to safety concerns based on these parameters.

CGM metrics collected during the last 4 weeks of the ONWARDS 1 complete trial (Weeks 74-78) supported the results observed in the main phase at Weeks 48-52 (Figure 9-3).

Figure 9-3 T2D – CGM percentage time above, below and in range



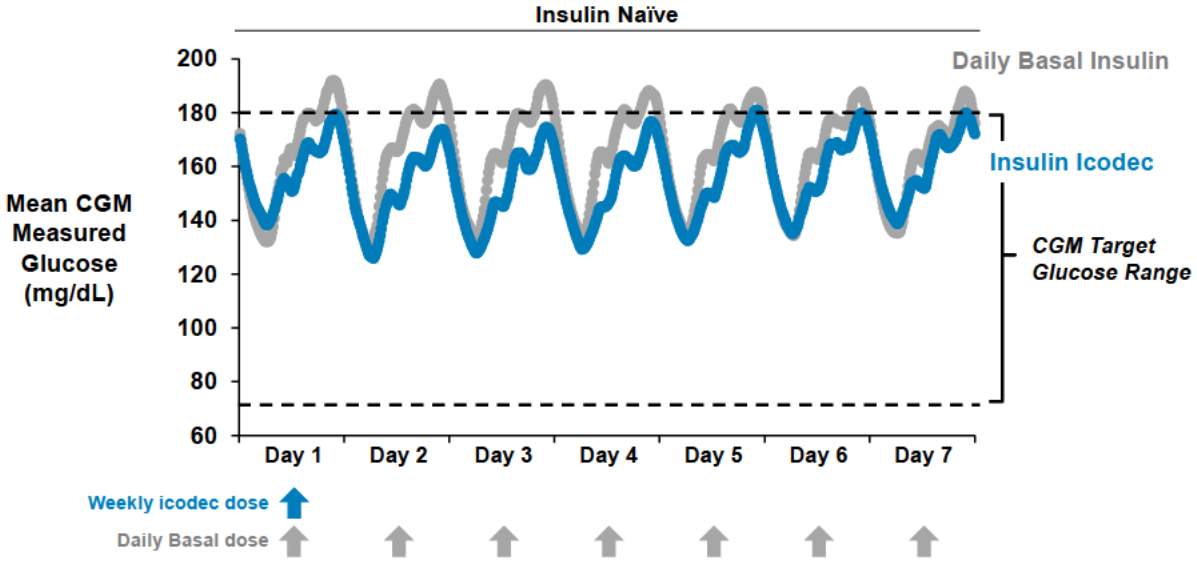
Abbreviations: CGM = continuous glucose monitoring; CI = confidence interval; ETD = estimated treatment difference; T2D = type 2 diabetes; TAR = time spent above range; TIR = time spent in range; TBR = time spent below range

Notes: observed data; Time spent is defined as 100 times the number of recorded measurements in a given range, divided by the total number of recorded measurements; *According to international consensus [28]

9.2.3 Mean glucose fluctuations over the week

In the ONWARDS 1 T2D population treated with insulin icodec, mean glucose values remained within the CGM target range of 70 to 180 mg/dL throughout the week, with glucose excursions that were generally small and consistent throughout each day and across the week. This result indicates that the glucose lowering effect of insulin icodec is maintained across the week and is similar each day as expected based on the insulin icodec PD profile, as assessed by GIR (Figure 6-2). Overall, these data indicate that weekly insulin icodec provided consistent and predictable daily glycemic patterns over the week after dosing (Figure 9-4).

Figure 9-4 T2D – Mean glucose fluctuations across the week based on CGM data-ONWARDS 1 (weeks 48 to 52)



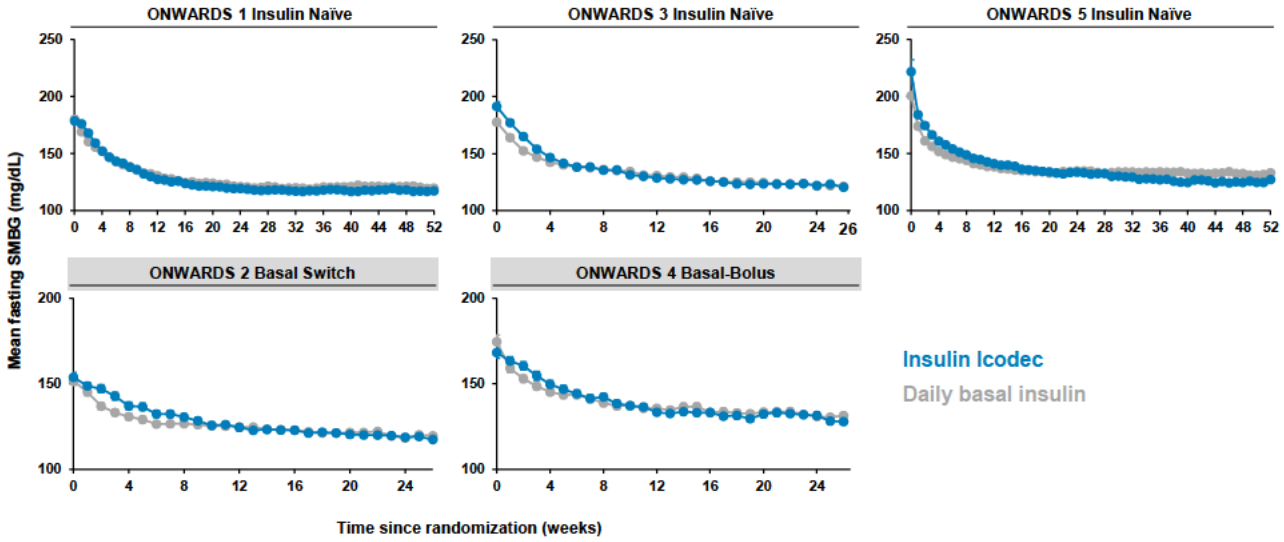
Abbreviations: CGM = continuous glucose monitoring; T2D = type 2 diabetes

9.2.4 Other efficacy assessments

The following observations further support insulin icodec efficacy in providing glycemic control:

- Fasting plasma glucose (FPG) was a supportive secondary endpoint in all ONWARDS trials, except ONWARDS 5. In T2D populations (ONWARDS 1-4), treatment with insulin icodec provided at least as much reduction in FPG as daily basal insulin.
- Participants with T2D treated with insulin icodec or daily basal insulin achieved a comparable glycemic control as measured by SMBG, supporting the results of the primary endpoint (change in HbA_{1c}). Mean pre-breakfast SMBG measurements over the course of a week also support the effectiveness of the titration algorithm used in the insulin icodec program (Figure 9-5).
- The differences in mean weekly doses of basal insulins between treatment arms were overall small and not consistently observed across all trials. This is consistent with the unit-vs-unit equivalence of insulin icodec vs daily basal insulins as predicted based on pre-clinical and phase 1 studies.

Figure 9-5 T2D – Mean fasting SMBG by treatment week



Abbreviations: SMBG = self-measured plasma glucose; T2D = type 2 diabetes

9.3 Hypoglycemia in people with T2D

Evaluation of hypoglycemia was a pre-specified assessment at the end of the main phase of the trial, therefore, the results presented in this section refer to the main phase unless otherwise specified. Most of the evaluation of hypoglycemia is based on data collected from the eDiary (SMBG-based), as pre-specified in the protocol. However, for some endpoints CGM-based data are also shown, providing an additional, complementary evaluation (for more details about analysis of hypoglycemia, please see Section 8.2.2.1).

Severe (level 3) or clinically significant (level 2) hypoglycemic episodes in ONWARDS T2D populations are presented in Table 9-5. Most of the hypoglycemic episodes occurred during the day. Nocturnal hypoglycemic episodes in participants with T2D are presented in Appendix A, Table 14-3.

Hypoglycemic episodes were defined as severe (level 3) when there was cognitive impairment, and the assistance of another person was needed for recovery. In the T2D populations either insulin naïve (ONWARDS 1, ONWARDS 3 and ONWARDS 5) or previously on basal-only (ONWARDS 2), 1 episode of severe hypoglycemia in 1589 participants was reported in the insulin icodec arm vs. 11 episodes in the daily basal insulin arm. In the basal-bolus trial (ONWARDS 4), 7 episodes of severe hypoglycemia were reported in 4 participants in the insulin icodec arm vs. 3 episodes in 2 participants in the daily basal insulin arm. In total, 4 episodes of level 3 hypoglycemia in 3 participants with T2D were nocturnal, and none occurred in the insulin icodec treatment arm. During the 26-week extension phase of the ONWARDS 1 trial, no additional severe hypoglycemic episodes occurred in the insulin icodec arm, while 3 severe episodes occurred in the daily basal insulin arm. Therefore, across all T2D populations, the risk of severe hypoglycemia (level 3) was very low, and similar between treatment arms.

Table 9-5 T2D – Hypoglycemic episodes by trial and classification

		Insulin Icodec (N = 1880)			Daily Basal insulin (N = 1878)		
Trial	**Classification**	**%**	**E**	**R**	**%**	**E**	**R**
Insulin naïve							
ONWARDS 1	**Level 2**	9.8	143	0.29	10.0	75	0.15
	Level 3	0.2	1	0.002	0.6	3	0.006
ONWARDS 3	**Level 2**	8.9	53	0.31	5.8	23	0.13
	Level 3	0	0		0.7	2	0.01
ONWARDS 5	**Level 2**	11.8	104	0.19	7.8	76	0.14
	Level 3	0	0		0.7	5	0.009
Basal switch							
ONWARDS 2	**Level 2**	14.1	113	0.73	7.2	41	0.27
	Level 3	0	0		0.4	1	0.007
Basal-bolus							
ONWARDS 4	**Level 2**	50.9	937	5.60	55.0	935	5.60
	Level 3	1.4	7	0.04	0.7	3	0.02

Abbreviations: % = percentage of participants with one or more episodes; E = number of episodes; R = rate (number of events per 1 PYE); PYE = Patient years of exposure (1 PYE = 365.25 days); T2D = type 2 diabetes

In ONWARDS 1, 3 and 5 (insulin naïve) and ONWARDS 2 (basal-only), most participants with T2D did not experience any clinically significant or severe (level 2 or level 3) hypoglycemic episode during the trials (85.9–90.2%). Overall, the proportion of participants experiencing a level 2 or level 3 hypoglycemic episode was similar between treatment arms. In line with what is expected in participants with T2D on a basal-bolus regimen, the proportion of participants in ONWARDS 4 (T2D basal-bolus) who did not experience a clinically significant or severe (level 2 or level 3) hypoglycemic episode was lower than in the other T2D trials, but still similar between treatment arms (48.5% vs. 44.3% in insulin icodec vs. daily basal insulin).

Although the risk of severe hypoglycemia in participants treated with insulin icodec was similar to the risk in participants treated with daily basal insulin, the occurrence of clinically significant (level 2) hypoglycemic episodes was higher with insulin icodec than daily basal insulin in ONWARDS 1, 2, 3 and 5. The rates of severe (level 3) or clinically significant (level 2) hypoglycemia in participants with T2D under a basal-bolus regimen (ONWARDS 4) were similar between insulin icodec and daily basal insulin. During the 26-week extension phase of ONWARDS 1, no increase in the rate of clinically significant (level 2) hypoglycemic episodes was observed in both treatment arms compared to main phase (from baseline to week 52). When considering the complete trial (from baseline to week 83), the rate of clinically significant hypoglycemic episodes remained higher in the insulin icodec arm compared to insulin glargine.

The estimated rate ratios of combined severe and clinically significant (level 2 + level 3) hypoglycemic episodes, as pre-specified endpoints of the ONWARDS program, are presented below. Given that in the insulin icodec arm only 1 episode of severe (level 3) occurred across insulin naïve and basal only ONWARDS trials, the higher rates observed in the insulin icodec arm

compared to daily basal insulin are driven by clinically significant (level 2) hypoglycemia (Table 9-6).

Table 9-6 T2D – Level 3* (severe) or level 2 (clinically significant) hypoglycemic episodes estimated rate ratio

Trial	Estimated Rate Ratio [95% CI] Insulin icodec/Daily basal insulin
Insulin naïve	
ONWARDS 1 (Main)	1.64 [0.98; 2.75]
ONWARDS 1 (Main + Extension)	1.63 [1.02; 2.61]
ONWARDS 3	1.82 [0.87; 3.80]
ONWARDS 5	1.17 [0.73; 1.86]
Basal switch	
ONWARDS 2	1.93 [0.93; 4.02]
Basal-bolus	
ONWARDS 4	0.99 [0.73; 1.33]

Abbreviations: CI = confidence interval; T2D = type 2 diabetes

Note: *Across all T2D trials, 8 severe hypoglycemic episodes (1 episode in ONWARDS 1 and 7 episodes in 4 subjects in ONWARDS 4) in the insulin icodec arm, and 14 in the daily basal insulin arm were reported.

When put into context, the rates calculated for ONWARDS 1 and 3 can be translated into the fact that a single insulin naïve T2D patient who starts treatment with insulin icodec would experience 1 additional clinically significant (level 2) hypoglycemic episode within the next 6–7 years compared to if started with daily insulin. When considering the rates observed in ONWARDS 5, 1 additional clinically significant hypoglycemic episode would occur within 24 years after starting treatment with insulin icodec instead of another daily basal insulin.

Level 2 hypoglycemic episodes in the insulin icodec arm were reported by a few individuals, some of whom experienced many episodes. For example:

- In ONWARDS 1 (main phase), 3 participants (0.6%) accounted for 61 of 143 (43%) level 2 episodes reported in the insulin icodec arm.
- In ONWARDS 3, 2 participants (0.7%) accounted for 15 of the total 53 (28%) level 2 episodes in the insulin icodec arm. No other participants in the insulin icodec arm had more than 4 episodes.

In the basal-bolus trial (ONWARDS 4), the proportion of participants with high frequency of hypoglycemic episodes was similar between treatment arms.

A post-hoc analysis of hypoglycemia has been performed using CGM data from ONWARDS 1, ONWARDS 2 and ONWARDS 4. As described in Section 8.2.2.1, by assessing hypoglycemia via CGM data, the reporting of hypoglycemia is independent of the frequency of SMBG measurements. The estimated rate ratios between insulin icodec and daily basal insulin for level 2 hypoglycemia are presented below, including nocturnal hypoglycemia (Table 9-7). The level 2 hypoglycemia rate ratios are lower with CGM data than with SMBG data, suggesting a smaller difference between treatments.

Table 9-7 Level 2 (clinically significant) hypoglycemic episodes estimated rate ratios – CGM-based

Trial	Estimated Rate Ratio (95% CI)
Insulin naïve	
ONWARDS 1 (Main)	
Total	1.23 [1.04; 1.45]
Nocturnal	1.02 [0.83; 1.26]
ONWARDS 1 (Main + Extension)	
Total	1.27 [1.08; 1.48]
Nocturnal	1.08 [0.89; 1.31]
ONWARDS 2	
Total	1.25 [0.97; 1.62]
Nocturnal	1.01 [0.72; 1.40]
Basal-bolus	
ONWARDS 4	
Total	1.20 [0.97; 1.47]
Nocturnal	0.87 [0.68; 1.11]

Abbreviations: CGM = continuous glucose monitoring; CI = confidence interval

Notes: Clinically significant hypoglycemia (level 2): interstitial glucose value of < 54 mg/dL for at least 15 minutes confirmed by CGM. The number of events was analyzed using a negative binomial regression model (log link) with treatment, region and personal CGM device use as fixed factors, and the logarithm of the time period for which the events are considered as an offset (derived based on number of recorded measurements). Nocturnal: The period between 00:01 and 05:59 (both included).
ONWARDS 1 (Main) based on weeks 0-4, 22-26, and 48-52, (Extension) based on weeks 0-4, 22-26, 48-52 and 74-78
ONWARDS 2 and 4 based on weeks 0-4 and 22-26.

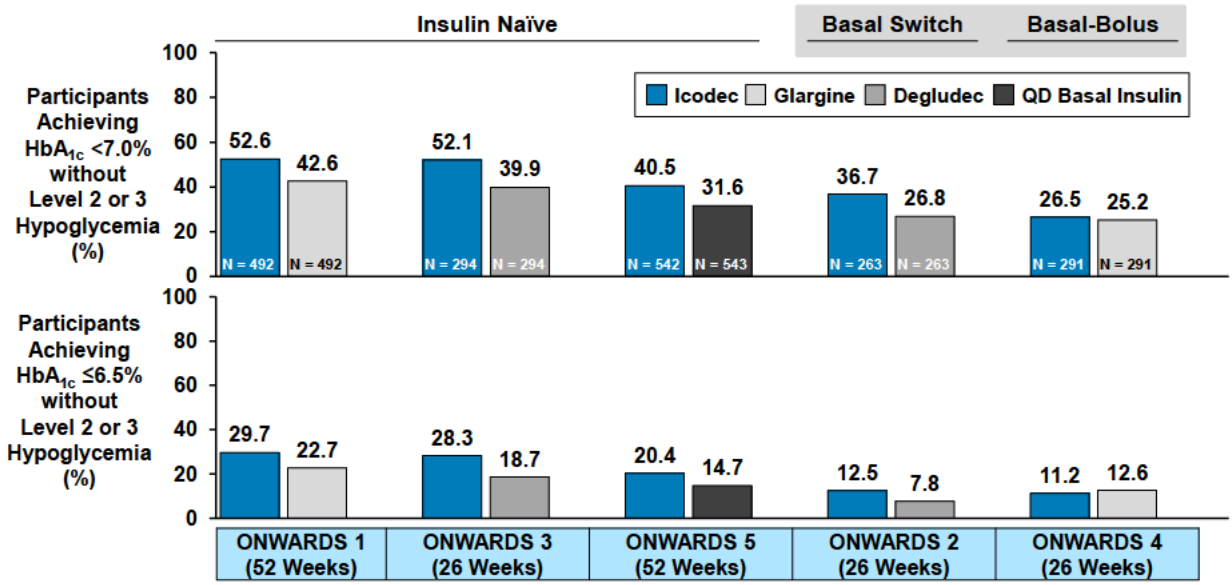
Although the overall rates of hypoglycemic episodes across ONWARDS 1 to 5 were higher in the insulin icodec arm, the number of episodes that were reported as SAEs was similar in the 2 treatment arms (3 in insulin icodec arm and 4 in daily basal insulin). Importantly, in insulin icodec-treated participants all SAEs associated with hypoglycemia were resolved and none led to permanent treatment discontinuation.

Duration of clinically significant or severe (level 2 or level 3) hypoglycemic episodes was similar between treatment arms. All episodes were manageable and resolved using the same methods as with daily basal insulins (data not shown).

9.4 Composite efficacy and safety assessments

To investigate whether glycemic control came at the cost of increased hypoglycemia, an analysis was performed to estimate the proportion of participants who achieved the HbA_{1c} targets (<7.0% or ≤6.5%) without experiencing any level 2 and level 3 hypoglycemic events in the previous 12 weeks. This analysis showed similar proportions of participants achieving HbA_{1c} targets without level 2 or level 3 hypoglycemia between treatment arms (Figure 9-6), suggesting that the glycemic control with insulin icodec was achieved without an increased risk of hypoglycemic episodes.

Figure 9-6 T2D – Estimated proportion of participants achieving HbA_{1c} targets without level 2 or level 3 hypoglycemia in the past 12 weeks



Abbreviations: % = estimated percentage of participants; HbA_{1c} = glycosylated hemoglobin; N = number of participants; T2D = type 2 diabetes

10 Clinical results in T1D

Summary

Trial population

- A total of 582 participants with T1D were randomized 1:1 in ONWARDS 6
- In the T1D population, more than 95% of enrolled participants completed the trial, with similar proportion in both treatment arms

Efficacy

In ONWARDS 6, once-weekly insulin icodec met the primary endpoint, demonstrating non-inferiority to insulin degludec for change in HbA_{1c}

To further support insulin icodec efficacy on glycemic control in participants with T1D, it was demonstrated that in the insulin icodec treatment group:

- Glucose time in range was comparable to daily basal insulin arm
- Time course to achieve glycemic improvement was similar to daily basal insulin arm

Hypoglycemia

In ONWARDS 6, hypoglycemic episodes were manageable and were resolved using the same methods as in current clinical practice for daily basal insulins

- 97% of participants with T1D did not experience any severe (level 3) hypoglycemic episode in either two treatment arms
- A higher rate of severe (level 3) was observed in the insulin icodec arm compared to insulin degludec and was partially driven by a few patients who reported many episodes
- The management and duration of the level 3 hypoglycemic episodes were comparable between treatment arms
- The rates for Level 2 or Level 3 hypoglycemic episodes were higher among patients receiving insulin icodec compared to insulin degludec, and were driven by level 2 episodes
- The duration of level 2 hypoglycemic episodes was similar between treatment arms
- Risk factors for level 2 or level 3 hypoglycemia are the same for icodec and insulin degludec, and in line with those reported for other daily basal insulins.

10.1 Trial population in ONWARDS 6

The participants enrolled in ONWARDS 6 represent a global population with T1D from 12 countries across North America, Europe, and Asia. Based on the data shown below, the population in ONWARDS 6 is considered representative of the intended T1D treatment population.

10.1.1 Baseline and demographic characteristics

Key baseline and demographic characteristics of the participants enrolled in the insulin icodec arm in ONWARDS 6 are presented in Table 10-1 and Table 10-2.

The overall disease-related baseline characteristics of the insulin icodec treated population were representative of a broad T1D population as seen in clinical practice in terms of treatment regimen, BMI, renal impairment, diabetes duration, HbA_{1c} and FPG levels. The overall demographic characteristics were also representative of typical T1D with regards to age, race, ethnicity, and country of origin.

Demographic and baseline characteristics were similar between participants in the insulin icodec and insulin degludec arms.

Table 10-1 T1D – Key demographic characteristics (ONWARDS 6)

	ONWARDS 6 N=582
Sex, N (%)	
Male	337 (57.9)
Female	245 (42.1)
Age (years)	
Mean (SD)	44.2 (14.1)
Age group, N (%)	
≥18 - <65 years	538 (92.4)
≥65 - <75 years	38 (6.5)
≥65 years	44 (7.6)
≥75 years	6 (1.0)
Race, N (%)	
White	448 (77.0)
Black or African American	11 (1.9)
Asian	123 (21.1)
Ethnicity, N (%)	
Not Hispanic or Latino	562 (96.6)
Hispanic or Latino	20 (3.4)
Region	
Europe	275 (47.3)
North America	191 (32.8)
Asia	116 (19.9)

Abbreviations: % = percentage of participants; N = number of participants; SD = standard deviation; T1D = type 1 diabetes

Table 10-2 T1D – Key baseline diabetes characteristics (ONWARDS 6)

	ONWARDS 6 N=582
BMI (kg/m^2)	
Mean (SD)	26.5 (4.8)
Renal function eGFR, N (%)	
Normal (≥90 mL/min/1.73m^2)	387 (66.5)
Mild impairment (≥60 -<90 mL/min/1.73m^2)	181 (31.1)
Moderate impairment (≥30 - <60 mL/min/1.73m^2)	14 (2.4)
Duration of diabetes, N (%)	
<10 years	157 (27.0)
≥10 years	425 (73.0)
HbA_{1c} (%)	
Mean (SD)	7.6 (0.9)
<8%, N (%)	378 (64.9)
≥8%, N (%)	204 (35.1)
FPG (mg/dL)	
Mean (SD)	175.7 (73.1)
History of cardiovascular disease, N (%)	
Yes	48 (8.2)
No	534 (91.8)

Abbreviations: % = percentage of participants; BMI = body mass index; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; N = number of participants; SD = standard deviation; T1D = type 1 diabetes

Notes: Data from main phase of ONWARDS 6. Baseline refers to week 0 except for renal function, these are evaluated at screening. Renal function categories are based on eGFR derived using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.

Participants from Europe, North America and Asia were included in the ONWARDS 6 insulin icodec arm, and the majority were White. The participants with T1D (ONWARDS 6) were generally young, with few participants ≥75 years included in ONWARDS 6 (n=6). Approximately one third of participants in ONWARDS 6 were from North America and there was good representation across race and ethnicity that aligns with US T1D demographics.

When considering only the US population, Black or African Americans enrolled in the US centers were 4.9% of the total US trial population in ONWARDS 6 (data not shown), which is in line with the percentage of African Americans living with T1D in US (2.9 – 4.7%).[91]

ONWARDS 6 covered people with long-standing T1D on basal-bolus regimen with a mean diabetes duration of 19.5 years in the insulin icodec arm. The mean baseline HbA_{1c} was 7.6% and mean FPG was 175.7 mg/dL. ONWARDS 6 included insulin icodec treated participants with various degrees of renal impairment, including 2.4% of participants with moderate renal impairment.

10.1.2 Participant disposition

In ONWARDS 6, participant disposition was similar between treatment arms (for main phase, see Table 10-3. The proportion of participants completing main phase was over 95% in both treatment arms, over 93% of participants completing the scheduled end-of-treatment visit without discontinuation of insulin icodec treatment. Hence, retention rates were adequate to preserve trial integrity and minimize the need for imputation.

The proportion of participants who discontinued the trial product was higher in the insulin icodec arm than in the insulin degludec arm.

In the ONWARDS 6 trial, a total of 5 participants indicated hypoglycemia or fear for hypoglycemia as the reason for permanent discontinuation of the trial product in the insulin icodec arm (1 participant reported “hypoglycemic episode” as the reason for discontinuation, while 4 participants indicated “hypoglycemia” or “fear of hypoglycemia” in the “other reason” category). In the insulin degludec arm, no one withdrew from the trial reporting a reason related to hypoglycemia (Table 10-3).

Corresponding tables including data from the extension phase of ONWARDS 6 can be found in Appendix A, Table 14-2.

Table 10-3 T1D – Participants disposition – main phase

	Insulin icodec		Insulin degludec	
	N	%	N	%
Randomized	290	100	292	100
Exposed	290	100	292	100
Permanent discontinuation of trial product	18	6.2	9	3.1
Adverse event	1	0.3	1	0.3
Hypoglycemic episode	1	0.3	0	
Protocol deviation	1	0.3	0	
Lost to follow up	0		1	0.3
Pregnancy	2	0.7	0	
Withdrawal of consent	4	1.4	3	1.0
Other	9	3.1	4	1.4
Withdrawn from trial	11	3.8	8	2.7
Patient's withdrawal consent	9	3.1	7	2.4
Lost to follow up	1	0.3	1	0.3
Investigator decision	0	0	0	0
Death	1	0.3	0	0
Site closure	0	0	0	0
Completed trial	277	95.5	285	97.6
Without permanent discontinuation	272	93.8	283	96.9
After permanent discontinuation	5	1.7	2	0.7

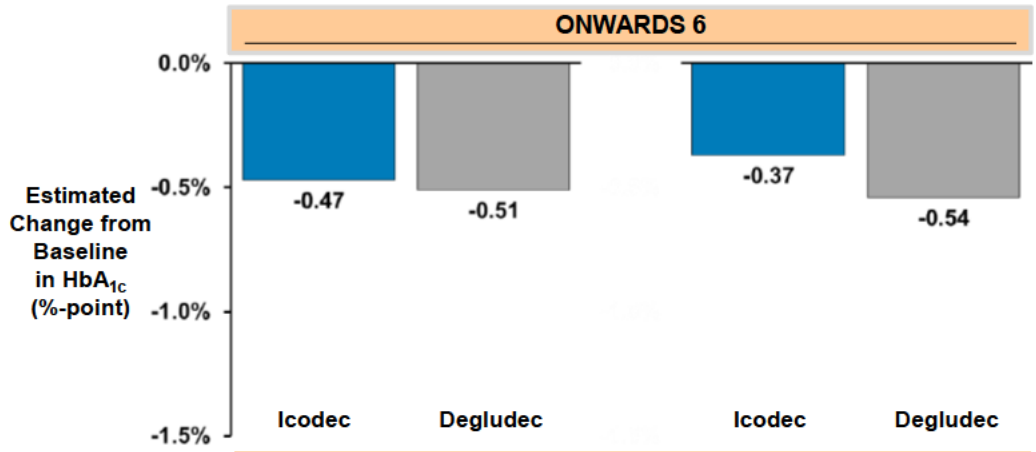
Abbreviations: % = percentage of participants; N = number of participants; T1D = type 1 diabetes

10.2 Efficacy in people with T1D

10.2.1 Change in HbA_{1c}

In the T1D population, insulin icodec demonstrated non-inferiority to insulin degludec in terms of change in HbA_{1c}, as the pre-specified primary hypothesis (from baseline to week 26). Although a slight increase in HbA_{1c} was observed in the insulin icodec arm at week 52 (end of the extension phase) in comparison to week 26 (end of the main trial phase), the reduction in HbA_{1c} from baseline to week 52 was clinically relevant Figure 10-1.

Figure 10-1 T1D – Change of HbA_{1c} from baseline to week 26 and week 52

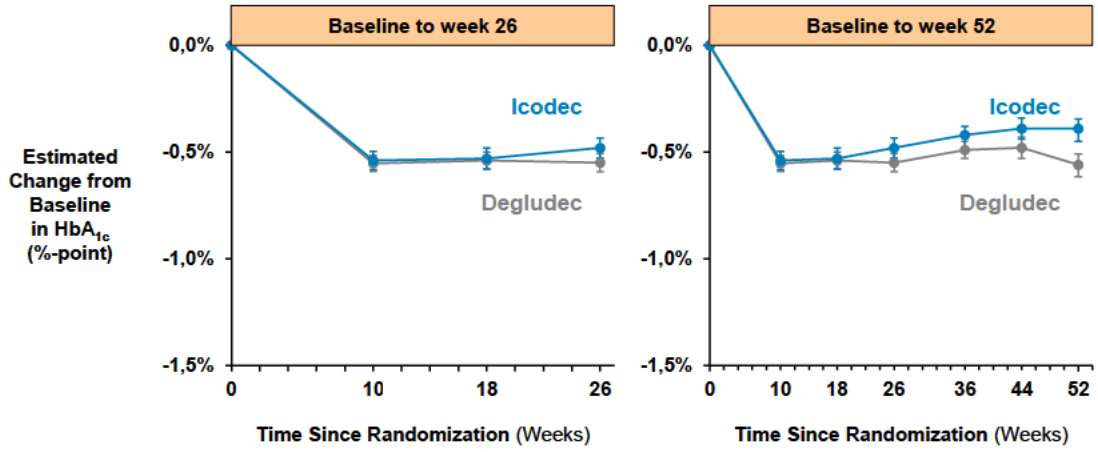


T1D Study	Week 26		Week 52	
Baseline HbA_{1c} (%)	7.6	7.6	7.6	7.6
Difference [95% CI]	**0.05** [-0.13, 0.23]		**0.17** [0.02, 0.31]	
p-value Non-Inferiority	0.0065		-	

Abbreviations: CI = confidence interval; Difference = estimated treatment difference; HbA_{1c} = glycosylated hemoglobin; T1D = type 1 diabetes

In the T1D population, HbA_{1c} decreased from baseline to week 10, after which it remained stable until week 26. Importantly, HbA_{1c} decrease by week in the insulin icodec treatment arm was comparable to insulin degludec, suggesting a similar impact on the glycemic effect, as measured by HbA_{1c} Figure 10-2.

Figure 10-2 T1D – HbA_{1c} by treatment week – Change from baseline



Abbreviations: HbA_{1c} = glycosylated hemoglobin; T1D = type 1 diabetes **Notes:** Observed data including data obtained after premature discontinuation; mean (symbol) and mean ± standard error to the mean (error bars).

10.2.2 CGM metrics

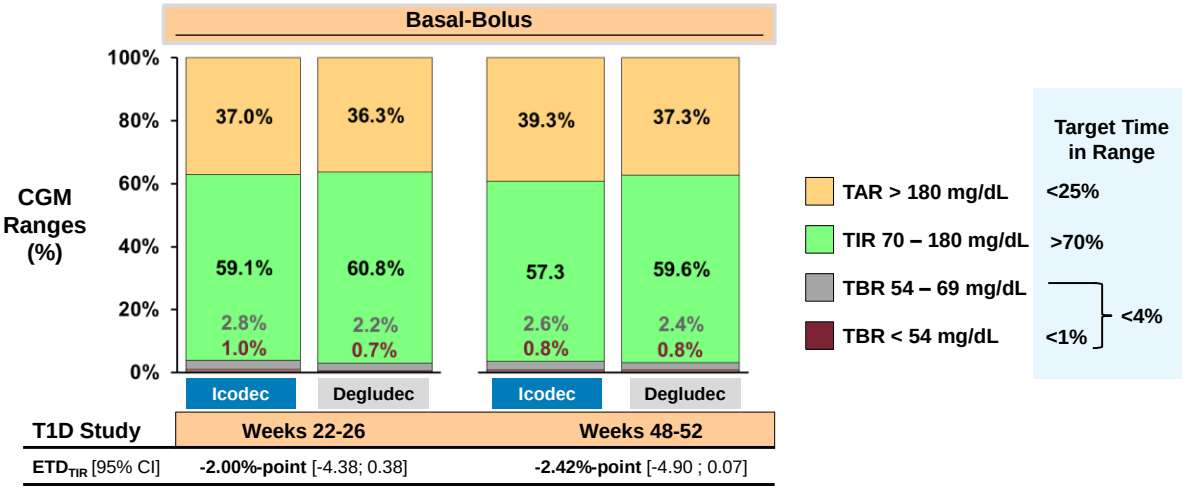
For the T1D population, CGM metrics were collected throughout the trial, and both participants and investigators were unblinded to the measurements. CGM data were not collected before randomization.

In ONWARDS 6, on average the percentage of time spent in range or above range was similar between the 2 treatment arms. In the insulin icodec arm, the mean time spent below 70 mg/dL was

within the recommended target range, while time spent below 54 mg/dL was 1% which corresponds to the threshold recommended by international consensus guidelines Figure 10-3. The estimated treatment difference in TIR between insulin icodec and insulin degludec observed at week 26 was not clinically meaningful, as it was below the 3%-point threshold defined in the international consensus guidelines.[24]

In general, CGM data collected at the end of the extension phase (weeks 48-52) supports the results observed in weeks 24-26. TIR results from week 48 to week 52 did not show a clinically meaningful difference between insulin icodec and insulin degludec although in the insulin icodec arm, a decrease in TIR was observed at week 52 compared to week 26. TBR <54 mg/dL between arms was not different during weeks 48-52, while the mean TBR <54 mg/dL in the insulin icodec arm was higher than in the insulin degludec arm during weeks 22-26. In addition, in the insulin icodec arm, observed mean TBR <54 mg/dL was on the threshold of the internationally recommended target (<1%) during weeks 22–26 (1.0%) and below the target during weeks 48–52 (0.8%), while at both time points observed mean TBR <70 mg/dL was below the recommended target of <4%.

Figure 10-3 T1D – CGM ranges at end of main phase and extension phase



Abbreviations: CGM = continuous glucose monitoring; CI = confidence interval; ETD = estimated treatment difference; T1D = type 1 diabetes; TAR = time spent above range; TIR = time spent in range; TBR = time spent below range

Notes: observed data; time spent is defined as 100 times the number of recorded measurements in a given range, divided by the total number of recorded measurements; * [24].

10.2.3 Patient reported outcomes (PROs)

DTSQ is a widely used PRO tool in diabetes research and is officially approved by World Health Organization (WHO) and the International Diabetes Federation (IDF) [92,93] and was used in ONWARDS 6 to assess treatment satisfaction from the patients' perspective. However, the PRO tool was not assessed per FDA COA Qualification program for use with once-weekly insulin. As described in Section 8, ONWARDS 6 was unblinded and therefore the results of the PROs may be biased, and the outcomes should be taken with caution. Participants were defined as responders if the change in score is >0.5SD in favorable direction, where SD is the standard deviation for all participants at baseline (using observed baseline data). In both treatment arms, an improvement from baseline in DTSQs total treatment satisfaction score was reported that can be translated to the

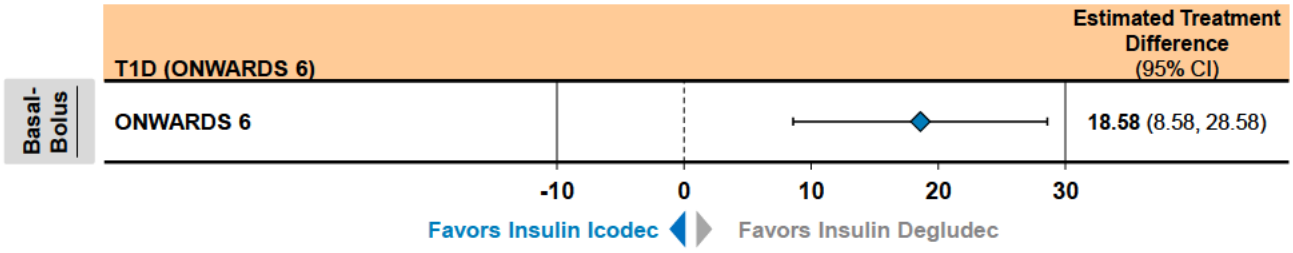
following proportions: among participants who completed treatment, 44.6% in the insulin icodec arm and 48.4% in the insulin degludec achieved a clinically meaningful improvement from baseline.[94, 95] However, the overall improvement in DTSQs total treatment satisfaction score in the insulin degludec arm, compared to the insulin icodec arm, was statistically significantly higher. This result may be linked to the complexity of initiating and getting used to a new concept of once-weekly insulin treatment for people with a mean diabetes duration of 20 years and treated by multiple daily injections. In addition, the PD profile over the week, implied new ways of adjusting bolus insulin which probably had an impact on the overall satisfaction of participants with T1D treated with insulin icodec. Nevertheless, the fact that almost half of participants with T1D treated with insulin icodec achieved a meaningful improvement of their overall treatment satisfaction suggests that even highly experienced people who are used to a traditional multi-daily injection regimen with a daily basal insulin may see weekly insulin icodec as a potential therapeutic option.

10.2.4 FPG and SMBG

Fasting plasma glucose (FPG) was a supportive secondary endpoint in ONWARDS 6.

For participants with T1D, the reduction in FPG at week 26 was larger for insulin degludec than for insulin icodec Figure 10-4. in contrast to mean SMBG data and HbA_{1c} reduction which were both comparable between the 2 treatment arms. FPG was usually evaluated on the day of titration before insulin icodec weekly injection, while SMBG was the mean of all SMBG measurements over the week. Therefore, the smaller observed reduction in FPG with insulin icodec was attributable to the waning pharmacodynamic effect on Days 5-7 (Section 6.3.2), rather than an overall lower efficacy.

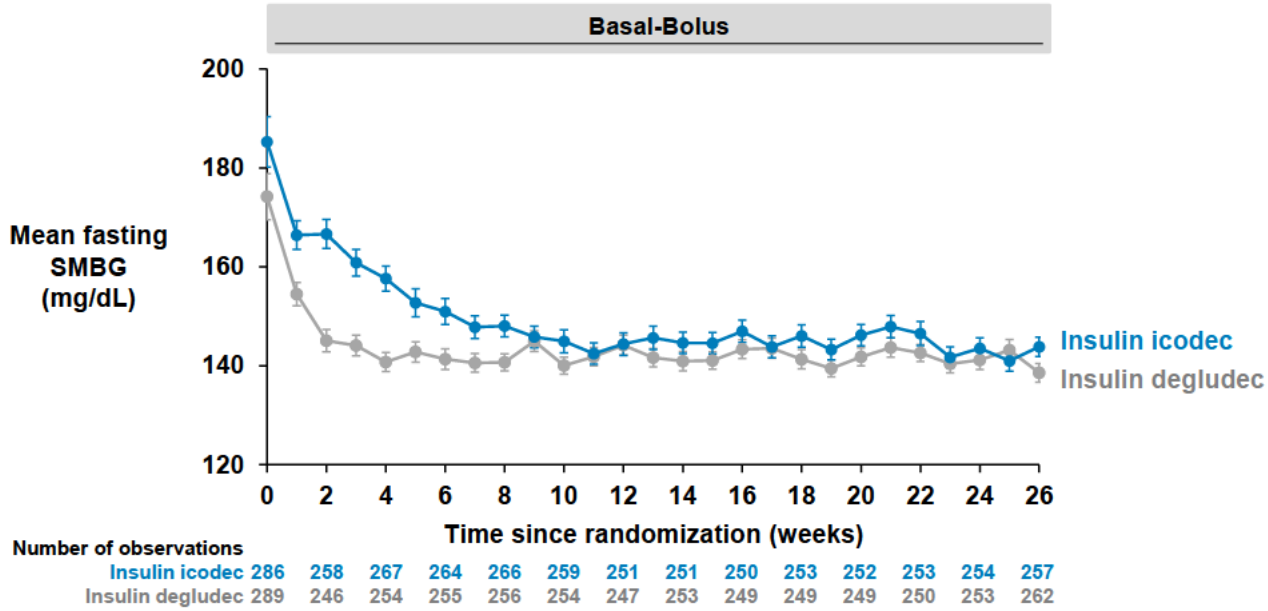
Figure 10-4 T1D – FPG (mg/dL) at planned end of treatment – change from baseline – plot of estimated differences



Abbreviation: CI = confidence interval; FPG: fasting plasma glucose; T1D = type 1 diabetes

For participants with T1D (ONWARDS 6), the mean fasting SMBGs did not reach the target of 80 to 130 mg/dL in either treatment arm. Insulin icodec was slower at bringing participants fasting SMBG towards the target in the initial 8 weeks compared to insulin degludec, whereafter the curves were comparable and they achieved similar fasting SMBG at steady state, indicating that the titration dynamics were similar in the insulin icodec and insulin degludec arm Figure 10-5.

Figure 10-5 T1D – Mean fasting self-measured plasma glucose during the entire week by treatment week



Abbreviation: SMBG: self-measured blood glucose

10.2.5 Weekly insulin dose

The mean weekly basal, total and bolus insulin dose during the last two weeks before landmark visit (weeks 24-26) are presented in Table 10-4.

Overall, the total insulin weekly dose was similar between treatments. However, a higher basal insulin dose along with a lower bolus insulin dose was observed in the insulin icodec arm compared to insulin degludec. Further discussion about differences between treatments in the relative bolus and basal doses is taken in Section 10.3.6.

Table 10-4 T1D – Estimated mean weekly insulin dose during the last 2 weeks of planned treatment

	Insulin icodec	Insulin degludec	ETR (icodec/degludec)
Total	310.52	322.68	0.96 [0.90; 1.03]
Basal	169.96	151.24	1.12 [1.07; 1.18]
Basal (U/kg)	2.21	1.97	1.12 [1.07; 1.18]
Bolus	131.86	161.42	0.82 [0.74; 0.90]

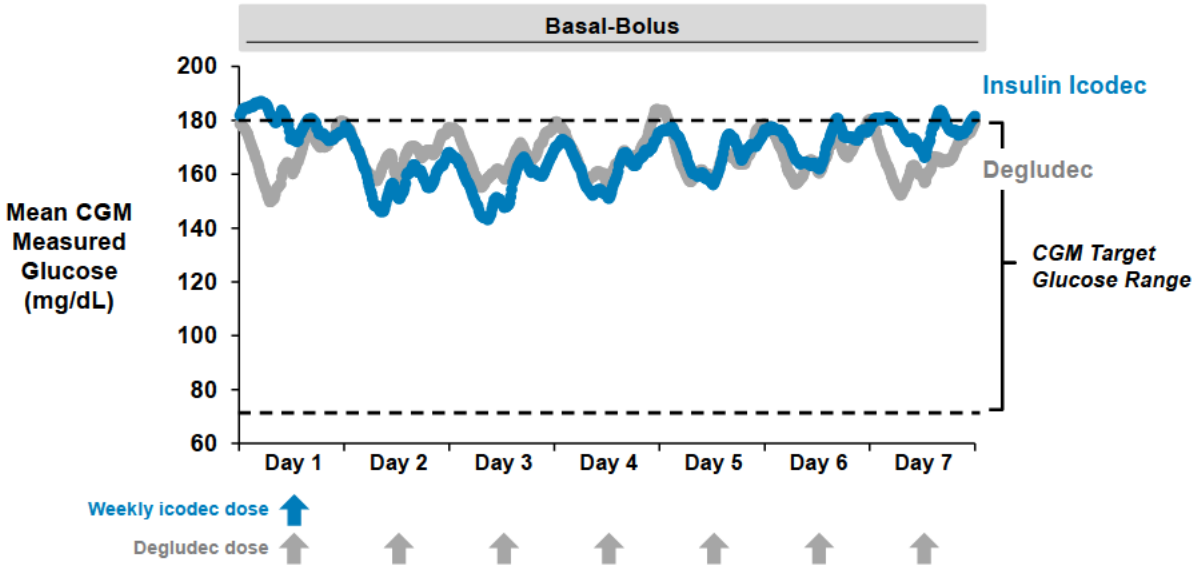
Abbreviations: ETR= estimated treatment ratio; T1D = type 1 diabetes; U = units
Notes: Values are estimated geometric mean.

10.2.6 Mean CGM fluctuation over the week

Across the week, the majority of CGM glucose values in participants with T1D treated with insulin icodec were within the target range (70 to 180 mg/dL). Although the weekly variability is more pronounced for insulin icodec, which is consistent with insulin icodec's PD profile, it is of a similar magnitude to the within day fluctuation of insulin degludec and insulin icodec. Being day 1 the day of insulin icodec weekly injection, the mean glucose in participants treated with insulin icodec was

lower during days 2 to 4 than on other days, as expected based on the PD profile Figure 10-6. Overall, these results indicate that the glucose lowering effect of insulin icodec is predictable and provides glycemic coverage that is maintained across the week.

Figure 10-6 T1D – Mean glucose fluctuations across the week based on CGM data (weeks 22 to 26)



Abbreviations: CGM = continuous glucose monitoring; T1D = type 1 diabetes

10.3 Hypoglycemia in people with T1D

10.3.1 Introduction

In order to assess the hypoglycemia risk with insulin icodec, statistical analyses of pre-specified secondary safety endpoints were conducted, including analysis of level 3 and level 2 hypoglycemic episodes, both separately and combined. These analyses were supported by post-hoc analyses of level 2 hypoglycemic episodes based on CGM data. Furthermore, to understand the root causes of hypoglycemia and to assess whether there are any predictors of increased hypoglycemia risk for insulin icodec, extensive analyses were conducted for participants with level 2 or level 3 hypoglycemic episodes, based on baseline and demographic characteristics.

Since evaluation of hypoglycemia was a pre-specified assessment at the end of the main phase of the trial (week 26), the results presented in this section are referring to the main phase, unless otherwise specified. For the same reason, most of the evaluation of hypoglycemia is based on data collected from the eDiary (SMBG-based), as pre-specified in the protocol. However, for some endpoints CGM-based data are also shown, providing an additional or more suitable evaluation (for more details about analysis of hypoglycemia, please see Section 8.2.2.1).

When evaluating hypoglycemia, it is important to keep in mind that participants in the ONWARDS 6 trial had been diagnosed with T1D at least 1 year prior to screening. They were therefore experienced users of daily basal insulins and some of them randomized to the insulin degludec arm may have continued their previous regimen. On the other hand, participants randomized in the insulin icodec arm needed to change from daily basal insulin to a new weekly

regimen. Furthermore, in ONWARDS 6 insulin icodec was compared to insulin degludec, which has a low steady state within subject day-to-day variability in glucose lowering effect and is the only basal insulin approved with a benefit in hypoglycemia risk reduction. Both a lower incidence rate (27% lower) and lower event rate (40% lower) in severe (level 3) hypoglycemia have been demonstrated for insulin degludec compared to insulin glargine U100 while maintaining similar glycemic control.[96]

10.3.2 Overview of hypoglycemia

As expected, the majority of participants with T1D experienced clinically significant or severe (level 2 or level 3) hypoglycemia in both treatment arms, with >98% of the episodes being level 2. Participants who reported level 3 hypoglycemic episodes were few (3.1%) and proportions similar between treatment arms (Table 10-5).

In the T1D population, a higher risk of clinically significant (level 2) or severe (level 3) hypoglycemic episodes was observed in the insulin icodec treatment arm compared to insulin degludec Figure 10-8. Most of the hypoglycemic episodes occurred during the day. The rates of nocturnal hypoglycemic episodes at all severity levels were higher in the insulin icodec arm compared with insulin degludec (Appendix A, Table 14-4). When considering the complete trial, the risk of hypoglycemia observed from baseline to week 57 did not increase compared to the period from baseline to week 26 in both treatment arms, with the rates of severe (level 3) hypoglycemia decreasing in both treatment arms.

Table 10-5 T1D – Hypoglycemic episodes by classification

		Insulin icodec			Insulin degludec		
Phase	**Classification**	**%**	**E**	**R**	**%**	**E**	**R**
Main	**Level 1**	99.3	10799	75.88	98.3	7402	51.36
	Level 2	84.8	2789	19.60	76.4	1478	10.26
	Level 3	3.1	47	0.33	3.1	17	0.12
Main + Ext	**Level 1**	99.3	20406	67.98	99.0	14819	47.87
	Level 2	90.3	5047	16.81	85.6	2811	9.08
	Level 3	4.5	56	0.19	4.1	25	0.08

Abbreviations: % = percentage of participants with one or more events; E = number of events; Ext = extension phase; Main = main phase; R = rate (number of events per 1 PYE); PYE = Patient years of exposure (1 PYE = 365.25 days); T1D = type 1 diabetes

While the proportions of participants with T1D experiencing a severe (level 3) hypoglycemic episodes were similar between treatment arms, a higher proportion of participants reported clinically significant (level 2) episodes in the insulin icodec than in the insulin degludec arm.

10.3.3 Severe hypoglycemia (level 3)

In ONWARDS 6, 96.9% of participants did not report any severe (level 3) hypoglycemia. The proportion of participants experiencing a severe (level 3) hypoglycemic episode was the same in both treatment arms (3.1%), while the number of severe hypoglycemic episodes was higher in the

insulin icodec arm in comparison with insulin degludec arm (47 vs. 17 in the insulin icodec and insulin degludec arm, respectively) reflecting that a few participants experienced many severe (level 3) hypoglycemic episodes. In particular, one participant in the insulin icodec arm reported 33 out of the 47 severe (level 3) hypoglycemic episodes (70%), while one participant in the insulin degludec arm reported 7 out of the 17 severe (level 3) hypoglycemic episodes (41%). Hypoglycemia in these participants is described in more details in Section 10.3.3.1.

Severe (level 3) nocturnal hypoglycemia occurred in 2 participants (0.7%) in the insulin icodec arm and 3 participants (1.0%) in the insulin degludec arm (Appendix A, Table 14-4).

The clinical presentation of severe (level 3) hypoglycemic episodes in participants with T1D was similar between treatment arms in terms of duration, management, and recovery. Most severe (level 3) episodes were managed without a visit to the clinic, the emergency room or the hospital (89.4% and 88.2% in the insulin icodec and insulin degludec arms, respectively), and were treated with eating or drinking carbohydrates only (83.0% and 76.5% in the insulin icodec and insulin degludec arm, respectively) (Table 10-6). In all insulin icodec cases, participants recovered after treatment (Appendix A, Table 14-5, “did the patient feel better after treatment?”). The most common symptoms for level 3 hypoglycemic episodes reported in the T1D population treated with insulin icodec were “feeling dizzy”, “impaired balance”, and “sweating”.

Table 10-6 T1D – Management of level 3 hypoglycemic episodes

	Insulin icodec		Insulin degludec	
	N	E (%)	N	E (%)
Total episodes (level 3)	9	47 (100)	9	17 (100)
Treatment*				
Something to eat or drink (carbohydrates) only	6	39 (83.0)	7	13 (76.5)
Intensive intervention	5	6 (12.8)	2	2 (11.8)
IV Glucose (drip) only	3	3 (6.4)	2	2 (11.8)
IV glucose and glucagon	1	2 (4.3)	0	
Glucagon only	1	1 (2.1)	0	
Medical assistance				
No	5	38 (80.9)	6	12 (70.6)
Unknown	1	1 (2.1)	1	2 (11.8)
Yes	6	8 (17.0)	3	3 (17.6)
Where did the patient get help				
Clinic/Emergency room/Hospital	4	5 (10.6)	2	2 (11.8)
Other	6	42 (89.4)	7	15 (88.2)
Convulsions or seizures				
No	8	46 (97.9)	7	15 (88.2)
Yes	1	1 (2.1)	2	2 (11.8)
Loss of consciousness or coma				
No	4	37 (78.7)	6	14 (82.4)
Yes	5	10 (21.3)	3	3 (17.6)

Abbreviations: % = percentage of events; E = number of events; IV = intravenous; N = number of participants with one or more episodes; T1D = type 1 diabetes

Note: the same participant could be reported in more than one category if different events from the same patient fell in different categories. The sum of the participants from each category is not equal to the total number of participants. The sum of the events from each category is equal to the total number of events. *Treatment not available for 2 episodes in the insulin icodec group and 2 episodes (1 participant) in the insulin degludec group.

Complete table in Appendix A, Table 14-5

The duration of severe hypoglycemic episodes was evaluated based on the eDiary reported by trial participants. Based on the available data, the majority of the severe (level 3) hypoglycemic episodes in the T1D population were shorter than 30 minutes in both treatment arms (Table 10-7), with median duration of 13 minutes in the insulin icodec arm and 14 minutes in insulin degludec arm.

To summarize, although in the ONWARDS 6 T1D population the rate of level 3 hypoglycemia was higher in the insulin icodec arm than in the insulin degludec arm, the number of participants experiencing a level 3 episode was similar between treatments. Participants and investigators elected to continue treatment with insulin icodec despite the level 3 episodes. Furthermore, in the two treatment arms the episodes were managed in the same way and the duration of the episodes was similar.

Table 10-7 T1D – Duration of severe (level 3) hypoglycemic episodes in participants with T1D based on eDiary

	Insulin icodec (E)	Insulin degludec (E)
Missing duration	3	8
Non missing duration	44	9
<30 minutes	34	6
30-<60 minutes	4	0
60-<90 minutes	2	1
90-<120 minutes	2	0
120-<150 minutes	0	1
180-<210 minutes	1	1
240-<270 minutes	1	0

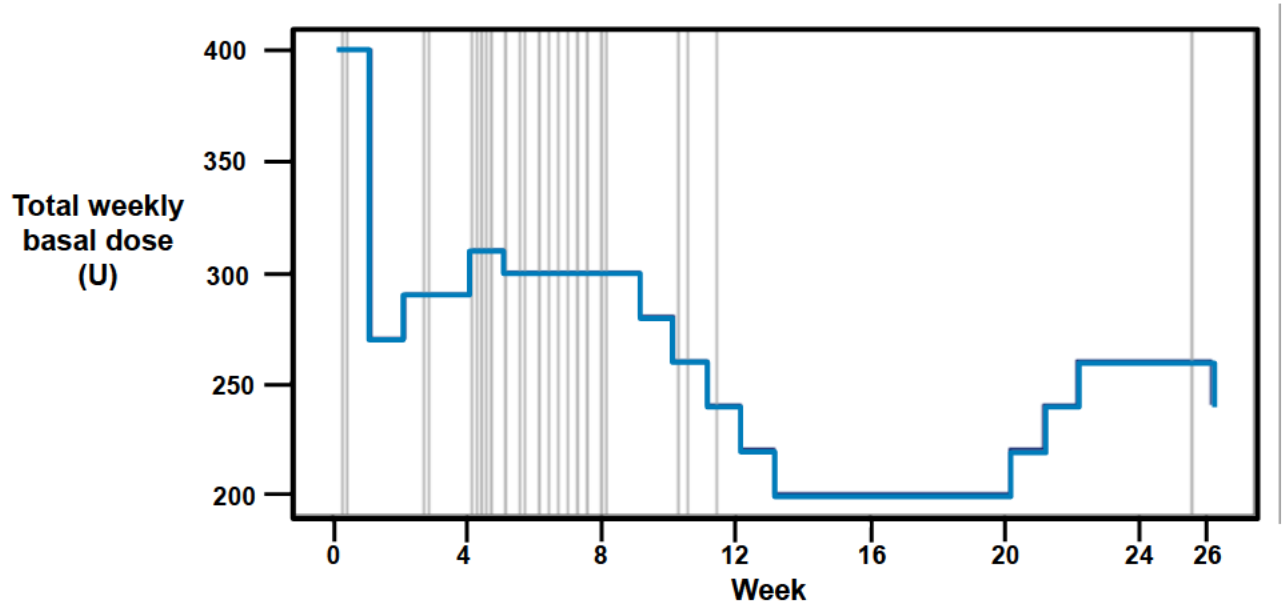
Abbreviations: E = number of episodes

During the 26-week extension of ONWARDS 6, there were 9 additional severe (level 3) hypoglycemic episodes in the insulin icodec arm and 8 in the insulin degludec arm.

10.3.3.1 Participant with many severe (level 3) hypoglycemic episodes

In the insulin icodec arm, one participant accounted for 33 out of the 47 severe (level 3) hypoglycemic episodes (70%). The majority of these episodes (32 out of 33) occurred during the first 12 weeks of treatment (i.e. the titration phase) and none of these episodes were reported as SAEs or led to hospitalization. Of note, the participant had life-style changes during the trial and lost a significant amount of body weight. The participant's insulin dose was not adjusted based on occurrence of severe hypoglycemia and on the changes in lifestyle, body weight and SMBG. After achieving the appropriate individualization of the insulin doses, only one additional severe (level 3) episode occurred Figure 10-7. Despite the many level 3 episodes, the investigator considered it safe and beneficial to keep the participant in the trial. The participant did not discontinue treatment with insulin icodec and remained in the trial until the end of the extension phase, where one additional severe (level 3) hypoglycemia episode in week 29 was experienced.

Figure 10-7 T1D – Distribution of level 3 hypoglycemic episodes and total weekly basal insulin dose in participant with 33 level 3 hypoglycemic episodes



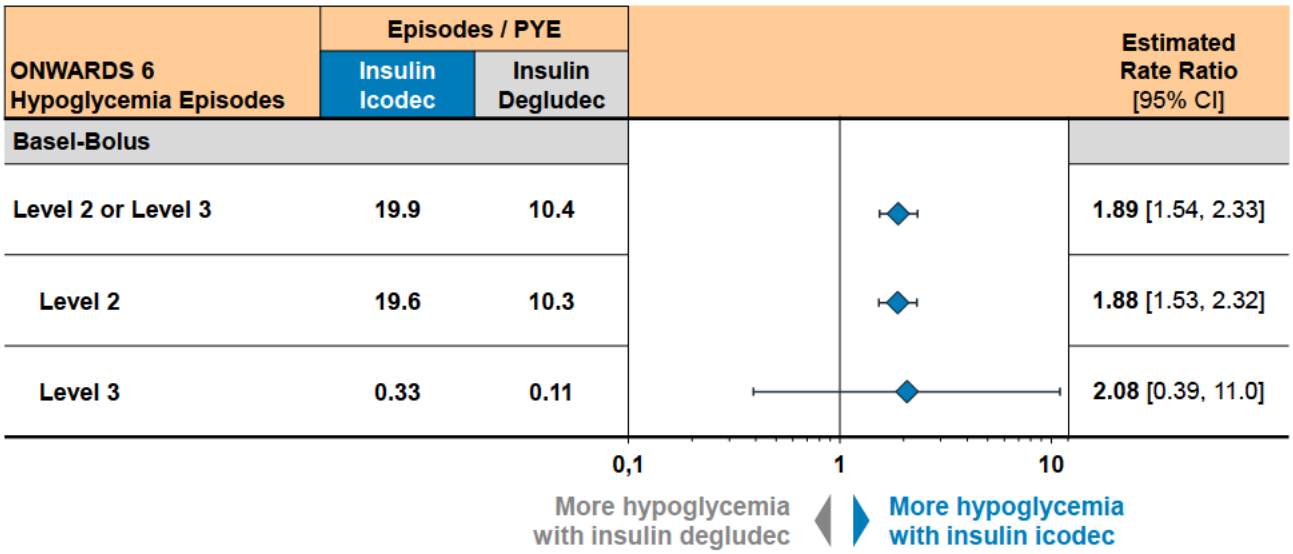
Abbreviations: T1D = type 1 diabetes; U = units
Note: vertical line = day with level 3 hypoglycemic episode

Similarly, in the insulin degludec arm, one participant accounted for 7 out of the 17 severe (level 3) hypoglycemic episodes. None of these episodes were reported as SAEs, and the participant did not discontinue treatment.

10.3.4 Severe (level 3) and clinically significant (level 2) hypoglycemia

As presented in section 8.2 and explained in the introduction above, combined severe and clinically significant hypoglycemia (level 3+level 2) was a pre-specified endpoint to evaluate hypoglycemia in the ONWARDS program. However, as shown above, level 3 hypoglycemia minimally contributed to the combined number of level 2 or level 3 episodes. Therefore, the results presented below are mostly driven by level 2 episodes, while level 3 episodes are described in detail in Section 10.3.3. The rates for level 2 or level 3 hypoglycemic episodeswere higher in the insulin icodec arm compared to insulin degludec (Figure 10-8).

Figure 10-8 T1D – Level 3 (severe) or level 2 (clinically significant) hypoglycemic episodes



Abbreviations: CI = confidence interval; PYE = Patient years of exposure (1 PYE = 365.25 days); T1D = type 1 diabetes

As presented in Section 10.3.3, the higher rate of level 3 hypoglycemia can, in large part, be explained by one participant who experienced multiple episodes and nevertheless decided to stay in the trial. In order to investigate the root cause of the higher rate of clinically significant (level 2) or severe (level 3) hypoglycemic episodes and their clinical impact, these episodes have been characterized in depth. This included the evaluation of the timing, duration of the episodes, potential association with SAEs, frequency and management and have been performed using both SMBG-based data, as prespecified in the protocol, and CGM-based data as a post-hoc and complimentary analysis when possible. These assessments are presented in the sections below.

10.3.5 Frequency of hypoglycemia (level 2 or level 3)

In order to understand the root cause of an excess of hypoglycemia among participants treated with insulin icodec, the frequency of the episodes was assessed.

In the T1D population, both treatment groups included participants who reported frequent hypoglycemic episodes Table 10-8. In the insulin icodec arm the proportion of participants with more than 10 episodes of level 2 or level 3 hypoglycemia was higher than in the insulin degludec arm. A residual excess of clinically significant or severe hypoglycemia remains in the insulin icodec arm. None of the participants with ≥20 severe or clinically significant hypoglycemic episodes discontinued the trial product.

The fact that the frequency of hypoglycemia is unevenly distributed among people with T1D is consistent with the literature.[97] [98]

Table 10-8 T1D – Participants with more frequent hypoglycemia (level 2 or level 3)

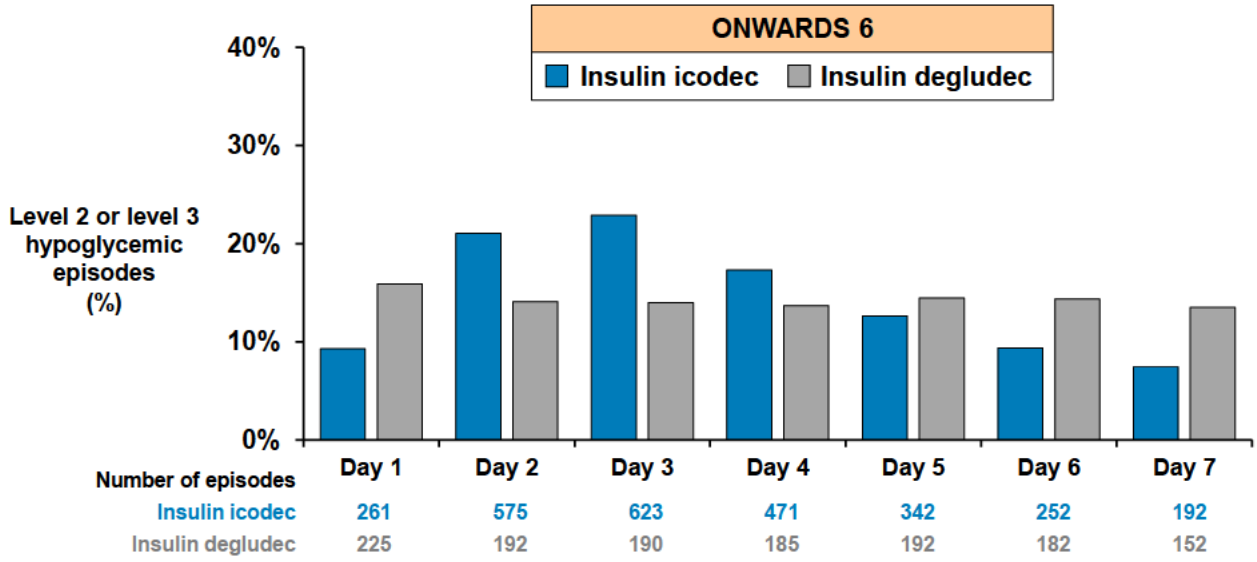
	Insulin icodec			Insulin degludec		
	N	%	E	N	%	E
No episodes	43	14.8	0	69	23.6	0
1–9 episodes	139	47.9	539	171	58.6	605
10–19 episodes	65	22.4	886	35	12.0	436
≥20 episodes	43	14.8	1411	17	5.8	454

Abbreviations: % = percentage of participants with one or more episodes, E = number of episodes; N = number of participants with one or more episodes

10.3.6 Occurrence of hypoglycemia over time (level 2 or level 3)

The majority of severe or clinically significant hypoglycemia (level 3 or level 2) in ONWARDS 6 occurred during days 2 to 4 after insulin icodec weekly administration. This pattern is consistent with the PD profile of insulin icodec (Figure 6-3) and with the glycemic levels observed by CGM over the week Figure 10-6, both of which show the greatest effects on days 2-4 after insulin icodec administration. The average proportion of level 2 or level 3 hypoglycemic episodes per day over the week is shown in Figure 10-9. This pattern is consistent throughout the trial.

Figure 10-9 T1D – Mean proportion of level 2 or level 3 hypoglycemic episodes over the week



Note: Day 1 is the day of weekly injection of insulin icodec. Data collected from baseline to week 26.

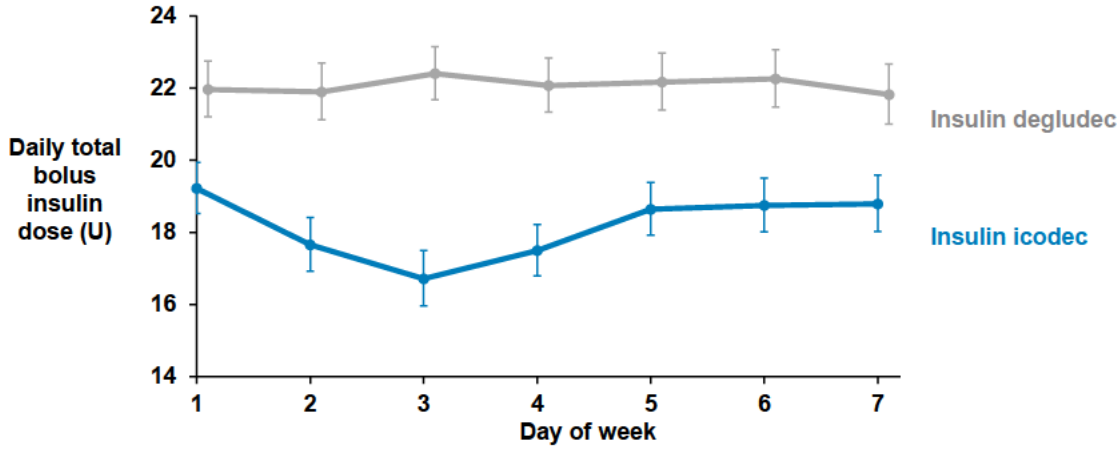
To better understand the root cause of the observed hypoglycemia pattern over the week, insulin icodec titration and dosing have been evaluated.

Titration dynamic and mean fasting pre-breakfast SMBG values over the week after the titration phase were similar between treatments and were associated with similar efficacy in glycemic control (as demonstrated by non-inferiority in change of HbA_{1c} and similar TIR). This suggests that the titration of insulin icodec was comparable to that of insulin degludec and is appropriate. Furthermore, the total weekly insulin doses were similar between treatment arms, supporting the

appropriateness of titration. However, a higher basal insulin dose was observed in the insulin icodec arm, whereas the bolus insulin dose was lower compared to the insulin degludec arm (Table 10-4).

Interestingly, when looking specifically to the end of the trial (week 24-26), an average reduction of 1 to 2 units in the bolus dose occurred during Days 2-4 compared to the rest of the week among participants of ONWARSD 6 randomized in the insulin icodec arm (Figure 10-10). It is important to note that although participants were allowed by protocol to change their bolus insulin dose, no specific instruction to take into account of icodec PD profile during the week was given. This suggests that the reduction in the bolus insulin dose was a reaction of participants and investigators to their observation of lower glycemia during those days, and an attempt to individualize the bolus insulin treatment. The observed reduction of the bolus dose on Days 2-4 in the insulin icodec arm corresponds to approximatively 5-10% of the total daily bolus dose which is likely too small compared to the PD effect of insulin icodec across the week and therefore not sufficient to change significantly the hypoglycemia rate.

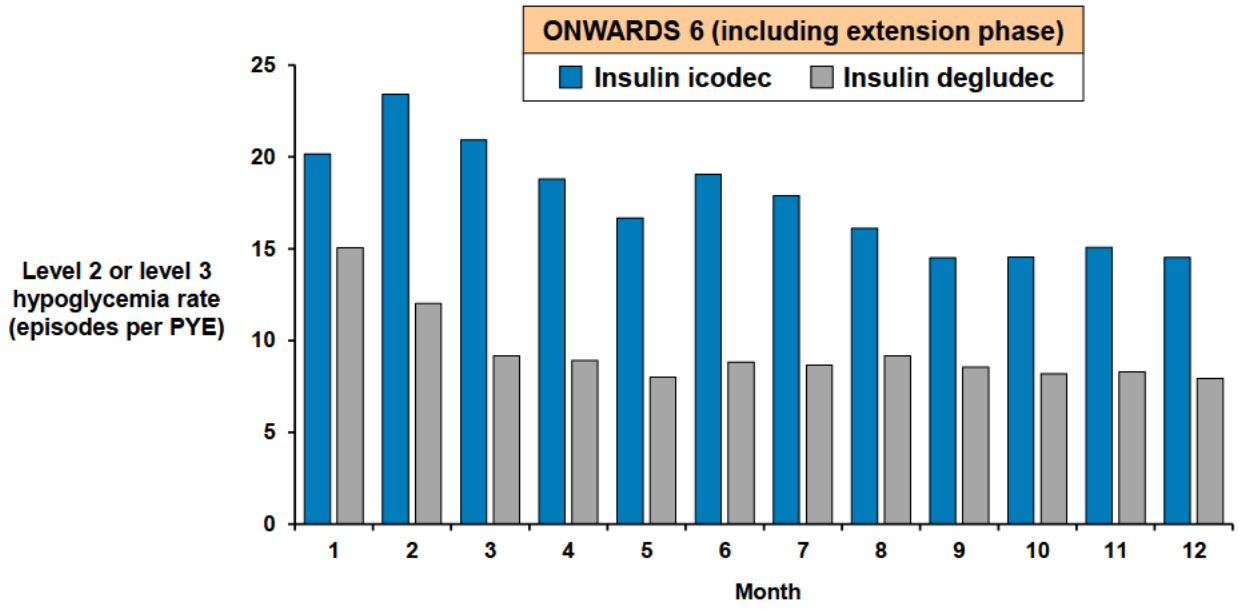
Figure 10-10 T1D – Average mean bolus insulin dose during weeks 24-26



Note: Actual daily total bolus insulin dose across an insulin icodec titration interval summed up for last 2 weeks of planned treatment (week 24-26) in ONWARDS 6

Consistent with literature reports,[99] the rate of hypoglycemic episodes was higher during the titration phase than in the maintenance phase with both treatments. The titration phase was pre-defined as the time from the administration of the first dose of trial product up until week 12, while the maintenance phase was defined as the time from week 12 to the planned end of treatment. There was no indication of an increase in the risk of severe (level 3) or clinically significant (level 2) hypoglycemic episodes over time in the insulin icodec arm Figure 10-11.

Figure 10-11 T1D – Rates of level 2 or level 3 hypoglycemic episodes by month



Abbreviations: PYE = Patient years of exposure (1 PYE = 365.25 days); T1D = type 1 diabetes

10.3.7 SAEs related to hypoglycemia

The proportion of participants and the rate of SAEs related to hypoglycemia were higher in the insulin icodec arm than in the insulin degludec arm for the T1D population (ONWARDS 6). In the main part of ONWARDS 6, 7 SAEs in the insulin icodec arm and 1 SAE in the insulin degludec arm were reported in association with hypoglycemia. One (1) SAE was associated with nocturnal hypoglycemia, it was resolved and did not lead to permanent treatment discontinuation. One (1) SAE was resolved in 2 days, while all other SAEs associated with hypoglycemia were resolved within one day, and none led to permanent treatment discontinuation Table 10-9 and Table 10-10.

Table 10-9 T1D – Hypoglycemic episodes reported as SAEs, by preferred term

	Insulin icodec		Insulin degludec	
	N (%)	E	N (%)	E
SAE	5 (1.7)	7	1 (0.3)	1
PT				
Hypoglycemia	4 (1.4)	6	0	
Hypoglycemic seizure	1 (0.3)	1	1 (0.3)	1
Severity				
Mild	0		0	
Moderate	2 (0.7)	2	0	
Severe	4 (1.4)	5	1 (0.3)	1
Outcome				
Recovered/resolved	5 (1.7)	7	1 (0.3)	1
Causality (as reported by the investigator)				
Unlikely	0		0	
Possible	2 (0.7)	2	1 (0.3)	1
Probable	4 (1.4)	5	0	

Abbreviations: % = percentage of participants; E = number of events; N = number of participants; PT = preferred term; SAE = serious adverse event; T1D = type 1 diabetes

Table 10-10 T1D – Patient level details about SAEs related to hypoglycemia

Trial product	Patient Age/Sex	Preferred term	Onset day	SAE Duration (Days)	Action on dosing	Outcome	Treatments
Insulin icodec	61 / M	Hypoglycemia	17	1	No change	Resolved	IV glucose
		Hypoglycemia	100	1	Reduced	Resolved	Oral carbs
		Hypoglycemia	108	1	Reduced	Resolved	Oral carbs
	27 / F	Hypoglycemia	129	1	Reduced	Resolved	Oral carbs, IM glucagon
	24 / M	Hypoglycemic seizure	164	1	Reduced	Resolved	IV glucose
	34 / M	Hypoglycemia	99	2	No change	Resolved	Oral carbs, IV glucose, glucagon
	19 / M	Hypoglycemia	164	1	Reduced	Resolved	Oral carbs
Insulin degludec	36 / F	Hypoglycemic seizure	55	4	Interrupted	Resolved	IV glucose

Abbreviations: IV = intravenous; IM = intramuscular; Oral carbs = oral carbohydrates (drinking or eating); SAE = serious adverse event; T1D = type 1 diabetes

During the extension phase of ONWARDS 6, additional SAEs associated to hypoglycemia occurred in both treatment arms. In the insulin icodec arm, 7 additional events were reported by 5 participants. Of these, 1 event was reported during the follow-up period (31 days after the end of treatment visit). In the insulin degludec arm, 2 additional events were reported by 2 participants.

In summary, in the insulin icodec arm, all SAEs associated with hypoglycemic episodes reported from baseline to week 57 were resolved in 1 or 2 days and none of these SAEs led to trial product discontinuation. Five (5) of the 14 SAEs associated with hypoglycemia were treated at a hospital. Four (4) of the SAEs associated with hypoglycemia were linked to physical activity, 4 were linked to skipped meals or reduced meal size and 1 was linked to a stomach infection.

10.3.8 CGM-based hypoglycemia (level 2)

Hypoglycemia analysis based on CGM data is described in Section 8.2.2.1.

A post-hoc analysis of level 2 hypoglycemia has been performed using CGM data that were collected throughout the ONWARDS 6 trial. The estimated rate ratios between insulin icodec and insulin degludec of level 2 hypoglycemia are presented below, include nocturnal episodes. As described in Section 8.2.2.1, CGM captures glycemia every 5 minutes throughout day and night thus providing objective and extensive data, whereas SMBG relies on the participant's decision to measure glycemia. Therefore, a difference in the hypoglycemia results when evaluated by CGM compared to SMBG was expected, and CGM-based hypoglycemia results should be considered complimentary to SMBG-based results. The estimated rate ratio between insulin icodec and insulin degludec of CGM-based level 2 hypoglycemia is closer to 1, than that SMBG-based (1.38 vs 1.88 with CGM- vs SMBG-based data) (Table 10-11).

Table 10-11 T1D – Level 2 hypoglycemic episodes estimated rate ratio – CGM-based

Trial	Estimated Rate Ratio [95% CI]
ONWARDS 6 Main	
• Overall	1.38 [1.17 ; 1.62]
• Nocturnal	1.28 [1.06 ; 1.56]
ONWARDS 6 Main + Extension	
• Overall	1.28 [1.09 ; 1.51]
• Nocturnal	1.20 [1.00 ; 1.45]

Abbreviations: CI = confidence interval; CGM = continuous glucose monitoring; T1D = type 1 diabetes.
Note: Nocturnal: The period between 00:01 and 05:59 (both included).

In ONWARDS 6, the duration of hypoglycemic episodes derived from CGM data was similar between the two treatment arms with a median duration of 60 minutes in both treatment arms, (Table 10-12).

Table 10-12 T1D – Duration of level 2 CGM-based hypoglycemia

	Insulin icodec		Insulin degludec	
	Median	P25; P75	Median	P25; P75
Duration (minutes)	60.0	40.0; 100.0	60.0	40.0; 95.0

Abbreviations: CGM = continuous glucose monitoring; T1D = type 1 diabetes
Note: CGM data were collected throughout the trial (from baseline to week 26). Based on 13883 episodes for insulin icodec and 9965 episodes for insulin degludec.

10.3.9 Evaluation of characteristics associated with hypoglycemic risk

In order to better characterize the higher risk of hypoglycemia observed among participants treated with insulin icodec, extensive post-hoc analyses of several intrinsic and extrinsic factors that may have an impact on the risk of hypoglycemia have been performed. Cut-offs for subgroups were selected based on guidelines - where available - or on previous experience. Where cut-offs were not easily identified (e.g., for diabetes duration), additional cut-offs were investigated, even though only one is presented here.

Since the number of hypoglycemic episodes based on CGM data are higher than those based on SMBG data, and due to the small number of participants falling in the analyzed subgroups, CGM-based data were used to estimate the rate ratio of level 2 hypoglycemia between treatments within subgroups and between subgroups within each treatment arm. However, please note that in some of the subgroups the number of participants is very low, and therefore the results should be taken with caution.

The estimated rate ratio of clinically significant (level 2) hypoglycemic episodes between insulin icodec and insulin degludec was similar across different subgroups, indicating that no unique risk factor for insulin icodec has been identified (Figure 10-12).

Figure 10-12 T1D – Treatment rate ratio of hypoglycemia across subgroups

Parameter		N (Icodec)	N (Degludec)	ERR [95% CI]
Overall		290	291	1.38 [1.17 ; 1,62]
Sex	Female	125	120	1.11 [0.86 ; 1.42]
	Male	165	171	1.67 [1.35 ; 2.07]
Age	18≤ to <65 years	267	270	1.35 [1.14 ; 1.59]
	65≤ years	23	21	2.05 [1.11 ; 3.76]
BMI	<25 kg/m²	105	135	1.42 [1.10 ; 1.83]
	25≤ to <30 kg/m²	118	101	1.37 [1.05 ; 1.79]
	30≤ to <35 kg/m²	46	41	1.27 [0.83 ; 1.93]
	≥35 kg/m²	21	14	2.11 [1.06 ; 4.20]
Diabetes duration	<10 years	75	82	1.52 [1.11 ; 2.08]
	≥10 years	215	209	1.34 [1.10 ; 1.61]
Baseline HbA_{1c}	<7%	79	70	1.32 [0.95 ; 1.82]
	7%≤ to <8%	110	118	1.44 [1.11 ; 1.88]
	8%≤ to <9%	72	80	1.25 [0.91 ; 1.71]
	≥9%	29	23	1.63 [0.94 ; 2.82]
CGM CV	≤36%	112	140	1.18 [0.94 ; 1.49]
	>36%	166	140	1.25 [1.02 ; 1.53]
Renal function	Normal function	197	190	1.40 [1.15 ; 1.72]
	Mild impairment	88	92	1.31 [0.98 ; 1.77]
	Moderate impairment	5	9	1.00 [0.33 ; 3.01]
United States	US	85	77	1.28 [0.94 ; 1.74]
	Non-US	205	214	1.43 [1.18 ; 1.73]
Region	Europe	136	138	1.41 [1.11 ; 1.79]
	North America	106	85	1.16 [0.87 ; 1.55]
	Asia	48	68	1.74 [1.20 ; 2.52]
Race	White	230	217	1.29 [1.07 ; 1.56]
	Asian	51	72	1.71 [1.19 ; 2.45]
	Black or African American	9	2	4.16 [0.86 ; 20.02]
Ethnicity	Not Hispanic or Latino	280	281	1.46 [1.23 ; 1.72]
	Hispanic or Latino	10	10	0.41 [0.17 ; 0.97]

[a]CGM CV was not assessed at baseline, subgroups are based on CGM data from week 0-2.

Abbreviations: BMI = body mass index; CGM = continuous glucose monitoring; CI = confidence interval; CV = coefficient of variation; eGFR = estimated glomerular filtration rate; ERR = estimated rate ratio; N = number of participants; T1D = type 1 diabetes; US = United States.

Notes: Renal function based on eGFR (normal function: ≥90 mL/min/1.73m^2, mild impairment: ≥60 mL/min/1.73m^2 to <90 mL/min/1.73m^2, moderate impairment: ≥30 mL/min/1.73m^{2}to <60 mL/min/1.73m^2).

Some of these characteristics are well-known risk factors for hypoglycemia and, as expected, were found associated with a higher rate of hypoglycemia in both treatment arms, such as higher glycemic variability (CGM CV%), longer duration of diabetes, and lower BMI. [97,100] These are in line with the ones reported in the literature for daily basal insulins, supporting that insulin icodec is similar to daily basal insulins in relation to the nature of hypoglycemic episodes (Figure 10-13).

Figure 10-13 T1D – Hypoglycemia risk by baseline and demographic characteristics

Parameter	Subgroup 1	Subgroup 2	Insulin treatment	N in subgroup 1	N in subgroup 2	Level 2 hypoglycemia (CGM)	ERR [95% CI]
Sex	Female	Male	Icodec	125	165		1.02 [0.81 ; 1.29]
			Degludec	120	171		1.54 [1.22 ; 1.95]
Age	≥65 years	18≤ to <65 years	Icodec	23	267		0.97 [0.62 ; 1.52]
			Degludec	21	270		0.64 [0.41 ; 1.00]
BMI	<25 kg/m²	25≤ to <30 kg/m²	Icodec	105	118		1.07 [0.82 ; 1.40]
			Degludec	135	101		1.03 [0.79 ; 1.34]
	30≤ to <35 kg/m²	25≤ to <30 kg/m²	Icodec	46	118		0.85 [0.60 ; 1.19]
			Degludec	41	101		0.91 [0.63 ; 1.32]
	≥35 kg/m²	25≤ to <30 kg/m²	Icodec	21	118		0.75 [0.47 ; 1.20]
			Degludec	14	101		0.49 [0.27 ; 0.86]
Diabetes duration	<10 years	≥10 years	Icodec	75	215		0.80 [0.62 ; 1.04]
			Degludec	82	209		0.71 [0.54 ; 0.92]
Baseline HbA_{1c}	<7%	≥9%	Icodec	79	29		0.76 [0.44 ; 1.31]
			Degludec	70	23		0.94 [0.53 ; 1.68]
	7%≤ to <8%	≥9%	Icodec	110	29		0.84 [0.51 ; 1.40]
			Degludec	118	23		0.95 [0.55 ; 1.64]
	8%≤ to <9%	≥9%	Icodec	72	29		0.75 [0.48 ; 1.15]
			Degludec	80	23		0.98 [0.61 ; 1.56]
CGM CV[a]	≤36%	>36%	Icodec	112	166		0.35 [0.28 ; 0.44]
			Degludec	140	140		0.37 [0.30 ; 0.46]
Renal function	Mild impairment	Normal function	Icodec	88	197		0.85 [0.66 ; 1.10]
			Degludec	92	190		0.91 [0.70 ; 1.18]
	Moderate impairment	Normal function	Icodec	5	197		0.58 [0.23 ; 1.42]
			Degludec	9	190		0.81 [0.41 ; 1.59]
United States	US	non-US	Icodec	85	205		1.24 [0.81 ; 1.92]
			Degludec	77	214		1.39 [0.89 ; 2.16]
Region	Europe	North America	Icodec	136	106		1.06 [0.82 ; 1.37]
			Degludec	138	85		0.87 [0.66 ; 1.14]
	Asia	North America	Icodec	48	106		0.98 [0.69 ; 1.38]
			Degludec	68	85		0.65 [0.47 ; 0.90]
Race	Asian	White	Icodec	51	230		0.84 [0.38 ; 1.85]
			Degludec	72	217		0.64 [0.30 ; 1.37]
	Black or African American	White	Icodec	9	230		1.03 [0.53 ; 2.03]
			Degludec	2	217		0.32 [0.08 ; 1.34]
Ethnicity	Hispanic or Latino	Not Hispanic or Latino	Icodec	10	280		0.62 [0.33 ; 1.17]
			Degludec	10	281		2.22 [1.17 ; 4.22]

[a]CGM CV was not assessed at baseline, subgroups are based on CGM data from week 0-2.

Abbreviations: BMI = body mass index; CGM = continuous glucose monitoring; CI = confidence interval; CV = coefficient of variation; eGFR = estimated glomerular filtration rate; ERR = estimated rate ratio; N = number of participants; T1D = type 1 diabetes; US = United States.

Notes: Renal function based on eGFR (normal function: ≥90 mL/min/1.73m², mild impairment: ≥60 mL/min/1.73m² to <90 mL/min/1.73m², moderate impairment: ≥30 mL/min/1.73m²to <60 mL/min/1.73m²).

Across all factors analyzed, glycemic variability has the most pronounced effect on the risk of hypoglycemia and is an example of how risk factors can be used to identify individuals with a reduced risk of hypoglycemia. Glycemic variability is a measure of the dynamic glucose variations that characterizes the amplitude, frequency, and duration of these fluctuations. Glycemic variability is expressed as the coefficient of variation (CV%) and is calculated as 100 × (standard deviation divided by mean glucose).[24] CV is a well-established risk factor for hypoglycemia and a clear cut off of ≤36% has been identified as associated with a lower risk of hypoglycemia.[24, 27,28, 101]. Glycemic variability is measured by CGM device which ensures data robustness and standardization. Moreover, CV is part of the standardized ambulatory glucose profile (AGP) report

– i.e. a summary of each patient's glucose data – which healthcare professionals, including non-diabetologists, use routinely to evaluate the glycemic control for patients. An extensive analysis of efficacy and safety parameters has been conducted in participants with T1D having low glycemic variability (CV) at the beginning of the trial and is presented below.

10.3.9.1 Efficacy and safety in subpopulations with CV % ≤36%

Glycemic variability is a measure of the dynamic glucose variations that characterizes the amplitude, frequency, and duration of these fluctuations. Glycemic variability is expressed as the coefficient of variation (CV%) and is calculated as 100 × (standard deviation divided by mean glucose).[24] CV is a well-established risk factor for hypoglycemia and a clear cut off of ≤36% has been identified as associated with a lower risk of hypoglycemia. [27, 100] Glycemic variability is measured by CGM device which ensures data robustness and standardization. Moreover, CV is part of the standardized ambulatory glucose profile (AGP) report [28] – i.e. a summary of each patient's glucose data – which healthcare professionals, including non-diabetologists, use routinely to evaluate the glycemic control for patients.

Below are presented efficacy and safety results in the subgroup of participants with CV ≤36% or >36%, for both treatment arms. It is important to note that CGM was not collected prior to randomization and therefore glycemic variability was not assessed prior to trial. However, average CV during the first 2 weeks of the trial was deemed to be appropriate to approximate glycemic variability at baseline and was used for these analyses. To evaluate robustness to the results, the same analyses have been performed using different cut-offs (CV ≤ and >32%, 34%, 38%, and 40%) and show that a lower risk of hypoglycemia is consistently associated with lower CV%, in both treatment arms, as expected.

Hypoglycemia – SMBG-based
There were no statistically significant treatment-by-subgroup interactions for any of the hypoglycemia endpoints.

The rates and the proportion of participants with level 2 or level 3 hypoglycemia (SMBG-based) were significantly lower with both insulins in the CV ≤36% subgroup compared to the rates in the respective total population, with an estimated rate ratio (insulin icodec vs insulin degludec) comparable in the CV ≤36% subgroup and the total ONWARDS 6 population.

By restricting the population to participants with CV ≤36%, the rate of level 2 or level 3 hypoglycemia is reduced from 19.92 to 9.99 episodes per year for insulin icodec and from 10.37 to 5.73 episodes per year for insulin degludec Table 10-13. The rate observed in the insulin icodec ≤36% CV subgroup (~10 episodes per year per patient) is comparable to the rate observed in all participants treated with insulin degludec, a marketed insulin with a well-known benefit in reducing hypoglycemia risk compared to other daily basal insulins, including insulin glargine.[96]

There were few severe (level 3) hypoglycemic episodes reported in the CV ≤36% subgroup; 3 (2.68%) participants reported a total of 5 episodes in the insulin icodec arm and 1 (0.71%) participant reported 1 episode in the insulin degludec arm.

In the CV ≤36% subgroup, there were no nocturnal severe (level 3) hypoglycemic episodes in the insulin icodec arm and 1 event of nocturnal severe hypoglycemia in the insulin degludec arm, while

1 SAE of hypoglycemia was reported in the insulin icodec arm and no SAEs related to hypoglycemia were reported in the insulin degludec arm.

Table 10-13 T1D – Level 2 or level 3 hypoglycemic episodes in total population and CV% subgroups

	Total population		CV% subgroup			
			≤36%		>36%	
	Insulin icodec	Insulin degludec	Insulin icodec	Insulin degludec	Insulin icodec	Insulin degludec
Participants, N (%)	247 (85.17)	223 (76.37)	78 (69.64)	86 (61.43)	158 (95.18)	127 (90.71)
Number of episodes	2836	1495	550	397	2085	1051
R	19.92	10.37	9.99	5.73	25.41	15.07
ERR [95% CI] Icodec/Degludec	1.89 [1.54; 2.33]		1.76 [1.29; 2.40]		1.64 [1.26; 2.13]	

Abbreviations: CI = confidence interval; CV = coefficient of variation; ERR = estimated rate ratio; N (%) = number (percentage) of participants; R = rate (number of events per 1 PYE); PYE = Patient years of exposure (1 PYE = 365.25 days); T1D = type 1 diabetes

Note: Participants with insufficient CGM data to categorize to a subgroup (i.e., those with <70% over the 2-week period [week 0–2]; n = 12 in each treatment arm) are not included in this table but are included in the source tables.

Hypoglycemia CGM-based

Hypoglycemia analysis based on CGM data is described in Section 8.2.2.1.

As observed with SMBG-based hypoglycemia, the rates with both insulins were lower in the CV ≤36% subgroup compared to the rates for the respective arms in the total ONWARDS 6 population. In the subgroup with CV ≤36%, the estimated rate ratio (insulin icodec vs insulin degludec) for level 2 hypoglycemic events was 1.18 $[0.94; 1.49]_{95\% CI,}$ indicating a reduction in the hypoglycemic risk in this subgroup compared to the total population (Table 10-14).

The improved hypoglycemia profile in the insulin icodec CV ≤36% subgroup is supported by the TBR results. As shown in Table 10-15, TBR (54 mg/dL and 70 mg/dL) was similar between insulin icodec and insulin degludec in the CV ≤36% subgroup, and well within the guideline-recommended targets (<4% of time below 70 mg/dL and <1% of time below 54 mg/dL).[24].

Table 10-14 T1D – Estimated rate ratio of level 2 hypoglycemic episodes in total population and CV% subgroups – CGM-based

	Total population	CV% subgroup	
		≤36%	>36%
ERR (95% CI)	1.38 [1.17; 1.62]	1.18 [0.94; 1.49]	1.25 [1.02; 1.53]

Abbreviations: CGM = continuous glucose monitoring; CI = confidence interval; CV = coefficient of variation; ERR = estimated rate ratio; T1D = type 1 diabetes

Note: Patients with insufficient CGM data to categorize to a subgroup (i.e., those with <70% over the 2-week period [week 0–2]; n = 12 in each treatment arm) are not included in the subgroup evaluation.

Adverse event profile

The AE profile in the insulin icodec CV ≤36% subgroup was similar to that in the total insulin icodec treatment arm, with no notable differences in the proportion of patients reporting AEs or the rates of AEs between insulin icodec and insulin degludec, and no unexpected clustering of events.

Glycemic control

In order to confirm that a low hypoglycemic risk did not come at the expenses of a less effective glycemic control, various efficacy parameters were analyzed in this subpopulation. In both treatment arms, in the CV ≤36% subgroup HbA_{1c} at week 26 was lower and TIR was higher compared to the total population. Glycemic control was similar between insulin icodec and insulin degludec for patients with CV ≤36% in terms of HbA_{1c} and TIR, with no statistically significant treatment-by-subgroup interaction for change in HbA_{1c} Table 10-15.

Table 10-15 T1D – Glycemic control in patients with T1D in ONWARDS 6 in the total population and in the glycemic variability CV% subgroups – full analysis set

	Total population		CV% subgroup			
			≤36%		>36%	
	Insulin icodec	Insulin degludec	Insulin icodec	Insulin degludec	Insulin icodec	Insulin degludec
HbA_{1c} (%)						
At week 26 (mean)	7.11	7.08	6.83	6.82	7.29	7.30
Mean change from baseline to week 26	-0.48	-0.55	-0.52	-0.62	-0.45	-0.48
FPG						
Mean change from baseline to week 26 (mg/dL)	-19.24	-32.42	-14.65	-33.11	-21.87	-29.07
Mean time in range (week 22–26)						
70–180 mg/dL	59.10	60.85	66.24	66.53	54.53	55.57
Mean time above range (week 22–26)						
>180 mg/dL	37.03	36.25	31.55	31.44	40.64	40.57
Mean time below range (week 22–26)						
<70 mg/dL	3.86	2.90	2.20	2.03	4.83	3.87
<54 mg/dL	1.02	0.68	0.39	0.36	1.37	1.04

Abbreviations: CV = coefficient of variation; FPG = fasting plasma glucose; HbA_{1c} = glycosylated hemoglobin; T1D = type 1 diabetes

Notes: Time in range is defined as 100 times the number of recorded measurements in glycemic range 70–180 mg/dL, both inclusive, divided by the total number of recorded measurements. Time spent above or below threshold is defined as 100 times the number of recorded measurements above/below the threshold, divided by the total number of recorded measurements.

Patients with insufficient CGM data to categorize to a subgroup (i.e., those with <70% over the 2-week period [week 0–2]; n = 12 in each treatment arm) are not included in this table but are included in the source tables.

10.4 Composite efficacy and safety assessment

As expected for people living with T1D, the estimated proportion of participants achieving HbA1c targets without reporting level 3 or 2 hypoglycemia in the last 12 weeks was low in both treatment arms (9.6% vs 16.7% for target HbA1c <7%, and 5.5% vs 7.6% for target HbA1c ≤6.5% in insulin degludec and insulin icodec arm, respectively).

10.5 Applicability of non-US data to US population with T1D

To assess if the results of the ONWARDS 6 trial which included people with T1D across 33 countries were representative of the US people with T1D, the same analyses of the main endpoints performed for the total population were also performed for the US and non-US populations and then compared. Details about the methods used for the comparison are given in Section 8.3.5.

In ONWARDS 6 the baseline and demographic characteristics can be considered comparable between US and non-US populations. US population did not differ from non-US population in

terms of efficacy of insulin icodec versus insulin degludec, based on the change of HbA_{1c} from baseline to week 26 (primary endpoint) and TIR 70-180 mg/dL. The exposure to the trial products was comparable between US and non-US population and participants with T1D did not display substantially different AE profiles for insulin icodec versus insulin degludec. In general, the rate of hypoglycemic events was similar between US and non-US populations except for severe (level 3) hypoglycemic episodes that had a higher rate among the non-US compared to US population in both treatment arms (Table 10-16). This imbalance was driven by the participants with 33 level 3 episodes in the insulin icodec arm and 17 level 3 episodes in the insulin degludec arm who both belonged to the non-US population. Thus, the efficacy and the safety profiles, including hypoglycemia, of insulin icodec based on global data appear to be applicable to a US population.

Table 10-16 T1D – Overview of clinically significant and severe hypoglycemic episodes in US and non-US populations

	Insulin icodec					Insulin degludec				
	Tot (N)	Sbj (N)	%	E	R	Tot (N)	Sbj (N)	%	E	R
Clinically significant (level 2)										
US	85	74	87.1	798	19.70	77	66	85.7	467	12.32
Non-US	205	172	83.9	1991	19.56	215	157	73.0	1011	9.52
Severe (level 3)										
US	85	2	2.4	3	0.07	77	3	3.9	3	0.08
Non-US	205	7	3.4	44	0.43	215	6	2.8	14	0.13

Abbreviations: Tot (N) = total number of subjects in the safety analysis set of the trial; Sbj (N) = number of subjects with one or more events; % = percentage of subjects with one or more events; E = number of events; R = rate (number of events per 1 PYE); PYE = Patient years of exposure (1 PYE = 365.25 days).

10.6 Applicability of non-US data to US population with T2D

The US population represents over 30% of the T2D ONWARDS population, with over 550 patient years of exposure to insulin icodec. The baseline and demographic characteristics are comparable between US and non-US populations for the T2D ONWARDS trials (data not shown). In the insulin icodec treatment arm,11.6% participants in the US population were Black or African American, which is in line with the proportion of African Americans living with diabetes in the US (12.7%).[102] The US population did not differ from the non-US population in terms of efficacy of insulin icodec versus daily basal insulin in any of the T2D trials, based on the primary endpoint (change in HbA_{1c} from baseline to landmark visit) and the confirmatory secondary endpoint for ONWARDS 1 (time in range 70-180 mg/dL). Exposure to insulin icodec was comparable between US and non-US populations. US and non-US populations did not display substantially different AE profiles for insulin icodec versus daily basal insulin. In general, the rate of hypoglycemic events was similar between US and non-US populations. Thus, the efficacy and safety profiles of insulin icodec based on global T2D data are considered applicable to the US T2D population.

11 General safety in people with T2D or T1D

Summary

In all ONWARDS trials (T2D and T1D), once-weekly insulin icodec had a safety profile similar to the well-established profile of daily basal insulins, with the exception of hypoglycemia.

- No unexpected findings or unacceptable risks were identified across the clinical development program
- The incidence of AEs was similar between the two treatment groups and across trials, and the majority of the events were non-serious and mild
- Fatal outcomes were rare and occurred at similar rates in both treatment arms
- In T2D, the incidence of SAEs was similar between treatment arms
- In T1D, the incidence of SAEs was higher in the insulin icodec arm (mainly accounted for by participants experiencing hypoglycemia)

To evaluate the safety of insulin icodec, data from T2D and T1D populations have been pooled, and data from extension phase of ONWARDS 1 and ONWARDS 6 have been included. Hypoglycemia is not reviewed in depth in this section as it is discussed above (Sections 1.6.2 and Section 10.3).

11.1 Exposure

In the ONWARDS trials the safety parameters have been evaluated in a total of 4340 participants, with a total exposure of 4246.47 patient-years, receiving either insulin icodec or daily basal insulin (Table 11-1). The exposure between treatment arms was similar within trials.

Table 11-1 Summary of the exposure by pool and trial

	Insulin icodec		Daily basal insulin	
	N	PYE	N	PYE
Type 2 diabetes				
Insulin naïve				
ONWARDS 1-ext	492	765.50	492	766.76
ONWARDS 3	293	170.90	294	171.13
ONWARDS 5	542	559.54	538	560.72
Basal switch				
ONWARDS 2	262	155.25	263	152.77
Basal-bolus				
ONWARDS 4	291	167.36	291	166.80
Type 1 diabetes				
ONWARDS 6-ext	290	300.16	292	309.58
Total				
Total	2170	2118.70	2170	2127.76

Abbreviations: N = Number of participants, PYE = Patient years of exposure (1 PYE = 365.25 days);
ext = main+extension phase

11.2 Adverse events

The pattern of the reported AEs was generally consistent between trials, with some differences observed mostly due to differences in trial duration, trial population and trial design.

11.2.1 Overview of AEs and SAEs

In T2D, the proportions of participants reporting AEs, SAEs, and severe AEs, were similar between those taking insulin icodec and daily basal insulin (Table 11-2). In T1D, AEs were reported by similar proportions of participants between treatment arms. However, among participants with T1D the incidences of SAEs and severe AEs were higher in the insulin icodec arm, which was mainly accounted for by participants experiencing hypoglycemia. SAEs related to hypoglycemic events in T1D are described in Section 10.3.7.

Table 11-2 Summary of AEs reported in ONWARDS trials

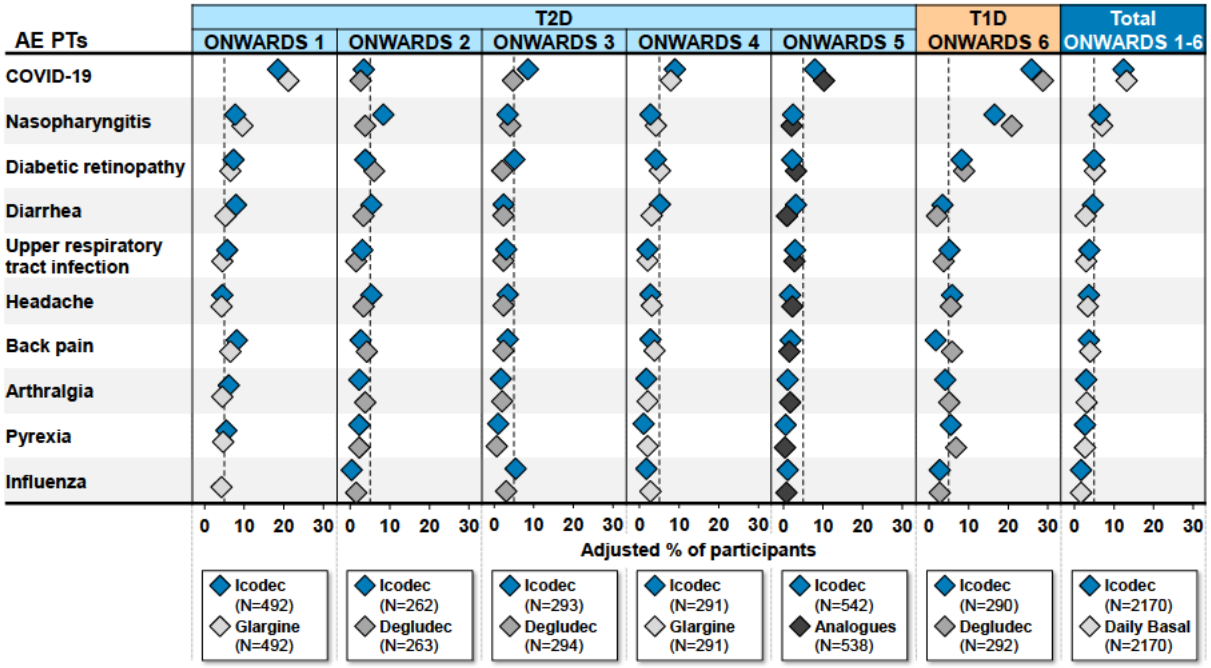
		Total AEs		SAEs		Severe AEs	
		Insulin icodec	Daily basal insulin	Insulin icodec	Daily basal insulin	Insulin icodec	Daily basal insulin
Type 2 diabetes							
Insulin naïve							
ONWARDS 1-ext	%	80.7	79.1	13.0	14.4	5.3	7.3
	E	1882	1823	95	119	38	61
	R	245.85	237.75	12.41	15.52	4.96	7.96
ONWARDS 3	%	60.4	56.8	5.1	5.1	4.4	1.4
	E	511	424	22	18	14	4
	R	299.01	247.76	12.87	10.52	8.19	2.34
ONWARDS 5	%	51.5	50.2	8.3	10.6	5.2	7.1
	E	819	795	69	85	34	63
	R	146.37	141.78	12.33	15.16	6.08	11.24
Basal switch							
ONWARDS 2	%	61.5	51.0	8.4	6.1	4.2	4.2
	E	466	328	30	20	17	13
	R	300.17	214.70	19.32	13.09	10.95	8.51
Basal-bolus							
ONWARDS 4	%	58.8	57.4	7.6	8.6	4.5	4.1
	E	455	550	35	33	20	14
	R	271.87	329.74	20.91	19.78	11.95	8.39
Type 1 diabetes							
ONWARDS 6-ext	%	82.8	80.8	8.3	6.8	6.9	3.1
	E	965	1146	39	25	28	10
	R	321.50	370.18	12.99	8.08	9.33	3.23

Abbreviations: AE = adverse event; SAE = serious adverse event; % = percentage of participants with one or more events; E = number of events; R = rate (number of adverse events per 100 PYE), PYE = patient years of exposure (1 PYE = 365.25 days); ext = main+extension phase.

The majority of AEs in both T2D and T1D were non-serious and mild. Fatal outcomes were rare in both T2D and T1D, with similar incidences in the 2 treatment arms. Deaths are discussed in Section 11.2.4.

The most commonly reported AEs (defined as reported by ≥5% participants in any trial or treatment arm) were consistent between treatment arms in all trials (Figure 11-1).

Figure 11-1 T2D and T1D – Adverse events by preferred term and trial – most frequent [≥5%]



Abbreviations: Adjusted % = percentage of participants with one or more events, calculated using the Cochran-Mantel-Haenszel method to account for differences between trials; AE = adverse event; N = number of participants in treatment arm; PT = preferred term; T1D = type 1 diabetes; T2D = type 2 diabetes

In the total ONWARDS trial population, no SAEs were reported by more than 1% of participants in the insulin icodec arm or daily basal insulin arm. The SAEs reported by more than 0.3% of the participants in either treatment arm in T2D and/or T1D are presented in Table 11-3. No pattern was seen with regards to time of onset. Although the incidences of SAEs related to COVID-19 (including COVID-19-related pneumonias) were higher among the insulin icodec-treated participants, a causal relationship between these events and insulin icodec has not been identified. In the T1D population, hypoglycemia was the only SAE reported in more than 1% of insulin icodec-treated participants. Hypoglycemic episodes reported as SAEs are defined in Section 8.2.2.1 and described in Section 10.3.7.

Table 11-3 T2D and T1D – Incidence of most frequently reported (>0.3%) SAEs by preferred term

	T2D pool		T1D		Total	
	Insulin icodec	Daily basal insulin	Insulin icodec	Insulin degludec	Insulin icodec	Daily basal insulin
	% * (N)	% * (N)	% (N)	% (N)	% * (N)	% * (N)
COVID-19 pneumonia	0.6 (12)	0.4 (7)	0.3 (1)	0	0.6 (13)	0.3 (7)
COVID-19	0.6 (11)	0.2 (4)	0.3 (1)	0.3 (1)	0.6 (12)	0.2 (5)
Acute myocardial infarction	0.6 (11)	0.5 (9)	0.3 (1)	0	0.6 (12)	0.4 (9)
Hypoglycemia	0.2 (3)	0.2 (4)	2.8 (8)	0.3 (1)	0.5 (11)	0.2 (5)
Pneumonia	0.4 (8)	0.2 (4)	0	0.3 (1)	0.4 (8)	0.2 (5)
Coronary artery disease	0.4 (8)	0.5 (9)	0	0	0.4 (8)	0.4 (9)
Angina unstable	0.2 (4)	0.1 (1)	0	0.7 (2)	0.2 (4)	0.1 (2)

Abbreviations: % = percentage of participants with one or more events; * percentage was adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials; N = number of participants with one or more events; SAE = serious adverse event; T1D = type 1 diabetes; T2D = type 2 diabetes.

11.2.2 Adverse events in subgroups

Since intrinsic and extrinsic factors may have an impact on the safety profile, various subgroups have been analyzed. The adverse event profile, including SAEs and severe AEs, in subgroups of participants based on intrinsic factors (sex, age, race, ethnicity, baseline BMI, baseline HbA_{1c}, diabetes duration, baseline renal function, baseline hepatic function) and extrinsic factors (region, pre-trial insulin treatment) was explored in both T2D pool and T1D populations. Overall, no treatment difference was found within each subgroup, indicating that the AE profile was not linked to intrinsic or extrinsic factors (data not shown).

11.2.3 Adverse events leading to permanent treatment discontinuation

In both T2D and T1D population, the proportions of participants with AEs leading to permanent treatment discontinuation were similar in the 2 treatment arms (Table 11-4).

Table 11-4 T2D and T1D – Participants experiencing an AE leading to treatment discontinuation

	T2D pool				T1D			
	Insulin icodec		Daily basal insulin		Insulin icodec		Insulin degludec	
	N	% *	N	% *	N	%	N	%
AEs leading to permanent treatment discontinuation	24	1.3	20	1.1	1	0.3	1	0.3
SAEs leading to permanent treatment discontinuation	12	0.6	15	0.8	1	0.3	0	

Abbreviations: N = number of participants with one or more events, % = percentage of participants with one or more events; (S)AE = (serious) adverse event; T1D = type 1 diabetes; T2D = type 2 diabetes; * percentage was adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials

In the reported AEs leading to permanent treatment discontinuation, no pattern with regards to the preferred term, the timing or type of AE was observed.

11.2.4 Deaths

Fatal outcomes were rare and reported for similar proportions of participants in the insulin icodec and daily basal insulin arms in all ONWARDS trials. The reasons for death were similar between the two treatment arms, with no clustering of events in any system organ class (Table 11-5). The total number of participants who had one or more fatal events was 15 (0.7%) in the insulin icodec arm and 14 (0.6%) in the daily basal insulin arm.

Table 11-5 T2D and T1D – Adverse events with fatal outcome by system organ class

	Insulin icodec N (%)	Daily basal insulin N (%)
T2D pool		
Infections and infestations	6 (0.3%)	3 (0.2%)
Cardiac disorders	3 (0.2%)	5 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.2%)	3 (0.2%)
Respiratory, thoracic and mediastinal	1 (0.1%)	1 (0.1%)
General disorders and administration site conditions	1 (0.1%)	3 (0.2%)
Renal and urinary disorders	1 (0.1%)	0
Gastrointestinal disorders	1 (0.1%)	1 (0.1%)
Vascular disorders	1 (0.1%)	0
Nervous system disorders	0	1 (0.1%)
Metabolism and nutrition disorders	0	1 (0.1%)
T1D		
Nervous system disorders	1 (0.1%)	0

Abbreviations: N = number of participants with one or more events; % = percentage of participants with one or more events; T1D = type 1 diabetes; T2D = type 2 diabetes; for T2D pool, percentages were adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials

11.3 Safety focus areas

Based on the therapeutic experience with insulins and regulatory feedback and requirements, several safety focus areas, as well as standard safety focus areas, were pre-defined for evaluation during the phase 3 program of insulin icodec.

No differences were identified between treatment arms in any of the safety focus areas, in terms of event rate per 100 PYE or proportion of participants (Table 11-6), with the exception of medication errors that were more frequent in the insulin icodec arm and are discussed in Section 11.3.2. Evaluation of cardiovascular disorders is presented in Section 11.3.1.

Table 11-6 T2D and T1D – Proportion of participants with AEs in the safety focus areas

	T2D pool				T1D			
	Insulin icodec		Daily basal insulin		Insulin icodec		Insulin degludec	
Safety focus area	**N (%)***	**R***	**N (%)***	**R***	**N (%)**	**R**	**N (%)**	**R**
Neoplasm	68 (3.6)	4.37	66 (3.5)	4.77	15 (5.2)	5.00	14 (4.8)	5.17
Retinal disorders	128 (6.8)	10.09	135 (7.2)	11.05	37 (12.8)	15.66	35 (12.0)	14.54
Hyperglycemia incl. DKA	14 (0.7)	0.88	22 (1.2)	1.32	1 (0.3)	0.33	2 (0.7)	0.65
Hypokalemia	2 (0.1)	0.13	2 (0.1)	0.07	1 (0.3)	0.33	0	
Other microvascular diabetic complications	14 (0.7)	0.80	22 (1.2)	1.37	2 (0.7)	0.67	2 (0.7)	0.65
Clinically meaningful peripheral oedema	26 (1.4)	1.67	24 (1.3)	1.17	3 (1.0)	1.00	3 (1.0)	0.97
Lipodystrophy	1 (0.1)	0.03	3 (0.2)	0.16	0		0	
Localized amyloidosis	0		0		0		0	
Injection site reactions[a]	42 (2.2)	6.67	35 (1.9)	4.13	1 (0.3)	0.67	2 (0.7)	0.65
Medication errors	23 (1.2)	1.93	26 (1.4)	2.52	16 (5.5)	6.00	7 (2.4)	2.58
Hypersensitivity reactions	69 (3.7)	4.52	78 (4.2)	5.38	36 (12.4)	14.66	41 (14.0)	15.50
Rare events[b]	88 (4.7)	5.47	95 (5.1)	6.00	23 (7.9)	7.66	13 (4.5)	4.52

Abbreviations: % = percentage of participants with one or more events; *percentages and rates were adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials; AE = adverse event; R = rate (number of adverse events per 100 PYE); PYE = patient years of exposure (1 PYE = 365.25 days); DKA = diabetic ketoacidosis; T1D = type 1 diabetes; T2D = type 2 diabetes

Notes: [a]56% of all injection site reactions and 76% of the injection site reactions observed in the insulin icodec arm were reported in ONWARDS 3 (double-dummy); [b]Safety evaluation of rare events did not suggest an increased risk of any specific rare event in the insulin icodec arm compared to the daily basal insulin arm.

11.3.1 Cardiovascular disorders

The risk of CV disorders was evaluated based on ECG data and adjudicated outcomes of selected, pre-defined CV events. In addition, a prospectively planned meta-analysis of MACE (CV death, myocardial infarction (MI) and stroke) has been carried out to further investigate the cardiovascular profile of insulin icodec. Time to occurrence of first EAC-confirmed MACE was analyzed by a Cox regression model stratified by trial and with treatment as explanatory variable. The meta-analysis was considered exploratory due to an anticipated low number of MACE events across the phase 3a program and no formal statistical hypothesis testing was performed.

Overall, in the ONWARDS trials, there was no indication of an increased risk of CV disorders in the insulin icodec arms compared to the daily basal insulin arms based on the evaluation of EAC-confirmed CV events, ECG data and meta-analysis of MACE from the ONWARDS trials.

Across the ONWARDS trials, 105 events in the insulin icodec arm were sent for adjudication, and 29 were confirmed as MACE by the EAC. In the daily basal insulin arm, 93 events were sent for adjudication of which 33 were confirmed as MACE by the EAC.

EAC-confirmed CV events were reported in similar proportions of participants in the 2 treatment arms in T2D trials (ONWARDS 1 to 5) and in T1D (ONWARDS 6) (Table 11-7).

Table 11-7 T2D and T1D – Proportion of participants with EAC-confirmed cardiovascular events

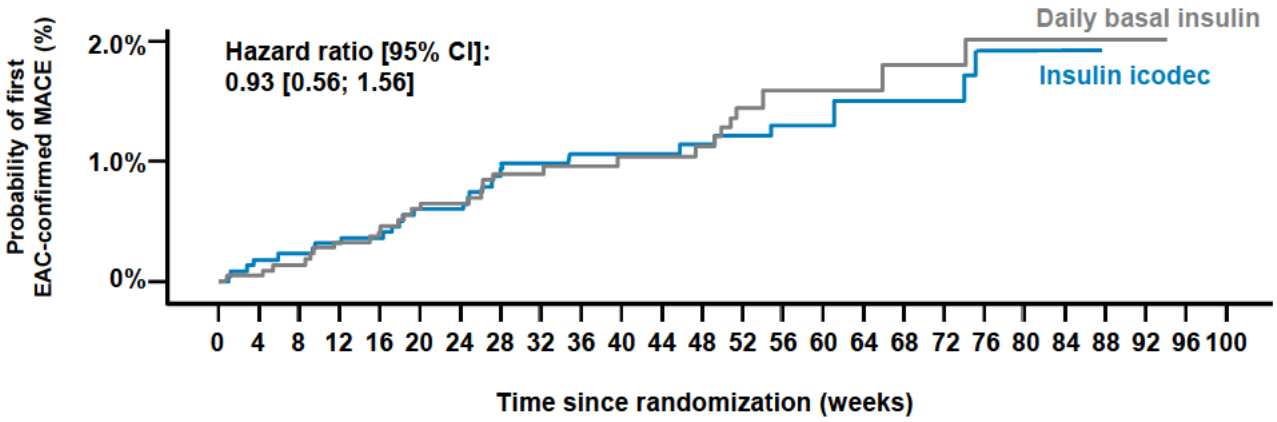
	T2D pool		T1D	
	Insulin icodec, %* (N)	Daily basal insulin, %* (N)	Insulin icodec, % (N)	Insulin degludec, % (N)
Acute coronary syndrome	1.2 (22)	0.8 (15)	0.3 (1)	0.7 (2)
Acute myocardial infarction	1.0 (19)	0.7 (14)	0.3 (1)	0
Hospitalization for unstable angina pectoris	0.2 (3)	0.1 (1)	0	0.7 (2)
Cerebrovascular event	0.3 (5)	0.6 (11)	0.7 (2)	0.3 (1)
Stroke	0.3 (5)	0.6 (11)	0.7 (2)	0.3 (1)
Heart failure	0.3 (5)	0.2 (4)	0.3 (1)	0
Heart failure hospitalization	0.3 (5)	0.2 (4)	0.3 (1)	0
Urgent heart failure visit	0	0.1 (1)	0	0
CV Death	0.1 (2)	0.4 (7)	0	0
Undetermined cause of death	0.2 (3)	0.1 (2)	0	0

Notes: CV = cardiovascular; EAC = event adjudication committee; N = number of participants with one or more events, % = percentage of participants with one or more events; T1D = type 1 diabetes; T2D = type 2 diabetes; *adjusted percentages were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials

There were no clinically relevant differences between insulin icodec and daily basal insulin in the improvement or deterioration of ECG categories.

The exploratory meta-analysis of MACE showed that participants treated with insulin icodec had a similar incidence of major adverse cardiovascular events (3-component MACE consisting of MI, stroke, or CV death) when compared to those treated with daily basal insulin. The estimated hazard-rate from the analysis of time to first EAC-confirmed MACE showed that the occurrence in the ONWARDS trials (pool of ONWARDS 1 to 6) was similar in the insulin icodec arm and daily basal insulin arm (HR: 0.84; 95% CI [0.48;1.49]) (Figure 11-2).

Figure 11-2 T2D and T1D – Time to first EAC confirmed MACE – cumulative incidence plot



Notes: Cumulative incidence estimate for first MACE during in-trial period.

Abbreviations: EAC: event adjudication committee; MACE = major adverse cardiovascular events with adjudication outcome of either CV death, myocardial infarction (acute myocardial infarction) or stroke (ischemic, hemorrhagic, or undetermined stroke)

11.3.2 Medication errors

Across phase 3a trials, a MedDRA search for medication errors (including misuse and abuse), identified 80 events in 72 participants with T2D or T1D across both treatment arms. Most of the events were mild, non-serious and all except one event in the daily basal insulin arm were reported as recovered.

The overall number of medication errors was comparable between the insulin icodec and daily basal insulin arms, with the exception for "accidental overdose" that was more frequent in the insulin icodec arm (Appendix A, Table 14-6).

In the trials with a higher single starting dose of insulin icodec (ONWARDS 2, 4 and 6), a cluster of overdose and dosing error events 25 events in 24 participants) was seen in the insulin icodec treatment arm during the first 9 days on trial product. This period corresponds to the first and second dose of insulin icodec indicating that these events occurred in relation to the higher single starting dose (see dosing initiation algorithm in Table 7-1). No similar clusters were seen in the comparator arm, as well as in the trials without single higher starting dose, where medication errors were reported at a lower frequency and more evenly distributed in time and across preferred terms.

In the insulin icodec arm, none of the overdose events occurring during the first 9 days was associated with level 3 hypoglycemia or additional adverse events, while one event was associated to level 2 hypoglycemia, another event to both level 1 and 2 hypoglycemia and six events to level 1 hypoglycemia.

In summary there were no severe clinical consequences from the overdoses reported in relation to the insulin icodec starting dose. The risk of medication errors for insulin icodec is described in the proposed label.

11.3.3 Immunogenicity

As for any protein-based drug, including insulins, treatment with insulin icodec may lead to the development of anti-insulin icodec antibodies which may affect the insulin icodec clinical effect.[103] Therefore, immunogenicity was assessed throughout the insulin icodec clinical development program, specifically in T2D populations naïve (ONWARDS 3), on basal-only prior to trial (ONWARDS 2) and on basal-bolus prior to trial (ONWARDS 4), and in people with T1D (ONWARDS 6).

In all populations, the likelihood that insulin icodec treatment induces anti-insulin icodec antibodies is considered high (70.2% to 82.1%) with the large majority cross-reacting with human insulin (66.7% to 78.5%).

Based on the statistical and descriptive analyses, the effect of anti-insulin icodec antibodies on pharmacokinetic properties of insulin icodec is considered of no clinical relevance (Figure 6-4), and the presence of anti-insulin icodec antibodies did not seem to affect either the overall efficacy or safety profile of insulin icodec. Furthermore, the presence of anti-insulin icodec antibodies did not appear to correlate with AEs such as injection site reactions or hypersensitivity reactions. The low number of systemic hypersensitivity events does not allow evaluation of their possible relationship to the presence of anti-insulin icodec antibodies.

11.4 Body weight

Basal insulin treatment is generally associated with weight gain.[104] As expected, body weight increased across trials and treatment arms, except for ONWARDS 2, where weight was unexpectedly stable for participants in the daily basal insulin arm. There was a trend of higher weight gain in the insulin icodec arm compared to the daily basal insulin arm (Table 11-8).

The weight increases and differences observed in ONWARDS 1-6 were reflective of the class effect of insulin treatment.[104]

Table 11-8 T2D and T1D – Body weight at end of treatment by trial – change from baseline

Trial	Estimated change from baseline (kg)		Treatment difference (kg)	
	Insulin icodec	Daily basal insulin	Estimate	[95% CI]
ONWARDS 1 (week 26)	2.29	1.83	0.46	[-0.12 ; 1.04]
ONWARDS 1 (week 78)	2.22	1.58	0.64	[-0.02 ; 1.30]
ONWARDS 2	1.40	-0.30	1.70	[0.76 ; 2.63]
ONWARDS 3	2.77	2.32	0.46	[-0.19 ; 1.10]
ONWARDS 4	2.73	2.16	0.57	[-0.39 ; 1.54]
ONWARDS 5	2.28	1.45	0.83	[-0.37 ; 2.02]
ONWARDS 6 (week 26)	1.29	1.01	0.28	[-0.37 ; 0.92]
ONWARDS 6 (week 52)	1.25	1.67	-0.42	[-1.20 ; 0.37]

Abbreviations: CI = confidence interval; T1D = type 1 diabetes; T2D = type 2 diabetes

12 Benefit/risk profile

12.1 Type 2 diabetes

Across all T2D ONWARDS trials, insulin icodec effectively reduced HbA_{1c} of a magnitude that is known to be associated to a significant reduction of the risk of macro- and microvascular complications.[29,30] Compared to daily basal insulins, insulin icodec was found to be statistically superior in HbA_{1c} reduction in T2D insulin naïve participants and participants switching from another daily basal insulin, and non-inferior in T2D participants on basal-bolus prior trial. Although statistical superiority was achieved, the clinical relevance of the difference between treatments has not been established.

As for all insulins, the main risk with insulin icodec is hypoglycemia. Importantly, in the ONWARDS program, 85.9-90.2% of participants with T2D treated with insulin icodec on basal only (either insulin naïve or on daily basal only prior to trial) and 48.5% of participants on basal-bolus did not experience any clinically significant or severe (level 2 or level 3) hypoglycemic episode. The risk of level 3 hypoglycemia in all T2D phase 3a trials was very low and similar between treatment arms (8 vs 14 episodes in insulin icodec arm vs daily basal insulin, over a total of 4340 participants with T2D). Novo Nordisk acknowledges that the rate of level 2 hypoglycemia was higher among participants treated with insulin icodec than with daily basal insulins, with a few participants contributing with many episodes. To put the rates observed in the clinical trials into context, they correspond to 1 additional level 2 hypoglycemic episode per person within the next 6–7 years if a person with T2D starts with insulin icodec instead of a daily basal insulin. The overall level 2 hypoglycemia rates were considered low and comparable to the rates reported in the literature for daily basal insulins.[105,106]

In addition to providing effective glycemic control, insulin icodec has been designed for once weekly administration, meaning a reduction from 365 injections to 52 injections of basal insulin per year, for people living with T2D needing insulin treatment. The literature currently lacks an evaluation of the comprehensive advantages associated with reducing basal insulin injections from daily to once weekly, as such option is currently not available for people in the need of insulin treatment. However, real-world evidence pertaining to once-weekly GLP-1 receptor agonists (GLP-1 RA) show that inherent benefits linked to this less frequent injection regimen include heightened treatment persistence and improved therapy adherence.[62,63] Although per design this has not been confirmed in the ONWARDS trials, insulin icodec has the potential to prevent delays in insulin therapy initiation and to improve adherence and persistence, similarly to what was observed with once-weekly GLP-1 RAs. It is well known that initiation of insulin treatment on time and therapy adherence are associated with a better glycemic control leading to long-term reduction of the risk of micro- and macrovascular complications.

In conclusion, Novo Nordisk considers that the benefit risk profile of insulin icodec in T2D is favorable and supports the approval of insulin icodec in T2D.

12.2 Type 1 diabetes

During the main phase of the ONWARDS 6 clinical trial, insulin icodec demonstrated non-inferior glycemic improvement from baseline compared to insulin degludec, assessed by change in HbA_{1c}.

The magnitude of HbA_{1c} reduction observed in the trial is known to be associated with a significant reduction in the risk of macro- and microvascular complications, including preventing blindness, kidney failure with need for dialysis, and amputation due to neuropathy. [31,32,33,9, 10]

As in type 2 diabetes, adherence remains a challenge in individuals with type 1 diabetes. Data coming from the literature on other drugs - both in the diabetes as well as in other therapeutic areas - suggest that given its once-weekly administration, insulin icodec has the potential to increase therapy adherence compared to once-daily insulins. As discussed in Section 2.3, high adherence directly correlates with better glycemic control and thus with the potential for a reduced risk of diabetes-related long-term complications. Improved prevention of short-term complications including symptomatic hyperglycemia and diabetic ketoacidosis is also associated with improved adherence. Therefore, insulin icodec may represent a valuable treatment alternative for people with T1D who perceive daily therapy adherence as a burden or who struggle with consistent daily insulin use for a number of reasons, and thus could greatly benefit from its unique once-weekly administration. It is important to note that neither these specific populations nor therapy adherence were specifically investigated in the ONWARDS 6 trial, because of the intrinsic limitations of a clinical trial setting. Nonetheless, healthcare providers will be able to identify patients for whom initiation or adherence are challenging, allowing the unique benefits of insulin icodec to be realized in practice.

The safety profile was similar between treatment arms except for hypoglycemia, where a higher risk was identified for insulin icodec compared to insulin degludec. When evaluating the risk of hypoglycemia for insulin icodec, it is important to consider the general limitations of a controlled clinical trial that may not directly translate into real world, and the unique aspects of ONWARDS 6, such as the daily insulin used as a comparator. However, since the impact of these factors is not known, these considerations are intended to provide context, and not to negate the acknowledged increased risk of hypoglycemia in individuals with type 1 diabetes. In this context, it is important to note that the comparator was insulin degludec, which is the only basal insulin approved with a reduced hypoglycemia risk over the commonly used insulin glargine with regards to severe hypoglycemia. [96] Moreover, it should be noted that the overall rate of clinically significant or severe hypoglycemia (level 2 or level 3) as assessed in ONWARDS 6 was not higher than previously published treat-to-target studies investigating insulin degludec or insulin glargine U300, reaching a similar glycemic control in T1D. Of note, the rates of clinically significant hypoglycemia or equivalent were between 18 and 43 hypoglycemic episodes per PYE, although the titration target and definition of episodes were slightly different, and participants were not wearing a CGM was not open.[45,46,47,48] Hence the between trial comparisons should be done with caution.

Hypoglycemia is an inherent risk of all insulins and therefore has been carefully analyzed throughout ONWARDS 6 by pre-specified as well as post-hoc analyses. The rates of severe (level 3) hypoglycemic episodes – defined as associated with severe cognitive impairment requiring external assistance for recovery – were higher in the insulin icodec arm compared to insulin degludec. The proportion of participants who did not experience any severe (level 3) hypoglycemic episodes was 97% in both treatment arms. Higher rates of severe hypoglycemia occurring in similar proportions of participants indicate that a few participants in the insulin icodec arm experienced multiple episodes, which is in line with what is reported for daily basal insulins in people living with T1D. In ONWARDS 6, this is illustrated by a single participant in the insulin icodec arm who

experienced multiple severe (level 3) hypoglycemic episodes. It is important to note that, despite many episodes, this participant remained in the trial and that the rates of severe hypoglycemia markedly reduced after appropriate individualization of the insulin doses.

The rates of clinically significant (level 2) hypoglycemic episodes – defined by SMBG value <54 mg/dL, independently of the symptoms – and the proportion of patients reporting them were higher in the insulin icodec arm compared to insulin degludec. For a comprehensive profiling of the hypoglycemic risk CGM-based data should be also considered, as providing a more objective assessment. The estimated rate ratio of level 2 hypoglycemia based on CGM was lower than that based on SMBG (1.38 vs 1.88). Furthermore, time spent below range (TBR), assessed by CGM, is a parameter that closely relates to hypoglycemia. Comparing the TBR in participants treated with insulin icodec to TBR targets as defined by international guidelines is relevant to put insulin icodec hypoglycemia risk into clinical context. In the insulin icodec arm, TBR was at or below the threshold of internationally recommended targets.[24] Moreover, consistent with the reassuring results observed on CGM-based hypoglycemia, TBR in participants treated with insulin icodec was only slightly higher than in participants treated with insulin degludec.

In order to assess whether insulin icodec carries specific hypoglycemia risks or if hypoglycemia in insulin icodec treated participants with T1D is unique in its clinical presentation, the nature of hypoglycemic episodes and potential risk factors were analyzed.

In both treatment arms, hypoglycemia was similar in terms of duration, management, and recovery, indicating that the clinical consequences of the episodes occurring with insulin icodec do not differ from those occurring with insulin degludec, and that the episodes can be managed in the same way as people living with T1D manage the hypoglycemia risk with daily basal insulins. Furthermore, an exhaustive analysis of demographic and baseline characteristics has been performed to identify specific factors that could be associated with a higher risk of severe or clinically significant hypoglycemia in the insulin icodec arm. The intrinsic characteristics identified were identical in both treatment arms and had a similar impact on the risk of hypoglycemia. Importantly, they were consistent with those already established for daily basal insulins, and therefore well known by healthcare practitioners, who routinely use them to evaluate the best insulin therapy for individuals with T1D.[97] Thus, similar to current clinical practice for daily insulins, these factors can be used by healthcare practitioners to make an assessment of the hypoglycemia risk on an individual basis and evaluate if the benefits of once-weekly insulin icodec are likely to outweigh the risks.

A higher risk of hypoglycemia occurred in Days 2-4 of the week consistently across the ONWARDS 6 trial, reflecting insulin icodec's glucose lowering profile. This predictable profile will be communicated to healthcare practitioners and patients, and can guide them to more closely monitor hypoglycemic risk on those days, as well as to adopt proactive actions to compensate the expected low glycemia, such as adjustment of bolus dose or careful planning of daily activities.

All data collected in ONWARDS 6 should be used in the context of real-world clinical practice, which takes into account the needs of people with T1D and how they are currently treated. Because of the complete absence of endogenous insulin, people with T1D rely on exogenous insulin or insulin analogs for life. Unfortunately, all currently available basal insulins carry a risk of hypoglycemia. People living with T1D are experienced users of insulins and have a good understanding of the risk of hypoglycemia and its management. Similarly, healthcare practitioners

understand the risk factors for hypoglycemia, both when initiating therapy and during the course of treatment. In order to identify the best therapy, individuals living with T1D and their healthcare practitioners currently work together to customize comprehensive treatment programs with the aim of achieving glycemic control, while minimizing the risk of hypoglycemia. These risks are continually reassessed, and adjustments can be made to the basal insulin based on the individual's changing status. The increasing use of CGM will provide additional information to the healthcare team allowing any needed dose adjustments to be made in a timely manner. Since both risk factors and management of hypoglycemia do not differ for insulin icodec vs currently available daily basal insulins, insulin icodec will be readily integrated into decision making and prescribing by practitioners.

In summary, the choice of basal insulin for a person living with T1D should be based on an accurate evaluation of that individual's characteristics and personal needs, balancing benefits and risks. Insulin icodec should be used to treat people with T1D when a benefit from a once-weekly posology can be anticipated and risks can be managed, based on the well characterized risk factors and weekly profile. As for any other insulin, in clinical practice, people with diabetes experiencing frequent episodes of severe (level 3) or clinically significant hypoglycemia (level 2) would likely be guided by their healthcare practitioners to decrease the insulin dose, relax the glycemic target or even switch to a different insulin.[107] Therefore, Novo Nordisk is of the opinion that the risk of hypoglycemia with insulin icodec treatment in individuals with T1D can be effectively mitigated by providing guidance to healthcare practitioners, who will consider the individual clinical situation and the product characteristics.

Based on the presented clinical data and adequate risk management, once-weekly insulin icodec is evaluated to be associated with a favorable benefit-risk profile and represents an alternative option to daily basal insulin for some people living with type 1 diabetes.

12.2.1 Risk mitigation

Data from the ONWARDS 6 clinical trial show that the risk of hypoglycemia is higher for insulin icodec, compared to insulin degludec in participants with T1D. However, as for daily basal insulins, hypoglycemia risk can be mitigated by carefully evaluating each individual's clinical history, baseline and demographic characteristics, lifestyle, as well as the product characteristics. As described, the occurrence of hypoglycemia with insulin icodec is characterized by the same well-known risk factors as daily basal insulins. To aid in appropriate patient selection, Novo Nordisk will reinforce measures for hypoglycemia mitigation, such as excluding people with T1D with hypoglycemia unawareness or recurrent severe hypoglycemia. If a patient experiences recurrent hypoglycemia while using insulin icodec, patients should consult their healthcare provider to consider treatment adjustments (e.g. adjustment of the titration target and/or dose reduction) or switch to other treatment options. Furthermore, data from ONWARDS 6 showed that hypoglycemia occurring with insulin icodec has a predictable pattern over the week, in line with the pharmacodynamic profile. Novo Nordisk will ensure that the higher hypoglycemia risk observed on the days with maximum glucose lowering effect (Days 2-4) will be communicated to the healthcare practitioners and people with T1D wishing to use insulin icodec, allowing for a safe use of insulin icodec in an individualized manner. The higher risk could also be mitigated by recommending wearing a CGM device, which will ensure a closer monitoring of glycemic level.

Novo Nordisk believes that these measures will guide patients and physicians to safely use once-weekly insulin icodec in people with T1D.

13 REFERENCES

1. Federation ID. IDF Diabetes Atlas, 10th Edition. Brussels, Belgium2021.
2. Centers for Disease and Control and Prevention. National Diabetes Statistics Report website [cited 2023 21 April].
3. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405-12.
4. American Diabetes Association. 13. Children and Adolescents:. Diabetes Care. 2019;42(Suppl 1):S148-S64.
5. Danne T, Becker D. Paediatric diabetes: achieving practical, effective insulin therapy in type 1 and type 2 diabetes. Acta Paediatr. 2007;96(11):1560-70.
6. Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care. 2005;28(1):186-212.
7. Khunti K, Millar-Jones D. Clinical inertia to insulin initiation and intensification in the UK: A focused literature review. Prim Care Diabetes. 2017;11(1):3-12.
8. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. Diabet Med. 2012;29(5):682-9.
9. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30-Year Follow-up. Diabetes Care. 2016;39(5):686-93.
10. The Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes. 1995;44(8):968-83.
11. Carr ALJ, Evans-Molina C, Oram RA. Precision medicine in type 1 diabetes. Diabetologia. 2022;65(11):1854-66.
12. Rosenstock J, Bain SC, Gowda A, Jódar E, Liang B, Lingvay I, et al. Weekly Icodec versus Daily Glargine U100 in Type 2 Diabetes without Previous Insulin. N Engl J Med. 2023;389(4):297-308.
13. Philis-Tsimikas A, Asong M, Franek E, Jia T, Rosenstock J, Stachlewska K, et al. Switching to once-weekly insulin icodec versus once-daily insulin degludec in individuals with basal insulin-treated type 2 diabetes (ONWARDS 2): a phase 3a, randomised, open label, multicentre, treat-to-target trial. Lancet Diabetes Endocrinol. 2023;11(6):414-25.
14. Lingvay I, Asong M, Desouza C, Gourdy P, Kar S, Vianna A, et al. Once-Weekly Insulin Icodec vs Once-Daily Insulin Degludec in Adults With Insulin-Naive Type 2 Diabetes: The ONWARDS 3 Randomized Clinical Trial. JAMA. 2023;330(3):228-37.
15. Mathieu C, Ásbjörnsdóttir B, Bajaj HS, Lane W, Matos ALSA, Murthy S, et al. Switching to once-weekly insulin icodec versus once-daily insulin glargine U100 in individuals with basal-bolus insulin-treated type 2 diabetes (ONWARDS 4): a phase 3a, randomised, open-label, multicentre, treat-to-target, non-inferiority trial. Lancet. 2023;401(10392):1929-40.
16. Bajaj HS, Aberle J, Davies M, Donatsky AM, Frederiksen M, Yavuz DG, et al. Once-Weekly Insulin Icodec With Dosing Guide App Versus Once-Daily Basal Insulin Analogues in Insulin-Naive Type 2 Diabetes (ONWARDS 5) : A Randomized Trial. Ann Intern Med. 2023;176(11):1476-85.
17. Russell-Jones D, Babazono T, Cailleteau R, Engberg S, Irace C, Kjaersgaard MIS, et al. Once-weekly insulin icodec versus once-daily insulin degludec as part of a basal-bolus

regimen in individuals with type 1 diabetes (ONWARDS 6): a phase 3a, randomised, open-label, treat-to-target trial. Lancet. 2023;402(10413):1636-47.
18. International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2017;40(1):155-7.
19. American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S55-S64.
20. Abraham MB, Jones TW, Naranjo D, Karges B, Oduwole A, Tauschmann M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes. 2018;19 Suppl 27:178-92.
21. Agiostratidou G, Anhalt H, Ball D, Blonde L, Gourgari E, Harriman KN, et al. Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care. 2017;40(12):1622-30.
22. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017;40(12):1631-40.
23. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384-95.
24. Battelino T, Alexander CM, Amiel SA, Arreaza-Rubin G, Beck RW, Bergenstal RM, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. Lancet Diabetes Endocrinol. 2023;11(1):42-57.
25. European Medicines Agency. Guidance on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus 2023 [16 Jan 2024].
26. Food and Drug Administration. Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products. Draft Guidance (fda.gov). 2023 [16 Jan 2024].
27. American Diabetes Association Professional Practice Committee. 6. Glycemic Goals and Hypoglycemia: Standards of Care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S111-S25.
28. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593-603.
29. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-53, Erratum 1999; 354: 602.
30. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577-89.
31. Aiello LP, Group DER. Diabetic retinopathy and other ocular findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care. 2014;37(1):17-23.
32. de Boer IH, Group DER. Kidney disease and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care. 2014;37(1):24-30.

33. Martin CL, Albers JW, Pop-Busui R, Group DER. Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care. 2014;37(1):31-8.
34. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet. 2018;391(10138):2449-62.
35. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. Endocrinol Metab Clin North Am. 2010;39(3):481-97.
36. Leahy JL. Pathogenesis of type 2 diabetes mellitus. Arch Med Res. 2005;36(3):197-209.
37. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am. 2004;88(4):787-835, ix.
38. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. Phys Ther. 2008;88(11):1322-35.
39. Mulnier HE, Seaman HE, Raleigh VS, Soedamah-Muthu SS, Colhoun HM, Lawrenson RA, et al. Risk of stroke in people with type 2 diabetes in the UK: a study using the General Practice Research Database. Diabetologia. 2006;49(12):2859-65.
40. Mahmood D, Singh BK, Akhtar M. Diabetic neuropathy: therapies on the horizon. J Pharm Pharmacol. 2009;61(9):1137-45.
41. Tahrani AA, Askwith T, Stevens MJ. Emerging drugs for diabetic neuropathy. Expert Opin Emerg Drugs. 2010;15(4):661-83.
42. Committee ADAPP. 7. Diabetes Technology: Standards of Care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S126-S44.
43. Ebekozien O, Mungmode A, Sanchez J, Rompicherla S, Demeterco-Berggren C, Weinstock RS, et al. Longitudinal Trends in Glycemic Outcomes and Technology Use for Over 48,000 People with Type 1 Diabetes (2016-2022) from the T1D Exchange Quality Improvement Collaborative. Diabetes Technol Ther. 2023;25(11):765-73.
44. Gandhi K, Ebekozien O, Noor N, McDonough RJ, Hsieh S, Miyazaki B, et al. Insulin Pump Utilization in 2017-2021 for More Than 22,000 Children and Adults With Type 1 Diabetes: A Multicenter Observational Study. Clin Diabetes. 2024;42(1):56-64.
45. Home PD, Bergenstal RM, Bolli GB, Ziemen M, Rojeski M, Espinasse M, et al. New Insulin Glargine 300 Units/mL Versus Glargine 100 Units/mL in People With Type 1 Diabetes: A Randomized, Phase 3a, Open-Label Clinical Trial (EDITION 4). Diabetes Care. 2015.
46. Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet. 2012;379(9825):1489-97.
47. Lane W, Bailey TS, Gerety G, Gumprecht J, Philis-Tsimikas A, Hansen CT, et al. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial. JAMA. 2017;318(1):33-44.
48. Battelino T, Danne T, Edelman SV, Choudhary P, Renard E, Westerbacka J, et al. Continuous glucose monitoring-based time-in-range using insulin glargine 300 units/ml versus insulin degludec 100 units/ml in type 1 diabetes: The head-to-head randomized controlled InRange trial. Diabetes Obes Metab. 2023;25(2):545-55.
49. Rosenbloom AL, Silverstein JH, Amemiya S, Zeitler P, Klingensmith GJ. Type 2 diabetes in children and adolescents. Pediatr Diabetes. 2009;10 Suppl 12:17-32.
50. Pinhas-Hamiel O, Zeitler P. Acute and chronic complications of type 2 diabetes mellitus in children and adolescents. Lancet. 2007;369(9575):1823-31.
51. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position

statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012;55(6):1577-96.
52. Morales J. The Pharmacologic Basis for Clinical Differences Among GLP-1 Receptor Agonists and DPP-4 Inhibitors. Postgraduate Medicine. 2011;123(6):189-201.
53. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015;58(3):429-42.
54. A cap on insulin costs benefits millions of Americans with diabetes [internet] 2023 [cited 2023 15 Apr].
55. Cowie CC, Casagrande SS, Menke A, Cissell MA, Eberhardt MS, Meigs JB, et al. Diabetes in America. 2018.
56. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 7. Diabetes Technology: Standards of Care in Diabetes-2023. Diabetes Care. 2023;46(Suppl 1):S111-S27.
57. Boonpattharatthiti K, Saensook T, Neelapaijit N, Sakunrag I, Krass I, Dhippayom T. The prevalence of adherence to insulin therapy in patients with diabetes: A systematic review and meta-analysis. Res Social Adm Pharm. 2024;20(3):255-95.
58. Riaz M, Basit A, Fawwad A, Yakoob Ahmedani M, Ali Rizvi Z. Factors associated with non-adherence to insulin in patients with type 1 diabetes. Pak J Med Sci. 2014;30(2):233-9.
59. Perez-Nieves M, Boye KS, Kiljanski J, Cao D, Lage MJ. Adherence to Basal Insulin Therapy Among People with Type 2 Diabetes: A Retrospective Cohort Study of Costs and Patient Outcomes. Diabetes Ther. 2018;9(3):1099-111.
60. Ceriello A. The glucose triad and its role in comprehensive glycaemic control: current status, future management. Int J Clin Pract. 2010;64(12):1705-11.
61. Donnelly LA, Morris AD, Evans JM, Darts Memo collaboration. Adherence to insulin and its association with glycaemic control in patients with type 2 diabetes. QJM. 2007;100(6):345-50.
62. Polonsky WH, Arora R, Faurby M, Fernandes J, Liebl A. Higher Rates of Persistence and Adherence in Patients with Type 2 Diabetes Initiating Once-Weekly vs Daily Injectable Glucagon-Like Peptide-1 Receptor Agonists in US Clinical Practice (STAY Study). Diabetes Ther. 2022;13(1):175-87.
63. Mody R, Huang Q, Yu M, Zhao R, Patel H, Grabner M, et al. Adherence, persistence, glycaemic control and costs among patients with type 2 diabetes initiating dulaglutide compared with liraglutide or exenatide once weekly at 12-month follow-up in a real-world setting in the United States. Diabetes Obes Metab. 2019;21(4):920-9.
64. McNamara M, Turner-Bowker DM, Westhead H, Yaworsky A, Palladino A, Gross H, et al. Factors Driving Patient Preferences for Growth Hormone Deficiency (GHD) Injection Regimen and Injection Device Features: A Discrete Choice Experiment. Patient Prefer Adherence. 2020;14:781-93.
65. Cutter G, Veneziano A, Grinspan A, Al-Banna M, Boyko A, Zakharova M, et al. Satisfaction and adherence with glatiramer acetate 40mg/mL TIW in RRMS after 12 months, and the effect of switching from 20mg/mL QD. Mult Scler Relat Disord. 2020;40:101957.
66. Reginster JY, Rabenda V. Patient preference in the management of postmenopausal osteoporosis with bisphosphonates. Clin Interv Aging. 2006;1(4):415-23.
67. Johannsson G, Gordon MB, Rasmussen MH, Holme Håkonsson I, Karges W, Sværke C, et al. Once-weekly somapacitan is effective and well tolerated in adults with GH deficiency: a randomized phase 3 trial. J Clin Endocrinol Metab. 2020.

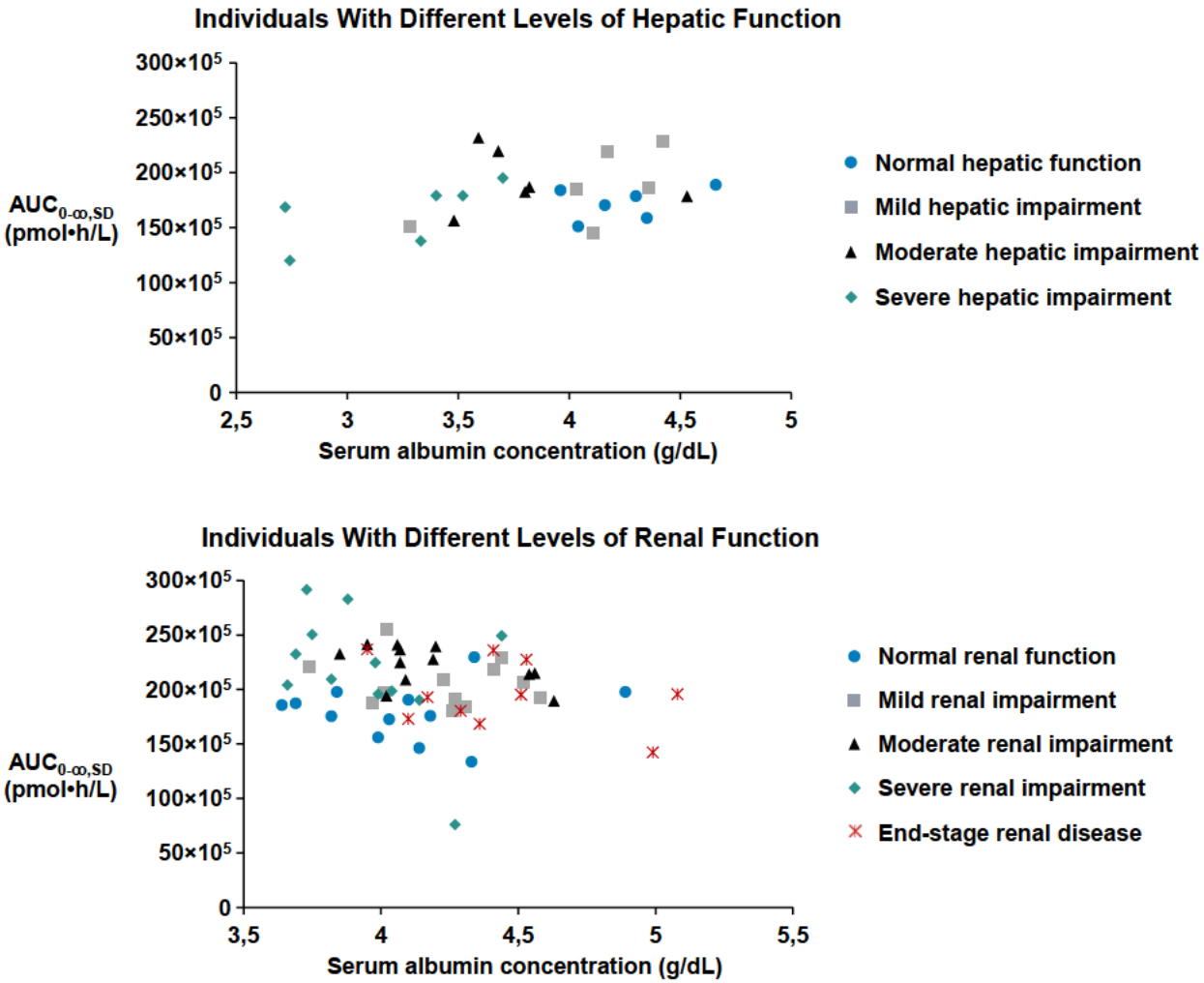
68. Johannsson G, Feldt-Rasmussen U, Håkonsson IH, Biering H, Rodien P, Tahara S, et al. Safety and convenience of once-weekly somapacitan in adult GH deficiency: a 26-week randomized, controlled trial. Eur J Endocrinol. 2018;178(5):491-9.
69. Committee ADAPP. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S52-S76.
70. Kunt T, Snoek FJ. Barriers to insulin initiation and intensification and how to overcome them. International Journal of Clinical Practice. 2009;63(164):6-10.
71. Vijan S, Hayward RA, Ronis DL, Hofer TP. Brief report: the burden of diabetes therapy: implications for the design of effective patient-centered treatment regimens. J Gen Intern Med. 2005;20(5):479-82.
72. Okemah J, Peng J, Quiñones M. Addressing Clinical Inertia in Type 2 Diabetes Mellitus: A Review. Adv Ther. 2018;35(11):1735-45.
73. Hauber AB, Johnson FR, Sauriol L, Lescrauwaet B. Risking health to avoid injections: preferences of Canadians with type 2 diabetes. Diabetes Care. 2005;28(9):2243-5.
74. Ali SN, Dang-Tan T, Valentine WJ, Hansen BB. Evaluation of the Clinical and Economic Burden of Poor Glycemic Control Associated with Therapeutic Inertia in Patients with Type 2 Diabetes in the United States. Adv Ther. 2020;37(2):869-82.
75. Ebekozien O, Noor N, Dimeglio L, Yau M, Rapaport JW-B, Hannon T, et al. 2022 State of Type 1 Diabetes in the U.S.—Real World T1D Exchange Multicenter Data from over 60,000 People. Diabetes. 2023;72.
76. Ekberg NR, Hartvig NV, Kaas A, Møller JB, Adolfsson P. Smart Pen Exposes Missed Basal Insulin Injections and Reveals the Impact on Glycemic Control in Adults With Type 1 Diabetes. J Diabetes Sci Technol. 2022:19322968221104142.
77. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Factors Associated with Injection Omission/Non-adherence in the Global Attitudes of Patients and Physicians in Insulin Therapy (GAPP) Study. Diabetes Obes Metab. 2012;9999(999A):10-1326.
78. Flores M, Amir M, Ahmed R, Alashi S, Li M, Wang X, et al. Causes of diabetic ketoacidosis among adults with type 1 diabetes mellitus: insulin pump users and non-users. BMJ Open Diabetes Res Care. 2020;8(2).
79. Nishimura E, Pridal L, Glendorf T, Hansen BF, Hubálek F, Kjeldsen T, et al. Molecular and pharmacological characterization of insulin icodec: a new basal insulin analog designed for once-weekly dosing. BMJ Open Diabetes Res Care. 2021;9(1).
80. Hubalek F, Refsgaard HHF, Gram-Nielsen S, Madsen P, Nishimura E, Munzel M, et al. Molecular engineering of safe and efficacious oral basal insulin. Nat Commun. 2020;11(1):3746.
81. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline E6(R1): Guideline for Good Clinical Practice. 10 Jun 1996.
82. MacIsaac RJ, Tsalamandris C, Panagiotopoulos S, Smith TJ, McNeil KJ, Jerums G. Nonalbuminuric renal insufficiency in type 2 diabetes. Diabetes Care. 2004;27(1):195-200.
83. Haahr H, Heise T. A Review of the Pharmacological Properties of Insulin Degludec and Their Clinical Relevance. Clinical Pharmacokinetics. 2014;53(9):787-800.
84. Rowland M, Tozer TN. Clinical pharmacokinetics and pharmacodynamics : concepts and applications. 4th ed. Philadelphia: Wolters Kluwer Health/Lippincott William & Wilkins. 2011.
85. Koehler G, Treiber G, Wutte A, Korsatko S, Mader JK, Semlitsch B, et al. Pharmacodynamics of the long-acting insulin analogues detemir and glargine following single-doses and under steady-state conditions in patients with type 1 diabetes. Diabetes Obes Metab. 2014;16(1):57-62.

86. Klein O, Lynge J, Endahl L, Damholt B, Nosek L, Heise T. Albumin-bound basal insulin analogues (insulin detemir and NN344): comparable time-action profiles but less variability than insulin glargine in type 2 diabetes. Diabetes Obesity & Metabolism. 2007;9(3):290-9.
87. Pieber TR, Arfelt KN, Cailleteau R, Hart M, Kar S, Mursic I, et al. Hypoglycaemia frequency and physiological response after double or triple doses of once-weekly insulin icodec vs once-daily insulin glargine U100 in type 2 diabetes: a randomised crossover trial. Diabetologia. 2023;66(8):1413-30.
88. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. Diabetes Care. 2023;46(Suppl 1):S140-S57.
89. Food and Drug Administration CaoC. Guidance for Industry. Non-Inferiority Clinical Trials to Establish Effectiveness. Nov 2016.
90. Chuang-Stein C, Beltangady M. Reporting cumulative proportion of subjects with an adverse event based on data from multiple studies. Pharm Stat. 2011;10(1):3-7.
91. Menke A, Orchard TJ, Imperatore G, Bullard KM, Mayer-Davis E, Cowie CC. The prevalence of type 1 diabetes in the United States. Epidemiology. 2013;24(5):773-4.
92. EMA. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. Rev. 2 ed22 Jun 2023.
93. Saisho Y. Use of Diabetes Treatment Satisfaction Questionnaire in Diabetes Care: Importance of Patient-Reported Outcomes. Int J Environ Res Public Health. 2018;15(5).
94. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003;41(5):582-92.
95. Mouelhi Y, Jouve E, Castelli C, Gentile S. How is the minimal clinically important difference established in health-related quality of life instruments? Review of anchors and methods. Health Qual Life Outcomes. 2020;18(1):136.
96. Novo Nordisk A/S. Tresiba® (insulin degludec), US Prescribing Information (PI). Jul 2022.
97. Giorda CB, Ozzello A, Gentile S, Aglialoro A, Chiambretti A, Baccetti F, et al. Incidence and risk factors for severe and symptomatic hypoglycemia in type 1 diabetes. Results of the HYPOS-1 study. Acta Diabetol. 2015;52(5):845-53.
98. Silbert R, Salcido-Montenegro A, Rodriguez-Gutierrez R, Katabi A, McCoy RG. Hypoglycemia Among Patients with Type 2 Diabetes: Epidemiology, Risk Factors, and Prevention Strategies. Curr Diab Rep. 2018;18(8):53.
99. Christiansen JS, Niskanen L, Rasmussen S, Johansen T, Fulcher G. Lower rates of hypoglycemia during maintenance treatment with insulin degludec/insulin aspart versus biphasic insulin aspart 30: a combined analysis of two Phase 3a studies in type 2 diabetes. J Diabetes. 2016;8(5):720-8.
100. Monnier L, Colette C, Wojtusciszyn A, Dejager S, Renard E, Molinari N, et al. Toward Defining the Threshold Between Low and High Glucose Variability in Diabetes. Diabetes Care. 2017;40(7):832-8.
101. Battelino T, Alexander CM, Amiel SA, Arreaza-Rubin G, Beck RW, Bergenstal RM, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. The Lancet Diabetes & Endocrinologic. 2023;11:42–57.
102. Surveillance - United States Diabetes Surveillance System (cdc.gov) 2023.
103. Jahn EM, Schneider CK. How to systematically evaluate immunogenicity of therapeutic proteins - regulatory considerations. N Biotechnol. 2009;25(5):280-6.
104. Blak BT, Smith HT, Hards M, Maguire A, Gimeno V. A retrospective database study of insulin initiation in patients with Type 2 diabetes in UK primary care. Diabet Med. 2012;29(8):e191-8.

105. Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T, et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care. 2012;35(12):2464-71.
106. Bode BW, Chaykin LB, Sussman AM, Warren ML, Niemeyer M, Rabol R, et al. Efficacy and safety of insulin degludec 200 U/mL and insulin degludec 100 U/mL in patients with type 2 diabetes (Begin: Compare). Endocr Pract. 2014;20(8):785-91.
107. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 6. Glycemic Targets: Standards of Care in Diabetes-2023. Diabetes Care. 2023;46(Suppl 1):S97-S110.
108. Little R, Rubin D. Statistical analysis with missing data. Sons. JW, editor. New York.: John Wiley & Sons. 1987.
109. Keene ON, Roger JH, Hartley BF, Kenward MG. Missing data sensitivity analysis for recurrent event data using controlled imputation. Pharm Stat. 2014;13(4):258-64.

14 Appendix A: Supporting figures and tables

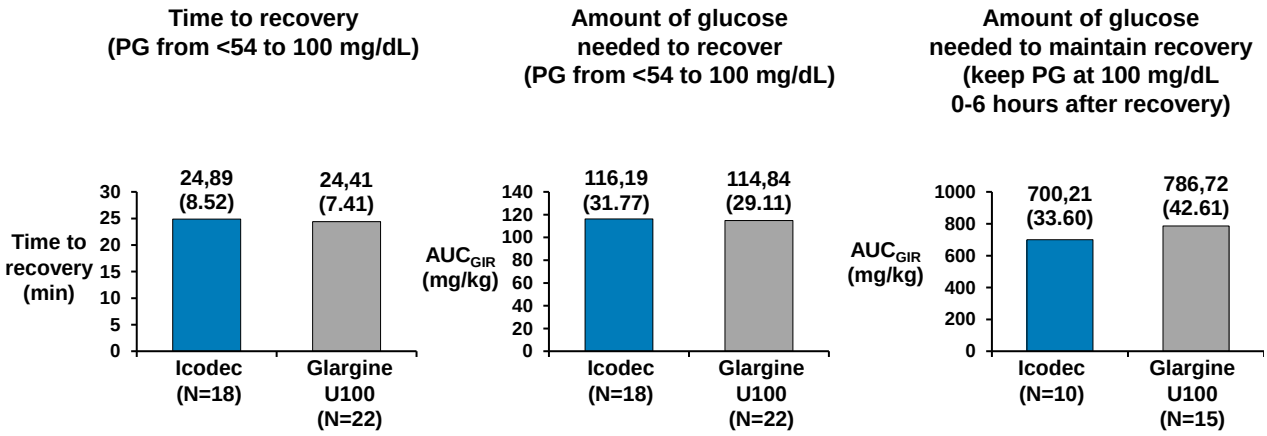
Figure 14-1 Total insulin icodec exposure versus baseline serum albumin concentration in individuals with different levels of hepatic or renal function



Abbreviations: AUC = area under the curve; CI = confidence interval; U = units

Notes: Top: Single dose of 1.5 U/kg insulin icodec (Trial 4570). Slope of log($AUC_{0-\infty,SD}$) versus log(baseline serum albumin) was not statistically significantly different from zero: 0.286, 95% CI [-0.102;0.674], p = 0.14. Bottom: Single dose of 1.5 U/kg insulin icodec (Trial 4226). Slope of log($AUC_{0-\infty,SD}$) versus log(baseline serum albumin) was not statistically significantly different from zero: -0.483, 95% CI [-1.367;0.401], p = 0.28.

Figure 14-2 Recovery from level 2 hypoglycemic episodes after triple doses of insulin icodec or insulin glargine U100 in individuals with T2D



Abbreviations: AUC = area under the curve; CV = coefficient of variation; GIR = glucose infusion rate; N = number of participants; PG = plasma glucose; SD = standard deviation; T2D = type 2 diabetes

Note: For time to PG recovery, mean and standard deviation (SD) are shown above the bars. For AUC_{GIR}, geometric mean (CV%) is shown above the bars. Trial 4462 was a crossover trial in individuals with T2D receiving double and triple doses of insulin icodec and insulin glargine U100 during insulin icodec treatment (for 6 weeks) and insulin glargine U100 treatment (for 11 days) at equimolar total weekly doses based on each participant's usual basal insulin dose. The double and triple doses were followed by hypoglycemia induction experiments, where PG was allowed to decrease to no less than 45 mg/dL. Thereafter, euglycemia was restored by constant IV glucose infusion (5.5 mg/kg/min) (left and middle panels) and maintained by variable glucose infusion (right panel).

Table 14-1 T2D – Participant disposition (including ONWARDS 1 extension)

	Insulin icodec		Daily basal insulin	
	N	%	N	%
Randomized	1882	100.0	1883	100
Exposed	1880	99.9	1878	99.7
Permanent discontinuation of trial product	122	6.5	113	6.0
Adverse event	33	1.8	26	1.4
Hypoglycemic episode	3	0.2	2	0.1
Protocol deviation	3	0.2	3	0.2
Lack of efficacy[a]	1	0.1	0	
Intensification to a basal bolus regime or continuous use of bolus insulin[b]	2	0.1	0	
Lost to follow up	16	0.9	22	1.2
Withdrawal of consent	31	1.6	36	1.9
Pregnancy	1	0.1	0	
Site closure	1	0.1	0	
Other	31	1.6	24	1.3
Withdrawn from trial	88	4.7	98	5.2
Withdrawal of consent by patient	43	2.3	45	2.4
Lost to follow up	21	1.1	30	1.6
Investigator decision	10	0.5	9	0.5
Death	12	0.6	14	0.7
Site closure	2	0.1	0	0
Completed trial*	1798	95.5	1793	95.2
Without permanent discontinuation of trial product	1760	93.5	1770	94.0
After permanent discontinuation of trial product	38	2.0	23	1.2

Abbreviations: N = number of participants; % = percentage of participants; T2D = type 2 diabetes

Notes: *week 78 visit in ONWARDS 1; [a]Lack of efficacy criterion applies to all trials except ONWARDS 5; [b]Intensification to a basal bolus regime or continuous use of bolus insulin only applies to ONWARDS 5.

Table 14-2 T1D – Participant disposition (including extension)

	Insulin icodec		Daily basal insulin	
	N	%	N	%
Randomized	290	100	292	100
Exposed	290	100	292	100
Permanent discontinuation of trial product	28	9.7	14	4.8
Adverse event	2	0.7	1	0.3
Hypoglycemic episode	1	0.3	0	
Protocol deviation	1	0.3	0	
Lost to follow up	0		1	0.3
Pregnancy	3	1.0	1	0.3
Withdrawal of consent	5	1.7	4	1.4
Other	16	5.5	7	2.4
Withdrawn from trial	16	5.5	11	3.8
Withdrawal of consent by patient	13	4.5	9	3.1
Lost to follow up	1	0.3	2	0.7
Investigator decision	1	0.3	0	0
Death	1	0.3	0	0
Completed trial (week 52)	274	94.5	282	96.6
Without permanent discontinuation of trial product	262	90.3	278	95.2
After permanent discontinuation of trial product	12	4.1	4	1.4

Abbreviations: N = number of participants; % = percentage of participants; T1D = type 1 diabetes

Table 14-3 T2D – Nocturnal hypoglycemic episodes - SMBG based

Trial	Classification	Insulin icodec (N = 1880)			Daily basal insulin (N = 1878)		
		%	E	R	%	E	R
Insulin naïve							
ONWARDS 1	**Level 1**	13.6	190	39.10	11.8	95	19.59
	Level 2	1.8	20	4.12	2.0	14	2.89
	Level 3	0			0.2	1	0.21
	Level 2+Level 3	1.8	20	4.12	2.2	15	3.09
ONWARDS 3	**Level 1**	8.2	40	23.41	7.8	37	21.62
	Level 2	0.3	2	1.17	1.4	5	2.92
	Level 3	0			0		
	Level 2+Level 3	0.3	2	1.17	1.4	5	2.92
ONWARDS 5	**Level 1**	8.9	107	19.12	8.6	213	37.99
	Level 2	2.0	13	2.32	2.0	18	3.21
	Level 3	0			0.2	1	0.18
	Level 2+Level 3	2.0	13	2.32	2.2	19	3.39
Basal switch							
ONWARDS 2	**Level 1**	22.9	144	92.76	13.3	102	66.77
	Level 2	6.1	32	20.61	3.4	13	8.51
	Level 3	0			0		
	Level 2+Level 3	6.1	32	20.61	3.4	13	8.51
Basal-bolus							
ONWARDS 4	**Level 1**	37.1	380	227.05	45.4	440	263.79
	Level 2	18.6	131	78.27	24.4	171	102.52
	Level 3	0			0.3	2	1.20
	Level 2+Level 3	18.6	131	78.27	24.7	173	103.72

Abbreviations: % = percentage of participants with or more events; N = number of participants; R = rate (number of adverse events per 100 PYE; 1 PYE = 365.25 days); T2D = type 2 diabetes

Note: Nocturnal hypoglycemic episodes are defined as episodes occurring between 00:01 and 05:59

Table 14-4 T1D – Nocturnal hypoglycemic episodes

Classification	Insulin icodec			Daily basal insulin		
	%	E	R	%	E	R
Level 1	73.8	980	6.89	58.6	734	5.09
Level 2	46.6	476	3.34	33.6	224	1.55
Level 3	0.7	5	0.04	1.0	3	0.02
Level 2 + Level 3	46.6	481	3.38	33.6	227	1.58

Abbreviations: % = percentage of participants with one or more events; E = number of events; R = rate (number of events per PYE; 1 PYE = 365.25 days); T1D = type 1 diabetes

Note: Nocturnal hypoglycemic episodes are defined as episodes occurring between 00:01 and 05:59

Table 14-5 T1D – Management of severe hypoglycemia (level 3)

	Ico			IDeg		
	N	E	(%)	N	E	(%)
Number of severe (level 3) hypoglycaemic episodes	9	47	(100.0)	9	17	(100.0)
Treatment(s) the patient received						
Glucagon	2	3	(6.4)	0		
Iv glucose (drip)	4	5	(10.6)	2	2	(11.8)
Something to drink or eat (carbohydrates)	7	42	(89.4)	7	13	(76.5)
Other	2	2	(4.3)	1	2	(11.8)
Treatment(s) the patient received, exclusive						
Intensive intervention	5	6	(12.8)	2	2	(11.8)
Something to drink or eat (carbohydrates), only	6	39	(83.0)	7	13	(76.5)
Other	2	2	(4.3)	1	2	(11.8)
Did the patient get help by a medical person to handle the episode?						
Yes	6	8	(17.0)	3	3	(17.6)
No	5	38	(80.9)	6	12	(70.6)
Unknown	1	1	(2.1)	1	2	(11.8)
Where did the patient get help?						
Clinic/emergency room/hospital	4	5	(10.6)	2	2	(11.8)
Other	6	42	(89.4)	7	15	(88.2)
Was the patient transported by ambulance?						
Yes	3	4	(8.5)	1	1	(5.9)
No	1	1	(2.1)	1	1	(5.9)
Missing	6	42	(89.4)	7	15	(88.2)
Did the patient experience convulsions or fits (Seizure)?						
Yes	1	1	(2.1)	2	2	(11.8)
No	8	46	(97.9)	7	15	(88.2)
Did the patient pass out (Loss of consciousness or coma)?						
Yes	5	10	(21.3)	3	3	(17.6)
No	4	37	(78.7)	6	14	(82.4)
Did the patient feel better after treatment?						
Yes	9	47	(100.0)	9	15	(88.2)
No	0			1	2	(11.8)

%: Percentage of events, E: Number of events, N: Number of subjects with one or more events. On-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit (FU2), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period. Main-on-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the end-date of the on-treatment period or the last planned visit in the main phase of the trial. Severe hypoglycaemia (level 3): Hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. Intensive intervention: Glucagon or iv glucose (drip).

Table 14-6 Medication errors by preferred term

	Insulin icodec		Daily basal insulin	
	N	E	N	E
TOTAL events	39	42	33	38
Accidental overdose	14	15	5	6
Incorrect dose administered	6	6	5	7
Prescribed overdose	5	5	0	
Overdose	4	4	4	4
Medication error	2	2	3	3
Product administration error	2	2	2	2
Underdose	2	2	5	5
Accidental underdose	1	1	0	
Product dispensing error	1	1	0	
Extra dose administered	1	1	1	1
Wrong product administered	1	2	6	6
Wrong dose	0		2	2
Intentional overdose	0		1	1
Drug abuse*	1	1	0	
Drug dependence	0		1	1

Abbreviations: N = number of participants with one or more events; E = number of events

Note: *"abuse" was reported as "dose abuse" in a participant who increased the dose of insulin icodec with 30U due to confusion and distraction, with no additional hypoglycemic episodes in the following weeks.

15 Appendix B: Statistical considerations

15.1 Missing data imputation for continuous endpoints

In the primary imputation model, missing values for the primary endpoint (regardless of treatment completion status) was imputed from trial participants, who had experienced an intercurrent event prior to the landmark visit and have a measurement at the landmark visit in the following way:

- First, one thousand (1000) copies of the dataset were generated for HbA_{1c}.
- Second, for participants who discontinued their randomized treatment or initiated treatment with bolus insulin for more than 2 weeks at any time prior to the landmark visit and have an HbA_{1c} measurement at the landmark visit, the change in HbA_{1c} from last available planned on-treatment value prior to the intercurrent event (LAOT-WOC) to the landmark visit was analyzed for each dataset copy using an analysis of covariance (ANCOVA) model with randomized treatment as fixed factor and LAOT-WOC value and the time point (study day) of this assessment as covariates. The estimated parameters, and their variances, from the model was used to impute missing HbA_{1c} values for the change from LAOT-WOC to the landmark visit and subsequently the missing HbA_{1c} value at the landmark visit.

In case the amount of data for the described imputation model (see second step above) was insufficient for meaningful imputation, the first alternative was the to simplify the imputation model by removing the following two covariates from the model: LAOT-WOC value and the time point (study day) of this assessment.

If the amount of data for this reduced model was still insufficient for meaningful imputation, a return-to-baseline imputation approach where missing values at landmark visit was imputed with baseline value adding a random error term. The random error term was considered normally distributed with mean zero and a standard deviation set equal to the estimated residual standard deviation of an ANCOVA analysis on the LAOT-WOC values. 1000 imputations were made.

Once missing data had been imputed, in each of the complete data sets, the endpoint was analyzed using the full ANCOVA model as specified in Section 8.3.5. The estimates and SDs for the 1000 data sets will be pooled to one estimate and associated SD using Rubin's rule[108].

The imputation model for primary and first alternative have underlying assumption that subjects with missing data behave similarly as subjects having an intercurrent event.

The imputation model for the second alternative has underlying assumption that subjects with missing data return to their baseline level.

An overview of which imputation approach that had to be applied can be found in Table 15-1.

Table 15-1 Imputation model for primary endpoint

	ONWARDS 1	ONWARDS 2	ONWARDS 3	ONWARDS 4	ONWARDS 5	ONWARDS 6
Including covariates*	X				X	X
Not including covariates		X	X			
Retrun-to-baseline				X		

Note: *covariates were last available HbA_{1c} value and study day of this assessment.

Missing values for the confirmatory secondary endpoint (TIR) and body weight was imputed in the same manner as the primary endpoint, whereas other continuous assessments were imputed by a return-to-baseline multiple imputation approach (if there was planned data collection at baseline) or based on trial participants in the comparator arm who had completed the trial and had a measurement at the landmark visit.

Intermediate missing CGM data (gaps in the profile) was not imputed. Following international consensus criteria, it was required that at least 70% of the planned CGM measurements during the last four weeks of treatment were available for endpoint data to be derived. Otherwise, the endpoint was set to being missing and imputed as described above.

15.2 Sensitivity analysis

A two-dimensional tipping point sensitivity analysis was performed on the primary and confirmatory endpoints to assess the robustness of the conclusions on non-inferiority and superiority respectively. Here, values, Δi, were added or subtracted to the imputed values (e.g., HbA_{1c}) before analyzing the data. A plot was constructed depicting which values of Δi would change the conclusion.

15.3 Missing data imputation for hypoglycemic episodes endpoints

Missing data for SMBG-based hypoglycemia was imputed in the following way:

For a subject with complete exposure time, L, i.e., no missing data, for any two disjoint time intervals [0, t0], [t0,L], the number of hypoglycemic episodes in the first interval, Y1, and in the second interval, Y2, are correlated, and it can be shown that the conditional distribution of Y2 given Y1 is also negative binomial. This result was used to impute missing data for Y2 when Y2 was missing.

The imputation steps conducted to impute missing hypoglycemic data based on the above result were then as follows:

Step 1

A Bayesian log-linear negative binomial model with offset was fitted to the observed data and independent samples were then drawn from the posterior distribution for the model parameters created by multiplying a noninformative prior with the likelihood function. The model parameters were the dispersion, intercept, treatment, region, stratification factors (ONWARDS 3 and 6), and

own CGM device use (yes/no) (ONWARDS 2 and 4). 1000 random samples of the model parameters were obtained.

Step 2

The parameters from step 1 were then used to calculate the linear predictors for the two time periods of observed data and missing data respectively, for subjects with missing data for Y2. This was done for each random sample of the parameters obtained. For L2, a reference-based approach was used to mimic an intention-to-treat (ITT) scenario where it was assumed that the event rate follows that of the comparator arm in the missing data period. I.e., the treatment effect parameter used was that of the comparator in this period.

Step 3

Then Y2|Y1 was simulated for subjects with missing data from a negative binomial distribution with parameters derived from step 1 and step 2 and the simulated value added to the observed value of Y1 to get an imputed value, Y, for the number of hypoglycemic episodes for the entire duration of the trial for a subject.

Step 4

For each imputed dataset, the number of hypoglycemic episodes was analyzed by a negative binomial model with treatment, region, stratification factors (ONWARDS 3 and 6), and own CGM device use (yes/no) (ONWARDS 2 and 4) as factors and with log of the planned trial duration as offset, i.e., as if the data were complete. The resulting estimates and their standard errors were then combined across imputations using Rubin's rule.

For further details please see reference [109]