FDA Briefing Document

BLA# 761326

Drug name: NNC0148-0287

Applicant: Novo Nordisk

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

May 24, 2024

Division of Diabetes, Lipid Disorders, and Obesity (DDLO)/ Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring biologics license application (BLA) 761326 for NNC0148-0287, a long-acting insulin analog product, to this Advisory Committee in order to gain the Committee's insights and opinions on the safety and efficacy of this product for the proposed indication to improve glycemic control in adults with diabetes mellitus. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

A1C	hemoglobin A1c
AC	Advisory Committee
ADA	American Diabetes Association
AESI	adverse event of special interest
ANCOVA	analysis of covariance
BLA	biologics license application
BMI	body mass index
CGM	continuous glucose monitoring
CI	confidence interval
Cmax	maximum serum concentration
CSII	continuous subcutaneous insulin infusion
C_{trough}	concentration immediately before next dose
CV	coefficient of variation
DCCT	Diabetes Control and Complications Trial
DDLO	Division of Diabetes, Lipid Disorders, and Obesity
DTSQs	Diabetes Treatment Satisfaction Questionnaire status version
E	event
EDC	electronic data capture
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
EMS	emergency medical service
ER	emergency room
FAS	full analysis set
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GIR	glucose infusion rate
GMI	glucose management indicator
H	hour
Ico	insulin icodec
IDeg	insulin degludec
IG	interstitial glucose
IGlar	insulin glargine

IP	investigational product
IR	incidence rate
IRR	incidence rate ratio
IV	intravenous
LS	least squares
MDII	multiple daily insulin injections
MedDRA	Medical Dictionary for Regulatory Activities
NCT	National Clinical Trial
NYHA	New York Heart Association
OCHEN	Office of Cardiology, Hematology, Endocrinology and Nephrology
ODA	once-daily basal insulin analogs
PD	pharmacodynamic
PG	plasma glucose
PK	pharmacokinetic
PRO	patient-reported outcome
PT	preferred term
PY	patient-years
PYE	patient-years of exposure
QD	once daily
QW	once weekly
RR	rate ratio
RTB	return-to-baseline
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SE	standard error
SMPG	self-measured plasma glucose
SS	steady state
$t_{1/2}$	half-life
T1D	type 1 diabetes
T2D	type 2 diabetes
TBR	time below range
TIR	time in range

Tmax	time to maximum serum concentration
U	unit
UKPDS	United Kingdom Prospective Diabetes Study
VRS	verbal rating scale
Y	year

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

To discuss whether the benefits of NNC0148-0287 (insulin icodec), a once-weekly insulin analog product, outweigh its risks for the proposed indication 'to improve glycemic control in adult patients with diabetes mellitus'. The focus of the meeting will be on the safety and efficacy of insulin icodec in patients with type 1 diabetes (T1D).

1.2 Context for Issues to Be Discussed at the AC

Diabetes mellitus is a chronic metabolic condition that can have serious and life-threatening complications. Diabetes affects an estimated 38 million people in the United States,[1] of which type 2 diabetes (T2D) accounts for 90 to 95% of all diagnosed cases of diabetes, while T1D accounts for 5 to 10%.[2,3] Patients with T1D require exogenous insulin treatment.[4] The American Diabetes Association (ADA) generally recommends that most patients with T1D be treated either with multiple daily insulin injections (MDII) of bolus and basal insulin, or with continuous subcutaneous insulin infusion (CSII) via an insulin pump with a rapid-acting insulin delivered as continuous basal insulin combined with mealtime boluses.[4-6] In the United States, approximately one-third of adult patients with T1D are managed with MDII.[7] Published reports suggest that the estimated prevalence of adherence to existing insulin therapies in adult T1D patients is approximately 53%,[8] with approximately 22% of patients missing at least one basal insulin dose over any 14-day period.[9] Nonadherence to insulin therapy is a precipitating factor for diabetic complications such as diabetic ketoacidosis.[10-12]

1.3 Brief Description of Issues for Discussion at the AC

The Applicant has developed insulin icodec as a long-acting insulin analog intended for once weekly (QW) subcutaneous (SC) administration (as a basal insulin) in adults with diabetes mellitus. Currently available basal insulin products need to be administered at least daily. In the insulin icodec clinical development program, efficacy was demonstrated in several studies of patients with T2D which investigated multiple treatment strategies including MDII; the achieved glycemic control was generally acceptable and not accompanied by a meaningful increase in hypoglycemia in the studies of patients with T2D. Efficacy of insulin icodec in combination with bolus insulin was also demonstrated in trial 4625 (hereafter referred to as ONWARDS 6), the single phase 3 trial conducted in patients with T1D. In ONWARDS 6, although confidence intervals for the difference between insulin icodec and the insulin degludec active comparator administered once daily for the primary endpoint of 'change in hemoglobin A1c (A1C) from baseline' were within the noninferiority margin and included zero, the point estimate of the treatment effect for insulin icodec was numerically smaller than the comparator. Moreover, the rate of hypoglycemic episodes was significantly higher in the insulin icodec arm compared to the insulin degludec arm. Although hypoglycemia is an expected adverse reaction caused by exogenous insulin use, the data from ONWARDS 6 show excess hypoglycemia caused by insulin icodec (versus the active comparator) without evidence of any additional glycemic control or other benefit. The patient-focused data collected in ONWARDS 6 were inadequate to inform whether patients with T1D preferred the once weekly basal insulin option to once daily. In light of the available safety and efficacy data, FDA requests that the advisory committee focus its discussion on the benefits and risks of insulin icodec in patients with T1D.

1.4 Draft Points for Consideration

Topics for discussion include:

- Discuss the benefits and risks of insulin icodec to improve glycemic control in adult patients with type 1 diabetes mellitus (T1D). Explain how you view the balance of benefits and risks in this population.
- Discuss the role of continuous glucose monitoring (CGM) devices and measures of glycemic variability to help reduce the risk of hypoglycemia in patients with T1D using insulin icodec.
- Discuss the proposed dosing and titration regimen and the extent to which the modeling data support alternative dosing strategies.
- Discuss the role of insulin icodec in the context of the available treatment armamentarium for patients with T1D.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

2.1.1 Condition

Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia. There are two main types of diabetes mellitus: T1D (characterized by T-cell-mediated autoimmune destruction of pancreatic β-cells, loss of insulin secretion, and the requirement for lifelong administration of exogenous insulin)[13,14] and T2D (characterized by β-cell dysfunction, resistance to insulin activity with inadequate insulin production to maintain euglycemia, and increased hepatic glucose output due to glucagon dysregulation).[15-18] As a result of chronic hyperglycemia, patients with diabetes mellitus are at an increased risk for microvascular (e.g., retinopathy, nephropathy and neuropathy)[19-22] and macrovascular (e.g., myocardial infarction, and stroke) complications.[22-24] Diabetes remains a leading cause of kidney failure,[25] adult-onset blindness,[26,27] and nontraumatic lower limb amputations.[28,29] Maintaining normoglycemia can reduce the risk of these diabetes-related complications. A1C is a biomarker that reflects the average glucose level in the previous 2 to 3 months,[30] and the treatment goal for most patients is to keep the A1C level below 7%.

2.1.2 Standard of Care

Lifelong administration of exogenous insulin is the cornerstone of therapy for T1D.[4] The American Diabetes Association (ADA) recommends multiple daily insulin injections (MDII) of bolus (to cover intake of carbohydrates and other macronutrients during meals) and basal insulin (to restrain gluconeogenesis and ketogenesis), or continuous subcutaneous insulin infusion (CSII) with a rapid-acting insulin delivered as continuous basal insulin combined with mealtime boluses via an insulin pump.[4-6]

Hypoglycemia is a major limiting factor in achieving glycemic control with exogenous insulin in patients with T1D.[31] The ADA classifies hypoglycemia as level 1, 2, or 3, defined as follows:

- Level 1: blood glucose concentration <70 mg/dL and ≥54 mg/dL,
- Level 2: blood glucose concentration <54 mg/dL, and
- Level 3: severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery, irrespective of glucose level.[30]

Major risk factors for hypoglycemia include recent level 2/3 hypoglycemia, impaired hypoglycemia awareness, end-stage kidney disease, cognitive impairment or dementia, and intensive insulin therapy (including MDII, CSII, or automated insulin delivery system).[30]

Some peer-reviewed literature suggests that the risk of hypoglycemia may be reduced in MDII regimens that use newer long-acting insulins with flatter pharmacodynamic profiles and longer half-lives.[32-39] A summary of pharmacokinetic and pharmacodynamic profiles of insulin icodec and approved basal insulin products is presented in Table 1.

Table 1. Pharmacokinetic and Pharmacodynamic Profiles of Insulin Icodec and Approved Basal Insulin Products (Not Including Biosimilar Insulin Products)

Proper Name Proprietary Name*	BLA# (Approval Date)	Time to Maximum PK Concentration (T_{max})	PK Elimination Half-Life ($t_{1/2}$)	Time of Peak Glucose-Lowering Effect
Insulin icodec[40]	BLA 761326	18.1 h	175 h	2-4 days
Insulin degludec (U100 and U200)				
Tresiba[41-44]	BLA 203314 (2015)	9 h	25 h	No pronounced peak
Insulin glargine (U100)				
Lantus[44,45]	BLA 021081 (2000)	12 h	12 h	No pronounced peak
Insulin glargine (U300)				
Toujeo[44,46]	BLA 206538 (2015)	12-16 h	19 h	No pronounced peak
Insulin isophane human (NPH)				
Humulin N[42,44,47]	BLA 018781 (1982)	4 h	4.4 h	2-8 h
Novolin N[42,44,48]	BLA 019959 (1991)	—	—	2-8 h

Source: Cited literature.
*Approved biosimilar insulin products are not included in this table.
Abbreviations: NPH, neutral protamine hagedorn; PD, pharmacodynamic; T1D, type 1 diabetes; T2D, type 2 diabetes; T_{max}, time to maximum plasma concentration

In addition to insulin replacement therapy, other therapeutic options for the management of T1D include pramlintide, an amylin analog indicated as adjunctive therapy to augment insulin therapy, and pancreas and pancreatic islet transplantation. These options are beyond the scope of this background document and will not be discussed further.

Adverse reactions associated with all insulin products include hypoglycemia, hypersensitivity reactions, injection site reactions, lipodystrophy, pruritus, rash, edema, and weight gain. Class labeling of insulin products also include the following Warnings and Precautions: never share an insulin pen or needle between patients; hyperglycemia or hypoglycemia, including due to medication errors or with changes in the insulin regimen; hypersensitivity reactions; hypokalemia; and fluid retention and congestive heart failure with concomitant use of a peroxisome proliferator-activated receptor-gamma agonists.

2.1.3 Unmet Medical Need

About one third of patients with T1D are managed with MDII.[7] Nonadherence to insulin therapy is a known precipitating factor for diabetic ketoacidosis in adult T1D populations.[10-12] Adherence to insulin therapy in adult patients with T1D was reported to be relatively low (52.6%, 95% confidence interval [CI]: 37.4 to 67.9%) in data from a meta-analysis of eight clinical trials.[8] The probability of missing at least one daily basal insulin dose over any 14-day period is estimated to be 22% (95% CI: 10 to 40%).[9]

Among patients with T2D using a daily basal insulin, a once weekly basal insulin would reduce the number of insulin injections from 365 per year to 52 per year. Such patients may positively view the option for a once weekly basal insulin.[49] U.S. survey data indicate that 91% of patients with T2D and 89%

of healthcare providers who manage patients with T2D would prefer a once weekly basal insulin product over another type of basal insulin.[50] Among patients with T1D who rely on an MDII regimen, a once weekly basal insulin would reduce the number of insulin injections from approximately 28 per week to 22 per week. In addition to requiring multiple daily insulin injections, such patients would also still require frequent glucose monitoring. For patients with T1D, it is not known whether a once weekly basal insulin would be preferred over other basal insulin options, or whether use would result in improved adherence and glycemic control.[51]

2.2 Pertinent Drug Development and Regulatory History

During the End-of-Phase-2 meeting, FDA provided advice and recommendations including:

- FDA noted that the data from pharmacokinetic (PK)/pharmacodynamic (PD) study 4225 conducted in patients with T1D suggested that the PD effect of insulin icodec is not "peakless" when dosed once weekly.
    - FDA advised that insulin icodec may not be ideally suited for use as a once weekly product, as the proposed regimen might lead to hypoglycemia.
- FDA agreed with an active comparator open-label study to demonstrate efficacy in T1D with the primary endpoint of A1C at 6 months. FDA noted, however, that meeting the prespecified noninferiority margin would not be sufficient to establish a favorable benefit-risk profile because the risk of hypoglycemia would also be taken into consideration.
    - FDA recommended that the T1D phase 3 study include a third arm evaluating insulin icodec dosed twice weekly.
    - FDA recommended that the study assess potential improvements in treatment satisfaction to offset any potential disadvantages related to glycemic profile.
    - FDA recommended that the Applicant assess the potential need for additional bolus dose adjustments.

3 Product, Mechanism of Action, and Indication

3.1 Drug Substance

Insulin icodec is an acylated long-acting human insulin analog produced by a process that includes expression of recombinant DNA in yeast (*Saccharomyces cerevisiae*), followed by chemical modification. Compared to human insulin, insulin icodec differs in that the amino acid Thr(B30) has been omitted, Tyr(A14) has been substituted with Glu, and Tyr(B16) and Phe(B25) have been substituted with His.[52] A C20 fatty-acid side chain has been added to the peptide backbone via the amino group in the side chain at Lys(B29). When insulin icodec is injected SC, the C20 fatty acid sidechain derivative binds strongly, but reversibly, to endogenous albumin, which results in decreased renal clearance and protection from metabolic degradation, and consequently prolonged pharmacodynamic activity.[52] Because there is >2000-fold excess of binding sites in the circulating albumin pool compared with the insulin icodec serum concentration, it is unlikely that albuminuria, intrinsic factors, or competitive protein binding will have a clinically relevant effect on the activity of this product.[52]

3.1.1 Drug Product

Insulin icodec (700 units/mL) is being developed in single-patient-use, prefilled FlexTouch pens in the following presentations:

- 1 mL (700 units/1 mL)
- 1.5 mL (1050 units/1.5 mL)
- 3 mL (2100 units/3 mL)

Each prefilled FlexTouch pen delivers doses in 10-unit increments and can deliver up to 700 units in a single injection. The FlexTouch pen platform is not a novel platform and has been approved for use with other insulin pen products manufactured by the Applicant.

3.1.2 Mechanism of Action

Insulin icodec lowers blood glucose by activating the insulin receptor to stimulate peripheral glucose uptake into skeletal muscle and fat, and inhibit glucose production by the liver.[53,54] Additionally, it inhibits lipolysis and proteolysis, and enhances protein synthesis.[54]

3.1.3 Proposed Indication

The Applicant's proposed indication is: Insulin icodec is a once-weekly long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus.

4 Summary of Issues for the AC

- Insulin icodec is a proposed insulin analog with a prolonged duration of action intended to support once weekly (QW) subcutaneous (SC) administration. Thus, insulin icodec reduces treatment burden in patients with T1D by reducing the number of basal insulin injections in comparison to daily basal insulins. However, insulin icodec does not have a peakless time-action profile throughout the dosing interval.
- In ONWARDS 6, weekly insulin icodec was noninferior (but not superior) to daily insulin degludec and was associated with 48 to 89% more level 2/3 hypoglycemia at Week 26, depending on the method of analysis. The highest risk period for hypoglycemia with insulin icodec coincides with its peak glucose-lowering effect which occurs on days 2 to 4 following each weekly injection. There were also more hypoglycemia-related serious adverse events reported among patients randomized to insulin icodec compared to insulin degludec. Thus, in the only study conducted in patients with T1D, insulin icodec was observed to have a higher risk of clinically meaningful hypoglycemia, in the absence of a lower A1C. Hypoglycemic episodes reported with insulin icodec and insulin degludec in ONWARDS 6 were of the same nature in terms of duration, management, and recovery.
- After discussion with FDA during the review cycle, to address FDA's concerns, the Applicant proposed several potential ways to support safe and effective use of insulin icodec in patients with T1D, including:
    - Limiting the use of insulin icodec to patients with T1D wearing a CGM device and patients without a history of hypoglycemia unawareness or recurrent hypoglycemia. In ONWARDS 6, subjects were required to use CGM devices and were excluded if they had history of hypoglycemia unawareness or recurrent hypoglycemia. Use of unblinded CGM affects patient behavior and hypoglycemia risk.[55,56] Thus, ONWARDS 6 may not be representative of patients without access to CGMs or patients with a history of recurrent hypoglycemia.

- Labeling alternative insulin dose titration strategies to reduce the risk of hypoglycemia (e.g., reducing the bolus insulin dose by approximately 30% between days 2 to 4 after each weekly insulin icodec injection). The Applicant's exploratory clinical pharmacology modeling analyses predicted that lowering the bolus insulin doses at the peak of insulin icodec's effect might reduce hypoglycemia risk.
- Indicating insulin icodec only for patients with a low % coefficient of variation (%CV). In exploratory post hoc analyses, the Applicant found that the subgroup of patients with low glycemic variability, as defined as percent coefficient of variation (%CV <36%), had hypoglycemia risk comparable to the entire cohort of patients on insulin degludec (i.e., with any %CV). This finding was consistent across a range of %CV cutpoints (%CV 32 to 40%) and was observed regardless of whether %CV was calculated by 4-point self-measured plasma glucose (SPMG) or continuous glucose monitoring (CGM). However, the risk of hypoglycemia was always higher in the insulin icodec arm, compared to insulin degludec arm, when assessing rates within identical %CV subgroups.
- Recommending that patients who experience recurrent hypoglycemia switch to other insulin treatment options and providing instructions in labeling to switch patients back to daily basal insulin products.
- Providing prescriber and patient training materials to help maximize benefit-risk.

- However, no clinical data are available to assess the impact of these proposed risk mitigation strategies (or confirm that a reduced risk of hypoglycemia can be achieved without decreasing efficacy).

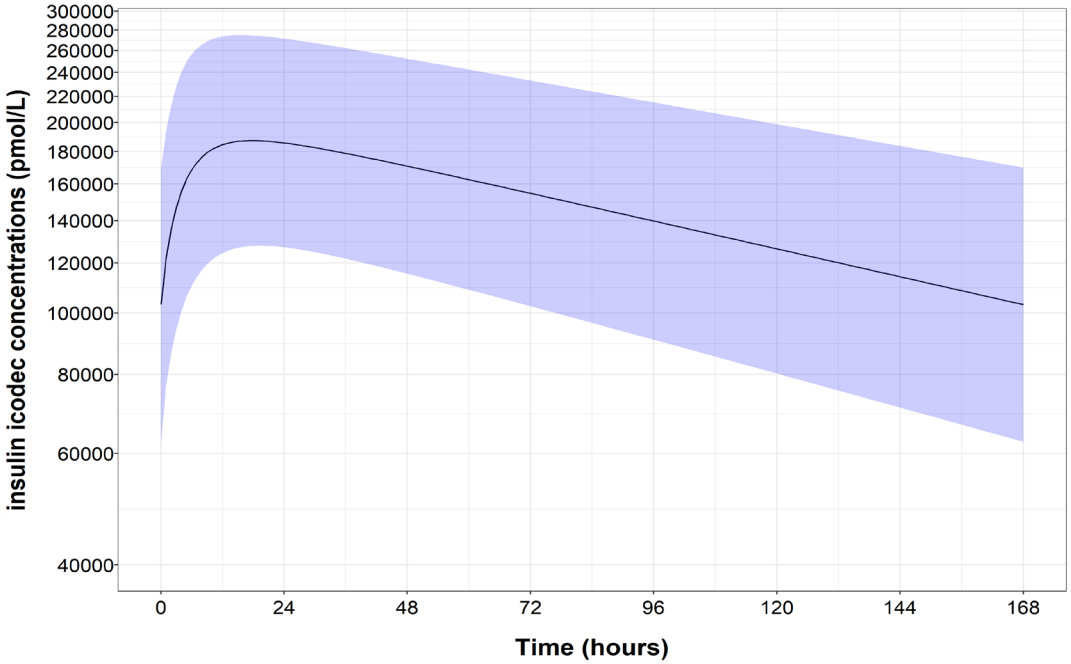
4.1 Clinical Pharmacology

The clinical pharmacology program comprised nine clinical studies to characterize the PK and PD characteristics of insulin icodec in patients with T1D (two studies), T2D (five studies), and in nondiabetic subjects with renal or hepatic impairment (two studies).

Study 4225 was a euglycemic clamp PK/PD study that evaluated the PK and the PD response to insulin icodec after weekly dosing (QW) for 8 weeks in subjects with T1D. Figure 1 shows the steady state PK profile of insulin icodec in 65 adult patients with T1D over one dosing interval after 8 weeks of QW dosing. The median time to maximum insulin icodec concentration (t_{max}) is reached at approximately 18.1 h (range: 12 to 119.9 h) then declines thereafter. The half-life ($t_{1/2}$) of insulin icodec was 174.6 h (geometric mean) with individual values ranging from 136.1 to 403.7 h. Geometric mean C_{max} was 185,139 (range: 105,200 to 442,900) pmol/L and geometric mean C_{trough} was 94,859 (range: 51,520 to 297,700) pmol/L.

Although the half-life of insulin icodec could be viewed as consistent with a dosing interval greater than daily, the rise and fall of insulin icodec plasma concentration during the week after dose administration may have implications in terms of using icodec as a once weekly basal insulin and is further discussed in Sections 4.4.3.3 and 4.4.4.

Figure 1. Geometric Mean Insulin Icodec Concentration Over a Dosing Interval After 8 Weeks of Weekly Dosing (Steady State) in Subjects With Type 1 Diabetes (Study 4225)

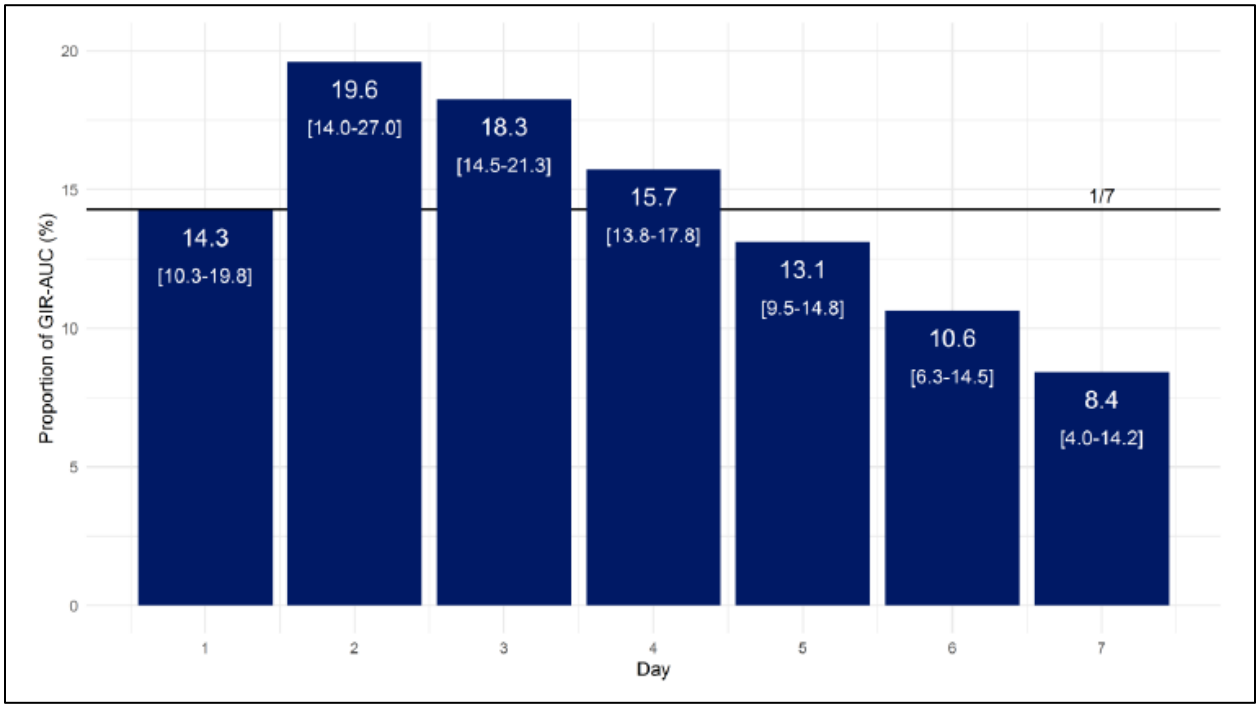


Source: Independent analysis of the Applicant's PK data in Study 4225 by FDA Pharmacometrics.
The black smooth line and shaded purple area show the geometric mean and 90% prediction interval, respectively.

For the PD assessment, subjects received an intravenous (IV) infusion of glucose such that the glucose infusion rate (GIR) was adjusted to maintain/clamp blood glucose concentration at a target level after insulin icodec SC administration. As insulin icodec plasma concentration increases, insulin action reduces glucose level and, consequently, the glucose infusion rate must be increased to maintain the target glycemic level. Because it is not feasible to clamp subjects for the entire 1-week proposed dosing interval, two separate euglycemic clamps were carried out: the first was started 16 h postdose and lasted 36 h to cover the expected time of maximum insulin icodec concentration, while the second clamp covered the last 30 h of the dosing interval. The Applicant modeled the GIR profile for the entire week.

Figure 2 shows a histogram of model-predicted glucose infusion rate for insulin icodec by day postdose at steady state. The GIR for individual days is expressed as a percentage of the entire week's GIR. The horizontal line corresponds to the ideal GIR expected if the glucose infusion rate was constant throughout the week. If GIR was constant, the fractional daily GIR would be approximately 14.3% (100%/7 days). Figure 2 shows that GIR for insulin icodec exceeds the daily ideal GIR line on Days 2 to 4 postdose and is below the ideal line on Days 5 to 7 postdose. This is consistent with the PK profile for insulin icodec over the dosing interval (Figure 1).

Figure 2. Distribution of Model-Predicted Glucose Infusion Rate (GIR) Effect Per Day in Caucasian Subjects With T1D Over a 1-Week Dosing Interval at Steady State (Study 4225)



Source: BLA 761326 in DARRTS (SDN 0001; April 10, 2023) Section 2.7.2. Summary of Clinical Pharmacology Studies page 86 of 245.
Values on the blue bars are the means and ranges of daily proportions of total weekly GIR-AUC.
Abbreviation: T1D, type 1 diabetes mellitus

Because the glucose lowering effect is not flat across the treatment interval but is higher on Days 2 to 4 and lower on Days 5 to 7, maintaining consistent glycemic control may require different compensatory adjustments to the individual daily bolus insulin doses over the dosing interval of insulin icodec.

No phase 2 study was conducted in patients with T1D to determine the optimal dosing strategy of insulin icodec and bolus insulin to mitigate the fluctuation of plasma glucose concentration observed on Days 2 to 4 postdose versus Days 5 to 7 postdose observed in phase 1 Study 4225.

During the review cycle, the Applicant conducted model-based assessments of alternative dosing and titration strategies for the weekly insulin icodec (titrating based on self-measured plasma glucose [SMPG] on different days of the week) and bolus insulin to optimize the safe and effective use of these products in patients with T1D. These assessments are described in Section 4.4.4. The Applicant identified that alternative weekly titration strategies for insulin icodec might compromise efficacy. In contrast, a dose reduction of bolus insulin on Days 2 to 4 was predicted to maintain glycemic control and optimize safety.

PK analyses showed that exposure was comparable across age, ethnicity, race (white, black, Japanese, Chinese, other Asian), sex, albumin, and type of diabetes. Body weight was found to have a clear effect on insulin icodec exposure, with exposure decreasing with increasing body weight (and vice versa). No body weight-related dose adjustment is required because dosing should be individualized to cover glycemic control needs. No clinically significant changes in area under the curve or C_{max} were noted in patients with hepatic impairment (mild and moderate) or renal impairment (from mild to end stage renal disease).

4.2 Review of the Clinical Trial Used to Support the T1D Indication

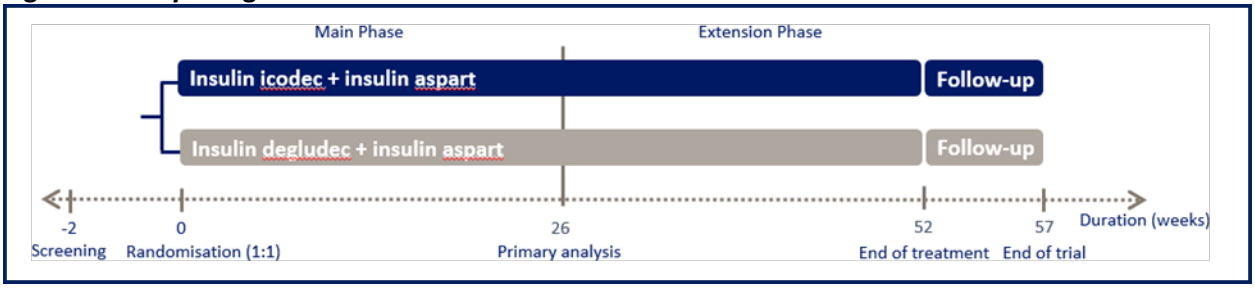
4.2.1 Clinical Development Program

The insulin icodec clinical development program consisted of 18 completed clinical trials, which included three phase 2 trials (T2D), and six phase 3 trials (1 T1D and 5 T2D, see Table 14). This briefing document will primarily focus on ONWARDS 6, the Applicant's sole phase 3 T1D trial used to support the efficacy and safety of insulin icodec to improve glycemic control in patients with T1D. The study design is presented in Figure 3 and an overview of study features is included in Section 7.2. In addition to ONWARDS 6, the Applicant conducted one phase 1 T1D trial (4225) which is described in Section 4.1.

4.2.2 Study Design

ONWARDS 6 was a 52-week, 1:1 randomized, open-label, active-controlled, parallel-group, multicenter, multinational, treat-to-target (mean pre-breakfast SMPG 80 to 130 mg/dL) trial. In this trial, the efficacy and safety of insulin icodec was compared to insulin degludec, both in combination with insulin aspart, in adult subjects with T1D (A1C <10% at screening). The trial duration was 59 weeks (2-week screening period, 26-week main treatment period, 26-week extension phase, and 5-week follow-up period (Figure 3). At Week 52, subjects were transferred to a marketed insulin product at the discretion of the investigator. Subjects were equipped with a continuous glucose monitoring (CGM) device (Dexcom G6) for the entire duration of the trial. Alerts for low or high glucose values were not blinded to either subjects or investigators.[1] Subjects also received a Roche Accu Check blood glucose meter and were instructed to measure a 4-point daily SMPG from Week 0 to the end of trial at pre-breakfast, pre-lunch, pre-dinner, and at bedtime. The measured SMPG values were transferred daily into an electronic diary (eDiary) by the subject.

Figure 3. Study Design of ONWARDS 6



Source: Reproduced from the Applicant's Clinical Study Report, Protocol NN1436-4625, labeled as Figure 4-1, page 21 of 93.
Abbreviation: V, visit

4.2.3 Study Subjects

Adults (age ≥18 years) with T1D diagnosed and treated with MDII for ≥1 year and had an A1C <10% at screening were eligible to participate in ONWARDS 6. Subjects were excluded if they met any of the following criteria: known hypersensitivity to investigational products (IP), female who is pregnant, breastfeeding or intends to become pregnant, cardiovascular event (myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischemic attack) within 180 days, New York Heart Association (NYHA) Class IV heart failure, renal (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) or hepatic (alanine aminotransferase ≥2.5× the laboratory upper limit of normal or

[1] The CGM device used in ONWARDS-6 was a Dexcom G6 that includes an "urgent low alarm" set at 55 mg/dL. Subjects could customize alerts for: "urgent low soon" (set at ≤55 mg/dL), "low" (<70 mg/dL), "high" (>200 mg/dL), "rise rate" (2 or 3 mg/dL/min), "fall rate" (2 or 3 mg/dL/min), and "signal loss".

bilirubin >1.5× upper limit of normal) impairment, known hypoglycemic unawareness (Clarke's questionnaire, question 8[57]), recurrent severe hypoglycemic episodes within the year, systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg, uncontrolled/unstable diabetic retinopathy/maculopathy, and malignant neoplasm within 5 years. A complete list of these inclusion/exclusion criteria can be found in the published report.[51]

Baseline demographics and clinical characteristics of the study populations for ONWARDS 1 to 6 are presented in Section 7.3. The data from ONWARDS 6 show that the T1D patient population randomized in this trial was predominantly white (77%), with a mean age 44 years, mean baseline A1C of 7.6%, body mass index of 27 kg/m^2, and estimated glomerular filtration rate (eGFR) of 98 mL/min/1.73 m^2. Fewer than 2% of subjects had an eGFR <60 mL/min/1.73 m^2, and no subjects randomized to insulin icodec had an eGFR <45 mL/min/1.73 m^2. Approximately 33% of subjects were enrolled from North America (28% from the United States).

4.2.4 Dosing of Investigational Products (IP)

The subjects randomized to the insulin icodec arm (administered with a prefilled pen injector) received a one-time loading dose to avoid hyperglycemia during the first week of treatment. The initial insulin icodec dose administered was equivalent to the total daily basal insulin dose before randomization ×7, plus a loading dose depending on the A1C level prior to randomization. If the A1C was <8% at screening, a one-time 50% loading dose was applied; if the A1C was ≥8%, a single 100% loading dose was applied (i.e., initial dose equivalent to the total daily basal insulin dose before randomization ×7 + 100%) to mitigate the risk of hyperglycemia. Subjects switching from insulin glargine U300 or basal insulin twice daily received a 50% loading dose of insulin icodec regardless of their A1C at screening. Subjects randomized to the insulin degludec arm were switched from their pretrial basal insulin analog according to local labeling.

The weekly basal dose adjustment was based on the lowest of three prebreakfast SMPG values measured 2 days before titration and on the day of titration (Table 2). If one or more SMPG values were missing, the dosage adjustment was performed based on the remaining value(s).

Table 2. Basal Insulin Dose Titration

Lowest SMPG Value	Insulin Icodec Dose Adjustment (Units/Week)	Insulin Degludec Dose Adjustment (Units/Day)
>130 mg/dL	+20	+3
80-130 mg/dL	0	0
<80 mg/dL)	−20	−3

Source: Clinical Study Protocol, pages 81-82 of 93.
Abbreviation: SMPG, self-monitored plasma glucose

The insulin aspart dose was adjusted weekly using the prespecified algorithm (Table 3) or based on carbohydrate counting at the investigator's discretion, with adjustments made during the first 8 weeks only for safety reasons. Weekly dose adjustments were based on the lowest preprandial or bedtime SMPG values measured the week prior to titration. The breakfast dose was adjusted based on the pre-lunch SMPG, lunch dose was adjusted based on the pre-dinner SMPG values, and dinner dose was adjusted based on bedtime SMPG.

Table 3. Bolus Insulin Dose Titration

Lowest Preprandial and Bedtime SMPG	Insulin Aspart Dosage Adjustment (Units)
>130 mg/dL	+1
80-130 mg/dL	0
<80 mg/dL	−1

Source: Clinical Study Protocol, page 81-82 of 93.
Abbreviation: SMPG, self-monitored plasma glucose

4.3 Efficacy Issues

4.3.1 Efficacy Endpoints and Methods

This section summarizes efficacy for ONWARDS 6. The primary endpoint for ONWARDS 6 was change from baseline in A1C at Week 26. No key secondary endpoints were prespecified for formal statistical testing with multiplicity adjustment. Other endpoints for descriptive purposes include:

- Change from baseline in A1C at Week 52
- Achieving A1C <7.0% at Week 26/52
- Change from baseline in fasting plasma glucose (FPG) at Week 26/52
- Time in range (70 to 180 mg/dL) (%) as measured by CGM (Weeks 22 to 26 / 48 to 52)
- Change from baseline in Diabetes Treatment Satisfaction Questionnaire status version (DTSQs) total treatment satisfaction score at Week 26/52

The prespecified primary analysis for comparing the "mean changes in A1C from baseline" is described as follows:

- **Full analysis set:** All randomized subjects. Subjects were analyzed according to randomized treatment.
- **Primary estimand:** Treatment policy estimand.
    - **Treatment condition**: Insulin icodec or insulin degludec, irrespective of adherence to randomized treatment and changes to antidiabetic background medication.
    - **Population**: Adults with T1D and at least one year of treatment with multiple daily insulin injections (basal and bolus insulin analog regimens).
    - **Intercurrent events**: Treatment discontinuation and withdrawal from the trial.
        - **Handling of data after intercurrent events**: All available data, regardless of treatment discontinuation was used in the analysis.
- **Population-level summary measure**: Mean difference in change from baseline in A1C.

The protocol-specified method for handling missing data was to impute missing data based on subjects who discontinued randomized treatment prior to the endpoint visit and had their endpoint measurement.

Table 4 lists the disposition of data capture for Week 26 and Week 52. For Week 26, there are 5 subjects who were off-treatment but had their Week 26 measurement on insulin icodec used to represent 16 subjects with missing data, and there are 2 subjects who were off-treatment but had their Week 26 measurement on insulin degludec used to represent 9 subjects with missing data. Likewise, for Week 52, there are 12 subjects who were off-treatment but had their Week 52 measurement on insulin icodec used to represent 20 subjects with missing data, and there are 2 subjects who were off-treatment but had their Week 52 measurement on insulin degludec used to represent 14 subjects with missing data.

Table 4. Disposition of Data Capture for A1C

Variable	Ico	IDeg
Number in FAS [N]	290	292
Number with Week 26 data [n (%)]	274 (94.5)	283 (96.9)
On treatment [n]	269	281
Off treatment [n]	5	2
Number without Week 26 data [n (%)]	16 (5.5)	9 (3.1)
Study discontinuation [n]	13	7
On treatment and in study [n]	3	2
Number with Week 52 data [n (%)]	270 (93.1)	278 (95.2)
On treatment [n]	258	276
Off treatment [n]	12	2
Number without Week 52 data [n (%)]	20 (6.9)	14 (4.8)
Study discontinuation [n]	16	12
On treatment and in study [n]	4	2

Source: FDA statistical reviewer based on submitted datasets.
N, Number contributing to the analysis; for A1C, N is the number in the FAS
Abbreviations: A1C, glycated hemoglobin; FAS, full analysis set; Ico, insulin icodec; IDeg, insulin degludec; n, number

The statistical analysis plan specified that in the case that the amount of data from subjects who discontinued randomized treatment prior to the endpoint visit and had their endpoint measurement for the imputation model was insufficient for meaningful imputation, the imputation model would be replaced by a return-to-baseline (RTB) approach; however, a precise definition for "insufficient for meaningful imputation" was not described. Given the small number of subjects who discontinued randomized treatment prior to the endpoint visit and had their endpoint measurement available to represent subjects with missing data, there is concern that the prespecified approach to handling missing data are not appropriate. Therefore, we consider the RTB imputation to be the most appropriate for the primary analysis, whereby the subjects endpoint measurement is drawn from a normal distribution centered at the subjects' baseline measurement with random error.

For each subject with missing Week 26/52 data, 1000 measurements were imputed, thus generating 1000 complete datasets. Each dataset was analyzed using analysis of covariance (ANCOVA) with treatment, region, pretrial basal insulin treatment, and A1C group at screening as fixed effects, and baseline A1C as a covariate. Rubin's rule was applied for inference.[58]

4.3.2 Efficacy Results

Table 5 displays the results for Week 26 and Week 52 based on the RTB analysis. There are reductions of A1C in both the insulin icodec and insulin degludec treatment arms. At Week 26, the primary objective of noninferiority of insulin icodec to insulin degludec is met as the upper bound of the confidence interval is less than 0.3 (i.e., prespecified noninferiority margin). At Week 52, reduction in A1C numerically favors insulin degludec. Further, the lower bound of the 95% confidence interval is greater than 0 and the upper bound of the 95% CI is less than 0.3. Subjects on insulin icodec showed a reduction in A1C ranging from −0.38 to −0.47, as observed by the treatment level least squares (LS) mean changes from baseline.

The proportion of subjects with A1C <7.0% at Week 26 and Week 52 is computed as the average number subjects with A1C <7.0% across the 1000 multiply imputed datasets divided by N.

Table 5. Results for A1C (%) and Proportion With A1C <7.0% at Week 26 and 52, Return-to-Baseline Approach to Missing Data

Baseline Mean (SD) [N]		
Insulin icodec		7.59 (0.96) [290]
Insulin degludec		7.63 (0.93) [292]
	Week 26	**Week 52**
LS Mean change from baseline (SE)		
Insulin icodec	-0.47 (0.04)	-0.38 (0.04)
Insulin degludec	-0.52 (0.04)	-0.52 (0.04)
Treatment difference (Ico – IDeg) (SE) (95% CI)		
	0.06 (0.05) (-0.05, 0.16)[a]	0.14 (0.06) (0.02, 0.25)
Average number of subjects with A1C <7.0% / N (%)[b,c]		
Insulin icodec	121 / 290 (42%)	116 / 290 (40%)
Insulin degludec	132 / 292 (45%)	118 / 292 (40%)

Source: FDA statistical reviewer; submitted datasets.
N, Number contributing to the analysis; for A1C, N is the number in the full analysis set
[a] One-sided P-value <0.001 for noninferiority
[b] Ninety subjects on insulin icodec and 82 subjects on insulin degludec had A1C <7.0% at baseline
[c] There are 116 subjects on insulin icodec and 129 on insulin degludec with known A1C <7.0% at Week 26. There are 109 subjects on insulin icodec and 116 on insulin degludec with known A1C<7.0% at Week 52.
Abbreviations: A1C, hemoglobin A1c; CI, confidence interval; Ico, insulin icodec; IDeg, insulin degludec; SD, standard deviation; SE, standard error

To check for the robustness of the conclusion of the primary analysis in departures to missing data, a two-way tipping point analysis as a sensitivity analysis was performed for the primary endpoint at Week 26 with respect to RTB. The results are fairly robust to departures in the assumption of handling missing data, as there exist unlikely but not clinically impossible scenarios where the conclusion of noninferiority tips to inferiority. For example, if the 16 subjects on insulin icodec with missing data had an average A1C increase of 1.47% from baseline and the 9 subjects on insulin degludec with missing data had an average A1C decrease of 1.86% from baseline, the conclusion from noninferiority changes to inferiority.

Secondary Endpoints

Table 6 lists the results of the efficacy endpoints of FPG, Time in Range, and DTSQ at Weeks 26 and 52.

- For FPG, both at Week 26 and Week 52, subjects on insulin icodec and insulin degludec demonstrated a reduction from baseline, however, subjects on insulin degludec showed a nominally significant larger reduction in FPG than subjects on insulin icodec as the lower bound of the 95% CI is greater than 0.
- For DTSQs, both at Week 26 and Week 52, subjects on insulin icodec and insulin degludec had an increase in DTSQs scores compared to baseline, however, changes in DTSQs scores on insulin degludec are nominally significantly higher than insulin icodec, as the upper bound of the 95% CIs are less than 0. The descriptive statistics for each item of DTSQs can be found in Section 7.4.4.
- For time in range (TIR) (70 to 180 mg/dL)(%) at Weeks 22 to 26 and Weeks 48 to 52, subjects on insulin degludec demonstrated numerically more TIR(%) than subjects on insulin icodec, however, this difference is not significant as the 95% CIs include 0.

Table 6. Results for Secondary Endpoints at Week 26 and 52

Variable	Insulin Icodec (Ico) FAS=290	Insulin Degludec (IDeg) FAS=292	Ico – IDeg (95% CI) [FPG, DTSQ, TIR]
FPG (mg/dL)			
Baseline mean (SD) [N]	179.2 (73.9) [276]	172.3 (72.3) [287]	
Number missing / N at Week 26[a]	20 / 276	13 / 287	
Adjusted mean change from baseline at Week 26	-15.1	-33.7	18.58 (8.58, 28.58)
Number missing / N at Week 52[a]	37 / 276	30 / 287	
Adjusted mean change from baseline at Week 52	-10.5	-33.8	23.35 (13.11, 33.59)
Time In Range (70-180 mg/dL) (%)			
Number missing / N at Weeks 22-26	29 / 290	20 / 292	
Adjusted mean at Week 22-26	59.1	61.1	-2.00 (-4.38, 0.38)
Number missing / N at Weeks 48-52	49 / 290	28 / 292	
Adjusted mean at Weeks 48-52	57.4	59.8	-2.42 (-4.90, 0.07)
DTSQs (Scores)[b]			
Baseline mean (SD) [N]	28.5 (5.5) [288]	28.3 (5.5) [291]	
Number missing / N at Week 26[a]	17 / 288	10 / 291	
Adjusted mean change from baseline at Week 26	2.0	3.1	-1.09 (-1.85, -0.34)
Number missing / N at Week 52[a]	28 / 288	14 / 291	
Adjusted mean change from baseline at Week 52	1.4	3.0	-1.59 (-2.51, -0.67)

Source: FDA statistical reviewer based on submitted datasets.
N, Number contributing to the analysis; for FPG and DTSQ, subjects with missing baseline measurements were excluded from the analysis.
[a] Subjects with missing baseline and missing endpoint measurements are not counted as they are excluded from the analysis.
[b] DTSQs scores are the summation of items 1, 4, 5, 6, 7, and 8. Of note, the Applicant did not provide evidence to support the content validity, other measurement properties (reliability, construct validity, responsiveness), and score interpretability (clinical meaningfulness) of the DTSQs. See Section 7.4 for limitations of DTSQs.
For FPG and DTSQ, subjects with missing data, the Week 26/52 imputed measurement was from a normal distribution with mean at the subjects baseline measurement with added variance. One-thousand datasets were generated. ANCOVA with treatment, region, pretrial basal insulin treatment, and A1C group at screening as fixed effects, and baseline measurement as a covariate was used for each dataset and Rubin's rule was applied.
For TIR, subjects with missing data, the imputed measurement was from a normal distribution with mean at the average of subjects on insulin degludec who completed treatment with added variance. One-thousand datasets were generated. ANOVA with treatment, region, pretrial basal insulin treatment, and A1C group at screening as fixed effects was used for each dataset; Rubin's rule was applied.
Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; CI, confidence interval; DTSQ, Diabetes Treatment Satisfaction Questionnaire; FAS, Full Analysis Set; FPG, fasting plasma glucose; A1C, hemoglobin A1c; Ico, insulin icodec; IDeg, insulin degludec; SD, standard deviation; TIR, time in range; U, unit.

4.3.3 Efficacy: Summary of Benefit

The Diabetes Control and Complications Trial (DCCT) determined that intensive glycemic control measured by A1C effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy and neuropathy of patients with T1D by a range of 35% to more than 70%.[59] Similarly, the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that intensive glycemic control measured by A1C reduces the incidence of microvascular complications.[60] Based on the DCCT and UKPDS, A1C is a validated surrogate endpoint for microvascular risk reduction in clinical trials in diabetes for antihyperglycemic drugs.

ONWARDS 6 demonstrated the efficacy of insulin icodec for glycemic control in patients with T1D. Insulin icodec was noninferior to insulin degludec in the change from baseline in A1C at Week 26. At

Week 52, the estimated treatment difference in change from baseline A1C nominally favors insulin degludec.

Results of the secondary endpoints for glycemic efficacy in ONWARDS 6 were consistent with the primary A1C endpoint in somewhat favoring insulin degludec. FPG is another indicator of glycemic control: at Week 52, the FPG showed an estimated treatment difference of 23 mg/dL favoring insulin degludec, which is nominally significant. TIR (70 to 180 mg/dL) (%) is a CGM based metric that exhibits moderate correlation with A1C.[56] However, TIR has not been established as a surrogate endpoint in clinical trials. In ONWARDS 6, neither treatment arm met the ADA target of 70% TIR and there was no significant difference between the treatment arms. However, the point estimate for TIR favored insulin degludec.

The DTSQs is an 8-item diabetes-specific patient-reported outcomes (PRO) instrument designed to assess current satisfaction with treatment and perceived frequency of hyperglycemia and hypoglycemia. Six items measure treatment satisfaction (satisfaction with current treatment, convenience, flexibility, satisfaction with own understanding of diabetes, and likelihood of continuing on or recommending current treatment). The remaining two items measure perceived frequency of hyperglycemia and frequency of hypoglycemia. Each of the treatment satisfaction items is rated on a 7-point verbal rating scale (VRS) ranging from 0 ("Very unsatisfied") to 6 ("Very satisfied"). Although the adjusted mean change from baseline at Weeks 26 and 52 in the DTSQs summary score were nominally significant in favor of insulin degludec, the clinical meaningfulness of these changes is unknown. Moreover, the Applicant did not submit an evidence dossier for the DTSQs and/or evidence to assess the fit-for-purpose of this instrument. FDA assessment also identified several issues with the instrument that limit the interpretability of the data collected in ONWARDS 6, as described in Section 7.4. FDA views the PRO data in the BLA as insufficient to draw conclusions about patient satisfaction with insulin icodec compared to patient satisfaction with insulin degludec (or other treatment options).

4.4 Safety Issues

4.4.1 Sources of Data for Safety

Safety of insulin icodec was primarily based on clinical data from the six completed phase 3 clinical trials for a total treatment exposure of 2,118 patient-years (PY). Generally, the safety findings in ONWARDS 6 were consistent with the known safety profiles of other basal insulin products: there were no clinically relevant numeric imbalances in serious adverse events (SAEs) or adverse events of special interest (AESI), except for the notable imbalance in hypoglycemia.

The Applicant performed safety analyses using the safety analysis set, defined as all subjects randomly assigned to trial treatment and who took at least one dose of insulin icodec. Subjects were analyzed according to the treatment they received, and the analysis included safety events that occurred during at least 5 weeks after the last dose of once daily (QD) basal insulin and 6 weeks after the last dose of QW insulin icodec. The following observation periods were used to evaluate safety:

- ***In-trial***, defined as the date from randomization up to any of the following: the last direct subject-site contact; subject withdrawal of consent; last subject-investigator contact for subjects lost to follow-up; or death.
- ***On-treatment***, defined as the date of the first dose of insulin icodec up to the first date of any of the following: end of trial visit, last date on insulin icodec plus 5 weeks for QD basal insulin and 6 weeks

for QW insulin icodec (baseline to Week 57), or end-date for the in-trial observation period. This period represents the time period a subject is exposed to insulin icodec.

- ***Main on-treatment***, defined as the date of the first dose of insulin icodec up to the first date of any of the following: end date of on-treatment period, or the last planned visit in the main period of the trial (Week 26 in ONWARDS 6).

4.4.2 Mean Weekly Insulin Dose and Body Weight

Data regarding bolus, basal and total insulin doses were collected at screening and during ONWARDS 6. Study investigators reported baseline insulin doses at screening by entering data into fields in the electronic data capture (EDC) system. During the treatment period, subjects self-reported doses taken in the eDiary. However, FDA noted significant discrepancies in the bolus and total insulin doses between the baseline and treatment periods in both the icodec and degludec treatment arms. The discrepancies with the baseline data were noted starting at Week 1 and persisted at all subsequent time points. The Applicant hypothesized that these discrepancies emerged because some investigators mistakenly reported the total daily bolus dose rather the individual bolus dose when entering baseline data in the EDC system, suggesting that reliable data on baseline bolus and total insulin doses are not available. For this reason, FDA focused its analyses of insulin dose on the data collected during the treatment period in the eDiary. Table 7 displays the summary statistics for weekly basal, bolus, and total insulin dose at Week 26 and Week 52. Total weekly insulin doses were similar at Week 26 and Week 52 across the two treatment arms (though numerically slightly greater at Week 52 in subjects randomized to insulin degludec). In contrast, the mean basal insulin dose was greater in subjects randomized to insulin icodec, whereas the mean bolus insulin dose was greater in subjects randomized to insulin degludec. Although reliable baseline insulin dose data are not available, it is unlikely that these differences between treatment arms were present at baseline.

Table 7. Summary Statistics for Weekly Basal, Bolus, and Total Insulin Dose at Weeks 26 and 52

Variable	Insulin Icodec (Safety Analysis Set=290)	Insulin Degludec (Safety Analysis Set=292)
Weekly basal insulin dose (U)		
Week 26: geometric mean (N)	179.0 (265)	148.7 (282)
Week 52: geometric mean (N)	178.0 (245)	148.0 (273)
Weekly bolus insulin dose (U)		
Week 26: geometric mean (N)	125.1 (270)	154.3 (278)
Week 52: geometric mean (N)	127.5 (248)	151.8 (272)
Weekly total insulin dose (U)		
Week 26: geometric mean (N)	309.6 (271)	312.2 (282)
Week 52: geometric mean (N)	301.0 (257)	312.4 (273)

Source: FDA statistical reviewer based on submitted datasets.
Safety analysis set: Subjects who were randomized and took at least one dose of trial product.
Abbreviation: N, number contributing to the analysis

In ONWARDS 6, the mean total weekly insulin dose (U) (basal, bolus, and total) from Weeks 24 to 26 and from Weeks 50 to 52 were evaluated and formally compared as secondary safety endpoints. The full analyses set and on treatment data were used in the analyses. For study subjects with missing data, the imputed log-transformed average weekly value during Weeks 24 to 26 and 50 to 52 was drawn from a normal distribution with mean at the subjects' log-transformed weekly screening response with added variance. One-thousand datasets were generated. The log-transformed response was analyzed using ANCOVA with treatment, region, pretrial basal insulin treatment, and A1C group at screening as fixed effects, and log-transformed weekly screening response as a covariate was used for each dataset and

Rubin's rule was applied. The point estimate of the log-transformed LS Means, treatment effect, and corresponding 95% confidence limits were exponentiated to transform back to the original scale.

Body weight (kg) was also analyzed as a secondary safety endpoint. At Weeks 26 and 52, subjects on insulin icodec showed no difference in change in body weight from subjects on insulin degludec, showing similar modest gains in body weight of 1.0 to 1.3 kg at both timepoints.

4.4.3 Increased Risk of Hypoglycemia With Insulin Icodec Versus Active Comparator

Although hypoglycemia is a known adverse effect of insulin therapy, an increased risk of level 2/3 hypoglycemia was observed in the insulin icodec arm compared to the active comparator insulin arm in ONWARDS 6. When considering the clinical relevance of this finding, it is important to note that the active comparator, insulin degludec, may be associated with less hypoglycemia risk than other marketed basal insulin products; daily Tresiba has a labeling claim for less hypoglycemia than daily insulin glargine in patients with T2D.[41] FDA's review of the hypoglycemia data are presented in the following sections.

4.4.3.1 Capture and Classification of Hypoglycemia

In the insulin icodec development program, events of hypoglycemia were assessed throughout the study (Day 1 through Week 57) and defined and identified according to the following three categories:

- **Level 1 hypoglycemia:** blood glucose <70 mg/dL and ≥54 mg/dL.
- **Level 2 (clinically significant) hypoglycemia:** blood glucose <54 mg/dL.
- **Level 3 (severe) hypoglycemia:** Episodes with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions.
- **Nocturnal hypoglycemia:** Episodes occurring between 00:01 and 05:59.

The definitions above are consistent with the 2024 American Diabetes Association (ADA) guidelines[30] and 2023 FDA draft guidance.[31] In ONWARDS 6, hypoglycemia events were captured by the trial blood glucose meter (Roche Accu Check). The CGM values were not to be relied on to document hypoglycemic episodes, but if a hypoglycemic episode was indicated by CGM, the subject was asked to measure their plasma glucose (PG) using the blood glucose meter for confirmation. Hypoglycemia events (levels 1 to 3) captured by blood glucose meter were reported in the eDiary, and episodes that met the criteria of an SAE were reported in the electronic case report form and a safety information form. Symptoms for all events hypoglycemic episodes were not reported.

4.4.3.2 Event Rates of Level 2/3 Hypoglycemia (SMPG and CGM)

A higher rate of level 2/3 hypoglycemia was reported with insulin icodec compared to insulin degludec in patients with T1D, rate ratio 1.8 (95% CI: 1.48, 2.18). The event rates of level 2/3 hypoglycemia (captured using SMPG) per 100 PY were 1700 and 916 for the insulin icodec-treated and insulin degludec-treated subjects, respectively, by Week 52 (Table 8). In the 52-week on-treatment period, most subjects had at least one episode of hypoglycemia (91% subjects in the insulin icodec arm, 86% of subjects in the insulin degludec arm), suggesting that the event-rate analysis is not driven by outliers.

Although the protocol for ONWARDS 6 specified that SMPG data should be obtained to confirm hypoglycemic episodes detected by CGM, FDA draft guidance issued since the conduct of ONWARDS 6 notes that CGM data and SMPG data provide complementary perspectives on the risk of hypoglycemia.[2] Event rates of level 2 hypoglycemia captured by CGM did not favor the insulin icodec arm (Table 8). The

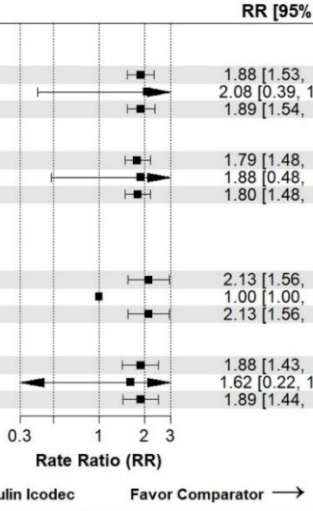
[2] Draft Guidance for Industry: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products. May 2023.

rates of nocturnal level 2 or level 2/3 hypoglycemia also were higher in the insulin icodec arm, regardless of how the events were captured (i.e., SMPG or CGM, Table 8). A higher rate of level 1 hypoglycemia was also reported for subjects randomized to the insulin icodec arm (i.e., 6,798 versus 4,787 events per 100 PY, respectively; data not shown). The rates of level 2/3 hypoglycemia reported across ONWARDS 1 to 6 are presented in Section 7.5.

Table 8. Event Rates of Level 2 or 3 Hypoglycemia—ONWARDS 6 (On-Treatment*)

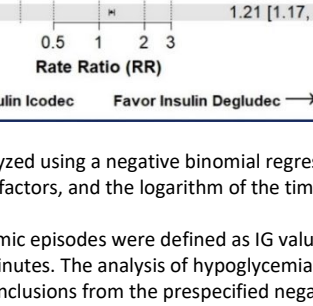
Hypoglycemic Episode (Level 2, Level 3) Capture: SMPG

	Insulin Icodec (N = 290)				Insulin Degludec (N = 292)				
	n	E	PY	Rate	n	E	PY	Rate	RR [95% CI]
Total									
Main (26 Weeks)									
Level 2	246	2789	142.3	1959.8	223	1478	144.1	1025.5	1.88 [1.53, 2.32]
Level 3	9	47	142.3	33.0	9	17	144.1	11.8	2.08 [0.39, 10.96]
Level 2 or Level 3	247	2836	142.3	1992.8	223	1495	144.1	1037.3	1.89 [1.54, 2.33]
Extension (52 Weeks)									
Level 2	262	5047	300.2	1681.4	250	2811	309.6	908.0	1.79 [1.48, 2.18]
Level 3	13	56	300.2	18.7	12	25	309.6	8.1	1.88 [0.48, 7.36]
Level 2 or Level 3	263	5103	300.2	1700.1	250	2836	309.6	916.1	1.80 [1.48, 2.18]
Nocturnal									
Main (26 Weeks)									
Level 2	135	476	142.3	334.5	98	224	144.1	155.4	2.13 [1.56, 2.91]
Level 3	2	5	142.3	3.5	3	3	144.1	2.1	1.00 [1.00, 1.00]
Level 2 or Level 3	135	481	142.3	338.0	98	227	144.1	157.5	2.13 [1.56, 2.91]
Extension (52 Weeks)									
Level 2	171	861	300.2	286.9	140	458	309.6	147.9	1.88 [1.43, 2.47]
Level 3	4	9	300.2	3.0	4	4	309.6	1.3	1.62 [0.22, 11.86]
Level 2 or Level 3	171	870	300.2	289.9	140	462	309.6	149.2	1.89 [1.44, 2.48]



Hypoglycemic Episode Capture (Level 2): CGM

	Ico (N = 290)				IDeg (N = 292)				
	n	E	PY	Rate	n	E	PY	Rate	RR [95% CI]
Total									
Main (26 Weeks)									
Level 2	288	13883	142.3	9756.1	284	9965	144.1	6915.3	1.42 [1.38, 1.45]
Extension (52 Weeks)									
Level 2	289	26986	300.2	8989.3	287	21623	309.6	6984.2	1.29 [1.26, 1.31]
Nocturnal									
Main (26 Weeks)									
Level 2	261	2790	142.3	1960.6	245	2135	144.1	1481.6	1.33 [1.26, 1.40]
Extension (52 Weeks)									
Level 2	272	5818	300.2	1938.0	267	4954	309.6	1600.1	1.21 [1.17, 1.26]



Source: ONWARDS 6 Clinical Study Report.

Analysis of hypoglycemic episodes captured using SMPG: The number of events is analyzed using a negative binomial regression model with treatment, region, A1C group at screening and pretrial basal insulin treatment as fixed factors, and the logarithm of the time period for which the events are considered as an offset.

Analysis of hypoglycemic episodes captured using CGM: Level 2 CGM-based hypoglycemic episodes were defined as IG values of <54 mg/dL for at least 15 minutes which ended when the CGM value was ≥54 mg/dL for at least 15 minutes. The analysis of hypoglycemia episodes captured using CGM was intended to be a descriptive analysis to assess the robustness of the conclusions from the prespecified negative binomial model analysis of hypoglycemic episodes captured using SMPG. Therefore, crude rate ratio and 95% confidence intervals were computed. The crude RR was not adjusted for any covariates.

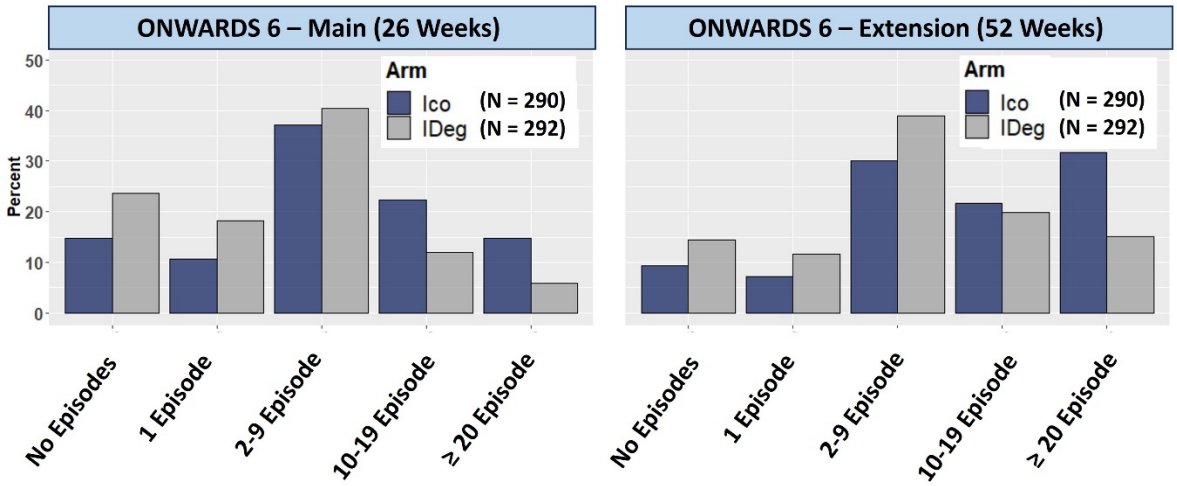
Comparative analysis was not performed for level 3 nocturnal hypoglycemia episodes because the number of events were low.

*Results based on in-trial analysis that considered hypoglycemic episodes during the entire trial duration regardless of the treatment exposure after randomization were consistent with the on-treatment analysis of ONWARDS 6. The proportion of subjects who discontinued treatment was small in ONWARDS 6 (6.2% in the insulin icodec arm and 3.1% in the insulin degludec arm). Those who discontinued treatment did not discontinue early in the trial.

Abbreviations: A1C, hemoglobin A1c; CGM, continuous glucose monitoring; E, number of events; Ico, Insulin icodec; IDeg, insulin degludec; N, number of subjects; n, number of subjects with one or more events; PY, patient years of exposure; rate, number of events per 100 PY; RR, rate ratio; SMPG, self-measured plasma glucose

The distribution of subjects by the number of level 2/3 hypoglycemic episodes (0, 1, 2 to 9, 10 to 19 and ≥20 episodes) during Weeks 0 to 26 and Weeks 0 to 52 was evaluated (Figure 4). Approximately 53.4% (155 of 290) of insulin icodec-treated subjects experienced 10 or more level 2/3 hypoglycemic events compared to 34.9% (102 of 292) of subjects randomized to the insulin degludec arm during the 52-week on-treatment period of ONWARDS 6. Similarly, the proportion of subjects experiencing frequent (>20) level 2/3 hypoglycemic episodes was higher in the insulin icodec arm (31.7% versus 15.1%, respectively).

Figure 4. Number of Level 2 or 3 Hypoglycemic Episodes Based on SMPG Data—ONWARDS 6 (On-Treatment)

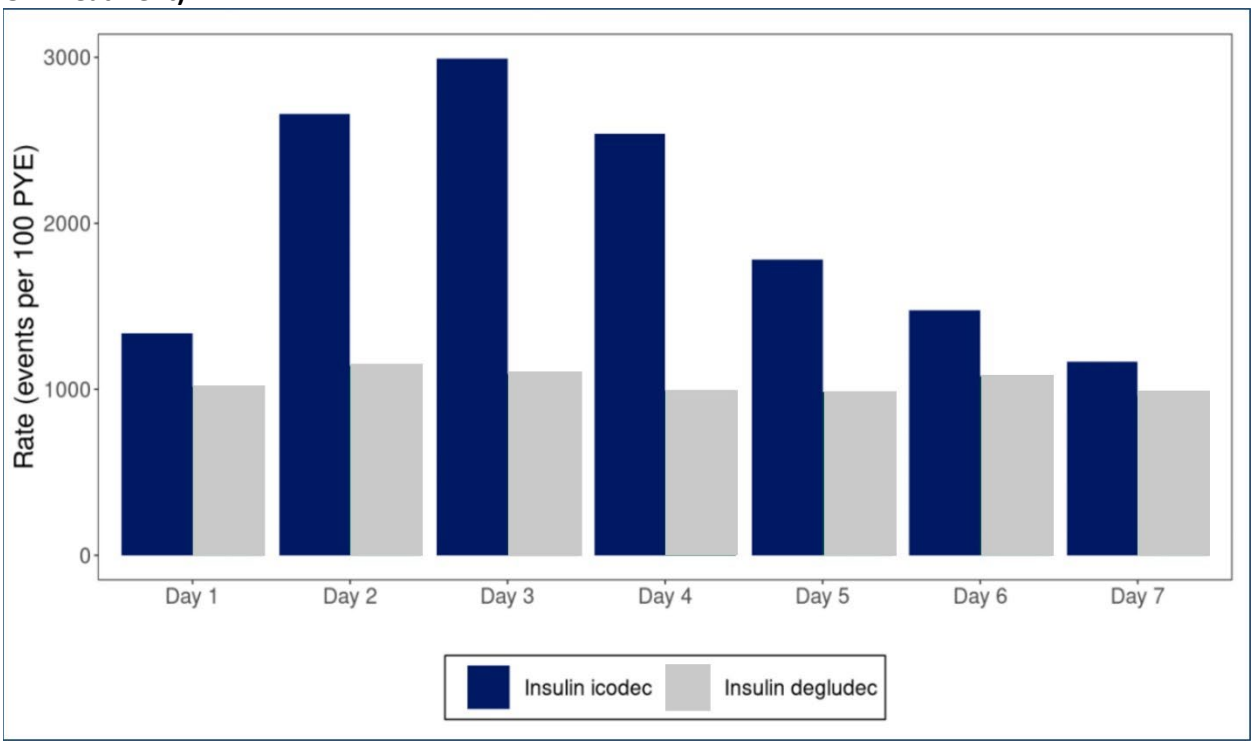


Source: ONWARDS 6 Clinical Study Report.
Abbreviations: Ico, insulin icodec; IDeg, insulin degludec; N, number of subjects; SMPG, self-measured plasma glucose.

4.4.3.3 Event Rates of Level 2/3 Hypoglycemia by Treatment Day (SMPG)

The rate of level 2/3 hypoglycemia in ONWARDS 6 by the day of the week following insulin icodec injections is presented in Figure 5. The peak hypoglycemia rates occurred on Days 2 to 4 after each injection, while the rates were similar for each day of the week in the insulin degludec arm. This finding is not unexpected based on the observed PK/PD profile of insulin icodec discussed in Section 4.1.

Figure 5. Rate of Level 2 or 3 Hypoglycemia (Based on SMPG) by Treatment Day—ONWARDS 6 (Main On-Treatment)



Source: Summary of Clinical Safety (Figure 2-11, page 120 of 217).
Level 2 hypoglycemia (plasma glucose <54 mg/dL confirmed by blood glucose meter), and level 3 hypoglycemia (severe cognitive impairment requiring external assistance for recovery). Observed data from the safety analysis set (SAS) for the main 26-week treatment period.
Abbreviations: PYE, patient years of exposure (1 PYE=365.25 days); SMPG, self-measured plasma glucose

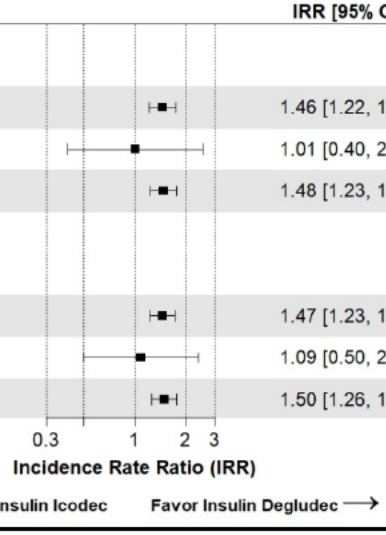
4.4.3.4 Incidence Rates of Level 2/3 Hypoglycemia (SMPG)

Additional analyses were performed to compare incidence rate of level 2 or combined level 2/3 hypoglycemia between the treatment arms (Table 9). This was to assess the robustness of the conclusions from the prespecified model as the total number of episodes can be driven largely by a few subjects who experience a large number of episodes. Incidence rate (IR) was defined as the number of subjects with at least one hypoglycemic episode divided by the time at risk. For subjects who experienced at least one event, time at risk was defined as the time from the first drug exposure to the first event. For subjects who did not experience an event, time at risk was set to equal the on-treatment period. The 95% CIs for the incidence rate ratio (IRR) were calculated using normal approximation. The analysis of incident hypoglycemia was intended to be descriptive and therefore, the IRR was not adjusted for covariates.

In ONWARDS 6, IRRs were consistent with the prespecified analysis results of event rate ratio, but showing a slightly lower risk of hypoglycemia. Over the 52-week exposure period, the results indicated a 50% higher risk of experiencing at least one level 2/3 hypoglycemia episode in the insulin icodec arm compared to subjects in the insulin degludec arm (IRR of 1.5 (95% CI: 1.26, 1.78)). The IR across all six phase 3 trials in the ONWARDS clinical program are presented in Section 7.6.

Table 9. Incidence Rate of Level 2 (Based on SMPG) or 3 Hypoglycemia—ONWARDS 6 (On-Treatment)

	Ico (N = 290)			IDeg (N = 292)			
	n	PY	Time At Risk	n	PY	Time At Risk	IRR [95% CI]
Main (26 Weeks)							
Level 2	246	142.3	43.3	223	144.1	57.3	1.46 [1.22, 1.75]
Level 3	9	142.3	139.7	9	144.1	141.0	1.01 [0.40, 2.54]
Level 2 or Level 3	247	142.3	42.8	223	144.1	57.1	1.48 [1.23, 1.77]
Extension (52 Weeks)							
Level 2	262	300.2	60.6	250	309.6	84.9	1.47 [1.23, 1.75]
Level 3	13	142.3	141.1	12	144.1	141.9	1.09 [0.50, 2.39]
Level 2 or Level 3	263	300.2	59.5	250	309.6	84.8	1.50 [1.26, 1.78]



Source: ONWARDS 6 Clinical Study Report.

Subjects with event refers to the number of subjects with one or more events; Time at risk definition: i) for subjects who experienced at least one event, time at risk was defined as the time from the first drug exposure to the first event, ii) for subjects who did not experience an event, time at risk was set to equal the on-treatment period. Ninety-five percent confidence intervals for the incidence rate ratio were calculated using normal approximation. The analysis of incident hypoglycemia was intended to be a descriptive analysis to assess the robustness of the conclusions from the prespecified negative binomial model. Therefore, the IRR was not adjusted for any covariates.

Abbreviations: N, number of subjects; n, number of subjects with one or more events; PY, patient-years of exposure; IRR, incidence rate ratio; SMPG, self-measured plasma glucose

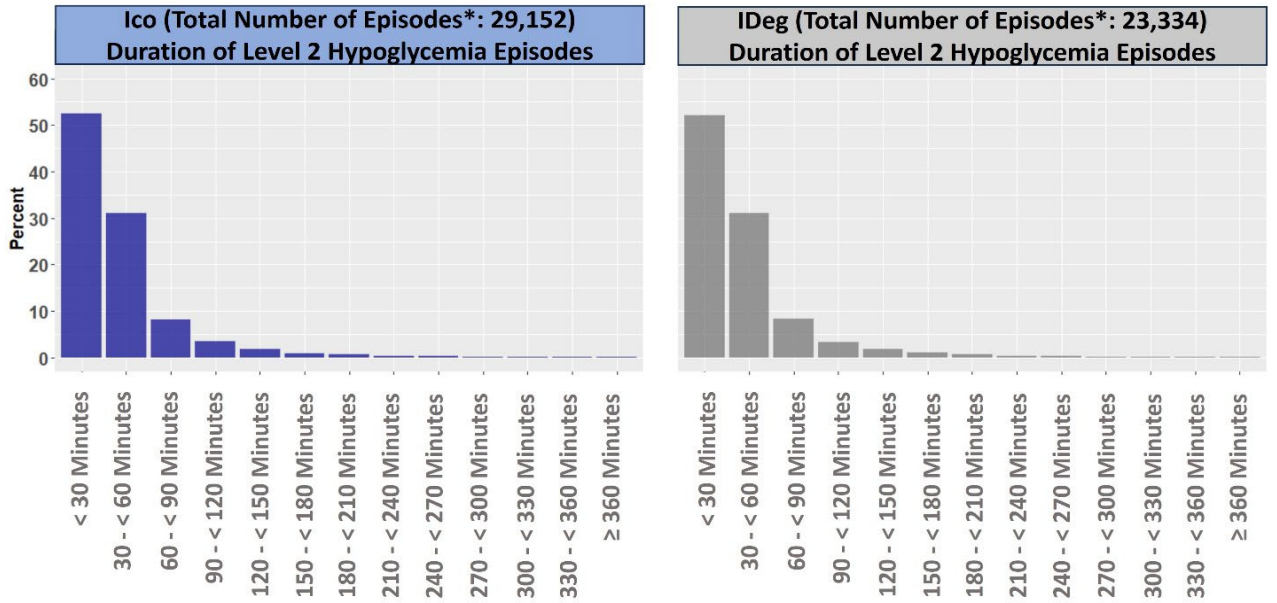
4.4.3.5 Duration of Level 2 Hypoglycemic Episodes (CGM)

CGM data from the 52-week on-treatment period of ONWARDS 6 was used to evaluate the duration of level 2 hypoglycemic episodes (Figure 6). The duration of level 2 hypoglycemia by CGM was defined as the period of time from when the interstitial glucose value was <54 mg/dL for at least 15 minutes to when interstitial glucose value was ≥54 mg/dL for at least 15 minutes, which is consistent with a recent international consensus statement on use of CGM in clinical trials.[61] Based on these analyses, it appears that the duration of level 2 episodes were similar between treatment arms, with numerically higher numbers of events in the insulin icodec arm (29,152 versus 23,334 in the insulin degludec arm). Notably, CGM captured far higher numbers of level 2 hypoglycemia events compared to SMPG (5,047 vs 2,811 events for the insulin icodec and insulin degludec arms, respectively; Table 8). Unlike SMPG, CGM measures glucose passively so reduces the barrier to data collection introduced by patient effort. Additionally, subjects may be more likely to measure SMPG with symptomatic events.

Figure 6. Duration (Minutes – Based on CGM) of Level 2 Hypoglycemia Episodes—ONWARDS 6 Extension (On-Treatment)

Variable	Ico	IDeg
Duration of episodes – based on CGM		
Number of episodes with missing duration	1	4
Descriptive statistics (duration, minutes)		
Mean (SD)	40.2 (41.8)	41.3 (45.6)
Median	25.0	25.0
P25; P75	20.0; 45.0	20.0; 45.0
Minimum; maximum	15.0; 730.0	15.0; 1225.0

Variable Total number of episodes among patients with nonmissing duration	Ico E (%)	IDeg E (%)
	29,152 (100)	23,334 (100)
Duration group		
<30 Minutes	15,301 (52.5)	12,162 (52.1)
30 - <60 Minutes	9063 (31.1)	7254 (31.1)
60 - <90 Minutes	2401 (8.2)	1945 (8.3)
90 - <120 Minutes	1031 (3.5)	767 (3.3)
120 - <150 Minutes	530 (1.8)	423 (1.8)
150 - <180 Minutes	275 (0.9)	237 (1.0)
180 - <210 Minutes	194 (0.7)	165 (0.7)
210 - <240 Minutes	106 (0.4)	103 (0.4)
240 - <270 Minutes	76 (0.3)	84 (0.4)
270 - <300 Minutes	55 (0.2)	47 (0.2)
300 - <330 Minutes	32 (0.1)	57 (0.2)
330 - <360 Minutes	34 (0.1)	35 (0.1)
≥360 Minutes	54 (0.2)	55 (0.2)

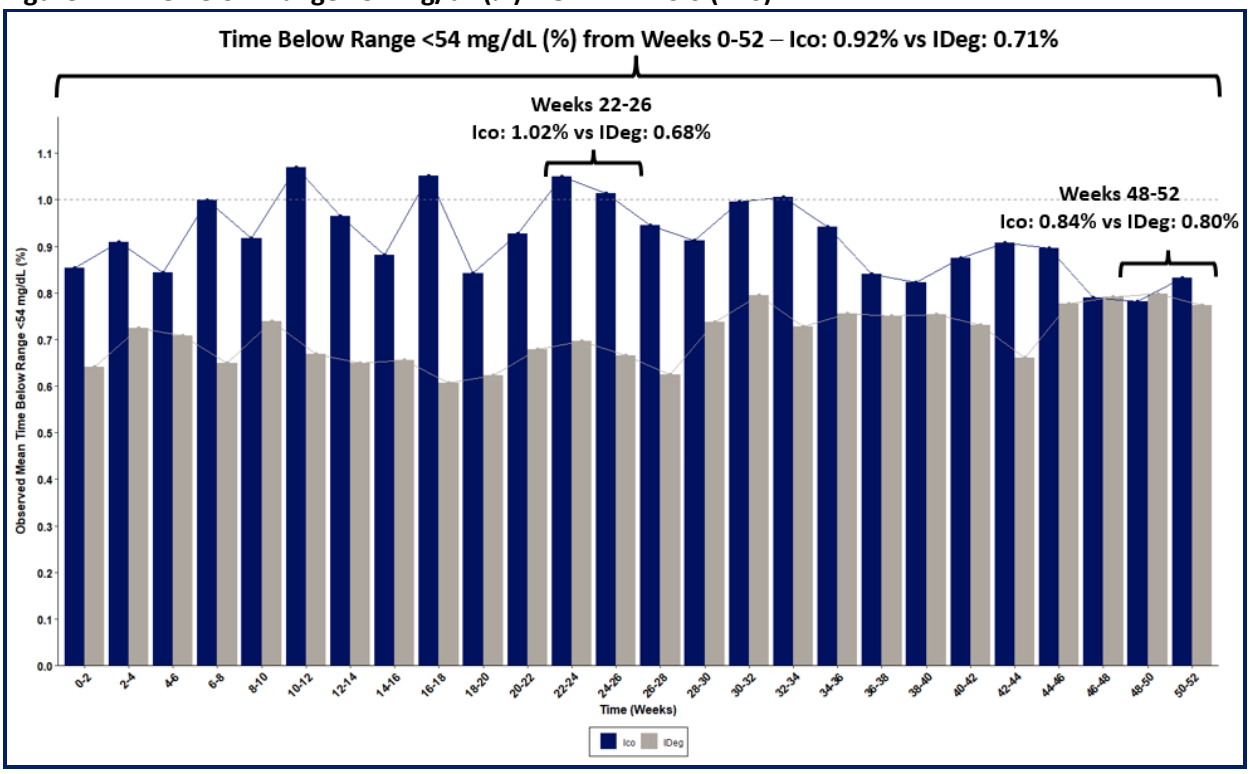


Source: ONWARDS 6 Clinical Study Report.
Level 2 hypoglycemic event was defined as starting with a CGM value of <54 mg/dL for at least 15 minutes and ending when the CGM value is ≥54 mg/dL for at least 15 minutes.
*Note: Total number of episodes among patients with non-missing duration.
Abbreviations: CGM, continuous glucose monitoring; E, number of events; Ico: insulin icodec; IDeg; insulin degludec; SD, standard deviation

TBR 54 mg/dL. Using CGM data, the time spent below range (TBR) 54 mg/dL during Weeks 22 to 26, 48 to 52, and 0 to 52 were assessed as safety endpoints (Figure 7). The mean TBR <54 mg/dL results were as follows:

- Weeks 22 to 26 was 1.02% for insulin icodec and 0.68% for insulin degludec.
- Weeks 48 to 52 was 0.84% for insulin icodec and 0.80% for insulin degludec.
- Weeks 0 to 52 was 0.92% for insulin icodec and 0.71% for insulin degludec.
- For Weeks 0 to 52 and 48 to 52 (but not 22 to 26), both treatment arms met the ADA-recommended glycemic goal of <1% (<15 minutes per day).[30]

Figure 7. Time Below Range <54 mg/dL (%)—ONWARDS 6 (FAS)



Source: Statistical analyst. sv.xpt, mdvisit.xpt, mdparm.xpt, adsl.xpt, adcgm.xpt.
Abbreviations: FAS, full analysis set; Ico, insulin icodec, IDeg, insulin degludec

4.4.3.6 Serious Adverse Events of Hypoglycemia

Severe hypoglycemia can progress to loss of consciousness, seizure, coma, or death.[30] In a survey of adults with T1D, approximately 20% of respondents experienced at least one severe hypoglycemic event in the prior year, suggesting that level 3 hypoglycemia is a common adverse effect of insulin therapy.[62] The incidence of hypoglycemic events requiring medical attention (i.e., an emergency department visit or hospitalization) among patients with T1D is estimated to be 3 to 5 episodes per 100 PY.[63,64]

An imbalance in serious adverse events (SAEs) of hypoglycemia was observed (Table 11) which did not favor the insulin icodec arm. At Week 52, 3.1% (9/290) of insulin icodec-treated subjects experienced 14 hypoglycemia SAEs (4.66 events/100 PY) compared to 1% (3/292) insulin degludec-treated subjects, who experienced 3 SAEs (1 event/100 PY). In the insulin icodec arm, treatment for hypoglycemia included: insulin icodec dose reduction in five subjects, glucagon administration in two subjects, and intravenous (IV) glucose infusion in four subjects. None of the SAEs in either treatment arm resulted in permanent discontinuation of IP or subject withdrawal from the trial.

Table 10. Serious Adverse Events of Hypoglycemia in Trial 4625 (On-Treatment)

Subj ID	Age (y)	Sex	BMI	MedDRA PT	Reported Term	Study Day	Action
Ico							
(b) (6)	61	Male	26.8	Hypoglycemia	Severe hypoglycemia	17	• Loss of consciousness • Administered IV glucose by emergency physician • Dose not changed
				Hypoglycemia	Severe hypoglycemia	100	• Loss of consciousness • Dose reduced
				Hypoglycemia	Severe hypoglycemia	108	• Loss of consciousness • Administered carbohydrates • Emergency physician contacted • Dose reduced
				Hypoglycemia	Severe hypoglycemia	219	• Shaking/sweating/confused • IV glucose administered in ER • Dose not changed
(b) (6)	30	Male	36.3	Hypoglycemia	Severe hypoglycemia	398	• IV glucose administered by paramedics at home • Not applicable*
	42	Male	27.2	Hypoglycemia	Severe hypoglycemia	264	• Loss of consciousness • Administered carbohydrates • Dose not changed
	27	Female	29.1	Hypoglycemia	Severe hypoglycemia	129	• Loss of consciousness • Glucagon administered by family member • Medial assistance was requested • Dose reduced
	24	Male	16.6	Hypoglycemic seizure	Severe hypoglycemia with seizure	164	• Loss of consciousness • Administered IV glucose in hospital • Dose reduced
	34	Male	35.1	Hypoglycemia	Severe hypoglycemia	99	• Loss of consciousness • Administered IV glucose by EMS and hospitalized • Dose reduced
	56	Male	26.7	Hypoglycemia	Severe hypoglycemia	357	• Confusion/dizziness/palpitations, trembling/difficulty speaking • Administered carbohydrates at ER • Dose not changed
	43	Male	31.3	Hypoglycemia	Severe hypoglycemia	225	• Drowsy/sweating/trembling • Administered carbohydrates • Dose reduced
				Hypoglycemia	Severe hypoglycemia	253	• Loss of consciousness • Administered glucagon by EMS • Dose not changed
				Hypoglycemia	Severe hypoglycemia	363	• Drowsy/sweating/trembling • Administered carbohydrates • Dose reduced
(b) (6)	19	Male	25.7	Hypoglycemia	Severe hypoglycemia	164	• Confusion (“cloudy consciousness”) • Administered carbohydrates • Dose reduced

Subj ID	Age (y)	Sex	BMI	MedDRA PT	Reported Term	Study Day	Action
IDeg (b) (6)	62	Female	28.8	Hypoglycemia	Severe hypoglycemia	253	• Loss of consciousness • Administered glucagon by spouse • Dose not changed
	79	Male	26.6	Hypoglycemic unconsciousness	Hypoglycemic unconsciousness	349	• Loss of consciousness • Administered glucagon and carbohydrates by EMT • Dose reduced
	36	Female	21.1	Hypoglycemic seizure	Hypoglycemic state with convulsions	55	• Loss of consciousness • Administered IV glucose at the hospital • Drug interrupted

Source: Derived from the Clinical Trial Report, Table 14.3.2.2, pages 379-387, of 999.
* Event occurred 1 month after IP was stopped (receiving insulin glargine and insulin lispro at the time of the event).
Abbreviations: BMI, body mass index; EMS, emergency medical service; EMT, emergency medical technician; ER, emergency room; IDeg, insulin degludec; Ico, insulin icodec; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; y, year

4.4.3.7 Management of Hypoglycemia

During the 52-week treatment period, there were 13 insulin icodec-treated subjects who experienced 56 level 3 hypoglycemic episodes versus 12 insulin degludec-treated subjects who experienced 25 events (Table 12). Most of these episodes were managed by administration of carbohydrates alone (i.e., 79% and 76% of subjects, respectively). Approximately 25% and 20% of level 3 hypoglycemic episodes were associated with loss of consciousness in insulin icodec and insulin degludec-treated subjects.

Table 11. Management of Level 3 Hypoglycemic Episodes

	Insulin Icodec			Insulin Degludec		
Variable	**N**	**E**	**%**	**N**	**E**	**%**
Number of severe (level 3) hypoglycemic episodes	**13**	**56**	**(100.0)**	**12**	**25**	**(100.0)**
Treatment(s) the patient received						
Glucagon	3	4	(7.1)	2	2	(8.0)
IV glucose (drip)	6	8	(14.3)	2	2	(8.0)
Something to drink or eat (carbohydrates)	9	47	(83.9)	9	20	(80.0)
Other	2	2	(3.6)	1	2	(8.0)
Treatment(s) the patient received, exclusive						
Intensive intervention	8	10	(17.9)	4	4	(16.0)
Something to drink or eat (carbohydrates), only	8	44	(78.6)	8	19	(76.0)
Other	2	2	(3.6)	1	2	(8.0)
Did the patient get help by a medical person to handle the episode?						
Yes	10	13	(23.2)	4	4	(16.0)
No	7	42	(75.0)	8	19	(76.0)
Unknown	1	1	(1.8)	1	2	(8.0)
Where did the patient get help?						
Clinic/emergency room/hospital	6	8	(14.3)	2	2	(8.0)
Other	9	48	(85.7)	10	23	(92.0)
Was the patient transported by ambulance?						
Yes	4	6	(10.7)	1	1	(4.0)
No	3	3	(5.4)	1	1	(4.0)
Missing	8	47	(83.9)	10	23	(92.0)

Variable	Insulin Icodec			Insulin Degludec		
	N	E	%	N	E	%
Did the patient experience convulsions or fits (seizure)?						
Yes	2	2	(3.6)	2	2	(8.0)
No	11	54	(96.4)	10	23	(92.0)
Did the patient pass out (loss of consciousness or coma)?						
Yes	9	14	(25.0)	5	5	(20.0)
No	6	42	(75.0)	7	20	(80.0)
Did the patient feel better after treatment?						
Yes	13	56	(100.0)	12	23	(92.0)
No	0			1	2	(8.0)

Source: Adapted from the Applicant's Regulatory Response (dated April 10, 2024).
Abbreviations: E, event; N, number with the event

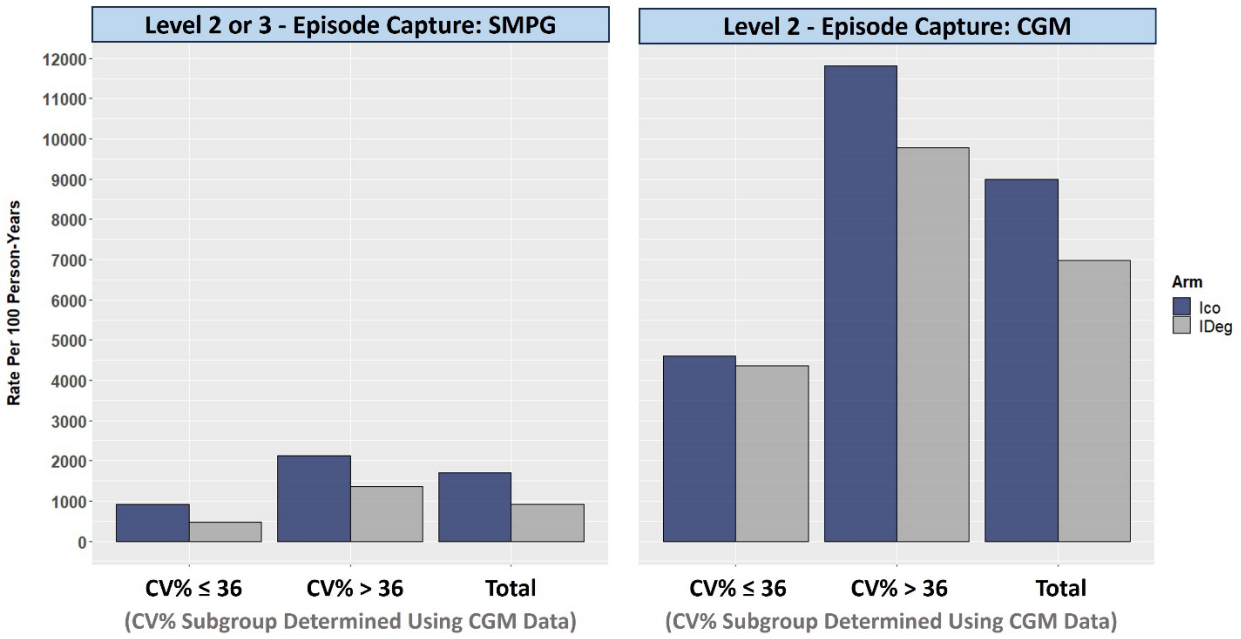
4.4.3.8 Exploratory Post Hoc Safety Analyses to Identify a Subgroup at Lower Risk for Hypoglycemia

The Applicant identified a subgroup of T1D subjects from ONWARDS 6 who had a lower risk of hypoglycemia compared to the total insulin icodec population and acceptable glycemic control, based on glycemic variability. 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 percent coefficient of variation (%CV) and is calculated as 100 × (standard deviation divided by mean glucose).[61]

The Applicant calculated %CV for each subject using data from the first 2 weeks after initiation of treatment. Numerically lower rates of level 2/3 hypoglycemic episodes were found in the CV ≤36% subgroup versus >36% captured by either SMPG or CGM (Figure 8).[3] However, the lower event rates did not change the observation that the rates of level 2/3 hypoglycemia in the insulin icodec arm were greater than the rates in the insulin degludec arm within each subgroup.

[3] Level 3 (severe) hypoglycemia is not classified based on glycemic criteria but defined qualitatively as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Thus, level 3 hypoglycemic events could not be obtained from CGM data alone, while the SMPG data included level 3 hypoglycemic events from eDiary (confirmed by investigator).

Figure 8. Event Rate of Level 2 or 3 Hypoglycemic Episodes by %CV (Cutpoint 36%, CGM-Derived %CV)—ONWARDS 6 (On-Treatment)



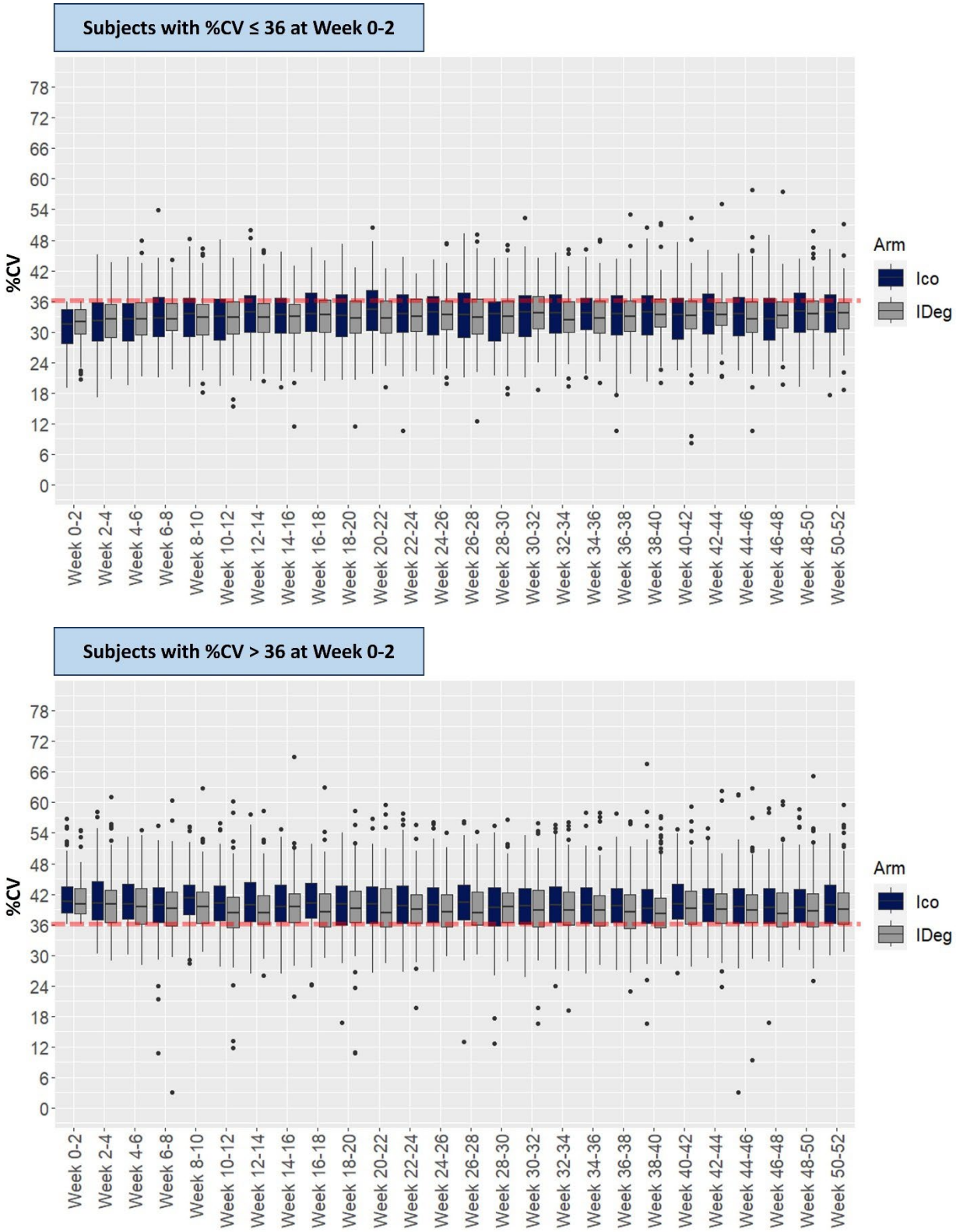
Level 2 or 3 Hypoglycemic Episode						
	%CV ≤ 36		%CV > 36		Total	
	Ico	IDeg	Ico	IDeg	Ico	IDeg
N	90	106	162	134	263	250
%	80.4	75.7	97.6	95.7	90.7	85.6
E	1076	711	3662	2035	5103	2836
Rate	922.2	475.9	2121.1	1353.8	1700.1	916.1

Level 2 - Episode Capture: CGM						
	%CV ≤ 36		%CV > 36		Total	
	Ico	IDeg	Ico	IDeg	Ico	IDeg
N	111	136	166	140	289	287
%	99.1	97.1	100.0	100.0	99.7	98.3
E	5378	6517	20401	14688	26986	21623
Rate	4609.0	4362.1	11816.5	9771.0	8990.6	6984.6

Source: Regulatory Response, February 2, 2024.
Abbreviations: %, percentage of subjects with one or more level 2 or level 3 hypoglycemic episode; CGM, continuous glucose monitoring; CV, coefficient of variation; E, number of hypoglycemic episodes; Ins Deg, insulin degludec; Ins Ico, insulin icodec; N, number of subjects with one or more level 2 or level 3 hypoglycemic episode; SMPG, self-measured plasma glucose

Additional exploratory analyses were performed to assess the variability of %CV within subgroups. Figure 9 shows the distribution of %CV through 52 weeks, which appears to be reasonably consistent throughout the trial period within each subgroup (i.e., for the %CV ≤36 subgroup, the median %CV for both arms was consistently below the red index line of 36%, and for the %CV >36 subgroup, was consistently above the red index line for both arms). Such exploratory analyses suggest that within-person variability of %CV remained relatively low, regardless of the treatment arm.

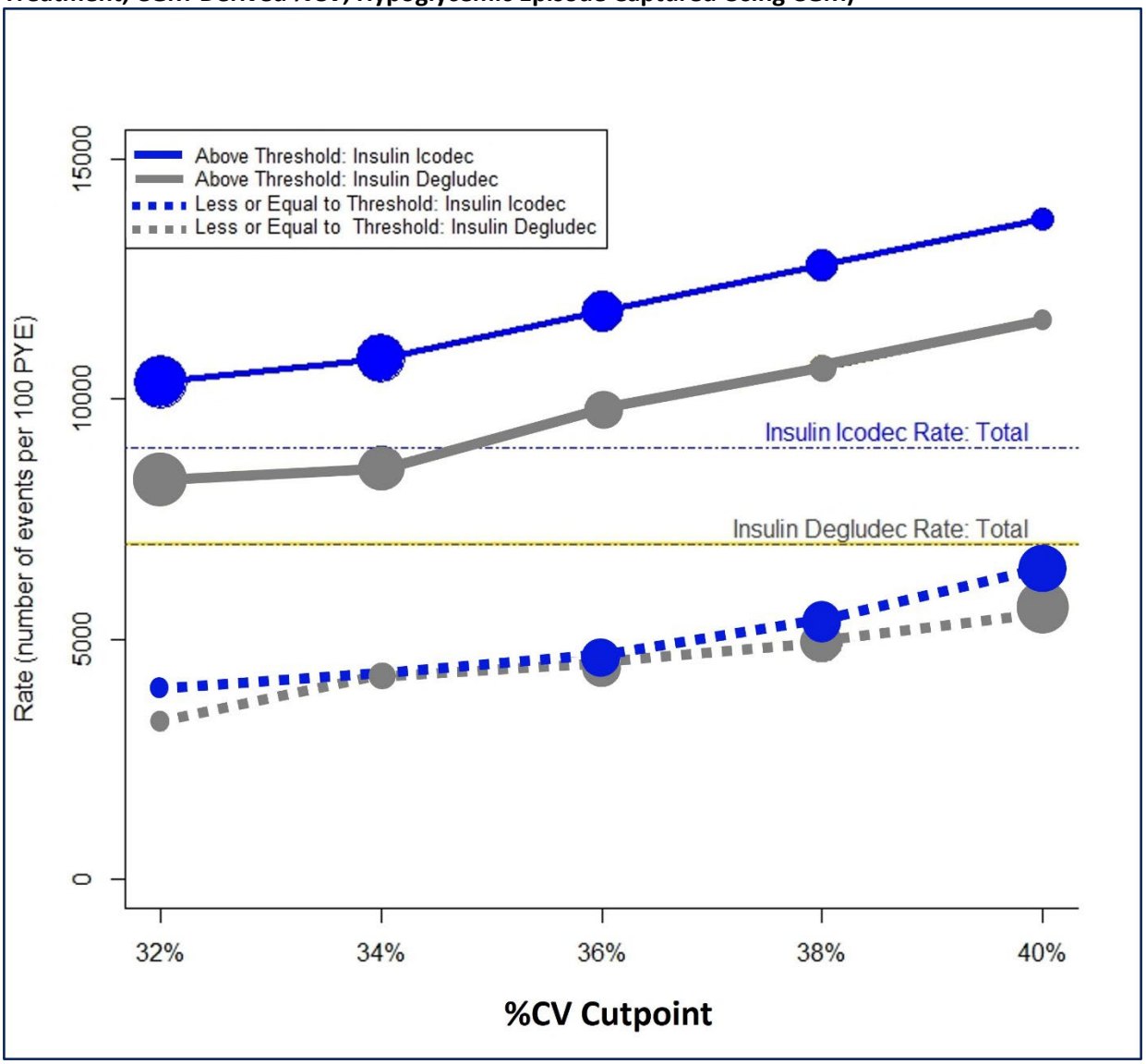
Figure 9. Distribution of %CV During the 52-Week Extension Period by %CV Subgroup (Cutpoint 36%, CGM-Derived %CV)—ONWARDS 6



Source: Regulatory Response, February 8, 2024.
Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation; Ins Deg, insulin degludec; Ins Ico, insulin icodec

Second, the consistency of subgroup results based on other %CV cutpoints were also evaluated in ONWARDS 6 to assess the pattern in hypoglycemia risk reduction and to determine whether a threshold effect existed. Exploration of the rates of level 2/3 hypoglycemic episodes by different %CV cutpoints from 32% to 40% indicated consistently lower rates of hypoglycemic episodes for the subgroup with lower %CV and when compared to the overall population (Figure 10).

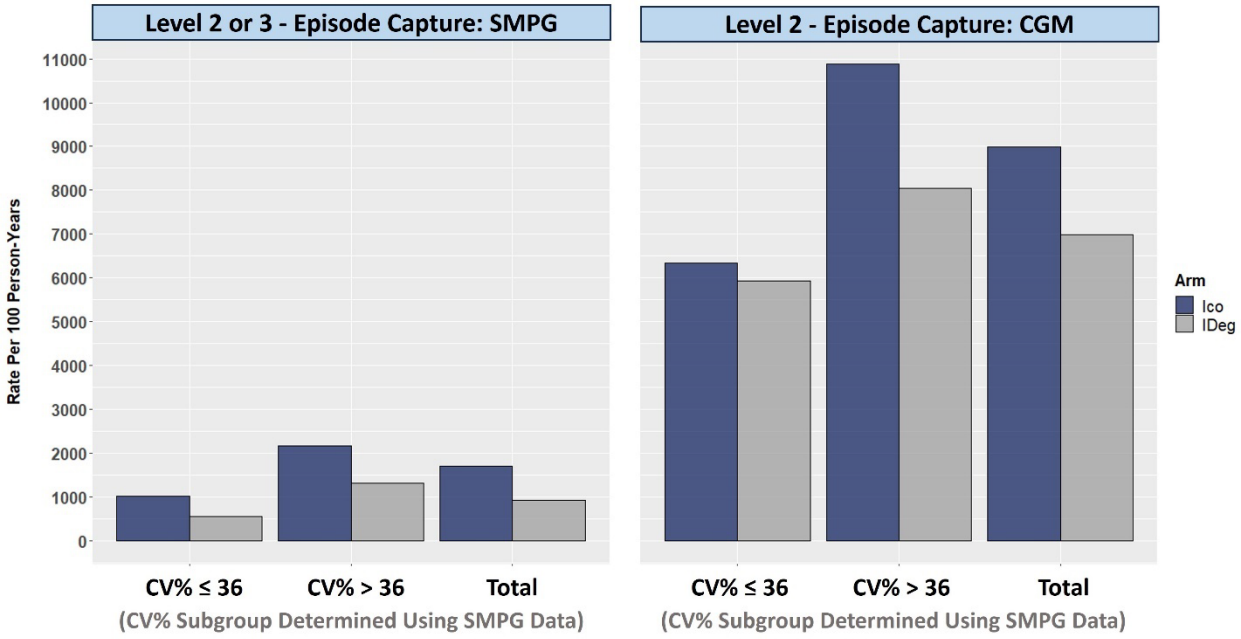
Figure 10. Event Rate of Level 2 or 3 Hypoglycemic Episodes by %CV Cutpoint—ONWARDS 6 (On-Treatment; CGM-Derived %CV, Hypoglycemic Episode Captured Using CGM)



Source: Regulatory Response, February 2, 2024.
Circle size is proportional to the sample size in the subgroup.
Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation

Third, the consistency of subgroup analyses results was assessed when %CV was calculated using 4-point SMPG values, measured during Weeks 0 to 2 after initiation of treatment. Numerically lower rates of level 2/3 hypoglycemic episodes were also observed for subjects with lower %CV, when %CV was determined using the 4-point SMPG profile data (i.e., daily preprandial and bedtime measurements) for the ≤36% (Figure 11) cutpoint.

Figure 11. Event Rate of Level 2 or 3 Hypoglycemic Episodes by %CV (Cutpoint 36%, 4-Point SMPG-Derived %CV)—ONWARDS 6 (On-Treatment)

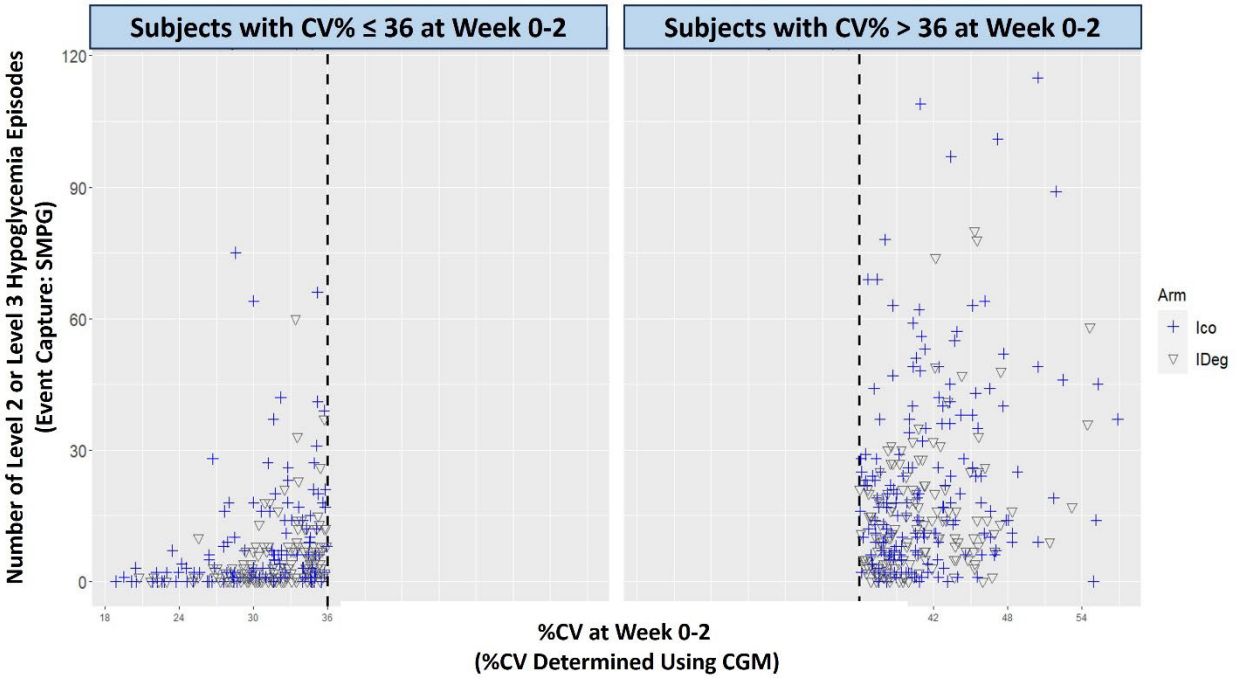


Level 2 or 3 - Episode Capture: SMPG							Level 2 - Episode Capture: CGM						
	CV% ≤ 36		CV% > 36		Total			CV% ≤ 36		CV% > 36		Total	
	Ico	IDeg	Ico	IDeg	Ico	IDeg		Ico	IDeg	Ico	IDeg	Ico	IDeg
N	98	116	163	133	263	250	N	118	143	168	143	289	287
%	82.4	79.5	97.0	92.4	90.7	85.6	%	99.2	98.0	100.0	99.3	99.7	98.3
E	1267	849	3719	1979	5103	2836	E	7943	9297	18786	12180	26986	21623
Rate	1011.3	541.1	2154.7	1306.5	1700.1	916.1	Rate	6339.7	5925.0	10884.2	8040.8	8990.6	6984.6

Source: Regulatory Response, March 18, 2024.
Four-point SMPG: Subjects measured preprandial and bedtime SMPG daily from Week 0 to end of trial at the following time points: pre-breakfast, pre-lunch, pre-dinner, and bedtime.
Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation; Ins Deg, insulin degludec; Ins Ico, insulin icodec; SMPG, self-measured plasma glucose

Fourth, the association between %CV and number of hypoglycemia episodes was assessed using CGM data. The number of level 2/3 hypoglycemic episodes are illustrated in Figure 12 by %CV subgroup determined using CGM. The exploratory analysis shows fewer level 2/3 hypoglycemia episodes for the subgroup with CV ≤36% compared to the subgroup with CV >36%.

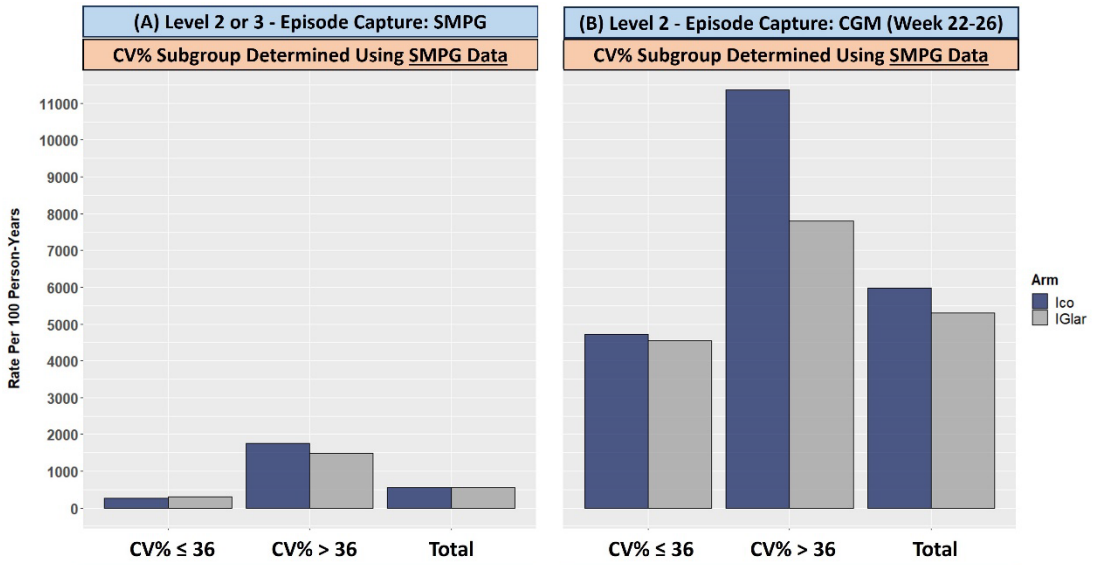
Figure 12. Number of Level 2 or 3 Hypoglycemic Episodes by %CV Subgroup—ONWARDS 6 (On-treatment; CGM-Derived %CV, Hypoglycemic Episode Captured Using CGM)



Source: Regulatory Response, February 2, 2024.
Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation; Ins Deg, insulin degludec; Ins Ico, insulin icodec; SMPG, self-measured plasma glucose

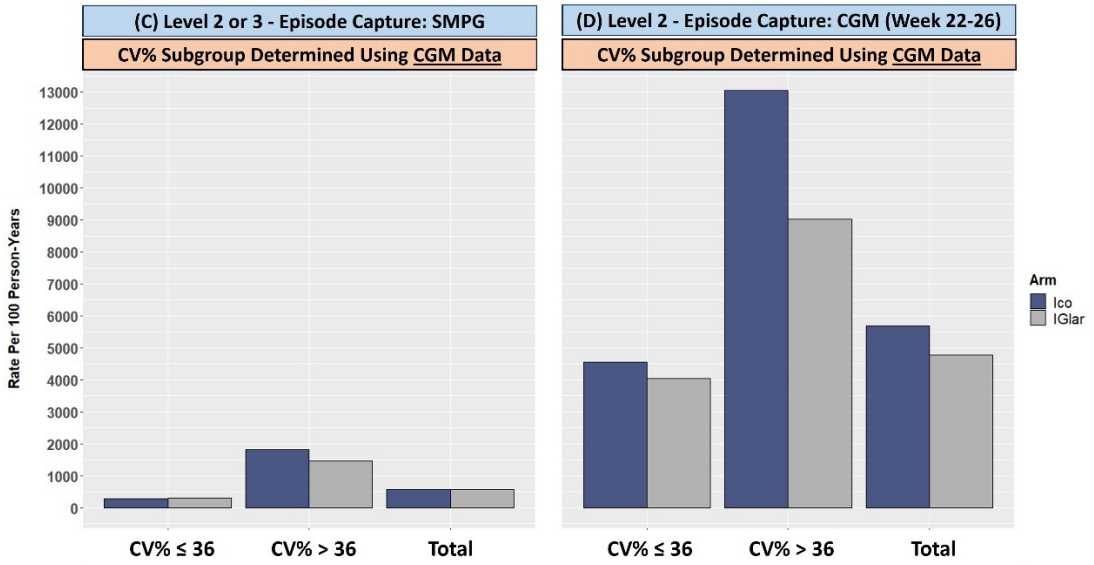
Fifth, the subgroup analysis based on %CV was revisited in ONWARDS 4 data. The ONWARDS 4 trial had subjects with T2D on basal-bolus insulin therapy and used a different daily basal insulin comparator (insulin glargine). Numerically lower rates of level 2 or level 3 hypoglycemic episodes were also observed for subjects with lower %CV in ONWARDS 4 (Figure 13).

Figure 13. Event Rate of Level 2 or 3 Hypoglycemic Episodes by %CV (Cutpoint 36%, SMPG-Derived %CV)—ONWARDS 4 (On-Treatment)



Level 2 or 3 - Episode Capture: SMPG						
	%CV ≤ 36		%CV > 36		Total	
	Ico	IGlar	Ico	IGlar	Ico	IGlar
N	101	108	49	53	150	162
%	43.7	48.4	86.0	85.5	51.6	55.7
E	360	388	584	537	944	938
Rate	269.0	301.6	1764.5	1490.9	564.1	562.4

Level 2 - Episode Capture: CGM (Week 22-26)						
	%CV ≤ 36		%CV > 36		Total	
	Ico	IGlar	Ico	IGlar	Ico	IGlar
N	153	137	48	52	201	189
%	71.5	66.5	90.6	88.1	69.1	64.9
E	721	643	408	334	1129	977
Rate	4716.4	4554.3	11368.6	7807.0	5979.9	5309.8



Level 2 or 3 - Episode Capture: SMPG						
	%CV ≤ 36		%CV > 36		Total	
	Ico	IGlar	Ico	IGlar	Ico	IGlar
N	88	96	43	44	150	162
%	44.0	50.8	89.6	81.5	51.6	55.7
E	337	327	514	465	944	938
Rate	290.7	293.7	1812.5	1463.0	564.1	562.4

Level 2 - Episode Capture: CGM (Week 22-26)						
	%CV ≤ 36		%CV > 36		Total	
	Ico	IGlar	Ico	IGlar	Ico	IGlar
N	135	119	44	46	179	165
%	71.8	65.0	97.8	90.2	61.5	56.7
E	615	517	414	332	1029	849
Rate	4558.0	4034.7	13055.4	9015.1	5688.2	4785.8

Source: Regulatory Response, March 18, 2024.
In ONWARDS 4, CGM data were available for Weeks 0 to 4 and 22 to 26, and during the follow-up period from Weeks 26 to 31. Level 2 episodes summarized in the table are level 2 hypoglycemic episodes captures in Weeks 0 to 4, 22 to 26, and 26 to 31.
Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation; E, event; Ico, insulin icodec; IGlar, insulin glargine; SMPG, self-measured plasma glucose

Section 7.7 describes the efficacy findings for changes in A1C and TIR (70 to 180 mg/dL)(%) by subgroups using %CV defined by both CGM and SMPG data during Weeks 0 to 2. Because these subgroups are based on postrandomization outcomes (i.e., %CV during Weeks 0 to 2), caution should be taken when drawing conclusions and efficacy results of subgroup analyses are all exploratory.

- Table 23 displays **subgroup results for A1C**. In general, subgroup results are consistent with the results of the overall population to establish the noninferiority of insulin icodec compared to insulin degludec at Week 26.
- Table 24 displays **subgroup results for TIR.** Subgroup results are consistent with the results of the overall population.

The Applicant's subgroup analyses have limitations, and the results should be interpreted with caution. The Applicant's choice of subgroup was post hoc. Importantly, the Applicant's proposal for risk mitigation suggests restricting the use of insulin icodec to T1D patients wearing a CGM device with CV ≤36% prior to initiation of insulin icodec treatment. The Applicant's assumption is that the pretreatment %CV levels will be comparable to post-treatment %CV levels. Data to confirm this assumption, however, was not provided.

4.4.4 Potential Alternative Dose Titration Schedules

The Applicant performed mechanistic glucose and insulin modelling and simulations to determine whether alternative dose-titration strategies for insulin icodec or insulin aspart (bolus insulin) could reduce the rate of level 2 hypoglycemia and maintain appropriate glycemic control in patients with T1D. In ONWARDS 6, insulin icodec was up- or down-titrated based on the lowest prebreakfast fasting plasma glucose (FPG) measured between Days 5 to 7, when the glucose lowering effect of insulin icodec is at its nadir. FDA asked the Applicant to investigate whether alternative titration strategies based on FPG measured on days coinciding with the time of peak glucose lowering effect could reduce the incidence of hypoglycemic events.

The study design of ONWARDS 6 did not allow for an evaluation of the independent effects of bolus and basal insulin separately. Therefore, a mechanistic modelling approach, based on data from ONWARDS 6 was supplemented with data from previous trials and literature, was developed to predict the separate effect of insulin icodec and bolus insulin dosing on glucose levels. The mechanistic glucose-insulin dynamics model predicted plasma glucose by modelling glucose turnover and taking into account carbohydrate intake as well as insulin icodec, insulin degludec and bolus insulin dosing. The mechanistic model consisted of both insulin PK models (with insulin aspart PK model borrowed from BLA 208751, Fiasp), an insulin effect compartment model, a meal intake model, glucose turnover model, and a CGM model. The model parameters were either estimated from current and previous trials (PK for insulins icodec, degludec and aspart) or determined from published literature (for the meal intake model, glucose turnover model, and CGM model). The mechanistic model used the glucose management indicator (GMI), calculated from the last 4 weeks of the simulated CGM data, as a surrogate for A1V.

Using modelling and simulation, the Applicant investigated the following three dose-titration scenarios as possible approaches to mitigate the risk of hypoglycemia:

- **First scenario**: Titrate insulin icodec dose based on the lowest FPG concentration measured between Days 2 to 4, instead of the last 3 days of the dosing interval (Days 5 to 7) as studied.
- **Second scenario**: Titrate insulin icodec dose based on the lowest FPG concentration measured between Days 3 to 5.

- **Third scenario**: Maintain the studied titration schedule for insulin icodec unchanged (i.e., based on Days 5 to 7), and reduce by 30% each pre-meal bolus insulin dose on Days 2 to 4 of each week.

The data in Table 13 summarize the model-predicted results for the mean weekly FPG at Week 26, mean GMI (or estimated A1C) at Week 26 and the rate of level 2 hypoglycemic events under different dose titration scenarios compared to the observed data. In addition to the three alternative titration scenarios, Table 13 shows the results from model-predictions based on the studied dose titration for insulin icodec (i.e., titration of insulin Icodec based on the lowest FPG of Days 5 to 7).

The model-predicted outcomes based on the per-protocol titration schedule used in study ONWARDS 6 are in agreement with the observed results from ONWARDS 6, suggesting the mechanistic model is able to predict the observed data.

The results from the two alternative titration scenarios for insulin icodec based on the lowest FPG of either Days 2 to 4 or Days 3 to 5 showed that both alternatives are predicted to result in about 30% decrease in the rate of hypoglycemic events compared to the per-protocol titration, with a drop in rate from 21.2 patient-years of exposure (PYE) to 14.7 PYE and 15.8 PYE for insulin icodec titration based on lowest FPG of Days 2 to 4 (first alternative scenario) and the lowest FPG of Days 3 to 5 (second alternative scenario), respectively. These rates of hypoglycemic events are close to those observed in the control arm of ONWARDS 6 with insulin degludec (rate of 10.4 PYE). Although these two alternatives titration scenarios are expected to reduce the rate of hypoglycemic events, they were predicted to compromise glycemic control and result in GMI-estimated A1C levels at Week 26 of about 7.6% (comparable to the baseline A1C values) and negligible change from baseline in A1C.

The third simulated dose titration scenario, in which insulin icodec is titrated per-protocol but the dose of bolus insulin is reduced weekly by 30% on Days 2 to 4, is predicted to reduce the rate of hypoglycemic events by about 40% from 21.2 PYE to 12.8 PYE, with a mean GMI-estimated A1C level at Week 26 of 7.26% (comparable to ONWARDS 6) and mean change from baseline in A1C of −0.37% (95%CI: −0.42% to −0.32%).

Table 12. Model-Predicted Endpoints for Alternative Titration Scenarios With Insulin Icodec and Bolus Insulin in Subjects With T1D (Compared to ONWARDS 6)

Titration Schedule	Week 26 FPG[a] (mg/dL)	Week 26 A1C (%)[b]	Change From Baseline in A1C (%)[b]	Rate of Level 2 Hypoglycemia (PYE)[c]
Observed data	160 (154-167)	7.15 (7.01-7.29)	−0.47 (−0.6; −0.33)	19.93
Model prediction based on:				
Lowest FPG Days 5-7 (per-protocol)	154 (152-157)	7.20 (7.16-7.25)[b]	−0.43 (-0.47; −0.38)[b]	21.22 (19.32-23.56)
Lowest FPG of Days 2-4	186 (183-189)	7.76 (7.69-7.83)[b]	0.13 (0.06; 0.20)[b]	14.67 (13.25-16.74)
Lowest FPG of Days 3-5	178 (175-181)	7.63 (7.57-7.70)[b]	−0.00 (−0.06; 0.07)[b]	15.47 (1398-1792)
Per-protocol for Icodec + 30% dose reduction of bolus insulin on Days 2-4	155 (152-157)	7.26 (7.21-7.31)[b]	−0.37 (−0.42; −0.32)[b]	12.76 (11.45-14.41)

Source: Regulatory Response, March 18, 2024.

[a] Week 26 FPG: mean self-measured or predicted pre-breakfast plasma glucose at Week 26. Values are means and 95% CI.

[b] GMI, calculated from the model-predicted CGM data, is used as a surrogate for A1C.

[c] Rate: events per PYE (1 PYE=365.25 days), calculated as the cumulative proportion of events over time. Values are means and 95% CI.

Abbreviations: A1C, hemoglobin A1c; CGM, continuous glucose monitoring; CI, confidence interval; GMI, glucose management indicator; FPG, fasting plasma glucose; PYE, patient-years of exposure; T1D, type 1 diabetes mellitus

The results from the mechanistic exposure-response modelling and simulations indicate that the alternative titration schedules for insulin icodec which lowers the risk of hypoglycemia may compromise glycemic control. In contrast, the alternative titration schedule for bolus insulin, with reduction of bolus

insulin dose by 30% on Days 2 to 4, is expected to reduce the risk of hypoglycemia and maintain glycemic control. Based on these results, the Applicant is proposing in labeling that patients with T1D consider reducing their bolus insulin dose between Days 2 and 4 after each weekly injection and that this dose reduction should be individualized. FDA notes that the feasibility and effectiveness of this approach has not been clinically evaluated. Furthermore, requiring patients with T1D who are already managing a complex MDII regimen to also adjust their bolus insulin dosing during select days of the week could require extra vigilance to prevent medication errors.

4.4.5 Safety Summary

In ONWARDS 6, insulin icodec was associated with 50 to 80% more clinically significant or severe hypoglycemia compared to insulin degludec at Week 52, depending on the method of analysis. These higher rates were observed regardless of whether the hypoglycemia events were captured actively using glucometers or passively using CGM devices and were also apparent whether the data were assessed by either event rate or incidence rate. The higher risk of hypoglycemia observed in the insulin icodec arm included a higher rate of hypoglycemia-related serious adverse events. The period of highest risk for hypoglycemia occurred on Days 2 to 4 and coincides with the peak glucose-lowering effect of this long-acting insulin analog. The higher rates are not exclusively associated with the loading dose or limited to the early dose titration phase at the start of use of insulin icodec. The higher rates were observed in the context of insulin dose data showing a higher basal-to-bolus dose ratio with insulin icodec compared to insulin degludec. The hypoglycemia events were similar in duration, management, and recovery to those observed in the insulin degludec group. The observed risk is consistent with the CGM-based TBR results which revealed greater TBR (%) in the insulin icodec group compared to insulin degludec.

Exploratory post hoc analyses were conducted to find a subgroup with a lower hypoglycemia risk in ONWARDS 6. Patients with lower glycemic variability, as measured by %CV, were found to be at lower risk of level 2/3 hypoglycemia when %CV was calculated by either CGM or SMPG. Across a broad range of %CV (32 to 40%), the risk of hypoglycemia was either lower than or comparable to the entire cohort of subjects on insulin degludec (cohort of subjects with any %CV). Similarly, lower numbers of level 2/3 events were observed based on post hoc analyses performed using the CV ≤36% cutpoint derived from SMPG and CGM in ONWARDS 4 (a clinical trial with a T2D population with more advanced disease on basal-bolus insulin therapy and compared to insulin glargine). Additionally, the %CV was found to be a relatively stable patient characteristic across the entire 52 weeks of ONWARDS 6. However, the risk of hypoglycemia was always higher in the insulin icodec arm, compared to insulin degludec arm, when assessing rates within identical %CV subgroups. In ONWARDS 6, glycemic efficacy was maintained in both ≤36% and >36% subgroups for both treatment arms but favored the insulin degludec arm within each %CV subgroup. Data were not provided to confirm that %CV during the first two weeks of treatment is representative of %CV on previous basal insulin therapy.

Given the existence of a pronounced peak in glucose lowering, alternative dose titration strategies were investigated in pharmacometric modelling involving modifications to the titration of both the basal and bolus component. Two of the three alternative titration approaches using alternative basal insulin titration strategies resulted in a reduced the risk of hypoglycemia but compromised efficacy. In contrast, a recommendation to reduce bolus insulin dosing by 30% on Days 2 to 4 was predicted to maintain glycemic control and optimize safety. No clinical studies were conducted to confirm the modelling results, or to confirm that patients could successfully titrate bolus insulin differently on specific days of the week without increasing medication errors.

5 Proposed Labeling to Mitigate Hypoglycemia Risk

The Applicant proposed labeling of insulin icodec to inform prescribers and patients about the risk of hypoglycemia. Relevant labeling proposals include the following:

- Labeling intended to restrict use in patients with T1D to those patients who wear a continuous glucose monitoring (CGM) device and whose glycemic variability (CV) is ≤36% prior to initiation of insulin icodec and without history of recurrent severe hypoglycemia or hypoglycemia unawareness.
- Labeling recommending discontinuation of product in patients who experience recurring hypoglycemia events.
- Labeling intended to inform patients and providers that the maximal glucose-lowering effect of insulin icodec occurs during Days 2 to 4 after each weekly injection.
    - Recommendations for patients with type 1 diabetes to consider reducing their bolus insulin dose between Days 2 and 4 after each weekly injection.

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7 Appendices

7.1 Table of Clinical Studies

Table 13. Overview of the Insulin Icodec Clinical Development Program

Study ID	Type of Trial	Design	Population (N)	Treatment	Treatment Duration
Phase 1 Trials					
NN1436-4314	SS PK/PD	Randomized, double-blind, double-dummy, active-controlled, single-center, multiple-dose, dose escalation	Caucasian T2D (50)	Insulin icodec SC QW vs. Insulin degludec SC QD	5 wks
NN1436-4226	PK	Single-center, single dose, open-label, parallel group	12 Healthy subjects and 46 with renal impairment (58)	Insulin icodec SC	Single dose
NN1436-4225	SS PK/PD	Randomized, 2-period crossover, single-center, open-label, multiple-dose	Caucasian T1D (66)	Insulin icodec SC QW vs. Insulin glargine (100 U/mL) SC QD	8 wks
NN1436-4422	SS PK/PD	Randomized, single-center, open-label, 2-period crossover, multiple-dose	Japanese T1D (24)	Insulin icodec SC QW vs. Insulin glargine (100 U/mL) SC QD	8 wks
NN1436-4462	SS PK/PD (assess hypoglycemia frequency/response to double/triple dose)	Randomized, single-center, open-label, 2-period crossover, multiple dose	Caucasian T2D (43)	Insulin icodec SC QW vs. Insulin glargine (100 U/mL) SC QD	6 wks
NN1436-4569	SS PK/PD	Single-center, open-label, one-period, multiple-dose	Caucasian T2D (46)	Insulin icodec SC QW Run-in period (1 wk) with Insulin degludec SC QD	8 wks
NN1436-4570	PK	2-center, single-dose, open-label, parallel-group	6 Healthy subjects and 19 with hepatic impairment (25)	Insulin icodec SC	Single dose
NN1436-4571	SS PK	Single-center, open-label, single group, multiple-dose	Chinese T2D (24)	Insulin icodec SC QW Run-in period (1-8 wks) with Insulin degludec SC QD	6 wks
NN1436-4572	PK/PD (assess injection region: abdomen, upper arm and thigh)	Randomized, single-center, open-label, 3-period crossover	Caucasian T2D (25)	Insulin icodec SC	Single dose ×3

Study ID	Type of Trial	Design	Population (N)	Treatment	Treatment Duration
Phase 2 Trials					
NN1436-4383	Safety and efficacy	Randomized, double-blind, double-dummy, active-controlled, parallel-group, stratified, multicenter, multinational, treat-to-target	Insulin-naïve T2D (247)	Insulin icodec SC QW vs. Insulin glargine (100 U/mL) SC QD	26 wks
NN1436-4465	Safety and efficacy (assess 3 titration algorithms)	Multinational, multicenter, randomized, open-label, active-controlled, parallel-group	Insulin-naïve T2D (205)	Insulin icodec SC QW vs. Insulin glargine (100 U/mL) SC QD	16 wks
NN1436-4466	Safety and efficacy (assess 2 switch approaches)	Randomized, multinational, multicenter, open-label, active-controlled, parallel-group (assess basal insulin switch)	Insulin-experienced T2D (154)	Insulin icodec SC QW vs. Insulin glargine (100 U/mL) SC QD	16 wks
Phase 3 Trials					
NN1436-4477 (ONWARDS 1)	Safety and efficacy	Randomized, open-label, parallel-group, active-controlled, multicenter, multinational, treat-to-target	Insulin naïve T2D (984)	Insulin icodec SC QW vs. Insulin glargine (100 U/mL) SC QD	78 (52*) wks
NN1436-4478 (ONWARDS 2)	Safety and efficacy	Randomized, open-label, active-controlled, parallel group, multicenter, multinational, treat-to-target	Insulin experienced T2D (526)	Insulin icodec SC QW vs. Insulin degludec SC QD	26 wks
NN1436-4479 (ONWARDS 3)	Safety and efficacy	Randomized, stratified, double-blinded, double dummy, active-controlled, parallel-group, multicenter, multiregional, treat-to-target	Insulin naïve T2D (588)	Insulin icodec SC QW vs. Insulin degludec SC QD	26 wks
NN1436-4480 (ONWARDS 4)	Safety and efficacy	Randomized, open-label, active-controlled, parallel group, multicenter, multinational, treat-to-target	Basal insulin treated T2D (582)	Insulin icodec SC QW + insulin aspart vs. Insulin glargine (100 U/mL) SC QD + insulin aspart	26 wks

Study ID	Type of Trial	Design	Population (N)	Treatment	Treatment Duration
NN1436-4481 (ONWARDS 5)	Safety and efficacy	Randomized, open-label, parallel-group, active-controlled, multicenter, multinational	Insulin naïve T2D (1085)	Insulin icodec SC QW vs. Basal insulin analogs SC QD	52 wks
NN1436-4625 (ONWARDS 6)	Safety and efficacy	Randomized, multicenter, multinational, open-label, active-controlled, parallel-group, treat-to-target	Basal/bolus insulin treated T1D (582)	Insulin icodec SC QW + insulin aspart vs. Insulin degludec SC QD + insulin aspart	52 (26*) wks

Source: Adapted from 5.2 Tabular Listing of All Clinical Trials.

* Duration of the main part of the trial.

Abbreviations: N, total study sample size; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; QW, once weekly; SC, subcutaneous; SS, steady state; T1D, type 1 diabetes; T2D, type 2 diabetes; wks, weeks

7.2 Trial Design Features of ONWARDS 6

Table 14. Overview of Study Design Features of ONWARDS 6 (Trial 4625)

Trial Identifier/Title	Trial Design and Primary Objective	Regimen/Route/ Schedule	Primary and Confirmatory Study Endpoints	Treatment Duration	No. of Subjects Randomized/Completed	Study Population and Study Sites
NN1436-4625* (ONWARDS 6) NCT04848480 ***Trial start date:*** 30 Apr 2021 ***Trial completion date:*** 02 December 2022 Data cut-off date: 21 December 2022 ***ARGUS Safety Database cut-off date:*** 22 Dec 2022 ***Title:*** Efficacy and safety of once weekly insulin icodec compared to once daily insulin degludec 100 units/mL, both in combination with insulin aspart, in adults with type 1 diabetes	***Design:*** Randomized, multicenter, multinational, open-label, active-controlled, parallel-group, treat-to-target ***Primary objective:*** To confirm the effect on glycemic control of QW insulin icodec in combination with insulin aspart, in subjects with T1D. This includes comparing the difference in change from baseline in A1C between QW insulin icodec and QD insulin degludec both in combination with insulin aspart after 26 weeks of treatment to a noninferiority limit of 0.3%	1:1 Allocation ***Starting dose:*** Ico SC QW + IAsp SC BID-QID[e] vs. IDeg SC QD + IAsp SC BID-QID[f] ***Treat-to-glycemic target:*** 80-130 mg/dL ***Basal dose titration:*** Weekly (based on the lowest of 2-3 pre-breakfast SMPG): Ico: ±20-unit increments IDeg: ±3-unit increments ***Bolus dose titration:*** Weekly (based on the lowest preprandial or bedtime SMPG): IAsp: ±1-unit increments	Primary Change from baseline in A1C at wk 26 (noninferiority)	52 wks • 26-wk main phase • 26-wk extension • 5-wk follow-up	Ico: 290/274 IDeg: 292/282	T1D ≥1 y ≥18 y Multiple daily insulin injections A1C ≤10% ***Conducted at 98 sites in 12 countries:*** Austria Canada Germany India Italy Japan Netherlands Russia Spain Turkey United Kingdom United States

Source: Adapted from Clinical Study Report.

* Ico SC: one-time additional dose at randomization consisting of the total daily basal insulin dose before randomization ×7 + 50% (if screening A1C <8%) or 100% (if screening A1C ≥8%) of their total daily basal insulin dose ×7. Subsequent weekly doses started at the total daily dose ×7.

† IDeg SC QD: switch from the previous basal insulin dose in accordance with local label. Ins Asp SC BID-QID: switch from previous bolus insulin done unit-to unit per meal. Ins Asp SC BID-QID: switch from previous bolus insulin done unit-to unit per meal.

Abbreviations: A1C, hemoglobin A1c; BID, twice daily; IAsp, insulin aspart; IDeg, insulin degludec; Ico, insulin icodec; NCT, National Clinical Trial; QD, daily; QID, four times daily; QW, every week; SC, subcutaneous; wks, weeks; SMPG, self-measured plasma glucose; T1D, type 1 diabetes mellitus; U, unit; v, versus; wk, week, Y, years

7.3 Baseline Characteristics and Subject Disposition for the ONWARDS Program

Table 15. Baseline Demographics—Full Analysis Set

	NN1436-4477 (ONWARDS 1)		NN1436-4478 (ONWARDS 2)		NN1436-4479 (ONWARDS 3)		NN1436-4480 (ONWARDS 4)		NN1436-4481 (ONWARDS 5)		NN1436-4625 (ONWARDS 6)	
Variable	**Ico N=492**	**IGlar N=492**	**Ico N=263**	**IDeg N=263**	**Ico N=294**	**IDeg N=294**	**Ico N=291**	**IGlar N=291**	**Ico N=542**	**ODA N=543**	**Ico N=292**	**IDeg N=290**
Sex, n (%)												
Female	197 (40.0)	229 (46.5)	101 (38.4)	123 (46.8)	109 (37.1)	110 (37.4)	137 (47.1)	141 (48.5)	233 (43.0)	230 (42.4)	125 (43.1)	120 (41.1)
Male	295 (60.0)	263 (53.5)	162 (61.6)	140 (53.2)	185 (62.9)	184 (62.6)	154 (52.9)	150 (51.5)	309 (57.0)	313 (57.6)	165 (56.9)	172 (58.9)
Age, years												
Mean (SD)	59.1 (10.05)	58.9 (9.85)	62.3 (9.79)	62.6 (8.42)	57.7 (10.19)	58.6 (9.74)	59.7 (10.13)	59.9 (9.92)	59.1 (10.79)	59.4 (10.15)	44.1 (14.07)	44.3 (14.07)
Median	60.0	60.0	63.0	63.0	58.0	59.0	61.0	61.0	59.5	60.0	42.5	45.0
Minimum, maximum	27.0, 84.0	28.0, 80.0	26.0, 86.0	37.0, 80.0	26.0, 78.0	33.0, 81.0	19.0, 85.0	21.0, 81.0	27.0, 94.0	27.0, 84.0	18.0, 82.0	18.0, 79.0
Age group, n (%)												
≥18 to <65	333 (67.7)	332 (67.5)	145 (55.1)	149 (56.7)	210 (71.4)	201 (68.4)	189 (64.9)	184 (63.2)	359 (66.2)	363 (66.9)	267 (92.1)	271 (92.8)
≥65	159 (32.3)	160 (32.5)	118 (44.9)	114 (43.3)	84 (28.6)	93 (31.6)	102 (35.1)	107 (36.8)	183 (33.8)	180 (33.1)	23 (7.9)	21 (7.2)
Race, n (%)[1,2]												
American Indian or Alaska Native	2 (<1)	0	2 (<1)	0	0	1 (<1)	0	1 (<1)	2 (<1)	1 (<1)	0	0
Asian	129 (26.2)	145 (29.5)	86 (32.7)	110 (41.8)	80 (27.2)	85 (28.9)	95 (32.6)	93 (32.0)	28 (5.2)	19 (3.5)	51 (17.6)	72 (24.7)
Black or African American	10 (2.0)	17 (3.5)	11 (4.2)	12 (4.6)	9 (3.1)	6 (2.0)	13 (4.5)	8 (2.7)	24 (4.4)	28 (5.2)	9 (3.1)	2 (<1)
Native Hawaiian or other Pacific Islander	2 (<1)	0	0	0	0	0	0	0	2 (<1)	1 (<1)	0	0
Not reported	0	0	0	0	15 (5.1)	16 (5.4)	0	1 (<1)	1 (<1)	0	0	0
White	333 (67.7)	317 (64.4)	161 (61.2)	137 (52.1)	179 (60.9)	175 (59.5)	183 (62.9)	187 (64.3)	478 (88.2)	493 (90.8)	230 (79.3)	218 (74.7)
Other	16 (3.3)	13 (2.6)	3 (1.1)	4 (1.5)	11 (3.7)	11 (3.7)	0	1 (<1)	7 (1.3)	1 (<1)	0	0
Ethnicity, n (%)[1]												
Hispanic or Latino	53 (10.8)	53 (10.8)	16 (6.1)	16 (6.1)	76 (25.9)	88 (29.9)	52 (17.9)	53 (18.2)	51 (9.4)	44 (8.1)	10 (3.4)	10 (3.4)
Not Hispanic or Latino	439 (89.2)	439 (89.2)	247 (93.9)	247 (93.9)	203 (69.0)	190 (64.6)	239 (82.1)	237 (81.4)	490 (90.4)	499 (91.9)	280 (96.6)	282 (96.6)
Not reported	0	0	0	0	15 (5.1)	16 (5.4)	0	1 (<1)	1 (<1)	0	0	0
Region, n (%)												
Africa	0	0	25 (9.5)	25 (9.5)	0	0	0	0	0	0	0	0
Asia	120 (24.4)	132 (26.8)	74 (28.1)	96 (36.5)	72 (24.5)	73 (24.8)	88 (30.2)	90 (30.9)	0	0	48 (16.6)	68 (23.3)
Europe	245 (49.8)	226 (45.9)	86 (32.7)	81 (30.8)	71 (24.1)	71 (24.1)	96 (33.0)	109 (37.5)	286 (52.8)	271 (49.9)	136 (46.9)	139 (47.6)
North America	108 (22.0)	112 (22.8)	78 (29.7)	61 (23.2)	75 (25.5)	74 (25.2)	74 (25.4)	59 (20.3)	256 (47.2)	272 (50.1)	106 (36.6)	85 (29.1)
South America	19 (3.9)	22 (4.5)	0	0	76 (25.9)	76 (25.9)	33 (11.3)	33 (11.3)	0	0	0	0
Country, n (%)												
Non-United States	384 (78.0)	380 (77.2)	185 (70.3)	202 (76.8)	245 (83.3)	248 (84.4)	217 (74.6)	232 (79.7)	381 (70.3)	357 (65.7)	205 (70.7)	215 (73.6)
United States	108 (22.0)	112 (22.8)	78 (29.7)	61 (23.2)	49 (16.7)	46 (15.6)	74 (25.4)	59 (20.3)	161 (29.7)	186 (34.3)	85 (29.3)	77 (26.4)

Variable	NN1436-4477 (ONWARDS 1)		NN1436-4478 (ONWARDS 2)		NN1436-4479 (ONWARDS 3)		NN1436-4480 (ONWARDS 4)		NN1436-4481 (ONWARDS 5)		NN1436-4625 (ONWARDS 6)	
	Ico N=492	IGlar N=492	Ico N=263	IDeg N=263	Ico N=294	IDeg N=294	Ico N=291	IGlar N=291	Ico N=542	ODA N=543	Ico N=292	IDeg N=290
Weight (kg)												
Mean (SD)	85.2 (17.74)	84.3 (17.63)	83.7 (18.44)	81.5 (17.14)	85.8 (20.10)	83.2 (18.22)	85.5 (17.63)	83.1 (17.29)	93.2 (22.52)	94.3 (21.53)	78.6 (17.62)	77.1 (16.78)
Median	83.7	83.5	83.9	81.3	84.9	81.5	84.6	81.6	90.8	92.2	77.2	75.8
Minimum, maximum	44.5, 140.0	43.3, 142.0	43.9, 136.8	40.8, 133.7	43.5, 151.4	45.8, 130.5	49.0, 136.7	41.3, 143.1	43.1, 208.4	49.5, 196.0	39.6, 160.3	41.0, 131.6
Missing	0	0	0	0	0	0	0	0	0	1	0	0
BMI at baseline (kg/m^2)												
Mean (SD)	30.0 (4.78)	30.1 (5.05)	29.5 (5.20)	29.2 (4.89)	29.9 (5.23)	29.2 (5.05)	30.5 (5.02)	30.0 (5.02)	32.6 (6.99)	33.0 (6.94)	26.8 (5.03)	26.2 (4.53)
Median	29.8	29.9	29.2	28.8	29.4	28.4	30.6	30.1	31.3	31.8	26.2	25.6
Minimum, maximum	15.4, 40.3	17.5, 40.3	16.9, 40.5	17.5, 40.6	16.6, 41.1	18.7, 40.4	18.1, 41.2	19.1, 40.4	18.8, 85.6	17.7, 69.4	16.6, 46.6	16.2, 40.3
Missing	0	0	0	0	0	0	0	0	0	1	0	0
Duration of diabetes (years)												
Mean (SD)	11.6 (6.66)	11.5 (6.75)	16.5 (8.36)	16.9 (7.92)	11.1 (6.61)	11.5 (6.54)	18.0 (9.09)	16.3 (7.65)	11.9 (6.91)	12.0 (7.60)	20.0 (13.20)	19.0 (12.88)
Median	11.1	10.3	15.5	16.2	10.5	10.7	16.8	15.8	11.2	11.2	18.4	16.6
Minimum, maximum	0.5, 41.3	0.8, 40.3	0.7, 51.3	0.8, 46.3	0.0, 40.7	0.7, 33.8	1.8, 59.6	0.6, 40.4	0.7, 40.4	0.2, 51.5	1.1, 59.6	1.1, 62.5
A1C at Baseline (%)												
Mean (SD)	8.5 (0.99)	8.4 (1.02)	8.2 (0.77)	8.1 (0.77)	8.6 (1.11)	8.5 (1.01)	8.3 (0.86)	8.3 (0.90)	9.0 (1.62)	8.9 (1.50)	7.6 (0.96)	7.6 (0.93)
Median	8.3	8.3	8.0	8.0	8.4	8.4	8.2	8.2	8.5	8.5	7.5	7.6
Minimum, maximum	6.6, 11.5	6.8, 12.8	6.7, 10.9	6.4, 11.0	6.8, 11.6	6.7, 11.5	6.6, 12.9	6.7, 12.0	6.3, 15.8	6.5, 16.3	5.1, 10.0	5.5, 10.1
Missing	0	0	0	0	0	0	0	0	0	1	0	0
FPG at Baseline (mg/dL)												
Mean (SD)	185.3 (48.96)	185.7 (51.66)	152.2 (47.47)	150.7 (40.92)	186.8 (54.20)	176.2 (45.90)	166.6 (54.10)	173.0 (63.46)	-	-	179.2 (73.86)	172.3 (72.30)
Median	180.2	174.8	146.0	147.8	176.6	167.6	158.6	163.1	-	-	169.4	156.8
Minimum, maximum	82.9, 405.5	73.9, 407.3	57.7, 337.0	52.3, 291.9	86.5, 437.9	81.1, 378.4	55.9, 405.5	57.7, 436.1	-	-	43.2, 441.5	39.6, 499.2
Missing	12	18	3	6	10	4	8	7	542	543	14	5
eGFR at Baseline (mL/min/1.73m^2)												
Mean (SD)	86.0 (18.19)	84.9 (19.58)	81.0 (18.81)	80.2 (19.86)	91.2 (19.54)	90.4 (18.33)	81.9 (20.48)	81.9 (20.27)	88.1 (21.11)	88.0 (20.31)	98.5 (18.71)	97.0 (19.62)
Median	88.0	87.0	83.0	84.0	95.0	94.0	82.0	85.0	92.0	92.0	99.0	98.0
Minimum, maximum	34.0, 129.0	26.0, 148.0	32.0, 140.0	32.0, 119.0	36.0, 140.0	32.0, 131.0	36.0, 149.0	33.0, 139.0	19.0, 130.0	17.0, 135.0	47.0, 161.0	36.0, 148.0
Missing	0	0	0	0	1	0	0	0	0	1	0	0

Source: Statistical analyst; adsl.xpt

[1] Subjects from France did not report race and ethnicity.

[2] Other includes two or more races and others (West Indian, Latino, Hispanic, South American, Egyptian, North American Aboriginal, and Arabic).

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; Ico, insulin icodec; IDeg, insulin degludec; IGlar, insulin glargine; ODA, once-daily basal insulin analogs; SD, standard deviation

Table 16. Analysis Populations and Subject Disposition—Full Analysis Set

	Main NN1436-4477 (ONWARDS 1)		Extension NN1436-4477 (ONWARDS 1)		NN1436-4478 (ONWARDS 2)		NN1436-4479 (ONWARDS 3)		NN1436-4480 (ONWARDS 4)		NN1436-4481 (ONWARDS 5)	
Variable	**Ico**	**IGlar**	**Ico**	**IGlar**	**Ico**	**IDeg**	**Ico**	**IDeg**	**Ico**	**IGlar**	**Ico**	**ODA**
Randomized[1]	492 (100.0)	492 (100.0)	492 (100.0)	492 (100.0)	263 (100.0)	263 (100.0)	294 (100.0)	294 (100.0)	291 (100.0)	291 (100.0)	542 (100.0)	543 (100.0)
Full analysis population[2]	492 (100.0)	492 (100.0)	492 (100.0)	492 (100.0)	263 (100.0)	263 (100.0)	294 (100.0)	294 (100.0)	291 (100.0)	291 (100.0)	542 (100.0)	543 (100.0)
Safety population[3]	492 (100.0)	492 (100.0)	492 (100.0)	492 (100.0)	262 (99.6)	263 (100.0)	293 (99.7)	294 (100.0)	291 (100.0)	291 (100.0)	542 (100.0)	538 (99.1)
Completed study	482 (98.0)	485 (98.6)	474 (96.3)	475 (96.5)	260 (98.9)	258 (98.1)	288 (98.0)	286 (97.3)	275 (94.5)	273 (93.8)	497 (91.7)	493 (90.8)
Discontinued study	10 (2.0)	7 (1.4)	18 (3.7)	17 (3.5)	3 (1.1)	5 (1.9)	6 (2.0)	8 (2.7)	16 (5.5)	18 (6.2)	45 (8.3)	50 (9.2)
Withdrawal of consent	3 (<1)	5 (1.0)	6 (1.2)	8 (1.6)	0	3 (1.1)	4 (1.4)	4 (1.4)	9 (3.1)	10 (3.4)	24 (4.4)	20 (3.7)
Lost to follow-up	2 (<1)	0	4 (<1)	4 (<1)	0	0	0	1 (<1)	3 (1.0)	6 (2.1)	14 (2.6)	19 (3.5)
Investigator decision	2 (<1)	0	4 (<1)	1 (<1)	1 (<1)	0	0	2 (<1)	2 (<1)	1 (<1)	3 (<1)	5 (<1)
Death	2 (<1)	2 (<1)	3 (<1)	4 (<1)	2 (<1)	2 (<1)	2 (<1)	1 (<1)	2 (<1)	1 (<1)	3 (<1)	6 (1.1)
Site closure	1 (<1)	0	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0
Completed treatment	475 (96.5)	480 (97.6)	466 (94.7)	472 (95.9)	256 (97.3)	253 (96.2)	281 (95.6)	283 (96.3)	274 (94.2)	269 (92.4)	483 (89.1)	493 (90.8)
Discontinued treatment	17 (3.5)	12 (2.4)	26 (5.3)	20 (4.1)	7 (2.7)	10 (3.8)	13 (4.4)	11 (3.7)	17 (5.8)	22 (7.6)	59 (10.9)	50 (9.2)
Adverse event	8 (1.6)	4 (<1)	12 (2.4)	7 (1.4)	5 (1.9)	3 (1.1)	4 (1.4)	2 (<1)	4 (1.4)	3 (1.0)	8 (1.5)	11 (2.0)
Hypoglycemic episode	0	1 (<1)	0	2 (<1)	0	0	0	0	0	0	3 (<1)	0
Protocol deviation	0	0	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Lack of efficacy	1 (<1)	0	1 (<1)	0	0	0	0	0	0	0	2 (<1)	0
Lost to follow-up	1 (<1)	0	3 (<1)	1 (<1)	0	0	0	1 (<1)	3 (1.0)	6 (2.1)	10 (1.8)	14 (2.6)
Pregnancy	0	0	0	0	0	0	0	0	0	0	1 (<1)	0
Site closure	1 (<1)	0	1 (<1)	0	0	0	0	0	0	0	0	0
Withdrawal of consent	2 (<1)	5 (1.0)	3 (<1)	6 (1.2)	0	2 (<1)	4 (1.4)	3 (1.0)	6 (2.1)	8 (2.7)	18 (3.3)	17 (3.1)
Other[4]	4 (<1)	2 (<1)	6 (1.2)	4 (<1)	1 (<1)	4 (1.5)	4 (1.4)	4 (1.4)	4 (1.4)	5 (1.7)	16 (3.0)	7 (1.3)

Source: Statistical analyst; adsl.xpt

[1] All subjects randomized.

[2] All subjects randomized. Subjects are analyzed according to the randomized treatment. In Study NN1436-4481, one subject (b) (6)) was randomized but excluded from the analysis because of the missing baseline A1C.

[3] All subjects randomly assigned to trial treatment and who took at least one dose of trial product. Subjects were analyzed according to the treatment they received.

[4] Includes family issues, personal reasons, moving or traveling, schedule conflicts.

Abbreviations: Ico, insulin icodec; IDeg, insulin degludec; IGlar, insulin glargine; ODA, once-daily basal insulin analogs

Table 17. Analysis Populations and Subject Disposition—Full Analysis Set, ONWARDS 6

	Main NN1436-4625 (ONWARDS 6)		Extension NN1436-4625 (ONWARDS 6)	
Variable	**Ico**	**IDeg**	**Ico**	**IDeg**
Randomized[1]	290 (100.0)	292 (100.0)	290 (100.0)	292 (100.0)
Full analysis population[2]	290 (100.0)	292 (100.0)	290 (100.0)	292 (100.0)
Safety population[3]	290 (100.0)	292 (100.0)	290 (100.0)	292 (100.0)
Completed study	279 (96.2)	284 (97.3)	274 (94.5)	281 (96.2)
Discontinued study	11 (3.8)	8 (2.7)	16 (5.5)	11 (3.8)
Withdrawal of consent	9 (3.1)	7 (2.4)	13 (4.5)	9 (3.1)
Lost to follow-up	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Investigator decision	0	0	1 (<1)	0
Death	1 (<1)	0	1 (<1)	0
Completed treatment	272 (93.8)	283 (96.9)	262 (90.3)	278 (95.2)
Discontinued treatment	18 (6.2)	9 (3.1)	28 (9.7)	14 (4.8)
Adverse event	1 (<1)	1 (<1)	2 (<1)	1 (<1)
Hypoglycemic episode	1 (<1)	0	1 (<1)	0
Protocol deviation	1 (<1)	0	1 (<1)	0
Lost to follow-up	0	1 (<1)	0	1 (<1)
Pregnancy	2 (<1)	0	3 (1.0)	1 (<1)
Withdrawal of consent	4 (1.4)	3 (1.0)	5 (1.7)	4 (1.4)
Other[4]	9 (3.1)	4 (1.4)	16 (5.5)	7 (2.4)

Source: Statistical analyst; adsl.xpt

[1] All subjects randomized.

[2] All subjects randomized. Subjects are analyzed according to the randomized treatment.

[3] All subjects randomly assigned to trial treatment and who took at least one dose of trial product. Subjects were analyzed according to the treatment they received.

[4] Includes personal reasons, moving or traveling, discomfort with frequent blood glucose testing, continuous glucose monitoring device, or electronic diary use. Of note, 7 of the 16 insulin icodec-treated subjects permanently discontinued treatment for the following reasons: participant decided to stop treatment owing to recurrent low blood sugars (n=1); participant stopped trial owing to blood glucose dropping frequently during the day as evidenced by continuous glucose monitoring (n=1); participant's request: insulin too unpredictable, making it difficult to manage glucose (n=1); concerns regarding the effect that investigational product had on blood glucose values, including the tendency for hypoglycemia (n=1); participant had very variable blood glucose control while using icodec and felt unsafe while using it owing to hypoglycemia (n=1); participant temporarily discontinued trial product owing to too many hypoglycemic episodes, and never reinitiated treatment (n=1); or difficult to gain glycemic control with investigational drug and risk of hypoglycemia (n=1).

Abbreviations: Ico, insulin icodec; IDeg, insulin degludec

7.4 Patient-Reported Outcomes (PRO) in ONWARDS 6

During protocol development for ONWARDS 6, FDA recommended that the trial evaluate the impact of insulin icodec on treatment satisfaction in patients with T1D to inform the benefit-risk assessment. In response, the Applicant added the **Diabetes Treatment Satisfaction Questionnaire status version** (DTSQs) as a supportive secondary endpoint in ONWARDS 6.[4] FDA recommended that the Applicant demonstrate that the DTSQ was fit-for-purpose, however the Applicant did not follow the recommendation to meet with FDA to discuss whether the DTSQs was fit-for-purpose for use in a registrational trial. The prespecified supportive secondary PRO-based efficacy endpoint in ONWARDS 6 was the change in the DTSQs in total treatment satisfaction score (6-item subset only, omitting the hypoglycemia/hyperglycemia domain) from baseline (Week 0) to Week 26.

7.4.1 DTSQ Instrument Description

The DTSQs is an 8-item diabetes-specific PRO instrument designed to assess current satisfaction with treatment and perceived frequency of hyperglycemia and hypoglycemia. Six items measure treatment satisfaction (satisfaction with current treatment, convenience, flexibility, satisfaction with own understanding of diabetes, and likelihood of continuing on or recommending current treatment). The remaining two items measure perceived frequency of hyperglycemia and frequency of hypoglycemia. Each of the treatment satisfaction items is rated on a 7-point verbal rating scale (VRS) ranging from 0 ("Very unsatisfied") to 6 ("Very satisfied"). The two items measuring perceived frequency of hyperglycemia and frequency of hypoglycemia are rated on 7-point VRS ranging from 0 ("None of the time") to 6 ("Most of the time"). The recall period (in the instructions) is over "the past few weeks;" however, some items (Items 2 and 3) have an embedded recall period ("recently"). The DTSQs was administered at baseline (Week 0) and Weeks 26 and 52. A copy of the instrument is in Section 7.4.3.

The DTSQs generates a total treatment satisfaction score and perceived hyperglycemia and hypoglycemia score:

- The **DTSQs Total Treatment Satisfaction Score** (items 1, 4 to 8) ranges from 0 to 36, where higher scores indicate greater satisfaction with treatment.
- The **DTSQs Perceived Hyperglycemia and Hypoglycemia Score** (items 2 and 3), where lower scores indicate more ideal blood glucose levels.

7.4.2 FDA Assessment of the DTSQs Instrument

The Applicant did not submit an evidence dossier for the DTSQs and/or evidence to assess the fit-for-purpose of this instrument. In the absence of data. FDA could not complete a fit-for-purpose

[4] There are two versions of the DTSQ: status and change. The DTSQ change version (DTSQc) uses the same eight-item question stems as the DTSQs but have different response options and asks respondents to assess changes in treatment satisfaction with their current treatment compared with their previous treatment and was designed to overcome any ceiling effect that may occur with the DTSQs (when treatment satisfaction is high at baseline). Each of the six items of the DTSQc is scored from +3 (e.g., much more satisfied now) to −3 (e.g., much less satisfied now). The DTSQc treatment satisfaction change score can thus range from +18 to −18.

assessment. However, the FDA assessment did identify several issues with the instrument that limit the interpretability of the data collected in ONWARDS 6, including the following:

- Treatment satisfaction is a multidimensional concept and can include multiple components, such as flexibility, convenience, satisfaction with efficacy, satisfaction with safety. While the DTSQs includes items that appear to assess some of these concepts, the submission did not include evidence (e.g., qualitative study protocols, concept elicitation/cognitive interview data and patient transcripts) to support that these concepts are being adequately assessed based on patient and clinician input.
    - Items are assessing satisfaction of patient's current treatment; however, subjects were taking more than one treatment in the trials.
    - The assessment frequency may not be sufficient and may have missed important information on the benefits of the product throughout the trial (DTSQs administered at baseline, Week 26 (primary timepoint), and Week 52).
    - It is unknown what improvement in the total treatment satisfaction score is meaningful to patients.
    - There are limited details regarding the methods used to translate and culturally adapt the instrument. As such, it is unknown whether the DTSQs is fit-for-purpose for all intended study populations in the multinational trial.

7.4.3 Diabetes Treatment Satisfaction Questionnaire Status (DTSQs)

Figure 14. Diabetes Treatment Satisfaction Questionnaire: DTSQs

Diabetes Treatment Satisfaction Questionnaire: DTSQs

The following questions are concerned with the treatment for your diabetes (including insulin, tablets and/or diet) and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

2. How often have you felt that your blood sugars have been unacceptably high recently?

most of the time	6	5	4	3	2	1	0	none of the time

3. How often have you felt that your blood sugars have been unacceptably low recently?

most of the time	6	5	4	3	2	1	0	none of the time

4. How convenient have you been finding your treatment to be recently?

very convenient	6	5	4	3	2	1	0	very inconvenient

5. How flexible have you been finding your treatment to be recently?

very flexible	6	5	4	3	2	1	0	very inflexible

6. How satisfied are you with your understanding of your diabetes?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

Yes, I would definitely recommend the treatment	6	5	4	3	2	1	0	No, I would definitely not recommend the treatment

8. How satisfied would you be to continue with your present form of treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

Please make sure that you have circled one number on each of the scales.

Source: Excerpt from the Applicant's Response to FDA Information Request, dated April 5, 2024.

7.4.4 DTSQs Item-level Data for ONWARDS 6

FDA could not complete a fit-for-purpose assessment for the DTSQs because an evidence dossier was not submitted in support of the instrument. However, whether the instrument is fit-for-purpose, the data collected through the DTSQs in ONWARDS 6 provide no evidence of a favorable impact on treatment satisfaction of insulin icodec in patients with T1D (see Table 19).

Table 18. Summary Statistics for DTSQs and Domain and Item Scores

	Ico	IDeg
FAS	290	292
DTSQ (scores) [Summation of items 1, 4, 5, 6, 7, 8]		
Week 0		
N	288	291
Mean (SD)	28.45 (5.52)	28.33 (5.53)
Median	29.00	29.00
Minimum; maximum	14.00; 36.00	9.00; 36.00
Week 26		
N	273	282
Mean (SD)	30.56 (5.06)	31.40 (5.04)
Median	32.00	33.00
Minimum; maximum	13.00; 36.00	10.00; 36.00
Week 52		
N	261	278
Mean (SD)	30.00 (6.20)	31.54 (5.04)
Median	32.00	33.00
Minimum; maximum	9.00; 36.00	10.00; 36.00
Item 1: How Satisfied Are You With Your Current Treatment		
Week 0		
N	288	292
Mean (SD)	4.91 (1.08)	4.88 (1.05)
Median	5.00	5.00
Minimum; maximum	0.00; 6.00	1.00; 6.00
Week 26		
N	273	282
Mean (SD)	5.16 (1.06)	5.40 (0.95)
Median	6.00	6.00
Minimum; maximum	0.00; 6.00	0.00; 6.00
Week 52		
N	261	278
Mean (SD)	5.04 (1.29)	5.42 (0.92)
Median	6.00	6.00
Minimum; maximum	0.00; 6.00	1.00; 6.00
Item 2: How Often Have You Felt That Blood Sugars Have Been Unacceptably High		
Week 0		
N	287	292
Mean (SD)	2.65 (1.36)	2.83 (1.41)
Median	3.00	3.00
Minimum; maximum	0.00; 6.00	0.00; 6.00
Week 26		
N	273	281
Mean (SD)	2.43 (1.45)	2.20 (1.38)
Median	2.00	2.00
Minimum; maximum	0.00; 6.00	0.00; 5.00
Week 52		
N	259	278
Mean (SD)	2.36 (1.44)	2.21 (1.32)
Median	2.00	2.00
Minimum; maximum	0.00; 6.00	0.00; 6.00

	Ico	IDeg
FAS	290	292
Item 3: How Often Have You Felt That Blood Sugars Have Been Unacceptably Low		
Week 0		
N	288	292
Mean (SD)	2.09 (1.35)	2.13 (1.39)
Median	2.00	2.00
Minimum; maximum	0.00; 6.00	0.00; 6.00
Week 26		
N	273	282
Mean (SD)	2.36 (1.44)	1.93 (1.38)
Median	2.00	2.00
Minimum; maximum	0.00; 6.00	0.00; 6.00
Week 52		
N	259	278
Mean (SD)	2.17 (1.51)	1.83 (1.29)
Median	2.00	2.00
Minimum; maximum	0.00; 6.00	0.00; 6.00
Item 4: How Convenient Have You Been Finding Your Treatment to be Recently		
Week 0		
N	288	292
Mean (SD)	4.49 (1.26)	4.51 (1.30)
Median	5.00	5.00
Minimum; maximum	1.00; 6.00	0.00; 6.00
Week 26		
N	273	282
Mean (SD)	5.08 (1.05)	5.11 (1.15)
Median	5.00	5.00
Minimum; maximum	2.00; 6.00	0.00; 6.00
Week 52		
N	261	278
Mean (SD)	5.17 (1.10)	5.09 (1.23)
Median	5.00	5.00
Minimum; maximum	1.00; 6.00	0.00; 6.00
Item 5: How Flexible Have You Been Finding Your Treatment to be Recently		
Week 0		
N	288	292
Mean (SD)	4.51 (1.35)	4.45 (1.32)
Median	5.00	5.00
Minimum; maximum	0.00; 6.00	1.00; 6.00
Week 26		
N	273	282
Mean (SD)	4.87 (1.22)	5.02 (1.25)
Median	5.00	5.00
Minimum; maximum	0.00; 6.00	0.00; 6.00
Week 52		
N	261	278
Mean (SD)	4.79 (1.39)	5.05 (1.20)
Median	5.00	5.00
Minimum; maximum	0.00; 6.00	0.00; 6.00

	Ico	IDeg
FAS	290	292
Item 6: How Satisfied Are You With Your Understanding of Your Diabetes		
Week 0		
N	288	292
Mean (SD)	4.92 (1.07)	4.85 (1.16)
Median	5.00	5.00
Minimum; maximum	0.00; 6.00	0.00; 6.00
Week 26		
N	273	282
Mean (SD)	5.15 (0.83)	5.16 (0.98)
Median	5.00	5.00
Minimum; maximum	3.00; 6.00	0.00; 6.00
Week 52		
N	261	278
Mean (SD)	5.12 (1.04)	5.22 (0.91)
Median	5.00	5.00
Minimum; maximum	0.00; 6.00	2.00; 6.00
Item 7: Would You Recommend Treatment to Someone Else With Your Kind of Diabetes		
Week 0		
N	288	291
Mean (SD)	4.92 (1.09)	4.94 (1.13)
Median	5.00	5.00
Minimum; maximum	2.00; 6.00	0.00; 6.00
Week 26		
N	273	282
Mean (SD)	5.11 (1.20)	5.39 (0.93)
Median	6.00	6.00
Minimum; maximum	0.00; 6.00	1.00; 6.00
Week 52		
N	261	278
Mean (SD)	4.97 (1.45)	5.45 (0.89)
Median	6.00	6.00
Minimum; maximum	0.00; 6.00	1.00; 6.00
Item 8: How Satisfied Would You be to Continue With Present Form of Treatment		
Week 0		
N	288	291
Mean (SD)	4.72 (1.11)	4.70 (1.22)
Median	5.00	5.00
Minimum; maximum	1.00; 6.00	0.00; 6.00
Week 26		
N	273	282
Mean (SD)	5.19 (1.13)	5.32 (1.01)
Median	6.00	6.00
Minimum; maximum	0.00; 6.00	0.00; 6.00
Week 52		
N	261	278
Mean (SD)	4.91 (1.49)	5.32 (1.05)
Median	6.00	6.00
Minimum; maximum	0.00; 6.00	0.00; 6.00

Source: FDA statistical reviewer based on submitted datasets.
Abbreviations: DTSQ, Diabetes Satisfaction Questionnaire; Ico, insulin icodec; IDeg, insulin degludec; SD, standard deviation

7.5 Level 2/3 Hypoglycemia Rates Reported in ONWARDS 1 to 6 (On-Treatment)

Table 19. Level 2 and Level 3 Hypoglycemia Rate Differences—ONWARDS 1 to 6 (On-Treatment)

Trial	Treatment Period	Hypoglycemic Episode	Insulin Icodec # Subjects/ N(%)/ PY/ E	Rate*: Insulin Icodec Estimate (95% CI)	Comparator # Subjects/ N(%)/ PY/ E	Rate*: Comparator Estimate (95% CI)	Rate Ratio† Estimate (95% CI)	Rate Difference* Estimate (95% CI)
ONWARDS 6	26 Weeks (Primary)	Level 2	290/ 246 (84.8)/ 142.3/ 2789	19.57 (16.75, 22.40)	292/ 223 (76.4)/ 144.1/ 1478	10.23 (8.71, 11.74)	1.88 (1.53, 2.32)	9.3471 (6.14, 12.55)
		Level 3	290/ 9 (3.1)/ 142.3/ 47	0.33 (0.01, 0.64)	292/ 9 (3.1)/ 144.12/ 17	0.12 (>−0.01, 0.24)	2.08 (0.39, 10.96)	0.21 (−0.13, 0.54)
		Level 2/3	290/ 247 (85.2)/ 142.3/ 2836	19.90 (17.03, 22.77)	292/ 223 (76.4)/ 144.1/ 1495	10.34 (8.81, 11.88)	1.89 (1.54, 2.33)	9.56 (6.30, 12.81)
	52 Weeks (Extension)	Level 2	290/ 262 (90.3)/ 300.2/ 5047	16.76 (14.46, 19.05)	292/ 250 (85.6)/ 309.6/ 2811	9.07 (7.82, 10.33)	1.79 (1.48, 2.18)	7.68 (5.07, 10.30)
		Level 3	290/ 13 (4.5)/ 300.2/ 56	0.18 (0.04, 0.33)	292/ 12 (4.1)/ 309.6/ 25	0.08 (0.01, 0.15)	1.88 (0.48, 7.36)	0.10 (−0.06, 0.26)
		Level 2/3	290/ 263 (90.7)/ 300.2/ 5103	16.94 (14.63, 19.25)	292/ 250 (85.6)/ 309.6/ 2836	9.15 (7.89, 10.42)	1.80 (1.48, 2.18)	7.78 (5.15, 10.42)
ONWARDS 1	52 Weeks (Primary)	Level 2	492/ 48 (9.8)/ 485.9/ 143	0.29 (0.19, 0.39)	492/ 49 (10.0)/ 485.0/ 75	0.16 (0.10, 0.22)	1.67 (0.99, 2.84)	0.13 (0.01, 0.25)
		Level 3	492/ 1 (0.2)/ 485.9/ 1	<0.01 (−0.01, 0.01)	492/ 3 (0.6)/ 485.0/ 3	<0.01 (-0.01, 0.01)	—	>−0.01 (−0.01, 0.01)
		Level 2/3	492/ 48 (9.8)/ 485.9/ 144	0.29 (0.19, 0.40)	492/ 52 (10.6%)/ 485.0/ 78	0.16 (0.10, 0.23)	1.64 (0.98, 2.75)	0.13 (0.01, 0.25)
	78 Weeks (Extension)	Level 2	492/ 61 (12.4)/ 765.5/ 226	0.29 (0.20, 0.39)	492/ 66 (13.4)/ 766.8/ 114	0.1503 (0.10, 0.20)	1.71 (1.06, 2.76)	0.14 (0.03, 0.25)
		Level 3	492/ 1 (0.2)/ 765.5/ 1	<0.01 (−0.01, 0.01)	492/ 6 (1.2)/ 766.8/ 7	0.01 (0, 0.02)	—	-0.01 (−0.02, 0.01)
		Level 2/3	492/ 61 (12.4)/ 765.5/ 227	0.29 (0.20, 0.39)	492/ 70 (14.2)/ 766.8/ 121	0.16 (0.10, 0.21)	1.63 (1.02, 2.61)	0.14 (0.03, 0.25)
ONWARDS 2	26 Weeks	Level 2	262/ 37 (14.1)/ 155.3/ 113	0.72 (0.37, 1.07)	263/ 19 (7.2)/ 152.8/ 41	0.26 (0.12, 0.41)	1.98 (0.95, 4.12)	0.46 (0.08, 0.83)
		Level 3	262/ 0 (0)/ 155.3/ 0	—	263/ 1 (0.4)/ 152.8/ 1	—	—	—
		Level 2/3	262/ 37 (14.1)/ 155.3/ 113	0.72 (0.37, 1.07)	263/ 19 (7.2)/ 152.8/ 42	0.27 (0.12, 0.42)	1.93 (0.93, 4.02)	0.45 (0.07, 0.83)

Trial	Treatment Period	Hypoglycemic Episode	Insulin Icodec # Subjects/ N(%)/ PY/ E	Rate*: Insulin Icodec Estimate (95% CI)	Comparator # Subjects/ N(%)/ PY/ E	Rate*: Comparator Estimate (95% CI)	Rate Ratio† Estimate (95% CI)	Rate Difference* Estimate (95% CI)
ONWARDS 3	26 Weeks	Level 2	293/ 26 (8.9)/ 170.9/ 53	0.32 (0.17, 0.48)	294/ 17 (5.8)/ 171.1/ 23	0.13 (0.06, 0.21)	2.09 (0.99, 4.41)	0.19 (0.01, 0.36
		Level 3	293/ 0 (0)/ 170.9/ 0	—	294/ 2 (0.7)/ 171.1/ 2	—	—	–
		Level 2/3	293/ 26 (8.9)/ 170.9/ 53	0.32 (0.17, 0.48)	294/ 18 (6.1)/ 171.1/ 25	0.15 (0.06, 0.23)	1.82 (0.87, 3.80)	0.18 (>0.00, 0.35
ONWARDS 4	26 Weeks	Level 2	291/ 148 (50.9)/ 167.4/ 937	5.57 (4.36, 6.78)	291/ 160 (55.0)/ 166.8/ 935	5.49 (4.30, 6.69)	0.99 (0.73, 1.34)	0.08 (−1.62, 1.78
		Level 3	291/ 4 (1.4)/ 167.4/ 7	0.04 (−0.01, 0.10)	291/ 2 (0.7)/ 166.8/ 3	0.02 (-0.02, 0.06)	2.19 (0.20, 24.44)	0.02 (−0.05, 0.09
		Level 2/3	291/ 150 (51.5)/ 167.4/ 944	5.61 (4.40, 6.82)	291/ 162 (55.7)/ 166.8/ 938	5.5290 (4.34, 6.72)	0.99 (0.73, 1.33)	0.08 (−1.61, 1.78
ONWARDS 5	52 Weeks	Level 2	542/ 64 (11.8)/ 559.5/ 104	0.19 (0.13, 0.25)	538/ 42 (7.8)/ 560.7/ 76	0.15 (0.10, 0.20)	1.23 (0.77, 1.98)	0.04 (−0.04, 0.12
		Level 3	542/ 0 (0)/ 559.5/ 0	—	538/ 4 (0.7)/ 560.7/ 5	—	—	–
		Level 2/3	542/ 64 (11.8)/ 559.5/ 104	0.19 (0.13, 0.25)	538/ 45 (8.4)/ 560.7/ 81	0.16 (0.10, 0.21)	1.17 (0.73, 1.86)	0.03 (−0.05, 0.11

Source: FDA safety statistical reviewer based on submitted datasets.

† Rate ratio: The number of events is analyzed using a negative binomial regression model with treatment, region, A1C group at screening and pretrial basal insulin treatment as fixed factors, and the logarithm of the time period for which the events are considered as an offset. Comparative analysis for level 3 hypoglycemic episodes were not performed in ONWARDS 1, 2, 3, and 5, because the number of level 3 episodes was low.

* Rate and rate difference: Rate by arm and rate difference between treatment arms was estimated using negative binomial model, using the NLMIXED procedure in SAS. Negative binomial model included randomized treatment as fixed factor and logarithm of the on-treatment period as offset but did not include any additional covariates in the model.

Abbreviations: OW1, ONWARDS1; OW2, ONWARDS2; %, percentage of subjects with one or more events; CI, confidence interval; E, number of events; N, number of subjects with one or more events; PY, patient-years of exposure; R, rate (number of events per patient years of treatment)

7.6 Incidence of Level 2/3 Hypoglycemia Reported in ONWARDS 1 to 6 (On-Treatment)

Table 20. Incidence Rates of Level 2 and Level 3 Hypoglycemia by Phase 3 Trial (On-Treatment)

			Insulin Icodec				Comparator				Incidence Rate Ratio (IRR)†
Trial	Treatment Period	Hypoglycemic Event	No. Subj.	N	PYE	Time at Risk*	No. Subj.	N	PYE	Time at Risk*	Estimate (95% CI)
Type 1 Diabetes Mellitus											
ONWARDS 6											
Primary	26 Wks	Level 2	290	246	142.3	43.3	292	223	144.1	57.3	1.46 (1.22, 1.75)
	26 Wks	Level 3	290	9	142.3	139.7	292	9	144.1	141.0	1.01 (0.40, 2.54)
	26 Wks	Level 2/3	290	247	142.3	42.8	292	223	144.1	57.1	1.48 (1.23, 1.77)
Extension	52 Wks	Level 2	290	262	300.2	60.6	292	250	309.6	84.9	1.47 (1.23, 1.75)
	52 Wks	Level 3	290	13	142.3	141.1	292	12	144.1	141.9	1.09 (0.50, 2.39)
	52 Wks	Level 2/3	290	263	300.2	59.5	292	250	309.6	84.8	1.50 (1.26, 1.78)
Type 2 Diabetes Mellitus											
ONWARDS 1											
Primary	52 Wks	Level 2	492	48	485.9	461.8	492	49	485.0	459.6	0.97 (0.65, 1.45)
	52 Wks	Level 3	492	1	485.9	485.7	492	3	485.0	484.4	0.33 (0.03, 3.20)
	52 Wks	Level 2/3	492	48	485.9	461.8	492	52	485.0	458.9	0.92 (0.62, 1.36)
Extension	78 Wks	Level 2	492	61	765.5	709.9	492	66	766.8	707.7	0.92 (0.65, 1.31)
	78 Wks	Level 3	492	1	765.5	764.7	492	6	766.8	763.8	0.17 (0.02, 1.38)
	78 Wks	Level 2/3	492	61	765.5	709.9	492	70	766.8	705.3	0.87 (0.61, 1.22)
ONWARDS 2	26 Wks	Level 2	262	37	155.2	143.3	263	19	152.8	145.2	1.97 (1.14, 3.43)
	26 Wks	Level 3	262	0	155.2	155.2	263	1	152.8	152.2	—
	26 Wks	Level 2/3	262	37	155.2	143.3	263	19	152.8	145.2	1.97 (1.14, 3.43)
ONWARDS 3	26 Wks	Level 2	293	26	170.9	163.6	294	17	171.1	165.9	1.55 (0.84, 2.86)
	26 Wks	Level 3	293	0	170.9	170.9	294	2	171.1	171.1	—
	26 Wks	Level 2/3	293	26	170.9	163.6	294	18	171.1	165.9	1.46 (0.80, 2.67)
ONWARDS 4	26 Wks	Level 2	291	148	167.4	110.3	291	160	166.8	106.7	0.89 (0.72, 1.12)
	26 Wks	Level 3	291	4	167.4	165.9	291	2	166.8	166.5	2.01 (0.37, 10.96)
	26 Wks	Level 2/3	291	150	167.4	109.5	291	162	166.8	106.4	0.90 (0.72, 1.12)
ONWARDS 5	52 Wks	Level 2	542	64	559.5	522.1	538	42	560.7	541.2	1.58 (1.07, 2.33)
	52 Wks	Level 3	542	0	559.5	559.5	538	4	560.7	557.9	—
	52 Wks	Level 2/3	542	64	560.7	522.1	538	45	559.5	539.2	1.47 (1.00, 2.15)

Source: FDA safety statistical reviewer based on submitted datasets.

* Time at risk: the time from first drug exposure to first event for subjects experiencing at least one event and for subjects with no events, is the PYE.

† Incidence rate is defined as the number of incident events divided by the person-time at risk. IRR = $(a/A_1)/(b/A_0)$, where a, exposed cases; b, unexposed cases; A_1, total exposed person time at $risk$; A_0, total unexposed person time at risk.

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; N, number of subjects with one or more events; OW, ONWARDS; PYE, patient-years of exposure

7.7 Exploratory Efficacy Analyses by %CV Subgroups

Table 22 displays the disposition of CV subgroups of ≤ 36% and > 36% during Weeks 0 to 2, based on CGM and SMPG data. For CGM-based CV subgroups, both insulin icodec and insulin degludec have 12 subjects who were not assigned to a level. For SMPG-based CV subgroups, insulin degludec has two subjects who were not assigned to a level, while there are three subjects on insulin icodec who were not assigned to a level.

Table 21. CV Subgroup Defined by CGM and SMPG (Weeks 0 to 2)

	CV ≤36%	CV >36%	Missing	Total
Defined by CGM (Weeks 0-2)				
Insulin degludec	140	140	12	292
Insulin icodec	112	166	12	290
Defined by SMPG (Weeks 0-2)				
Insulin degludec	146	144	2	292
Insulin icodec	119	168	3	290

Source: FDA statistical reviewer based on submitted datasets.
Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation; SMPG, self-measured plasma glucose

Table 22. Results for A1C (%) at Weeks 26 and 52: ONWARDS 6, CV Subgroup, RTB

Defined by CGM (Weeks 0-2)				
	CV ≤36%		**CV >36%**	
Baseline mean (SD) [N]				
Insulin Degludec	7.42 (0.88) [140]		7.78 (0.90) [140]	
Insulin Icodec	7.35 (0.95) [112]		7.74 (0.94) [166]	
Missing endpoint data[a] / N				
	Week 26	**Week 52**	**Week 26**	**Week 52**
Insulin Degludec	3 /140	5 /140	4 / 140	5 /140
Insulin Icodec	9 / 112	11 / 112	5 / 166	6 / 166
LS Mean change from baseline (SE)				
Insulin Degludec	−0.59 (0.05)	−0.50 (0.06)	−0.47 (0.06)	−0.54 (0.06)
Insulin Icodec	−0.50 (0.06)	−0.41 (0.07)	−0.44 (0.05)	−0.36 (0.05)
Treatment difference (Ico – IDeg) (SE) (95% CI)				
	0.09 (0.08)	0.09 (0.09)	0.03 (0.08)	0.18 (0.08)
	(−0.06, 0.24)	(−0.09, 0.27)	(−0.12, 0.19)	(0.03, 0.34)
Defined by SMPG (Weeks 0-2)				
	CV ≤36%		**CV >36%**	
Baseline mean (SD) [N]				
Insulin Degludec	7.43 (0.92) [146]		7.85 (0.89) [144]	
Insulin Icodec	7.38 (0.99) [119]		7.74 (0.91) [168]	
Missing endpoint data[a] / N				
	Week 26	**Week 52**	**Week 26**	**Week 52**
Insulin Degludec	3 / 146	4 / 146	6 / 144	10 / 144
Insulin Icodec	7 / 119	8 / 119	8 / 168	11 / 168
LS Mean change from baseline (SE)				
Insulin Degludec	−0.61 (0.05)	−0.55 (0.06)	−0.42 (0.05)	−0.48 (0.06)
Insulin Icodec	−0.50 (0.06)	−0.41 (0.06)	−0.46 (0.05)	−0.38 (0.05)
Treatment difference (Ico – IDeg) (95% CI) (SE)				
	0.11 (0.08)	0.14 (0.09)	−0.04 (0.07)	0.10 (0.08)
	(−0.05, 0.27)	(−0.03, 0.31)	(−0.18, 0.10)	(−0.06, 0.25)

Source: FDA statistical reviewer based on submitted datasets.
N, number contributing to the analysis; subjects not assigned to a subgroup level are excluded from the analysis.
[a] Subjects not assigned to a subgroup level are not counted as they are excluded from the analysis.
The same analysis methods for the total population are applied to each subgroup level.
Abbreviations: CV, coefficient of variation; A1C, hemoglobin A1c; Ico, insulin icodec; IDeg, insulin icodec; RTB, return-to-baseline; SD, standard deviation; SE, standard error

Table 23. Results for Time in Range (70 to 180 mg/dL) (%): ONWARDS 6, CV Subgroup

	Defined by CGM (Weeks 0-2)			
	CV ≤36%		CV >36%	
Missing endpoint data[a] / N				
	Weeks 22-26	**Weeks 48-52**	**Weeks 22-26**	**Weeks 48-52**
Insulin degludec	5 /140	10 / 140	10 / 140	12 / 140
Insulin icodec	14 / 112	17 / 112	11 / 166	27 / 166
LS Mean				
Insulin degludec	66.53	63.09	56.32	57.30
Insulin icodec	65.30	62.30	54.63	54.28
Treatment difference (Ico – IDeg) (95% CI)				
	−1.24	−0.78	−1.68	−3.02
	(−5.05, 2.57)	(−4.93, 3.36)	(−4.58, 1.21)	(−6.07, 0.02)
	Defined by SMPG (Weeks 0-2)			
	CV ≤36%		CV >36%	
Missing endpoint data[a] / N				
	Weeks 22-26	**Weeks 48-52**	**Weeks 22-26**	**Weeks 48-52**
Insulin degludec	7 / 146	9 / 146	12 / 144	18 / 144
Insulin icodec	12 / 119	18 / 119	15 / 168	30 / 168
LS Mean				
Insulin degludec	66.66	64.10	55.44	55.60
Insulin icodec	65.70	62.40	54.34	53.80
Treatment difference (Ico – IDeg) (95% CI)				
	−0.95	−1.70	−1.10	−1.80
	(−4.67, 2.76)	(−5.64, 2.24)	(−3.97, 1.76)	(−4.90, 1.31)

Source: FDA statistical reviewer based on submitted datasets.

N, Number contributing to the analysis; subjects not assigned to a subgroup level are excluded from the analysis.

[a] Subjects not assigned to a subgroup level are not counted as they are excluded from the analysis.

The same analysis methods for the total population are applied to each subgroup level.

Abbreviations: CGM, continuous glucose monitoring; CI, confidence interval; CV, coefficient of variation; Ico, insulin icodec; IDeg, insulin icodec; LS, least squares; SMPG, self-measured plasma glucose