Weekly Icodec vs Daily Glargine U100 in Insulin-Naïve Type 2 Diabetes

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ABSTRACT

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BACKGROUND

Insulin icodec (icodec) is an investigational once-weekly basal insulin analog for the management of diabetes. **METHODS**

ONWARDS 1 is a 78-week randomized, open-label, treat-to-target phase 3a trial (52-week main phase+26-week extension+5-week follow-up), in insulin-naïve adults with type 2 diabetes (glycated hemoglobin 7–11%) randomized 1:1 to icodec or once-daily glargine U100 (N=492/arm). The primary end point was change in glycated hemoglobin (baseline to week 52); the confirmatory secondary end point was time in glycemic range (TIR; 70–180 mg/dL; weeks 48–52). Hypoglycemic episodes (baseline to weeks 52 and 83) were recorded.

RESULTS

Baseline characteristics were similar between arms. Mean glycated hemoglobin reduction at 52 weeks was greater with icodec (8.50% to 6.93%; mean change, −1.55 %-points) versus glargine (8.44% to 7.12%; mean change, −1.35 %-points); estimated treatment difference (ETD; [95% CI], −0.19 [−0.36, −0.03] %-points) confirmed icodec noninferiority (P<0.0001) and superiority (P=0.0210). TIR was significantly greater with icodec (71.9%) than glargine (66.9%) (ETD [95% CI], 4.27 [1.92, 6.62] %-points; P=0.0004), confirming superiority. Combined clinically significant or severe hypoglycemia rates were 0.29 events/patient-year of exposure (PYE) for icodec and 0.15 events/PYE for glargine with an estimated rate ratio [ERR; 95% CI] of 1.64 [0.98, 2.75]) at week 52, and 0.30 events/PYE vs 0.15 events/PYE (ERR [95% CI], 1.63 [1.02, 2.61]) at week 83. No new safety signals were identified, and incidences of adverse events were similar between arms.

CONCLUSIONS

Glycemic control improved significantly with once-weekly icodec versus once-daily glargine. Combined clinically significant or severe hypoglycemia rates remained <one event/PYE in both arms.

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Current treatment guidelines for type 2 diabetes recommend a stepwise approach with incretin-based therapies as first-line injectable treatments; however, the initiation of once- or twice-daily basal insulin analogs to aid glycemic control remains widely used.[1,2]

Concerns regarding daily injections and reduced treatment adherence contribute substantially to suboptimal glycemic control for many people with type 2 diabetes.[3,4] Patients generally prefer fewer injections,[5] and the benefits of reducing injection frequency are supported by clinical evidence from weekly glucagon-like peptide 1 receptor agonists (GLP-1 RAs), which showed improved treatment adherence and glycemic control .[6] Conceivably, the observed benefits of once-weekly injectable GLP-1 RAs in type 2 diabetes might, by analogy, be relevant if a once-weekly insulin were available.[7,8]

Insulin icodec (icodec) provides basal insulin coverage over a full week following a single subcutaneous injection.[9] A short-term, proof-of-concept, phase 2 trial in people with insulin-naïve type 2 diabetes comparing once-weekly icodec with once-daily insulin glargine U100 (glargine U100) showed similar glycemic control and low rates of hypoglycemia across treatment arms.[10]

The phase 3a clinical development program, ONWARDS, evaluateds the efficacy and safety of once-weekly icodec across diverse populations and comparator treatments, as described previously.[11] We designed the present trial, ONWARDS 1, which had the longest duration among ONWARDS trials, to investigate the efficacy and long-term safety of once-weekly icodec compared with once-daily glargine U100, both in combination with non-insulin glucose-lowering treatments (including GLP-1 RAs and sodium-glucose cotransporter 2 [SGLT2] inhibitors), in people with insulin-naïve type 2 diabetes.

METHODS

TRIAL DESIGN

This 78-week, randomized, open-label, treat-to-target, phase 3a trial was conducted at 143 sites in 12 countries (Croatia, India, Israel, Italy, Japan, Mexico, Poland, Russia, Slovakia, Spain, UK, USA). The overall trial duration was approximately 85 weeks, comprising: screening period (up to 2 weeks), 78-week randomized treatment period (including 52-week main and 26-week extension phases), and a 5-week follow-up period during which study treatments were discontinued (Fig. S1).[11] The protocol is posted at **NEJM.org**.

Insulin naïve adults (≥ 18 years old) with type 2 diabetes and glycated hemoglobin values 7–11% (53.0–96.7 mmol/mol) and body mass indexes of 40 kg/m^2 or less at screening were eligible.[11] Full inclusion and exclusion are provided in Table S1.

TRIAL TREATMENT

Participants were randomized 1:1 to receive once-weekly icodec or once-daily glargine U100 using an interactive web response system. Icodec (700 U/mL; Novo Nordisk A/S) or glargine U100 (100 U/mL; Sanofi-Aventis) were administered subcutaneously using prefilled pen injectors. Starting dosages for icodec and glargine U100 were 70 U/week and 10 U/day, respectively. As this was a treat-to-target trial, insulin doses were titrated to enable participants to achieve a pre-breakfast self-measured blood glucose target of 80–130 mg/dL (4.4–7.2 mmol/L). Pre-trial non-insulin glucose-lowering treatments were continued following randomization, except for sulfonylureas and glinides, which were discontinued. At randomization, each participant received a blood glucose meter (Accu-Chek®; Roche Diabetes Care, Inc.), along with a double-blinded continuous glucose monitoring device (Dexcom G6; Dexcom Inc.), and education on device use. Further details are in the Supplementary Appendix.

EFFICACY END POINTS

The primary trial end point was absolute change in glycated hemoglobin level (%-point) from baseline to week 52. The estimand was defined as the treatment difference between icodec and glargine U100 in change in glycated hemoglobin level from baseline to week 52 for all randomized participants, irrespective of treatment adherence and changes in background glucose-lowering treatments.

The confirmatory key secondary end point was the proportion of time spent in the target glycemic range of 70–180 mg/dL (3.9–10.0 mmol/L) in weeks 48–52, as measured by blinded continuous

glucose monitoring. The supportive secondary efficacy end point was change in fasting plasma glucose from baseline to week 52.

SAFETY END POINTS

Supportive secondary safety end points were number of clinically significant (level 2; <54 mg/dL [<3.0 mmol/L]), severe (level 3), or combined clinically significant and severe hypoglycemic episodes from baseline to week 52 (classifications described in Supplementary materials); time spent below (<54 mg/dL [<3.0 mmol/L]) or above (>180 mg/dL [>10 mmol/L]) target glycemic range in weeks 48–52; mean weekly insulin dose in weeks 50–52; and change in body weight from baseline to week 52.

The prespecified safety end points encompassing the extension phase were the number of clinically significant, severe, or combined clinically significant and severe hypoglycemic episodes (baseline to week 83).

ADDITIONAL ASSESSMENTS

Additional prespecified exploratory assessments included: proportion of participants achieving glycated hemoglobin <7%, and proportion of participants achieving glycated hemoglobin <7% without clinically significant or severe hypoglycemia in the preceding 12 weeks (both at weeks 52 and 78); change in glycated hemoglobin level, fasting plasma glucose, and body weight from baseline to week 78; proportion of time spent in, above, or below target glucose range in weeks 74–78; and mean weekly insulin dose in weeks 76–78. A post hoc analysis assessed insulin dose by body weight (U/kg) at weeks 50–52 and 76–78.

Adverse and serious adverse events were recorded from baseline to week 83. For participants who discontinued trial treatment prematurely, adverse events were recorded until the discontinuation follow-up visit at week 78. An independent, external, event adjudication committee performed ongoing blinded adjudication of select adverse events, namely acute coronary syndrome, cerebrovascular events, heart failure, and all-cause death.

TRIAL OVERSIGHT

Before trial start, the protocol, consent form, and all other relevant documents were reviewed and approved by an independent ethics committee or institutional review board, according to local regulations. All participants provided written informed consent. The trial was conducted in accordance with the principles of the Declaration of Helsinki and in accordance with Good Clinical Practice Guidelines of the International Council for Harmonisation.

STATISTICAL ANALYSIS

A detailed description of the statistical analyses has been published;[11] these are briefly summarized here and further details are in the **Supplementary Appendix**.

The primary hypothesis was that icodec is noninferior to glargine U100 for glycated hemoglobin level change from baseline to week 52 (prespecified noninferiority margin: 0.3%-points). If noninferiority was confirmed, hierarchical confirmatory testing assessed icodec superiority compared with glargine U100 for time spent in target glycemic range, and then for change in glycated hemoglobin level (baseline to week 52).

The sample size was determined to fulfill the US Food and Drug Administration requirement of at least 300 participants completing 78 weeks of icodec treatment, to provide sufficient marginal power for the primary and confirmatory secondary hypotheses. Assuming no treatment difference for treatment completers without an intercurrent event and a treatment difference of 0.3%-points in favor of the comparator for participants experiencing an intercurrent event leading to a mean treatment difference of 0.03%-points in favor of the comparator, 970 participants would provide sufficient power of 99% to declare noninferiority.

The full analysis set included all randomized participants, and the safety analysis set included all randomized participants who received at least one treatment dose. Efficacy end points were analyzed using the full analysis set and the 'in-trial' period. Safety end points were assessed using the safety analysis set (descriptive statistics) and the full analysis set (statistical analyses, unless otherwise specified) during the 'main-on-treatment' period (main phase) or 'on-treatment' period (complete trial). Details of the statistical analyses and trial periods can be found in the Supplementary Appendix and **Table S2**.

ROLE OF THE FUNDING SOURCE AND AUTHOR CONTRIBUTIONS

The trial was funded by Novo Nordisk. Investigators were responsible for trial conduct, data collection and trial-related medical decisions, data interpretation, manuscript drafting and all decisions regarding publication. Representatives of Novo Nordisk were involved in: the trial design and conduct; data collection, management, analysis, and interpretation; and preparation, review, and approval of the manuscript. A medical writer (Erin Aldera PhD of Oxford PharmaGenesis Ltd), funded by Novo Nordisk, provided medical writing support under the direction of the authors.

RESULTS

PARTICIPANTS

Of 1192 participants screened between November 25, 2020, and December 01, 2022, 176 (14.8%) failed screening and 492 were randomized to each treatment arm (Fig. 1). All participants received at least one dose of trial treatment, and 954 (97.0%) completed the week 52 visit without discontinuing treatment (icodec, 475 [96.5%]; glargine U100, 479 [97.4%]); 953 participants (96.8%) completed the week 78 visit (icodec, 476 [96.7%]; glargine U100, 477 [97.0%]), of whom 466 (94.7%) receiving icodec and 472 (95.9%) receiving glargine U100 did so without permanent treatment discontinuation (Fig. S2). Demographics and baseline characteristics were broadly similar between treatment arms, except for the higher proportion of men in the icodec arm (Table 1).

EFFICACY END POINTS

At baseline, observed mean glycated hemoglobin level was 8.50% with icodec, and 8.44% with glargine U100; at week 52, estimated mean glycated hemoglobin level was 6.93% and 7.12%, respectively. The estimated mean change in glycated hemoglobin level from baseline to week 52 was −1.55 %-points for icodec and −1.35 %-points with glargine U100, with an estimated treatment difference (95% confidence interval [CI]) of −0.19 (−0.36, −0.03) %-points (Fig. 1A and Table 2), confirming noninferiority (P<0.001) and superiority (P=0.021) of icodec. At extension phase end (week 78), the glycated hemoglobin reduction with icodec was sustained (estimated treatment difference [95% CI] −0.11 [−0.22, 0.00] %-points).

In weeks 48–52, participants receiving icodec spent a significantly greater proportion of time in target glycemic range compared with glargine U100 (71.9% vs. 66.9%, estimated difference [95% CI] of 4.27 [1.92, 6.62] %-points; P<0.001), translating to approximately 1 hour and 1 minute additional time spent in range per day, and confirming superiority of icodec (Fig. 1B and Table 2). In weeks 74–78, this difference was maintained (icodec, 70.2%; glargine U100, 64.8%; estimated treatment difference [95% CI], 4.41 [1.92, 6.90] %-points), translating to approximately 1 hour and 4 minutes more time spent in range per day with icodec (Fig. 1B and Table 2).

At week 52, a greater proportion of participants receiving icodec compared with glargine U100 achieved glycated hemoglobin <7% (estimated percentage57.6% vs. 45.4%), and glycated hemoglobin <7% without clinically significant or severe hypoglycemia (estimated percentage: 52.6% vs. 42.6%). Similar findings were observed at week 78 (Fig. 1C and Table 2).

Estimated mean change in fasting plasma glucose (baseline to week 52) was similar between treatment arms (icodec, −60 mg/dL [−3.3 mmol/L]; glargine U100, −60 mg/dL [−3.3 mmol/L]; estimated treatment difference [95% CI], −0.24 [−4.89, 4.41] mg/dL or −0.01 [−0.27, −0.24] mmol/L;) (Table 2). Findings were similar at week 78.

SAFETY END POINTS

No difference was detected in the proportion of time spent below target glycemic range (<54 mg/dL [<3 mmol/L]) at weeks 48–52 with icodec or glargine U100 (estimated treatment ratio [95% CI], 1.27 [0.94, 1.71]) (Table 3). The proportion of time above target glycemic range (>180 mg/dL [10 mmol/L]) was lower with icodec than glargine U100 (estimated treatment difference [95% CI], −4.58 [−6.99, −2.17] %-points), translating to approximately 1 hour and 6 minutes less time spent above target range per day. Similar findings were observed for weeks 74–78 (Table 3).

The estimated mean weekly insulin dosage was 214 U/week (~31 U/day) and 222 U/week (~32 U/day) for weeks 50–52, and 224 U/week (~32 U/day) and 234 U/week (~33 U/day) for weeks 76–78 in the icodec and glargine U100 arms, respectively (Fig. S3 and Table 3).

There was no evidence of difference in the estimated mean change in body weight from baseline to week 52: 2.3 kg with icodec, and 1.8 kg with glargine U100 (estimated treatment difference [95% CI], 0.46 [−0.12, 1.04] kg) (Table 3). Similar changes were observed at week 78 (Table 3).

From baseline to week 83, 226 clinically significant hypoglycemic events occurred in 61 participants receiving icodec compared with 114 events in 66 participants receiving glargine U100 (Table 3). One episode of severe hypoglycemia occurred with icodec and seven episodes with glargine U100. Incidences of hypoglycemic events were similar between arms at week 52 and week 83 (Table 3). Over the trial duration, three participants (0.6%) receiving icodec experienced 105 of the 226 clinically significant hypoglycemic events (Table S3). Hypoglycemia rates in both treatment arms were below one hypoglycemia event per patient-year of exposure (PYE) at trial completion. From baseline to week 52, rates of clinically significant hypoglycemia were 0.29 vs. 0.15 events per PYE for icodec versus glargine U100, respectively (estimated rate ratio [95% CI]: 1.67 [0.99, 2.84]), and rates of combined clinically significant and severe hypoglycemia were 0.30 vs. 0.16 events per PYE for icodec and glargine U100, respectively (estimated rate ratio [95% CI]: 1.64 [0.98, 2.75]). At week 83, the rates of clinically significant and combined clinically significant and severe hypoglycemia remained below one event per PYE for both icodec and glargine U100 (0.30 vs. 0.15 events per PYE, estimated rate ratio [95% CI] 1.71 [1.06, 2.76]; and 0.30 vs. 0.16 event per PYE, estimated rate ratio [95% CI] 1.63 [1.02, 2.61], respectively; Fig. S4).

From baseline to week 83, 1882 adverse events occurred in 397 participants receiving icodec, and 1823 in 389 participants receiving glargine U100 (Table 3). Most were non-serious, mild or moderate in severity, and were determined by the investigator as unlikely to be related to trial treatment. Ninety-five serious adverse events occurred in 64 participants receiving icodec, compared with 119 events in 71 participants receiving glargine U100. All serious adverse events in the icodec arm were considered unlikely to be related to trial treatment. Adverse events by system organ class are shown in Fig. S5. While on treatment, five deaths occurred in the icodec and three deaths occurred in the glargine U100 arm (Table 3).

DISCUSSION

ONWARDS 1 was the longest trial in the ONWARDS development program for insulin icodec and supports the potential of this weekly insulin to facilitate basal insulin initiation and to improve glycemic control and treatment adherence by reducing the insulin injection burden for insulin-naïve people with type 2 diabetes requiring insulin therapy. The primary end point was met, with noninferiority and statistical superiority of once-weekly icodec compared with once-daily glargine U100 confirmed for change in glycated hemoglobin from baseline to week 52.

This reduction in glycated hemoglobin with icodec was maintained to week 78. A slight further reduction in glycated hemoglobin in the glargine U100 arm led to a statistically nonsignificant difference at week 78. Despite this, participants receiving icodec spent significantly more time in target glycemic range than those receiving glargine U100 at weeks 48-52 (additional 1 hour and 1 minute per day) and weeks 74-78 (additional 1 hour and 4 minutes per day). The International Consensus on Time in Range recommends that over 70% of continuous glucose monitoring measurements fall within the target glycemic range.[12] This was on average achieved in both trial phases with icodec, but not with glargine U100. Notably, despite the differences in hypoglycemia rates, there was no evidence of a difference between treatment arms in time spent below range (<54 mg/dL [<3.0 mmol/L]), which generally remained below the internationally recommended target (<1%) in both arms during both trial phases.[12-14]

Fasting plasma glucose levels were similar between treatment arms; this is observed consistently across other ONWARDS trials (Mathieu *et al*[15] and Philis-Tsimikas et al).[16] Fasting glucose measurements alone may not reflect the consistent glucose-lowering profile throughout the day with once-weekly icodec compared with once-daily treatments; the greater amount of time spent in glycemic range throughout the day and the significant decrease in glycated hemoglobin levels may provide a more accurate picture.

Although the rate of clinically significant or severe hypoglycemic episodes differed at week 83 with icodec compared with glargine U100, overall rates of these hypoglycemic episodes remained below one event/patient-year of exposure throughout the trial, which is comparable to rates reported previously for other basal insulin analog trials in insulin naïve type 2 diabetes, despite the caveat of differing trial designs.[17-19] Furthermore, the incidence of these episodes was similar between treatment arms throughout the trial. It is worth noting that the rate of clinically significant hypoglycemia in the icodec arm may have been influenced by three out of 492 participants (0.6%) experiencing 105 of the 226 clinically significant hypoglycemic events (54, 37, and 14 events, respectively). Moreover, at weeks 52 and 78, more participants receiving icodec than those receiving glargine U100 achieved a glycated hemoglobin of <7% without clinically significant or severe hypoglycemia in the preceding 12 weeks. Notably, only one episode of severe hypoglycemia occurred with icodec and seven with glargine U100, during this 18-month trial.

Our trial has several limitations. Unlike our phase 2 study,[10] the present trial did not have a double-blind, double-dummy design, a feature intended to limit the burden on trial participants from the number of injections that would be required over a long duration of time. However, ONWARDS 3 (NCT04795531) used a double-blind, double-dummy design to compare icodec with degludec in people with insulin-naïve type 2 diabetes and confirm the phase 2 study findings.[12] Furthermore, the continuous glucose monitoring would have been more informative if maintained throughout the trial. Although the blinding of these measurements was a strength for the assessment of glucose metrics, this prevented their use for insulin dose adjustments, which might have further reduced the occurrence of hypoglycemic events. Glargine U100 was selected as the comparator in this trial as it is the most-commonly used once-daily basal insulin. However, the efficacy and safety of icodec versus second generation basal insulin analogs have been assessed in ONWARDS 2[16] and 3 (vs. degludec), while ONWARDS 5 (NCT04760626) has compared icodec with a range of basal insulin analogs (including glargine U300 and degludec).[12]

Our trial has several strengths, the first of which is the long duration of the randomized treatment period and safety follow-up. Furthermore, this trial recruited a large, multinational cohort that was fairly representative of people with type 2 diabetes who require insulin despite the availability of newer non-insulin glucose-lowering treatments (Table S4). Participants could continue most background non-insulin glucose-lowering treatments, and blinded continuous glucose monitoring data allowed more objective and detailed assessments.

Taken together, the findings of the current trial highlight the totality of evidence for glycemic control with icodec, allowing more people with long-standing diabetes on non-insulin glucose-lowering

agents including GLP-1RAs and SGLT-2 inhibitors to achieve glycated hemoglobin <7%, and spend more time in range and also to achieve glycated hemoglobin <7% without clinically significant or severe hypoglycemia compared with glargine U100, while combined clinically significant or severe hypoglycemia remained well below one event per patient-year of exposure with both treatments..

In conclusion, once-weekly icodec offered improved glycemic control compared with once-daily glargine U100 in people with type 2 diabetes who were previously insulin naïve.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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FIGURE LEGEND

Figure 1. Change in Glycated Hemoglobin Level from Baseline to Week 78 (A), Continuous Glucose Monitoring Ranges for Weeks 48–52 and Weeks 74–78 (B), and Achievement of Glycated Hemoglobin Targets (C). Clinically significant (level 2) hypoglycemia: blood glucose <54 mg/dL (<3.0 mmol/L) confirmed by blood glucose meter; severe (level 3) hypoglycemia: no specific glucose threshold, but hypoglycemia was associated with severe cognitive impairment requiring external assistance for recovery. Error bars represent SEM. *Estimated mean values at weeks 52 and 78, derived based on multiple imputation. Glargine denotes insulin glargine U100, HbA_{1C} glycated hemoglobin, icodec insulin icodec, and SEM standard error of the mean.

TABLES

Table 1. Demographics and Baseline Characteristics*

	Icodec (n=492)	**Glargine (n=492)**
Male — no. (%)	295 (60.0)	263 (53.5)
Age — years†	59.1±10.1	58.9±9.9
Body weight — kg†	85.2±17.7	84.3±17.6
Body mass index — kg/m^{2}†	30.0±4.8	30.1±5.1
Diabetes duration — years†	11.6±6.7	11.5±6.8
Glycated hemoglobin — %†	8.5±1.0	8.4±1.0
Fasting plasma glucose — mg/dL (mmol/L)†	185.3±49.0 (10.3±2.7)	185.7±51.7 (10.3±2.9)
eGFR — mL/min/1.73m^{2}†	86.1±18.2	84.9±19.6
Non-insulin glucose-lowering agents at screening — no. (%)		
Metformin	449 (91.3)	436 (88.6)
Sulfonylureas	219 (44.5)	227 (46.1)
SGLT2 inhibitors	187 (38.0)	172 (35.0)
DPP-4 inhibitors	178 (36.2)	170 (34.6)
GLP-1 RAs	83 (16.9)	92 (18.7)
Thiazolidinediones	25 (5.1)	24 (4.9)
Alpha-glucosidase inhibitors	23 (4.7)	22 (4.5)
Glinides	11 (2.2)	15 (3.0)

*eGFR denotes estimated glomerular filtration rate, DPP-4 dipeptidyl peptidase-4, GLP-1 RA glucagon-like peptide-1 receptor agonist, glargine insulin glargine U100, icodec insulin icodec, and SGLT2 sodium-glucose cotransporter 2.

†Mean±standard deviation.

Table 2. Summary of Efficacy Findings.*

	Icodec (n=492)	Glargine (n=492)	Icodec vs. Glargine (95% CI), P value
Glycated hemoglobin — %			
Observed mean glycated hemoglobin level (baseline)	8.50	8.44	
Estimated mean ±SEM glycated hemoglobin level (week 52)	6.93 ±0.06	7.12 ±0.05	
Estimated mean ±SEM glycated hemoglobin level (week 78)	6.92 ±0.04	7.03 ±0.04	
Estimated mean ±SEM absolute change from baseline to week 52	−1.55 ±0.06	−1.35 ±0.05	ETD: −0.19 (−0.36, −0.03) %-points, $p<0.0001$[†]; P=0.0210[‡]
Estimated mean ±SEM absolute change from baseline to week 78	−1.55 ±0.04	−1.44 ±0.04	ETD: −0.11 (−0.22, 0.00) %-points, P=0.0506[§]
Composite end points — %			
Proportion of participants achieving glycated hemoglobin <7% (week 52)	57.6	45.4	EOR: 1.63 (1.24, 2.14)[¶]
Proportion of participants achieving glycated hemoglobin <7% at (week 78)	56.8	49.1	EOR: 1.37 (1.04, 1.80)[¶]
Proportion of participants achieving glycated hemoglobin <7% without clinically significant (level 2) or severe (level 3) hypoglycemia (week 52)	52.6	42.6	EOR: 1.49 (1.15, 1.94)[¶]
Proportion of participants achieving glycated hemoglobin <7% without clinically significant (level 2) or severe (level 3) hypoglycemia (week 78)	54.5	46.4	EOR: 1.38 (1.06, 1.80)[¶]
Observed mean time in range (70–180 mg/dL [3.9–10.0 mmol/L]) — %			
Weeks 48–52	71.9	66.9	ETD: 4.27 (1.92, 6.62) %-points, P=0.0004[‖]
Weeks 74–78	70.2	64.8	ETD: 4.41 (1.92, 6.90) %-points, P=0.0005[††]
Fasting plasma glucose — mg/dL; mmol/L			
Observed mean (SD) fasting plasma glucose (baseline)	185 (49); 10.3 (2.7)	186 (51.66); 10.31 (2.87)	
Estimated mean ±SEM fasting plasma glucose (week 52)	125 ±1.67; 6.95 ±0.09	125 ±1.68; 6.96 ±0.09	
Estimated mean ±SEM fasting plasma glucose (week 78)	126 ±1.77; 6.97 ±0.10	126 ±1.77; 7.02 ±0.10	
Estimated mean change from baseline to week 52	−60.32; −3.35	−60.08; −3.33	ETD: −0.24 (−4.89, 4.41); −0.01 (−0.27, 0.24)[§]

Estimated mean change from baseline to week 78	−59.83; −3.32	−59.09; −3.28	ETD: −0.74 (−5.66, 4.17); −0.04 (−0.31, 0.23)[§]

*ANCOVA denotes analysis of covariance, ANOVA analysis of variance, CI confidence interval, EOR estimated odds ratio (icodec/glargine U100), ETD estimated treatment difference (icodec – glargine U100), glargine insulin glargine U100, icodec insulin icodec, SD standard deviation, and SEM standard error of the mean.

[†]ANCOVA testing for noninferiority (margin: 0.3%), with region and randomized treatment as fixed factors, and baseline glycated hemoglobin as a covariate.

[‡]ANCOVA testing for superiority, with region and randomized treatment as fixed factors, and baseline glycated hemoglobin as a covariate.

[§]ANCOVA testing, with region and randomized treatment as fixed factors, and baseline glycated hemoglobin as a covariate.

[¶]Logistic regression model testing, with region and randomized treatment as fixed factors, and baseline glycated hemoglobin as a covariate.

[‖]ANOVA testing for superiority, with region and randomized treatment as fixed factors.

[††]ANOVA testing, with region and randomized treatment as fixed factors.

Table 3. Summary of Safety End Points and Adverse Events.*

	Icodec (n=492)	Glargine (n=492)	Icodec vs. Glargine (95% CI), P value
Observed mean time below range (<54 mg/dL) — %			
Week 48–52	0.3	0.2	ETR: 1.27 (0.94, 1.71) %-points, P=0.1134[†]
Week 74–78	0.3	0.2	ETR: 1.20 (0.89, 1.61) %-points, P=0.2346[†]
Observed mean time above range (>180 mg/dL) — %			
Weeks 48–52	26.9	32.3	ETR: −4.58(−6.99, −2.17) %-points[‡]
Weeks 74–78	29.6	34.2	ETR: −4.65 (−7.20, −2.10) %-points[‡]
Estimated mean weekly insulin dosage — U/week (~U/day)			
Weeks 50–52	214 (~31)	222 (~32)	ETR: 0.96 (0.89, 1.05)[‡]
Weeks 76–78	224 (~32)	234 (~33)	ETR: 0.96 (0.87, 1.04)[‡]
Post hoc analysis of estimated mean weekly insulin dosage — U/kg			
Weeks 50–52	2.5	2.6	ETR: 0.95 (0.88, 1.03)[‡]
Weeks 76–78	2.6	2.8	ETR: 0.95 (0.87, 1.03) [‡]
Body weight, kg			
Observed mean (SD) body weight (baseline)	85.17 (17.74)	84.31 (17.63)	
Estimated mean±SEM body weight (week 52)	87.03±0.21	86.57±0.21	
Estimated mean±SEM body weight (week 78)	86.95±0.24	86.31±0.23	
Estimated mean±SEM change from baseline to week 52	2.29±0.2	1.83±0.2	ETD: 0.46 (−0.12, 1.04)[§]
Estimated mean±SEM change from baseline to week 78	2.22±0.2	1.58±0.2	ETD: 0.64 (−0.02, 1.30)[§]

	Icodec (n=492)		Glargine (n=492)	
Overall hypoglycemic episodes observed in the safety analysis set (baseline to week 52)				
	Incidence, no. (%)	**Events (rate[¶])**	**Incidence, no. (%)**	**Events (rate[¶])**
Hypoglycemia alert value (level 1)	232 (47.2)	1447 (2.98)	191 (38.8)	632 (1.30)
Clinically significant (level 2) hypoglycemia[‖]	48 (9.8)	143 (0.29)	49 (10.0)	75 (0.15)
Severe (level 3) hypoglycemia[††]	1 (0.2)	1 (0.002)	3 (0.6)	3 (0.006)
Combined clinically significant (level 2) or severe (level 3) hypoglycemia	48 (9.8)	144 (0.30)	52 (10.6)	78 (0.16)
Overall hypoglycemic episodes observed in the safety analysis set (baseline to week 83)				
	Incidence, no. (%)	**Events (rate[¶])**	**Incidence, no. (%)**	**Events (rate[¶])**
Hypoglycemia alert value (level 1)	278 (56.5)	2308 (3.02)	239 (48.6)	1067 (1.39)
Clinically significant (level 2) hypoglycemia[‖]	61 (12.4)	226 (0.30)	66 (13.4)	144 (0.15)
Severe (level 3) hypoglycemia[††]	1 (0.2)	1 (0.001)	6 (1.2)	7 (0.009)
Combined clinically significant (level 2) or severe (level 3) hypoglycemia	61 (12.4)	227 (0.30)	70 (14.2)	121 (0.16)
Adverse events				
	Icodec (n=492)		**Glargine U100 (n=492)**	

	no. (%)	Events (rate[¶])	no. (%)	Events (rate[¶])
Adverse events (week 78)	397 (80.7)	1882 (245.85)	389 (79.1)	1823 (237.75)
Serious	64 (13.0)	95 (12.41)	71 (14.4)	119 (15.52)
Severity				
Severe	26 (5.3)	38 (4.96)	36 (7.3)	61 (7.96)
Moderate	192 (39.0)	401 (52.38)	183 (37.2)	397 (51.78)
Mild	351 (71.3)	1443 (188.50)	340 (69.1)	1365 (178.02)
Related to basal insulin				
Probable	30 (6.1)	43 (5.62)	33 (6.7)	51 (6.65)
Possible	46 (9.3)	67 (8.75)	39 (7.9)	60 (7.83)
Safety focus area				
Hypersensitivity	33 (6.7)	48 (0.06)	39 (7.9)	61 0.08)
Serious	0		1 (0.2)	1 (0.001)
Injection-site reactions	7 (1.4)	7 (0.01)	12 (2.4)	12 (0.02)
Serious	0		0	
Medication errors, including misuse and abuse	4 (0.8)	4 (0.005)	1 (0.2)	2 (0.003)
Serious	0		0	
Adjudicated events	**Icodec (no.)**		**Glargine (no.)**	
Acute coronary syndrome				
Acute myocardial infarction (STEMI)	4		3	
Acute myocardial infarction (NSTEMI)	4		4	
Hospitalization for unstable angina pectoris	3		0	
Cerebrovascular event				
Ischemic stroke	1		4	
Hemorrhagic stroke	1		0	
Heart failure				
Heart failure hospitalization	2		2	
Fatal events				
Cardiovascular death	1		3	
Non-cardiovascular death	4[‡‡]		1[§§]	

*ANCOVA denotes analysis of covariance, ANOVA analysis of variance, CI confidence interval, ETD estimated treatment difference (icodec – glargine), ETR estimated treatment ratio (icodec/glargine), glargine insulin glargine U100, icodec insulin icodec, no. number of participants with one or more events, NSTEMI non-ST-segment elevation myocardial infarction, PYE patient-years of exposure (1 PYE=365.25 days), SD standard deviation, SEM standard error of the mean, and STEMI ST-segment elevation myocardial infarction.

[†]Negative binomial model testing on the number of recorded measurements below range, with a log-link function and the logarithm of the total number of recorded measurements as an offset. Region and randomized treatment were included as fixed factors.

[‡]ANOVA testing, with region and randomized treatment as fixed factors (log transformation was applied for analyses of mean weekly insulin dose).

[§]ANCOVA testing, with region and randomized treatment as fixed factors, and baseline body weight as a covariate.

[¶]Rate denotes the number of events per PYE.

[‖]Clinically significant (level 2) hypoglycemia: blood glucose <54 mg/dL (<3.0 mmol/L) confirmed by blood glucose meter.

[††]Severe (level 3) hypoglycemia: no specific glucose threshold, but hypoglycemia was associated with severe cognitive impairment requiring external assistance for recovery.

[‡‡] Two deaths related to cancer, one to coronavirus disease during 2019, and one to intestinal obstruction and sepsis.

[§§] Death from an unknown cause: the event was judged to be possibly related to the trial treatment by the investigator.