ORIGINAL ARTICLE

Weekly Icodec versus Daily Glargine U100 in Type 2 Diabetes without Previous Insulin

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ABSTRACT

BACKGROUND

Insulin icodec is an investigational once-weekly basal insulin analogue for diabetes management.

METHODS

We conducted a 78-week randomized, open-label, treat-to-target phase 3a trial (including a 52-week main phase and a 26-week extension phase, plus a 5-week follow-up period) involving adults with type 2 diabetes (glycated hemoglobin level, 7 to 11%) who had not previously received insulin. Participants were randomly assigned in a 1:1 ratio to receive once-weekly insulin icodec or once-daily insulin glargine U100. The primary end point was the change in the glycated hemoglobin level from baseline to week 52; the confirmatory secondary end point was the percentage of time spent in the glycemic range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter) in weeks 48 to 52. Hypoglycemic episodes (from baseline to weeks 52 and 83) were recorded.

RESULTS

Each group included 492 participants. Baseline characteristics were similar in the two groups. The mean reduction in the glycated hemoglobin level at 52 weeks was greater with icodec than with glargine U100 (from 8.50% to 6.93% with icodec [mean change, –1.55 percentage points] and from 8.44% to 7.12% with glargine U100 [mean change, –1.35 percentage points]); the estimated between-group difference (–0.19 percentage points; 95% confidence interval [CI], −0.36 to −0.03) confirmed the noninferiority (P<0.001) and superiority (P=0.02) of icodec. The percentage of time spent in the glycemic range of 70 to 180 mg per deciliter was significantly higher with icodec than with glargine U100 (71.9% vs. 66.9%; estimated between-group difference, 4.27 percentage points [95% CI, 1.92 to 6.62]; P<0.001), which confirmed superiority. Rates of combined clinically significant or severe hypoglycemia were 0.30 events per person-year of exposure with icodec and 0.16 events per person-year of exposure with glargine U100 at week 52 (estimated rate ratio, 1.64; 95% CI, 0.98 to 2.75) and 0.30 and 0.16 events per person-year of exposure, respectively, at week 83 (estimated rate ratio, 1.63; 95% CI, 1.02 to 2.61). No new safety signals were identified, and incidences of adverse events were similar in the two groups.

CONCLUSIONS

Glycemic control was significantly better with once-weekly insulin icodec than with once-daily insulin glargine U100. (Funded by Novo Nordisk; ONWARDS 1 ClinicalTrials.gov number, NCT04460885.)

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

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

Insulin icodec provides basal insulin coverage over a full week after a single subcutaneous injection.[9] A short-term, proof-of-concept, phase 2 trial involving persons with type 2 diabetes who had not previously received insulin compared once-weekly insulin icodec with once-daily insulin glargine U100 and showed similar glycemic control and low rates of hypoglycemia in the two trial groups.[10]

A phase 3a clinical development program, ONWARDS, evaluated the efficacy and safety of once-weekly insulin icodec across diverse populations and comparator treatments, as previously described.[11] Three trials involved participants with type 2 diabetes who had not previously received insulin: ONWARDS 1 (this trial), ONWARDS 3 (a randomized, double-blind 26-week trial with a 5-week follow-up period), and ONWARDS 5 (a 52-week, open-label trial with a 5-week follow-up period and real-world elements). ONWARDS 2 and 4 involved participants who had previously received insulin, and ONWARDS 6 involved participants with type 1 diabetes. The present trial, ONWARDS 1, investigated the efficacy and long-term safety of once-weekly insulin icodec as compared with once-daily insulin glargine U100, both in combination with noninsulin glucose-lowering treatments (including GLP-1 receptor agonists and sodium–glucose cotransporter 2 [SGLT2] inhibitors), in persons with type 2 diabetes who had not previously received insulin.

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, United Kingdom, and United States). The overall trial duration was approximately 85 weeks, comprising a screening period (up to 2 weeks), a 78-week randomized treatment period (including a 52-week main phase and a 26-week extension phase), and a 5-week follow-up period during which trial treatments were discontinued (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[11] The protocol is also available at NEJM.org.

Adults (≥18 years of age) with type 2 diabetes who had not previously received insulin and who had a glycated hemoglobin level of 7 to 11% (53.0 to 96.7 mmol per mole) and a body-mass index (the weight in kilograms divided by the square of the height in meters) of 40 or less at screening were eligible.[11] Full inclusion and exclusion criteria are provided in Table S1.

Trial Treatment

Participants were randomly assigned in a 1:1 ratio to receive once-weekly insulin icodec or once-daily insulin glargine U100 with the use of an interactive Web-response system. Icodec (700 U per milliliter; Novo Nordisk) or glargine U100 (100 U per milliliter; Sanofi-Aventis) were administered subcutaneously with the use of prefilled pen injectors. The starting dose was 70 U per week for icodec and 10 U per day for glargine U100. Because this was a treat-to-target trial, insulin doses were adjusted to enable participants to reach a prebreakfast self-measured blood glucose target of 80 to 130 mg per deciliter (4.4 to 7.2 mmol per liter). Pretrial noninsulin glucose-lowering treatments were continued after randomization, except for sulfonylureas and glinides, which were discontinued. At randomization, each participant received a blood glucose meter (Accu-Chek, Roche Diabetes Care), along with a double-blind continuous glucose-

monitoring device (Dexcom G6, Dexcom) and education on device use. Further details are provided in the Supplementary Appendix.

EFFICACY END POINTS

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

The confirmatory key secondary end point was the percentage of time spent in the target glycemic range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter) in weeks 48 to 52, as measured by blinded continuous glucose monitoring. The supportive secondary efficacy end point was the change in the fasting plasma glucose level from baseline to week 52.

SAFETY END POINTS

Secondary safety end points were the number of hypoglycemic episodes characterized as clinically significant (level 2; glucose level, <54 mg per deciliter [<3.0 mmol per liter]), severe (level 3), or combined clinically significant or severe from baseline to week 52 (classifications are described in the Supplementary Appendix); the time spent with glucose levels of less than 54 mg per deciliter or more than 180 mg per deciliter in weeks 48 to 52; the mean weekly insulin dose in weeks 50 to 52; and the 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, and combined clinically significant or severe hypoglycemic episodes (baseline to week 83).

ADDITIONAL ASSESSMENTS

Additional prespecified exploratory assessments included the percentage of participants with a glycated hemoglobin level below 7% and the percentage of participants with a glycated hemoglobin level below 7% without clinically significant or severe hypoglycemia in the preceding 12 weeks (both at weeks 52 and 78); the change in the glycated hemoglobin level, the fasting plasma glucose level, and body weight from baseline to week 78; the percentages of time spent in the target glycemic range, with glucose levels of less than 54 mg per deciliter, and with glucose levels of more than 180 mg per deciliter in weeks 74 to 78; and the mean weekly insulin dose in weeks 76 to 78. A post hoc analysis assessed insulin doses according to body weight (U per kilogram) at weeks 50 to 52 and 76 to 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 death from any cause.

TRIAL OVERSIGHT

Before the start of the trial, 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 the participants provided written informed consent. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation.

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 who was funded by Novo Nordisk provided medical writing assistance under the direction of the authors.

STATISTICAL ANALYSIS

A detailed description of the statistical analyses has been published[11]; these are briefly summarized here, with further details provided in the Supplementary Appendix. The primary hypothesis was that icodec is noninferior to glargine U100 with respect to the change in the glycated hemo-

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Icodec (N=492)	Glargine U100 (N=492)
Male sex — no. (%)	295 (60.0)	263 (53.5)
Age — yr	59.1±10.1	58.9±9.9
Body weight — kg	85.2±17.7	84.3±17.6
Body-mass index	30.0±4.8	30.1±5.1
Diabetes duration — yr	11.6±6.7	11.5±6.8
Glycated hemoglobin level — %	8.5±1.0	8.4±1.0
Fasting plasma glucose level — mg/dl	185.3±49.0	185.7±51.7
Estimated GFR — ml/min/1.73 m^2	86.1±18.2	84.9±19.6
Noninsulin 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 receptor agonists	83 (16.9)	92 (18.7)
Thiazolidinediones	25 (5.1)	24 (4.9)
α-Glucosidase inhibitors	23 (4.7)	22 (4.5)
Glinides	11 (2.2)	15 (3.0)

* Plus–minus values are means ±SD. Participants in the trial received either once-weekly insulin icodec or once-daily insulin glargine U100. To convert values for glycated hemoglobin to millimoles per mole, multiply by 10.93 and then subtract 23.50. To convert values for glucose to millimoles per liter, multiply by 0.05551. DPP-4 denotes dipeptidyl peptidase 4, GFR glomerular filtration rate, GLP-1 glucagon-like peptide-1, and SGLT2 sodium–glucose cotransporter 2.

globin level from baseline to week 52 (prespecified noninferiority margin, 0.3 percentage points). If noninferiority was confirmed, hierarchical confirmatory testing assessed the superiority of icodec to glargine U100 with respect to the time spent in the target glycemic range and then with respect to the change in the glycated hemoglobin level from baseline to week 52.

The sample size was chosen to fulfill the 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. Under the assumption that there would be no between-group difference in the change in the glycated hemoglobin level among participants who completed treatment without an intercurrent event and a difference of 0.3 percentage points in favor of the comparator among participants having an intercurrent event, which would lead to a mean between-group difference of 0.03 percentage points in favor of the comparator, we calculated that 970 participants would provide the trial with 99% power to declare noninferiority.

The full analysis set included all randomly assigned participants; the safety analysis set included all randomly assigned participants who received at least one treatment dose. Efficacy end points were analyzed with the use of the full analysis set and data from the "in-trial" period (i.e., from randomization to last contact, withdrawal, or death). Safety end points were assessed with the use of the safety analysis set (descriptive statistics) and the full analysis set (statistical analyses, unless otherwise specified) during the "main on-treatment" period (52-week main phase) or "on-treatment" period (complete trial, to week 83). Details of the statistical analyses and trial periods are provided in the Supplementary Appendix, including Table S2.

RESULTS

PARTICIPANTS

Of 1192 persons screened between November 25, 2020, and December 1, 2022, a total of 176 (14.8%) had screening failure and 32 withdrew before randomization; 492 were randomly assigned to each trial group (Fig. S2). All 984 participants received at least one dose of trial treatment, and 954 (97.0%) completed the week 52 visit without discontinuing treatment (475 [96.5%] in the icodec group and 479 [97.4%] in the glargine U100 group); 953 participants (96.8%) completed the week 78 visit (476 [96.7%] in the icodec group and 477 [97.0%] in the glargine U100 group), of whom 466 (94.7%) receiving icodec and 472 (95.9%) receiving glargine U100 did so without permanent treatment discontinuation. The two trial groups were broadly similar with respect to baseline characteristics, including clinical variables and race and ethnic group: 67.4% of the participants in the icodec group and 64.4% of those in the glargine U100 group were White; 26.2% and 29.5%, respectively, were Asian; 2.0% and 3.5%, respectively, were Black; and 10.8% in each group were Hispanic or Latino. However, the percentage of

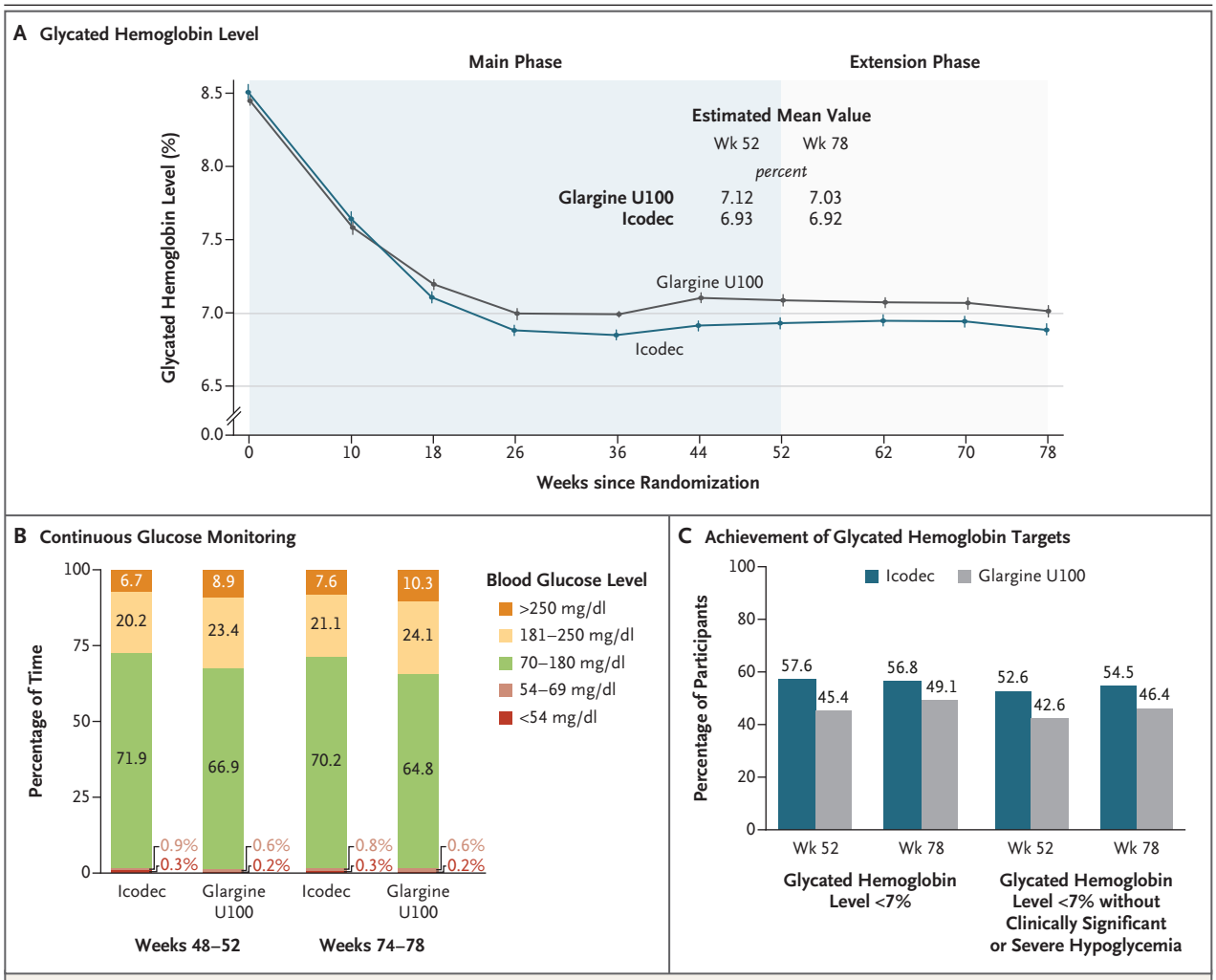

Figure 1. Key End Points.

Panel A shows mean glycated hemoglobin levels from baseline to week 78 among participants who received either once-weekly insulin icodec or once-daily insulin glargine U100. Estimated mean values at weeks 52 and 78 were derived on the basis of multiple imputation. To convert values for glycated hemoglobin to millimoles per mole, multiply by 10.93 and then subtract 23.50. Error bars indicate standard errors. Panel B shows the percentage of time spent at various glucose levels in weeks 48 to 52 and in weeks 74 to 78 as measured by continuous glucose monitoring. The target glycemic range was 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter). To convert values for glucose to millimoles per liter, multiply by 0.05551. Panel C shows the estimated percentage of participants who reached a glycated hemoglobin level below 7% and the percentage who reached a glycated hemoglobin level below 7% without clinically significant or severe hypoglycemia in the preceding 12 weeks. Clinically significant hypoglycemia (level 2) is defined as a blood glucose level of less than 54 mg per deciliter (<3.0 mmol per liter), confirmed with a blood glucose meter. Severe hypoglycemia (level 3) is defined as hypoglycemia with severe cognitive impairment requiring external assistance for recovery.

participants who were men was higher in the icodec group than in the glargine U100 group (Table 1).

EFFICACY END POINTS

At baseline, the observed mean glycated hemoglobin level was 8.50% in the icodec group and 8.44% in the glargine U100 group; at week 52, the estimated mean glycated hemoglobin level was 6.93% and 7.12%, respectively. The estimated mean change in the glycated hemoglobin level from baseline to week 52 was –1.55 percentage points with icodec and –1.35 percentage points with glargine U100, with an estimated

Table 2. Summary of Efficacy Findings.*

Variable	Icodec (N=492)	Glargine U100 (N=492)	Difference or Odds Ratio (95% CI)	P Value
Glycated hemoglobin level — %				
Observed mean level at baseline	8.50	8.44		
Estimated mean level				
At wk 52	6.93±0.06	7.12±0.05		
At wk 78	6.92±0.04	7.03±0.04		
Estimated mean absolute change from baseline				
To wk 52	−1.55±0.06	−1.35±0.05	−0.19 (−0.36 to −0.03)†	<0.001‡; 0.02§
To wk 78	−1.55±0.04	−1.44±0.04	−0.11 (−0.22 to 0.00)†	0.05¶
Composite end points				
Glycated hemoglobin level <7% — % of participants				
At wk 52	57.6	45.4	1.63 (1.24 to 2.14)‖	
At wk 78	56.8	49.1	1.37 (1.04 to 1.80)‖	
Glycated hemoglobin level <7% without clinically significant or severe hypoglycemia — % of participants				
At wk 52	52.6	42.6	1.49 (1.15 to 1.94)‖	
At wk 78	54.5	46.4	1.38 (1.06 to 1.80)‖	
Observed mean time in target glycemic range of 70–180 mg/dl — %				
Wk 48–52	71.9	66.9	4.27 (1.92 to 6.62)†	<0.001**
Wk 74–78	70.2	64.8	4.41 (1.92 to 6.90)†	<0.001††
Fasting plasma glucose level — mg/dl				
Observed mean level at baseline	185.31±48.96	185.71±51.66		
Estimated mean level				
At wk 52	125.19±1.67	125.43±1.68		
At wk 78	125.68±1.77	126.42±1.77		
Estimated mean change from baseline				
To wk 52	−60.32	−60.08	−0.24 (−4.89 to 4.41)†¶	
To wk 78	−59.83	−59.09	−0.74 (−5.66 to 4.17)†¶	

* Plus–minus values are means ±SE, except values for observed mean fasting plasma glucose level at baseline, which are expressed as means ±SD. To convert values for glycated hemoglobin to millimoles per mole, multiply by 10.93 and then subtract 23.50. To convert values for glucose to millimoles per liter, multiply by 0.05551.

† Value is the estimated difference between the groups (icodec minus glargine U100). Differences are in percentage points except for estimated mean change from baseline in fasting plasma glucose level.

‡ Analysis-of-covariance testing for noninferiority (margin, 0.3 percentage points) was performed, with geographic region and randomly assigned treatment as fixed factors and baseline glycated hemoglobin level as a covariate.

§ Analysis-of-covariance testing for superiority was performed, with geographic region and randomly assigned treatment as fixed factors and baseline glycated hemoglobin level as a covariate.

¶ Analysis-of-covariance testing was performed, with geographic region and randomly assigned treatment as fixed factors and baseline glycated hemoglobin level as a covariate.

‖ Value is the estimated odds ratio (icodec:glargine U100). These end points were analyzed with a logistic-regression model, with geographic region and randomly assigned treatment as fixed factors and baseline glycated hemoglobin level as a covariate.

** Analysis-of-variance testing for superiority was performed, with geographic region and randomly assigned treatment as fixed factors.

†† Analysis-of-variance testing was performed, with geographic region and randomly assigned treatment as fixed factors.

treatment difference of −0.19 percentage points (95% confidence interval [CI], −0.36 to −0.03) (Fig. 1A and Table 2), which confirmed the noninferiority (P<0.001) and superiority (P=0.02) of icodec. At the end of the extension phase (week 78), the reduction in glycated hemoglobin level with icodec was sustained (estimated treatment difference, −0.11 percentage points; 95% CI, −0.22 to 0.00).

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

At week 52, higher percentages of participants receiving icodec than those receiving glargine U100 reached a glycated hemoglobin level below 7% (estimated percentage, 57.6% vs. 45.4%) and a glycated hemoglobin level below 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).

The estimated mean change in the fasting plasma glucose level (baseline to week 52) was similar in the two trial groups (−60.32 mg per deciliter [−3.35 mmol per liter] in the icodec group and −60.08 mg per deciliter [−3.33 mmol per liter] in the glargine U100 group; estimated treatment difference, −0.24 mg per deciliter [95% CI, −4.89 to 4.41], or −0.01 mmol per liter [95% CI, −0.27 to 0.24]) (Table 2). Findings were similar at week 78.

SAFETY END POINTS

No significant difference was detected in the percentage of time spent with glucose levels of less than 54 mg per deciliter at weeks 48 to 52 with icodec or glargine U100 (estimated treatment ratio, 1.27; 95% CI, 0.94 to 1.71) (Table 3). The percentage of time spent with glucose levels of more than 180 mg per deciliter was lower with icodec than with glargine U100 (estimated treatment difference, −4.58 percentage points; 95% CI, −6.99 to −2.17), which translated to approximately 1 hour and 6 minutes less time spent with glucose levels above the target glycemic range per day. Similar findings were observed for weeks 74 to 78.

The estimated mean weekly insulin dose was 214 U per week (approximately 31 U per day) in the icodec group and 222 U per week (approximately 32 U per day) in the glargine U100 group in weeks 50 to 52 (Table 3 and Fig. S3). The estimated dose was 224 U per week (approximately 32 U per day) and 234 U per week (approximately 33 U per day), respectively, in weeks 76 to 78.

There was no evidence of a substantial difference in the estimated mean change in body weight from baseline to week 52: 2.29 kg with icodec and 1.83 kg with glargine U100 (estimated treatment difference, 0.46 kg; 95% CI, −0.12 to 1.04) (Table 3). Similar changes were observed at week 78.

From baseline to week 83, a total of 226 clinically significant hypoglycemic events occurred in 61 participants (12.4%) receiving icodec, as compared with 114 events in 66 participants (13.4%) receiving glargine U100 (Table 3). One episode of severe hypoglycemia occurred with icodec, and 7 episodes occurred with glargine U100. Incidences of hypoglycemic events were similar in the two groups at week 52 and week 83. Over the trial duration, 3 participants (0.6%) receiving icodec had 105 of the 226 clinically significant hypoglycemic events (Table S3). Hypoglycemia rates in both trial groups were below one hypoglycemic event per person-year of exposure at trial completion. From baseline to week 52, rates of clinically significant hypoglycemia were 0.29 events per person-year of exposure for icodec and 0.15 events per person-year of exposure for glargine U100 (estimated rate ratio, 1.67; 95% CI, 0.99 to 2.84), and rates of combined clinically significant or severe hypoglycemia were 0.30 and 0.16 events per person-year of exposure, respectively (estimated rate ratio, 1.64; 95% CI, 0.98 to 2.75). At week 83, the rates of clinically significant hypoglycemia remained below one event per person-year of exposure for both icodec and glargine U100 (0.30

Table 3. Summary of Safety End Points.*

Variable	Icodec (N = 492)	Glargine U100 (N = 492)	Ratio or Difference (95% CI)
Observed mean time with glucose levels <54 mg/dl — %			
Wk 48–52	0.3	0.2	1.27 (0.94 to 1.71)†‡
Wk 74–78	0.3	0.2	1.20 (0.89 to 1.61)†‡
Observed mean time with glucose levels >180 mg/dl — %			
Wk 48–52	26.9	32.3	−4.58 (−6.99 to −2.17)§
Wk 74–78	29.6	34.2	−4.65 (−7.20 to −2.10)§
Estimated mean weekly insulin dose — U/wk (~U/day)			
Wk 50–52	214 (~31)	222 (~32)	0.96 (0.89 to 1.05)†¶
Wk 76–78	224 (~32)	234 (~33)	0.96 (0.87 to 1.04)†¶
Post hoc analysis of estimated mean weekly insulin dose — U/kg			
Wk 50–52	2.5	2.6	0.95 (0.88 to 1.03)†¶
Wk 76–78	2.6	2.8	0.95 (0.87 to 1.03)† ¶
Body weight — kg			
Observed mean weight at baseline	85.17±17.74	84.31±17.63	
Estimated mean weight			
At wk 52	87.03±0.21	86.57±0.21	
At wk 78	86.95±0.24	86.31±0.23	
Estimated mean change from baseline			
To wk 52	2.29±0.21	1.83±0.21	0.46 (−0.12 to 1.04)§‖
To wk 78	2.22±0.24	1.58±0.23	0.64 (−0.02 to 1.30)§‖
Overall hypoglycemic episodes, safety analysis, baseline to wk 52 — no. of participants (%) [events data]			
Hypoglycemia alert value**	232 (47.2) [1447 events; 2.98/PYE]	191 (38.8) [632 events; 1.30/PYE]	
Clinically significant hypoglycemia††	48 (9.8) [143 events; 0.29/PYE]	49 (10.0) [75 events; 0.15/PYE]	
Severe hypoglycemia‡‡	1 (0.2) [1 event; <0.01/PYE]	3 (0.6) [3 events; 0.01/PYE]	
Combined clinically significant or severe hypoglycemia	48 (9.8) [144 events; 0.30/PYE]	52 (10.6) [78 events; 0.16/PYE]	
Overall hypoglycemic episodes, safety analysis, baseline to wk 83 — no. of participants (%) [events data]			
Hypoglycemia alert**	278 (56.5) [2308 events; 3.02/PYE]	239 (48.6) [1067 events; 1.39/PYE]	
Clinically significant hypoglycemia††	61 (12.4) [226 events; 0.30/PYE]	66 (13.4) [114 events; 0.15/PYE]	

Severe hypoglycemia‡‡‡	1 (0.2) [1 event; <0.01/PYE]	6 (1.2) [7 events; 0.01/PYE]
Combined clinically significant or severe hypoglycemia	61 (12.4) [227 events; 0.30/PYE]	70 (14.2) [121 events; 0.16/PYE]

* Plus–minus values are means ±SE, except values for observed mean weight at baseline, which are expressed as means ±SD. One person-year of exposure (PYE) is equal to 365.25 days. To convert values for glucose to millimoles per liter, multiply by 0.05551.
† Value is the estimated ratio (icodec:glargine U100).
‡ P=0.11 for weeks 48 to 52 and P=0.23 for weeks 74 to 78. A negative binomial model was used to analyze 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. Geographic region and randomly assigned treatment were included as fixed factors.
§ Value is the estimated difference between the groups (icodec minus glargine U100). For observed mean time with glucose level above 180 mg per deciliter, the difference is in percentage points.
¶ Analysis-of-variance testing was conducted, with geographic region and randomly assigned treatment as fixed factors (log transformation was applied for analyses of mean weekly insulin dose).
‖ Analysis-of-covariance testing was conducted, with geographic region and randomly assigned treatment as fixed factors and baseline body weight as a covariate.
** The hypoglycemia alert level (level 1) is defined as a blood glucose level of less than 70 mg per deciliter (<3.9 mmol per liter) or greater than or equal to 54 mg per deciliter (≥3.0 mmol per liter), confirmed with a blood glucose meter.
†† Clinically significant hypoglycemia (level 2) is defined as a blood glucose level of less than 54 mg per deciliter (<3.0 mmol per liter), confirmed with a blood glucose meter.
‡‡ Severe hypoglycemia (level 3) is defined as hypoglycemia with severe cognitive impairment requiring external assistance for recovery.

vs. 0.15 events per person-year of exposure; estimated rate ratio, 1.71 [95% CI, 1.06 and 2.76]), as did the rates of combined clinically significant or severe hypoglycemia (0.30 vs. 0.16 events per person-year of exposure; estimated rate ratio, 1.63 [95% CI, 1.02 to 2.61]) (Fig. S4).

ADVERSE EVENTS

From baseline to week 83, a total of 1882 adverse events occurred in 397 participants receiving icodec and 1823 events occurred in 389 participants receiving glargine U100 (Table 4). Most events were nonserious, mild or moderate in severity, and were assessed by the investigator as being unlikely to be related to trial treatment. A total of 95 serious adverse events occurred in 64 participants receiving icodec, as compared with 119 events in 71 participants receiving glargine U100. All serious adverse events in the icodec group were considered unlikely to be related to trial treatment. Adverse events according to system organ class are shown in Fig. S5. During treatment, five deaths occurred in the icodec group and four deaths occurred in the glargine U100 group (Table 4).

DISCUSSION

ONWARDS 1, the longest trial in the ONWARDS development program for insulin icodec, showed that this weekly insulin regimen facilitated the initiation of basal insulin treatment and improved glycemic control and potentially treatment adherence through reducing the insulin injection burden for persons with type 2 diabetes who had not previously received insulin. The noninferiority and statistical superiority of once-weekly icodec to once-daily glargine U100 with respect to the change in the glycated hemoglobin level from baseline to week 52 (primary end point) was confirmed.

This reduction in the glycated hemoglobin level with icodec was maintained to week 78. A slight further reduction in the glycated hemoglobin level with glargine U100 led to the nonsignificance of the between-group difference at week 78. However, participants receiving icodec spent significantly more time in the target glycemic range than those receiving glargine U100 in weeks 48 to 52 (additional 1 hour and 1 minute per day) and weeks 74 to 78 (additional 1 hour and 4 minutes per day). The International Con-

Table 4. Summary of Adverse Events.*

Variable	Icodec (N=492)	Glargine U100 (N=492)
Overall events at wk 78 — no. of participants (%) [events data]		
Any	397 (80.7) [1882 events; 2.46/PYE]	389 (79.1) [1823 events; 2.38/PYE]
Serious	64 (13.0) [95 events; 0.12/PYE]	71 (14.4) [119 events; 0.16/PYE]
Severity — no. of participants (%) [events data]		
Severe	26 (5.3) [38 events; 0.05/PYE]	36 (7.3) [61 events; 0.08/PYE]
Moderate	192 (39.0) [401 events; 0.52/PYE]	183 (37.2) [397 events; 0.52/PYE]
Mild	351 (71.3) [1443 events; 1.88/PYE]	340 (69.1) [1365 events; 1.78/PYE]
Related to basal insulin — no. of participants (%) [events data]		
Probable	30 (6.1) [43 events; 0.06/PYE]	33 (6.7) [51 events; 0.07/PYE]
Possible	46 (9.3) [67 events; 0.09/PYE]	39 (7.9) [60 events; 0.08/PYE]
Safety focus area — no. of participants (%) [events data]		
Hypersensitivity		
Any	33 (6.7) [48 events; 0.06/PYE]	39 (7.9) [61 events; 0.08/PYE]
Serious	0	1 (0.2) [1 event; <0.01/PYE]
Injection-site reactions		
Any	7 (1.4) [7 events; 0.01/PYE]	12 (2.4) [12 events; 0.02/PYE]
Serious	0	0
Medication errors, including misuse and abuse		
Any	4 (0.8) [4 events; <0.01/PYE]	1 (0.2) [2 events; <0.01/PYE])
Serious	0	0
Adjudicated events — no. of participants		
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: hospitalization for heart failure	2	2
Fatal events		
Death from cardiovascular causes	1	3
Death from noncardiovascular causes	4†	1‡

* One person-year of exposure (PYE) is equal to 365.25 days. NSTEMI denotes non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.
† Two deaths were related to cancer, one to coronavirus disease 2019, and one to intestinal obstruction and sepsis.
‡ One death from an unknown cause was judged to be possibly related to the trial treatment by the investigator.

sensus on Time in Range recommends that more than 70% of continuous glucose monitoring measurements fall within the target glycemic range.[12] This was achieved on average in both trial phases with icodec, but not with glargine U100. Despite higher hypoglycemia rates in the icodec group (0.29 events with icodec vs. 0.15 events with glargine U100 per person-year of

exposure), there was no evidence of a substantial difference between the trial groups in the time spent with glucose levels of less than 54 mg per deciliter, which generally remained below the internationally recommended target (<1%) in both groups during both trial phases.[12-14]

Fasting plasma glucose levels were similar in the two groups; this finding was observed consistently across other ONWARDS trials.[15,16] Fasting glucose measurements alone may not reflect the consistent glucose-lowering profile throughout the day with once-weekly icodec as compared with once-daily treatments; the greater amount of time spent in the target 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 slightly more in the icodec group than in the glargine U100 group, overall rates of these hypoglycemic episodes remained below one event per person-year of exposure throughout the trial, which is similar to rates reported previously in other trials of daily basal insulin analogues involving persons with type 2 diabetes who had not previously received insulin, despite the caveat of differing trial designs.[17-19] Furthermore, the incidence of clinically significant episodes was similar in the icodec group (12.4%) and the glargine U100 group (13.4%) throughout the trial. Of note, the rate of clinically significant hypoglycemia in the icodec group may have been influenced by 3 of 492 participants (0.6%) having 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 reached a glycated hemoglobin level below 7% without clinically significant or severe hypoglycemia in the preceding 12 weeks. Only 1 episode of severe hypoglycemia occurred with icodec and 7 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 because we 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 (ClinicalTrials.gov number, NCT04795531) used a double-blind, double-dummy design to compare icodec with degludec in persons with type 2 diabetes who had not previously received insulin and to confirm the phase 2 study findings.[11] Continuous glucose monitoring (performed during specific periods within the present trial) would have been more informative if maintained throughout the trial. Although the blinding of glucose measurements was a strength for the assessment of glucose metrics, this prevented their use for insulin dose adjustments, which could have further reduced the occurrence of hypoglycemic events. Glargine U100 was selected as the comparator in the present trial because it is the most commonly used once-daily basal insulin; the efficacy and safety of icodec as compared with second-generation basal insulin analogues have been assessed in ONWARDS 2[16] and 3 (vs. degludec), whereas ONWARDS 5 (NCT04760626) has compared icodec with a range of basal insulin analogues (including glargine U300 and degludec).[11]

Our trial has several strengths, particularly the long duration of the randomized treatment period and safety follow-up. Furthermore, the large, multinational cohort consisted of diverse participants representative of persons with type 2 diabetes for whom insulin treatment is warranted despite the availability of newer noninsulin glucose-lowering treatments, except for the low proportions of Black and Latino participants (Table S4). Participants could continue most background noninsulin glucose-lowering treatments, and blinded continuous glucose monitoring data allowed for more detailed assessments of glycemic and safety variables.

Taken together, the findings of the current trial highlight the totality of evidence for glycemic control with icodec. Among persons with long-standing diabetes taking noninsulin glucose-lowering agents including GLP-1 receptor agonists and SGLT-2 inhibitors, those who received icodec were more likely to reach a glycated hemoglobin level below 7% than those who received glargine U100, and they spent more time in the target glycemic range and were more likely to reach a glycated hemoglobin level below 7% without clinically significant or severe hypoglycemia. In this phase 3a trial, we found that once-weekly insulin icodec offered better glycemic control than once-daily insulin glargine U100 in persons with type 2 diabetes who had not previously received insulin.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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