

Original Article

Once-Weekly Insulin Icodec: Safety Profile in Type 2 and Type 1 Diabetes Based on a Pooled Analysis of ONWARDS 1-6



Harpreet S. Bajaj, MD^{1,*}, Sofie Bech Andersen, PhD², Boryana Hristova, MD², Satish Hulkund, MSc³, Monika Kellerer, MD PhD⁴, Yiming Mu, MD⁵, Siri Vinther, PhD², Ildiko Lingvay, MD⁶

¹ LMC Diabetes and Endocrinology, Brampton, Ontario, Canada

² Novo Nordisk A/S, Søborg, Denmark

³ Novo Nordisk India Private Limited, Bangalore, India

⁴ Division of Internal Medicine 1, Department of Diabetes and Endocrinology, Marienhospital, Stuttgart, Germany

⁵ Department of Endocrinology, The First Medical Center, Chinese People's Liberation Army General Hospital, Beijing, China

⁶ Division of Endocrinology, Department of Internal Medicine and Peter O'Donnell Jr. School of Public Health, University of Texas Southwestern Medical Center, Dallas, Texas, USA

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ABSTRACT

Objective: To describe the safety profile of once-weekly insulin icodec (icodec), focusing on aspects beyond hypoglycemia, in a pooled population from the ONWARDS phase 3a trials.

Methods: ONWARDS 1-6 investigated the efficacy and safety of icodec versus once-daily basal insulin comparators in insulin-naïve and insulin-experienced adults with type 2 diabetes, and insulin-experienced adults with type 1 diabetes. Adverse event (AE) data from all trial periods were pooled. Hypersensitivity, injection-site reactions, and medication errors, as well as microvascular and macrovascular (including time to first major adverse cardiovascular event [MACE]) complications, were among the safety areas evaluated.

Results: Total treatment exposure was 2118.70 and 2127.76 patient-years of exposure (PYE) in the icodec ($n = 2170$) and comparator groups ($n = 2170$), respectively. Adjusted rates (events/100 PYE) were similar for icodec and comparators for all AEs (248.49 vs 242.53), serious AEs (14.51 vs 14.03), and severe AEs (7.92 vs 7.50), respectively. Adjusted rates of hypersensitivity were 5.88 and 6.74 events/100 PYE in the icodec and comparator groups, respectively. Most injection-site reactions were mild; adjusted rates: 5.86 and 3.66 events/100 PYE, respectively. Medication error rates were 2.47 and 2.53 events/100 PYE, respectively. Time to first MACE was similar between groups (hazard ratio [95% confidence interval]: 0.93 [0.56–1.56]). Adjusted rates for other AEs were broadly similar between groups.

Conclusion: Based on a detailed evaluation of safety focus areas across the ONWARDS 1-6 trials, the safety profile of once-weekly icodec was generally similar to that of once-daily basal insulin comparators in individuals with type 2 diabetes or type 1 diabetes.

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Abbreviations: AE, adverse event; degludec, insulin degludec; DKA, diabetic ketoacidosis; EAC, event adjudication committee; glargine, insulin glargine; HbA1c, glycated hemoglobin A1c; icodec, insulin icodec; MACE, major adverse cardiovascular event; MedDRA, Medical Dictionary for Regulatory Activities; PD, pharmacodynamic; PK, pharmacokinetic; PYE, patient-years of exposure; PYO, patient-years of observation; SAE, serious adverse event; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus.

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* Address correspondence to Dr Harpreet S. Bajaj, LMC Diabetes and Endocrinology, 2979 Bovaird Drive East, Brampton, Ontario L6S 0C6, Canada.

E-mail address: harpreet.bajaj@lmc.ca (H.S. Bajaj).

Introduction

Insulin is an important component of the treatment strategy for individuals with type 2 diabetes (T2D) and type 1 diabetes (T1D).¹⁻⁵ However, insulin use remains associated with adverse events (AEs) such as hypoglycemia, hypersensitivity, injection-site reactions, and medication errors.⁶⁻⁸ Therefore, it is important to assess the incidence of these AEs when insulin analogs are developed to evaluate their benefit-risk profile fully.

Insulin icodec (icodec) is a once-weekly basal insulin analog developed for the treatment of T2D and T1D, with the aim of

reducing the frequency of basal insulin administration from 365 injections/year to 52 injections/year. This reduced injection frequency could decrease treatment burden and may positively impact treatment adherence.^{9,10} The efficacy and safety of once-weekly icodec versus once-daily basal insulin comparators were investigated in the ONWARDS phase 3a clinical development program.¹¹ Across a range of clinical scenarios in insulin-naïve and insulin-experienced individuals with T2D, and insulin-experienced individuals with T1D, the randomized ONWARDS 1-6 trials (NCT04460885, NCT04770532, NCT04795531, NCT04880850, NCT04760626, and NCT04848480) demonstrated the statistical noninferiority or superiority of icodec to once-daily comparators with regard to change in glycated hemoglobin (HbA1c) from baseline to the primary analysis time point.¹²⁻¹⁷ In addition, no statistically significant differences in the rates of combined clinically significant (level 2) hypoglycemia (blood glucose <54 mg/dL [<3.0 mmol/L]) or severe (level 3) hypoglycemia (hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery) were observed with icodec versus once-daily comparators,¹²⁻¹⁶ except for in ONWARDS 6, in which the rate of combined clinically significant or severe hypoglycemia was statistically significantly higher in the icodec group than in the insulin degludec (degludec) group.¹⁷

The aim of this present analysis was to assess the overall safety profile of once-weekly icodec versus once-daily basal insulin comparators in a pooled population of participants from the ONWARDS 1-6 trials. To complement a previous participant-level, post hoc meta-analysis that focused on hypoglycemia and glycemic efficacy in individuals with T2D,¹⁸ the present pooled analysis investigates relevant safety focus areas of once-weekly icodec beyond hypoglycemia in both T2D and T1D.

Methods

Trial Design

The ONWARDS 1-6 trial designs have been described previously and are summarized in [Supplementary Table 1](#).¹¹⁻¹⁷ In brief, ONWARDS 1-6 were phase 3a, randomized, open-label (except ONWARDS 3, which was double-blinded), multinational, multicenter trials that investigated the efficacy and safety of icodec in insulin-naïve (ONWARDS 1, 3, 5) and insulin-experienced (ONWARDS 2, 4) adults (aged ≥ 18 years) with T2D, and in insulin-experienced adults with T1D receiving basal-bolus insulin (ONWARDS 6). ONWARDS 3 used a double-dummy design in which participants received 1 weekly and 7 daily injections each week to maintain blinding.

Participants were randomized (1:1) to receive once-weekly icodec (700 U/mL) or once-daily doses of: insulin glargine (glargine) U100 (ONWARDS 1, 4); degludec (ONWARDS 2, 3, 6); or degludec, glargine U100, or glargine U300 (ONWARDS 5). In the basal-bolus insulin trials in individuals with T2D (ONWARDS 4) or T1D (ONWARDS 6), participants in both groups also received 2-4 daily aspart injections.

The primary endpoint of each trial (change in HbA1c from baseline) was assessed at the end of the main phase (week 26 in ONWARDS 2, 3, 4, and 6; week 52 in ONWARDS 1 and 5). ONWARDS 1 and 6 also included a 26-week extension phase after the primary analysis to assess long-term safety. All 6 trials included a 5-week follow-up period between the end of treatment visit and the end of trial visit, in which safety data were collected; during this period participants were transferred to a suitable marketed product.

ONWARDS 1-6 were conducted in accordance with the principles of the Declaration of Helsinki and the relevant laws and

Highlights

- Insulin icodec (icodec) is a once-weekly basal insulin analog developed for the treatment of both type 2 diabetes and type 1 diabetes; by decreasing the frequency of basal insulin administration from 365 injections per year to 52 injections per year, it has the potential to reduce treatment burden
- This analysis pools a large amount of safety data from 6 phase 3a trials that evaluated the efficacy and safety of icodec compared with contemporary once-daily basal insulin treatments (insulin degludec, insulin glargine U100, and insulin glargine U300) across different patient populations, specifically insulin-naïve and insulin-experienced people with type 2 diabetes and insulin-experienced people with type 1 diabetes
- Based on a detailed evaluation of the reported adverse events, focusing on aspects beyond hypoglycemia, the safety profile of once-weekly icodec was shown to be generally similar to that of once-daily basal insulin comparators

Clinical Relevance

This analysis, leveraging the safety data from ONWARDS 1-6, shows that the overall safety profiles of insulin icodec (icodec) and currently used daily basal insulins, including insulin degludec and insulin glargine, are comparable in people with type 2 diabetes or type 1 diabetes. This finding should help to reassure physicians regarding patient safety when using icodec.

institutional guidelines of each participating country and site. Written informed consent was obtained from all participants before study entry.

Outcomes

Safety focus areas typically assessed for all insulins were also evaluated for icodec during the ONWARDS 1-6 trials.¹²⁻¹⁸ Safety data from all periods (main phase, extension phase, and follow-up period) of the trials were pooled.

The following predefined Medical Dictionary for Regulatory Activities (MedDRA; version 24.1) searches were used to capture AEs related to safety focus areas: hypersensitivity reactions; injection-site reactions; medication errors; diabetic retinopathy or maculopathy (assessed before randomization and at the end of treatment); other microvascular diabetic complications (including renal, dermal, and neurological diabetic complications); hyperglycemia (including diabetic ketoacidosis [DKA]); neoplasms (benign, unspecified, and malignant [malignant neoplasms were confirmed with an additional search using MedDRA version 25.1]); peripheral edema; hypokalemia; lipodystrophy; and localized amyloidosis. Cardiovascular-related events (acute coronary syndrome, cerebrovascular events, heart failure, and cardiovascular-related death), as independently assessed by an event adjudication committee (EAC), were also evaluated. AEs and serious AEs (SAEs) were defined based on standard safety reporting.¹⁹

A meta-analysis was conducted to evaluate the time to first EAC-confirmed major adverse cardiovascular event (MACE) for icodec versus once-daily comparators, using a 3-point composite outcome of cardiovascular death, acute myocardial infarction, and stroke.

Statistical Analyses

The number and proportion of participants who experienced an AE, the number of AEs, and the rate of AEs (number of AEs per 100 patient-years of exposure [PYE] or 100 patient-years of observation [PYO]; 1 PYE or 1 PYO = 365.25 days) were assessed in the pooled icodec group versus the pooled once-daily comparator group. The AE data derived from the predefined MedDRA searches were evaluated using descriptive statistics. Proportions and rates were adjusted using the Cochran-Mantel-Haenszel method to minimize the potential risk of confounding caused by differences in the trial populations.

AEs were assessed during the on-treatment period or the in-trial period. The on-treatment period was from the date of the first dose of trial product to the first date of either: the end of trial visit; the last date receiving trial treatment plus 6 additional weeks for those receiving icodec or 5 additional weeks for those receiving once-daily comparators; or the end date for the in-trial observation period. The in-trial period was from the onset date on or after the day of randomization to no later than the last participant-site contact, the last participant-investigator contact (for participants lost to follow-up), or the withdrawal/death date for participants who withdrew or died. Both periods were assessed using the safety analysis set, which comprised all participants who had received ≥ 1 dose of icodec or comparator. The duration of AEs was calculated as the end date minus the start date plus 1 day, meaning that events commencing and resolving on the same calendar day were recorded as having a duration of 1 day, despite potentially occurring over just a few hours.

A Cox proportional hazards model was used to compare treatment groups by estimating hazard ratios for time to first EAC-confirmed MACE. The model included treatment as a fixed effect (reference: once-daily comparator) and was stratified by trial. Participants were censored at the end of their in-trial observation period.

Results

Participants and Exposure

The overall ONWARDS pooled population included 4340 participants with T2D or T1D: 2170 each in the icodec and once-daily comparator groups. The icodec group and the once-daily comparator group had similar total exposure to trial treatment (2118.70 PYE and 2127.76 PYE, respectively) and total PYO (2155.16 PYO and 2156.66 PYO, respectively). Baseline characteristics of

participants in the pooled icodec and once-daily comparator groups were broadly similar (Supplementary Table 2).

Overall AEs

Overall, the proportion of participants who experienced any AE in the on-treatment period was 65.7% in the icodec group (rate: 248.49 events/100 PYE) and 62.8% in the once-daily comparator group (242.53 events/100 PYE) (Table 1). In the on-treatment period, the proportion of participants who experienced an event and the event rate were comparable between the icodec and once-daily comparator groups, respectively, for SAEs (8.8% [14.51 events/100 PYE] and 9.4% [14.03 events/100 PYE]), severe AEs (5.1% [7.92 events/100 PYE] and 5.1% [7.50 events/100 PYE]), fatal events (0.7% [1.10 events/100 PYE] and 0.6% [0.88 events/100 PYE]), and AEs leading to permanent discontinuation of trial product (1.2% [1.61 events/100 PYE] and 1.0% [1.57 events/100 PYE]). The proportion of participants who experienced AEs judged to be probably related to trial product by the investigator was 4.4% in the icodec group and 3.9% in the once-daily comparator group, with reported rates of 7.51 events/100 PYE and 7.22 events/100 PYE, respectively.

Safety Focus Areas

Hypersensitivity and Systemic Hypersensitivity Reactions

The proportion of participants with any hypersensitivity reaction in the on-treatment period was 4.8% in the icodec group (5.88 events/100 PYE) and 5.5% in the once-daily comparator group (6.74 events/100 PYE) (Table 2). Systemic hypersensitivity reactions (as defined in the protocols and assessed by investigators) were rare, occurring in 0.6% of participants receiving icodec and 0.4% of participants receiving once-daily comparators. There were 2 SAEs of systemic hypersensitivity in the icodec group (anaphylactic reaction [associated with a different medicine and unlikely to be related to icodec] and urticaria [probably related to icodec]) and 1 SAE of systemic hypersensitivity in the once-daily comparator group (anaphylactic reaction [possibly related to comparator]). All 3 events were subsequently resolved.

Injection-Site Reactions

The proportion of participants who experienced injection-site reactions in the on-treatment period was similar between groups (icodec: 2.0%; once-daily comparators: 1.7%); the rate was 5.86 events/100 PYE in the icodec group and 3.66 events/100 PYE in the once-daily comparator group (Table 2). The most common adverse events were injection-site reactions for the icodec group (29 of 82

Table 1
Summary of Adverse Events in the Pooled Phase 3a ONWARDS Trial Population (On-Treatment)

Summary	Icodec				Once-daily insulin comparator			
	N = 2170		PYE = 2118.70		N = 2170		PYE = 2127.76	
	n	Adjusted %	E	Adjusted R	n	Adjusted %	E	Adjusted R
AEs	1425	65.7	5098	248.49	1363	62.8	5066	242.53
Serious AEs	192	8.8	290	14.51	204	9.4	300	14.03
Severe AEs	111	5.1	151	7.92	110	5.1	165	7.50
Fatal events	15	0.7	20	1.10	14	0.6	19	0.88
AEs probably related to trial product	96	4.4	141	7.51	84	3.9	143	7.22
AEs possibly related to trial product	145	6.7	210	11.40	118	5.4	223	11.42
AEs leading to permanent discontinuation of trial product	25	1.2	33	1.61	21	1.0	31	1.57
AEs leading to temporary discontinuation of trial product	36	1.7	65	3.45	61	2.8	107	4.69

Abbreviations: %, proportion of participants with ≥ 1 AE; AE, adverse event; degludec, insulin degludec; E, number of AEs; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; icodec, insulin icodec; n, number of participants with ≥ 1 AE; PYE, patient-years of exposure (1 PYE = 365.25 days); R, rate (number of AEs per 100 PYE).

Once-daily comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2, 3, and 6, degludec; ONWARDS 5, degludec, glargine U100, or glargine U300. Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials.

Table 2

Summary of Safety Focus Areas Based on Predefined Medical Dictionary for Regulatory Activities Searches in the Pooled Phase 3a ONWARDS Trial Population

Safety focus area Predefined MedDRA term	Icodec				Once-daily insulin comparator			
	N = 2170		PYE = 2118.70 PYO = 2155.16		N = 2170		PYE = 2127.76 PYO = 2156.66	
	n	Adjusted %	E	Adjusted R	n	Adjusted %	E	Adjusted R
Hypersensitivity reaction ^a	105	4.8	131	5.88	119	5.5	152	6.74
Systemic hypersensitivity reaction ^b	12	0.6	15	0.79	8	0.4	9	0.42
Injection-site reaction	43	2.0	82	5.86	37	1.7	67	3.66
Medication error ^c	39	1.8	42	2.47	33	1.5	38	2.53
Diabetic retinopathy or maculopathy (in trial)	168	7.7	210	10.83	171	7.9	225	11.43
Other microvascular diabetic complication (in trial)	16	0.7	16	0.77	24	1.1	24	1.26
Hyperglycemia ^d	15	0.7	16	0.81	24	1.1	25	1.23
Neoplasm (in trial)	83	3.8	96	4.38	82	3.8	103	4.85
Malignant neoplasm ^e	21	1.0	23	1.08	23	1.1	31	1.48
Peripheral edema	29	1.3	32	1.58	27	1.2	29	1.15
Hypokalemia	3	0.1	3	0.15	2	0.1	2	0.06
Lipodystrophy (in trial)	1	0.0	1	0.03	3	0.1	3	0.14
Localized amyloidosis	0	—	—	—	0	—	—	—

Abbreviations: %, proportion of participants with ≥ 1 AE; AE, adverse event; degludec, insulin degludec; E, number of AEs; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; icodec, insulin icodec; MedDRA, Medical Dictionary for Regulatory Activities; n, number of participants with ≥ 1 AE; PYE, patient-years of exposure (1 PYE = 365.25 days) (on-treatment period); PYO, patient-years of observation (1 PYO = 365.25 days) (in-trial period); R, rate (number of AEs per 100 PYE [on-treatment period]; number of AEs per 100 PYO [in-trial period]).

Data presented are AEs that occurred in the on-treatment period unless otherwise specified. Once-daily comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2, 3, and 6, degludec; ONWARDS 5, degludec, glargine U100, or glargine U300. Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials.

^a Standardized MedDRA query includes many events with various etiologies.

^b Protocol-defined with additional data collection.

^c Standardized MedDRA query includes events related to misuse and abuse.

^d Standardized MedDRA query includes events related to diabetic ketoacidosis.

^e MedDRA version 25.1 was used to confirm the number of malignant neoplasms.

events) and injection-site pain for the once-daily comparator group (31 of 67 events). Of the 149 injection-site reaction events recorded in ONWARDS 1–6, 84 occurred during ONWARDS 3, the double-blind double-dummy trial; 62 of these were in the icodec group (with 2 participants accounting for 24 of the events). Of these 62 events, 35 were judged by the investigator as probably or possibly related to icodec and 21 as probably or possibly related to placebo. In the once-daily comparator group, 19 of the 22 injection-site reactions were judged by the investigator as probably or possibly related to degludec and 4 as probably or possibly related to placebo. Across the remaining trials (ONWARDS 1, 2, 4, 5, and 6), there were 20 injection-site reaction events with icodec and 45 events with the once-daily comparators. All injection-site reaction events were nonserious; most were mild and were considered resolved in both pooled groups. The median duration (first quartile; third quartile) of injection-site reaction events was similar between pooled groups (icodec: 5.50 [3.00; 16.25] days; once-daily comparators: 7.00 [1.00; 43.00] days).

Medication Errors

The proportion of participants who experienced medication errors in the on-treatment period was 1.8% for the icodec group and 1.5% for the once-daily comparator group; 42 events occurred in the icodec group and 38 events in the once-daily comparator group (Table 2). Of the 42 events in the icodec group, 25 events in 24 participants occurred during the first 10 days after treatment initiation in the 3 trials that included a one-time additional dose at treatment initiation (ONWARDS 2, 4, and 6); of these 25 events, 15 occurred at the second injection dose. Most medication errors were reported as accidental overdose or dosing error, and none were associated with severe hypoglycemia. For 8 of the 24 participants, investigators reported 11 episodes of alert value (level 1) hypoglycemia and 3 episodes of clinically significant (level 2) hypoglycemia as being associated with the medication error. These

hypoglycemic episodes occurred at a median time (first quartile; third quartile) of 2 (1; 3) days after the medication error. One medication error in the icodec group (double dose received owing to an administration error [200 U on 2 consecutive days]) was considered serious; this error did not result in a hypoglycemic episode (the participant was admitted to hospital after double dosing for measures to prevent hypoglycemia). Two medication errors in the once-daily comparator group were also considered serious; both errors happened after treatment with the trial product was completed. One was an overdose due to a mix-up between aspart (100 U) and degludec; this error did not lead to hypoglycemia. The other was an accidental overdose of 170 U of degludec instead of 24 U on 1 day, followed the next day by 150 U of degludec instead of 22 U; this error was co-reported with severe hypoglycemia during hospitalization.

Diabetic Retinopathy or Maculopathy

The proportion of participants with diabetic retinopathy or maculopathy events in the in-trial period was 7.7% in the icodec group and 7.9% in the once-daily comparator group; corresponding rates were 10.83 events/100 PYO and 11.43 events/100 PYO, respectively (Table 2). The most common event in this safety focus area for the icodec and once-daily comparator groups, respectively, was diabetic retinopathy (125 of 210 events and 125 of 225 events), followed by macular edema (17 events and 6 events), diabetic retinal edema (7 events and 16 events), retinopathy hypertensive (11 events and 8 events), nonproliferative retinopathy (6 events and 6 events), and retinal hemorrhage (6 events and 0 events). All SAEs related to diabetic retinopathy or maculopathy occurred in participants with T2D; 2 events in 2 participants were reported in the icodec group (retinal vein occlusion and retinopathy hypertensive) compared with 4 events in 3 participants in the once-daily comparator group (all diabetic retinal edema).

Other Microvascular Diabetic Complications

The proportion of participants with other microvascular diabetic complications in the in-trial period was 0.7% in the icodex group and 1.1% in the once-daily comparator group (Table 2). For both groups, the most common event for this safety area of interest was diabetic neuropathy (8 of 16 events in the icodex group; 14 of 24 events in the once-daily comparator group). Although no SAEs were reported in participants with T1D, 2 participants with T2D experienced SAEs: 1 who received icodex (diabetic foot infection) and 1 who received a once-daily comparator (diabetic neuropathy).

Hyperglycemia, Including DKA

The proportion of participants who experienced hyperglycemia events in the on-treatment period was 0.7% in the icodex group and 1.1% in the once-daily comparator group; rates of hyperglycemia were 0.81/100 PYE and 1.23/100 PYE, respectively (Table 2). The most common AE in the icodex group (8 of 16 events) and the once-daily comparator group (15 of 25 events) was hyperglycemia, followed by exacerbation of diabetes mellitus (3 events in the icodex group vs 2 events in the once-daily comparator group) and HbA1c increased (1 event in the icodex group vs 3 events in the once-daily comparator group). SAEs related to this safety focus area were DKA (1 event in the icodex group), ketonuria (1 event in the icodex group), hyperglycemia (2 events in the once-daily comparator group), and blood glucose increased (1 event in the once-daily comparator group). The SAE of DKA occurred in an individual with T1D who had completed icodex treatment and

switched to daily basal insulin ≥ 1 month before the event; it was considered to be related to a gastrointestinal infection.

Neoplasms

The proportion of participants with neoplasms in the in-trial period was 3.8% in both the icodex and the once-daily comparator groups; the rate of neoplasms was 4.38/100 PYO and 4.85/100 PYO, respectively (Table 2). SAEs related to neoplasms were experienced by 21 participants in the icodex group (24 events) and 26 participants in the once-daily comparator group (30 events). Serious events of malignant neoplasms were reported in 18 participants in the icodex group (20 events) and 20 participants in the once-daily comparator group (24 events).

Hypokalemia, Lipodystrophy, and Localized Amyloidosis

In the on-treatment period, the proportion of participants with hypokalemia was 0.1% in both the icodex and once-daily comparator groups, and that for lipodystrophy was 0.0% and 0.1% in the icodex and once-daily comparator groups, respectively, whereas there were no localized amyloidosis events in any group across the trials (Table 2).

Cardiovascular-Related Events

The proportion of participants with EAC-confirmed cardiovascular events in the in-trial period in each group is shown in Table 3. Cardiovascular death was reported for 2 participants in the icodex group (0.1%; 1 event of acute myocardial infarction and 1 event of other cardiovascular causes [peripheral arterial disease])

Table 3

Summary of Event Adjudication Committee-Confirmed Cardiovascular Events in the Pooled Phase 3a ONWARDS Trial Population

Summary	Icodex				Once-daily insulin comparator			
	N = 2170		PYO = 2155.2		N = 2170		PYO = 2156.7	
	n	Adjusted %	E	Adjusted R	n	Adjusted %	E	Adjusted R
Acute coronary syndrome	23	1.1	23	1.05	17	0.8	17	0.74
Acute myocardial infarction ^a	20	0.9	20	0.96	14	0.6	14	0.61
STEMI	7	0.3	7	0.28	8	0.4	8	0.41
NSTEMI	13	0.6	13	0.68	6	0.3	6	0.20
Undetermined	0	—	—	—	0	—	—	—
Hospitalization for unstable angina pectoris	3	0.1	3	0.09	3	0.1	3	0.13
Cerebrovascular event	7	0.3	7	0.38	12	0.6	12	0.57
Stroke ^a	7	0.3	7	0.38	12	0.6	12	0.57
Ischemic stroke	5	0.2	5	0.31	12	0.6	12	0.57
Hemorrhagic stroke	2	0.1	2	0.07	0	—	—	—
Undetermined stroke	0	—	—	—	0	—	—	—
Heart failure	6	0.3	7	0.28	4	0.2	5	0.30
Heart failure hospitalization	6	0.3	7	0.28	4	0.2	4	0.22
Urgent heart failure visit	0	—	—	—	1	0.0	1	0.08
Cardiovascular death ^a	2	0.1	2	0.11	7	0.3	7	0.33
Acute myocardial infarction	1	0.0	1	0.03	2	0.1	2	0.12
Sudden cardiac death	0	—	—	—	3	0.1	3	0.10
Heart failure	0	—	—	—	0	—	—	—
Stroke	0	—	—	—	1	0.0	1	0.08
Cardiovascular procedure	0	—	—	—	1	0.0	1	0.03
Cardiovascular hemorrhage	0	—	—	—	0	—	—	—
Other cardiovascular causes	1	0.0	1	0.08	0	—	—	—
Undetermined cause of death	3	0.1	3	0.16	2	0.1	2	0.09

Abbreviations: %, proportion of participants with ≥ 1 AE; AE, adverse event; degludec, insulin degludec; E, number of AEs; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; icodex, insulin icodex; MACE, major adverse cardiovascular event; n, number of participants with ≥ 1 AE; NSTEMI, non-ST-segment-elevation myocardial infarction; PYO, patient-years of observation (1 PYO = 365.25 days); R, rate (number of AEs per 100 PYO); STEMI, ST-segment-elevation myocardial infarction. In-trial status is defined based on the onset date, as decided by the EAC. In-trial period: from the onset date on or after the day of randomization to no later than the date of the last direct participant-site contact, the last participant-investigator contact (for participants lost to follow-up), withdrawal (for participants who withdrew their informed consent), or death (for participants who died before the date of last contact or withdrawal). Once-daily comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2, 3, and 6, degludec; ONWARDS 5, degludec, glargine U100, or glargine U300. Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials.

^a Component of the 3-point MACE analysis.

compared with 7 participants in the once-daily comparator group (0.3%; 2 events of acute myocardial infarction, 3 events of sudden cardiac death, 1 event of stroke, and 1 of the immediate complications of a cardiovascular procedure). Cause of death was undetermined for 3 participants (0.1%) in the icodec group and for 2 participants (0.1%) in the once-daily comparator group. The proportion of participants with EAC-confirmed first occurrence of MACE in the in-trial period was similar between groups (icodec: 1.3%; once-daily comparators: 1.4%); the rate of this occurrence was 1.42 events/100 PYO in the icodec group and 1.31 events/100 PYO in the once-daily comparator group. The time to first EAC-confirmed occurrence of MACE was also similar between groups: hazard ratio (95% confidence interval), 0.93 (0.56–1.56) (Figure).

Discussion

This pooled analysis of safety data from the phase 3a ONWARDS trials was performed to provide an overview of the safety profile of once-weekly icodec, focusing on predefined safety events beyond hypoglycemia. Among these predefined events, medication errors related to the administration of a one-time additional icodec dose at treatment initiation in insulin-experienced participants who switched therapy differed from those in insulin-naïve participants, who do not require an additional dose to start icodec treatment. Medication errors in the insulin-experienced subgroup are therefore addressed separately in this report and are further described in the icodec label and risk management plan.^{20,21} With the exception of this specific scenario, the predefined safety events were not primarily influenced by insulin dose or differences between T1D and T2D pathophysiology. Consequently, as most of them (including injection-site reactions, medication errors, and hyperglycemia/DKA) were infrequent, conducting separate formal analyses by diabetes type or prior insulin use would have limited statistical power and yield unreliable estimates. Safety data were therefore pooled irrespective of diabetes type and prior insulin use to increase the precision of the event rate estimates and to enable a comprehensive evaluation across clinically heterogeneous, but mechanistically similar, populations receiving basal insulin

therapy. Overall, the analysis of safety focus areas beyond hypoglycemia provides reassuring evidence that the proportions of participants experiencing AEs and the rates of various classes of AEs were broadly similar in the pooled icodec and once-daily comparator groups.

Hypersensitivity, one of the safety focus areas examined, was found to be comparable between the icodec and once-daily comparator groups; notably, the standardized MedDRA query captured AEs with various etiologies, which were unlikely to be related to basal insulin treatment. Moreover, the proportion of participants with protocol-defined systemic hypersensitivity was low across groups.

In both pooled groups, all injection-site reactions were nonserious. Across the open-label studies, the number of reported injection-site reactions was numerically lower with icodec than with once-daily comparators; in contrast, in ONWARDS 3, a double-blind double-dummy trial, the rate of injection-site reactions was numerically higher in the icodec group than in the once-daily comparator group.^{12–17} Indeed, over half of the injection-site reactions occurred in ONWARDS 3; this disparity was partly due to a few participants with many reported events.¹⁴ The greater number of injection-site reactions in ONWARDS 3 should be interpreted in the context of its double-dummy design, in which participants received 1 weekly and 7 daily injections each week, substantially increasing the injection-site reaction burden, although reporting bias in open-label trials cannot be excluded.

The overall proportion of participants with medication errors was similarly low in both treatment groups. Of note, a cluster of medication errors associated with the one-time additional dose of icodec at treatment initiation (per protocol) in ONWARDS 2, 4, and 6 (ie, trials in which insulin-experienced individuals switched from a daily basal insulin to a once-weekly basal insulin) was observed.^{13,15,17} Reassuringly, these events were associated only with alert value (level 1) or clinically significant (level 2) hypoglycemia, and none resulted in severe (level 3) hypoglycemia. The occurrence of medication errors highlights the importance of adequate training for health care professionals and individuals initiating insulin to reduce the risk of medication errors.²² It is also

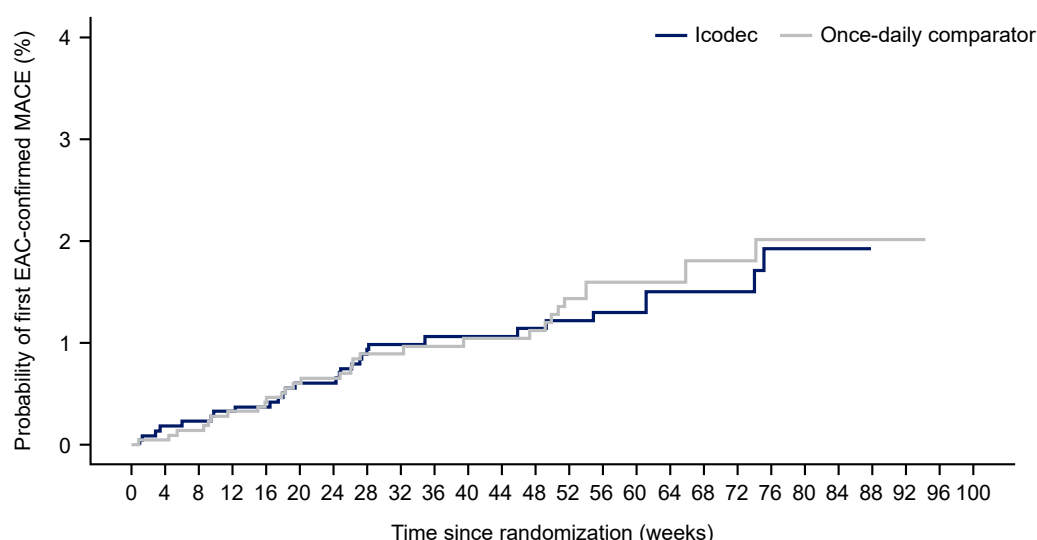


Fig. Time to first EAC-confirmed MACE in the pooled phase 3a ONWARDS trial population. Cumulative incidence estimate for the first EAC-confirmed MACE during the in-trial period. In-trial period: from the onset date on or after the day of randomization to no later than the date of the last direct participant-site contact, the last participant-investigator contact (for participants lost to follow-up), withdrawal (for participants who withdrew their informed consent), or death (for participants who died before the date of last contact or withdrawal). Once-daily comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2, 3, and 6, degludec; ONWARDS 5, degludec, glargine U100, or glargine U300. Degludec, insulin degludec; EAC, event adjudication committee; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; icodec, insulin icodec; MACE, major adverse cardiovascular event.

important that health care professionals take the time to explain the icodec dosing regimen to individuals with diabetes and that individuals carefully read the instructions in the icodec package leaflet.²⁰ A patient/caregiver guide addressing how to avoid medication errors, developed in conjunction with the European Medicines Agency,²³ has been translated into relevant languages in the European Union member states where icodec is available. The one-time additional icodec dose is administered when switching from daily basal insulin to prevent a potential transient increase in fasting glucose levels and thus achieve quicker glycemic control; however, for individuals with T2D, modeling analysis suggests that omission of the one-time additional dose did not show sustained clinically relevant effects.²⁴ Moreover, while icodec may be co-administered with other non-insulin glucose-lowering therapies, dose reduction or discontinuation may be necessary and careful monitoring is advised.²²

Diabetic retinopathy and maculopathy occurred with similar incidence and rates in the icodec and once-daily comparator groups. Rapid and substantial reductions in HbA1c have been historically associated with early worsening of diabetic retinopathy,^{25,26} and this remains an important consideration when interpreting retinopathy outcomes. Accordingly, in clinical practice, individuals who achieve marked improvements in glycemic control should continue to receive appropriate ophthalmologic monitoring in line with current recommendations.²⁶

DKA is a serious safety concern, particularly for people with T1D.²⁷ Notably, the rate of AEs of hyperglycemia including DKA across the pooled ONWARDS 1-6 population was low and similar between groups. One SAE of DKA was recorded in a participant with T1D in the icodec group, but the event occurred in the follow-up period after switching to a marketed once-daily insulin and was considered unrelated to icodec.

As a once-weekly insulin, icodec has a prolonged half-life, and based on general pharmacokinetic (PK) principles, near complete clearance requires approximately 5 half-lives.^{28,29} Consistent with PK/pharmacodynamic (PD) modeling of switching and treatment discontinuation, icodec exposure declines gradually over several weeks rather than abruptly after a single missed dose,²⁴ suggesting that a missed weekly injection is unlikely to result in sudden loss of basal insulin coverage. While these PK/PD assessments were conducted in participants with T2D, the pharmacologic properties of icodec are expected to be comparable in individuals with T1D and thus may help to contextualize potential coverage gaps in this population. Building on these PK/PD considerations, during intercurrent illness, current clinical use guidance for icodec recommends frequent glucose monitoring and the temporary use of intensification of rapid-acting insulin, while continuing basal insulin, to reduce the risk of DKA in susceptible individuals.²² If glycemic deterioration occurs and the timing of the last icodec dose limits timely basal adjustment, short-acting insulin may be required until recovery.^{20,22} In this pooled analysis, AEs were captured during the on-treatment period, which included events occurring up to 6 weeks after the last icodec dose and up to 5 weeks after the last once-daily comparator dose.

Cardiovascular-related events, including MACE, were uncommon and occurred at similar rates in the icodec and comparator groups. However, the low number of events (58) limits the precision of the estimated treatment effect, cardiovascular safety remains incompletely established. This pooled analysis is insufficient on its own to replace a dedicated cardiovascular outcomes trial or establish cardiovascular neutrality. A key strength of this study is the large sample size of the pooled population from all 6 phase 3a ONWARDS trials ($N = 4340$, equally divided between icodec and the once-daily comparator groups), which encompasses participants from 33 countries across 5 continents. Pooling

of these trials allowed for improved characterization of rare but clinically meaningful AEs and for a broader and more comprehensive assessment of icodec safety than could be achieved through analysis of the individual trials alone. Overall, the findings from this pooled population are consistent with, and provide greater confidence in, the safety evaluations for each of the individual trials.

Based on data from this study and from the clinical development program, icodec has shown improved treatment satisfaction while maintaining comparable efficacy and safety to daily basal insulin across a broad population of individuals with T2D.^{10,22} The reduced treatment burden may be particularly beneficial for those who struggle with managing dosing or those who prefer or need a simpler regimen.

A limitation of this study is the inherent variation in study design and participant populations (insulin-naïve T2D, insulin-experienced T2D, and T1D) across the ONWARDS 1-6 trials, which may have confounded the results. While the Cochran-Mantel-Haenszel method was used to reduce the risk of confounding owing to differences in participant numbers across the trials, it should be noted that statistical adjustment cannot fully account for underlying differences in disease pathophysiology. In addition, the durations of the ONWARDS trials were relatively short in the context of evaluating certain safety focus areas, such as neoplasms, particularly because the presence or history of malignant neoplasms was an exclusion criterion in ONWARDS 1-4 and 6.¹¹ Furthermore, statistical analysis of the differences in the rate of AEs between groups could not be conducted owing to the small number of participants who experienced events associated with most safety focus areas. It should also be noted that the overall small proportion of first EAC-confirmed occurrence of MACE, although expected and considered sufficient for the evaluation of MACE for this type of analysis, cannot compare with the statistical power or number of events required for formal cardiovascular outcomes trial analyses. Finally, 5 of the 6 ONWARDS trials had an open-label design, which may have resulted in reporting biases; however, given that the overall safety profile was broadly similar between icodec and once-daily comparators, the impact of any reporting bias is likely to be insubstantial.

Conclusions

Overall, the safety profile of once-weekly icodec was found to be comparable to that of once-daily basal insulin comparators. This was based on a detailed evaluation of safety focus areas beyond hypoglycemia across 6 phase 3a clinical trials in individuals with T2D or T1D. This study provides additional information regarding the safety profile of icodec. Observations from the use of icodec in the postmarketing setting will further enrich the knowledge base about the safety profile of this once-weekly basal insulin therapy.

Disclosure

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