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Once-Weekly Insulin for Type 2 Diabetes without Previous Insulin Treatment

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ABSTRACT

BACKGROUND

It is thought that a reduction in the frequency of basal insulin injections might facilitate treatment acceptance and adherence among patients with type 2 diabetes. Insulin icodec is a basal insulin analogue designed for once-weekly administration that is in development for the treatment of diabetes.

METHODS

We conducted a 26-week, randomized, double-blind, double-dummy, phase 2 trial to investigate the efficacy and safety of once-weekly insulin icodec as compared with once-daily insulin glargine U100 in patients who had not previously received long-term insulin treatment and whose type 2 diabetes was inadequately controlled (glycated hemoglobin level, 7.0 to 9.5%) while taking metformin with or without a dipeptidyl peptidase 4 inhibitor. The primary end point was the change in glycated hemoglobin level from baseline to week 26. Safety end points, including episodes of hypoglycemia and insulin-related adverse events, were also evaluated.

RESULTS

A total of 247 participants were randomly assigned (1:1) to receive icodec or glargine. Baseline characteristics were similar in the two groups; the mean baseline glycated hemoglobin level was 8.09% in the icodec group and 7.96% in the glargine group. The estimated mean change from baseline in the glycated hemoglobin level was -1.33 percentage points in the icodec group and -1.15 percentage points in the glargine group, to estimated means of 6.69% and 6.87%, respectively, at week 26; the estimated between-group difference in the change from baseline was -0.18 percentage points (95% CI, -0.38 to 0.02 , $P=0.08$). The observed rates of hypoglycemia with severity of level 2 (blood glucose level, <54 mg per deciliter) or level 3 (severe cognitive impairment) were low (icodec group, 0.53 events per patient-year; glargine group, 0.46 events per patient-year; estimated rate ratio, 1.09; 95% CI, 0.45 to 2.65). There was no between-group difference in insulin-related key adverse events, and rates of hypersensitivity and injection-site reactions were low. Most adverse events were mild, and no serious events were deemed to be related to the trial medications.

CONCLUSIONS

Once-weekly treatment with insulin icodec had glucose-lowering efficacy and a safety profile similar to those of once-daily insulin glargine U100 in patients with type 2 diabetes. (Funded by Novo Nordisk; NN1436-4383 ClinicalTrials.gov number, NCT03751657.)

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*A list of principal investigators in this trial is available in the Supplementary Appendix, available at NEJM.org.

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E VOLVING GUIDELINES FOR STANDARDS of care from the American Diabetes Association and the European Association for the Study of Diabetes recommend treatment escalation when individualized glycemic targets are not reached in patients with type 2 diabetes.^{1,2} Despite these recommendations, clinical inertia is highly prevalent in the management of type 2 diabetes, with the longest delays reported for insulin initiation (median time from initiation of treatment with one or more oral antidiabetic drugs to initiation of insulin treatment, 1.2 to 4.9 years).^{3,4} Previous data have indicated that patients with type 2 diabetes would generally prefer fewer injections and greater flexibility than is typical of the current once-daily treatment options.⁵ Therefore, reducing the number of injections could potentially increase acceptance of and adherence to insulin treatment among patients with type 2 diabetes,⁶ thereby potentially improving glycemic control.

Insulin icodec (proposed international non-proprietary name) is a basal insulin analogue administered once weekly that is in development for the treatment of patients with diabetes. With a time to maximum concentration of 16 hours and a half-life of approximately 1 week, insulin icodec has a pharmacokinetic and pharmacodynamic profile suitable for once-weekly injection.⁷ Here, we report the findings of a phase 2 clinical trial designed to investigate the efficacy and safety of once-weekly insulin icodec as compared with once-daily insulin glargine U100 in patients who had not received insulin previously and whose type 2 diabetes was inadequately controlled while taking metformin with or without a dipeptidyl peptidase 4 inhibitor.

METHODS

TRIAL DESIGN

We conducted a 26-week, randomized, double-blind, double-dummy, treat-to-target, active-controlled, parallel-group, multinational phase 2 trial. Patients were randomly assigned in a 1:1 ratio to receive either once-weekly subcutaneous icodec plus once-daily placebo or once-daily subcutaneous glargine plus once-weekly placebo; randomization was stratified according to dipeptidyl peptidase 4 inhibitor use (Fig. S1 in the Supplementary Appendix, available with the full text of

this article at NEJM.org). The trial included a 2-week screening period, a 26-week treatment period, and a 5-week follow-up period. The treatment exposure period was defined as the period from the date of first dose of icodec or glargine until the last follow-up visit or the day of the last dose of icodec or glargine plus 5 weeks (for glargine) or 6 weeks (for icodec), whichever came first. The treatment exposure period without ancillary treatment was defined as the period from the date of first dose of icodec or glargine until the initiation of ancillary treatment (defined as any diabetes medication other than the trial drugs, metformin, or a dipeptidyl peptidase 4 inhibitor), an increase in metformin or dipeptidyl peptidase 4 inhibitor doses, or the end date of the treatment exposure period if no ancillary treatment was initiated.

Patients who were 18 to 75 years of age and who had not previously received long-term insulin treatment, who had received a diagnosis of type 2 diabetes at least 180 days before screening, who were receiving stable daily doses of metformin with or without dipeptidyl peptidase 4 inhibitor, and who had a glycated hemoglobin level of 7.0 to 9.5% were eligible for enrollment. Previous short-term insulin treatment (maximum of 14 days) or previous insulin treatment for gestational diabetes were allowed. The inclusion and exclusion criteria are summarized in Table S1.

TREATMENT

The starting dose of icodec was 70 U once per week, and the starting dose of glargine was 10 U once per day. After randomization, insulin doses were adjusted weekly to achieve a pre-breakfast patient-measured blood glucose target of 70 to 108 mg per deciliter (3.9 to 6.0 mmol per liter). The adjustment algorithm, which was based on the three preceding patient-measured blood glucose levels, is summarized in Table S2. Once-weekly injections were performed with a pen injector, and once-daily injections were performed with a vial and syringe.

EFFICACY END POINTS

The primary end point was the change in the glycated hemoglobin level from baseline to week 26, with the primary “estimand” (a precisely defined estimated measure of treatment effect) being the trial-product estimand, defined as the

between-group difference in the change in glycated hemoglobin level from baseline to week 26 among all patients who underwent randomization, had all patients continued to receive the trial product without receiving ancillary therapies. A more detailed explanation of the rationale for estimands and of the estimands used in this trial is provided in the Supplementary Appendix. Key secondary end points included the changes in fasting plasma glucose level, body weight, and the mean of the 9-point patient-measured blood glucose profile from baseline to week 26 and the mean weekly insulin dose during the last 2 weeks of treatment. In addition, the time spent with the blood glucose level in the tight glycemic range of 70 to 140 mg per deciliter (3.9 to 7.8 mmol per liter), monitored by flash glucose monitoring (FreeStyle Libre Pro) during the last 2 weeks of treatment, was a prespecified exploratory end point. Both the investigators and the patients were unaware of the flash glucose monitoring results. Only patients with at least 70% flash glucose monitoring coverage over 13 days were included in the analysis.

SAFETY END POINTS

Key safety end points included the number of adverse events during the treatment exposure period from baseline to week 31 (end of the 5-week follow-up period), including serious adverse events, the number of overall and nocturnal hypoglycemic alert events (level 1; blood glucose level, ≥ 54 and < 70 mg per deciliter [≥ 3.0 and < 3.9 mmol per liter], confirmed by blood glucose meter), the number of hypoglycemic events that were either clinically significant (level 2; < 54 mg per deciliter [< 3.0 mmol per liter], confirmed by blood glucose meter) or severe (level 3; severe cognitive impairment requiring external assistance for recovery), and the number of severe hypoglycemic events only. Whenever a hypoglycemic event was suspected, patient-measured blood glucose levels were obtained to provide confirmation. In addition, all hypoglycemic events confirmed during patient-measured blood glucose monitoring were recorded, even if the patient was asymptomatic. Reported major adverse cardiovascular events, hypersensitivity, and injection-site reactions were adjudicated by an independent, external committee, the members of which were unaware of the treatment-group assignments.

TRIAL OVERSIGHT

The trial was conducted in compliance with the principles of the Declaration of Helsinki and in accordance with Good Clinical Practice guidelines of the International Conference for Harmonisation. The protocol, which is available at NEJM.org, was reviewed and approved by the appropriate institutional review boards and independent ethics committees. All patients provided written informed consent before trial entry.

A combination of academic authors and authors who are employees of the sponsor participated in developing the trial concept and design and in collecting the data. All the authors were involved in the analysis and interpretation of data and participated in preparing the manuscript that was submitted, with the support of a medical writing agency (paid for by Novo Nordisk). The first, fifth, sixth, and seventh authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All the authors read and approved the submitted version of the manuscript.

STATISTICAL ANALYSIS

All presented analyses, with the exception of the incidence of hypoglycemia, were prespecified. The sample size was determined such that the width of the two-sided 95% confidence interval for the between-group difference, under an assumption of normally distributed data for the change in glycated hemoglobin level from baseline to 26 weeks, was 0.5 percentage points. The standard deviation for the glycated hemoglobin level was expected to be 1.0% for all treatment groups on the basis of previous observations with glargine. A total of 246 patients, with 123 in each treatment group, would meet this requirement. The trial was not powered to detect significant differences between the treatments in any of the end points, and no adjustment for multiplicity was applied.

All efficacy end points were summarized and analyzed with the trial-product estimand period (treatment exposure period without ancillary treatment) and the full analysis set, defined as all patients who underwent randomization (Table S3). Safety end points were summarized with the use of the treatment exposure period and the safety analysis set, defined as all patients who received at least one dose of trial medication,

and were analyzed with the use of the full analysis set.

The change from baseline in glycated hemoglobin level after 26 weeks was analyzed with a linear mixed model for repeated measures with an unstructured covariance matrix. The model included the use of a dipeptidyl peptidase 4 inhibitor (yes or no), geographic region, assigned treatment, and visit as fixed factors and baseline glycated hemoglobin level as covariate. Interactions between visit and all factors and covariates were also included in the model. Missing data were imputed with a mixed model for repeated measures to reflect the primary estimand. The estimated mean treatment difference and the confidence interval are provided together with the corresponding two-sided P value. In the following, this mixed model for repeated measures will be referred to as the “standard” mixed model for repeated measures. The binary response end points, defined as whether a patient had had a hypoglycemic event or met a specific glycated hemoglobin target (<7% or ≤6.5%) at 26 weeks, were analyzed with a logistic-regression model with the same factors and covariates (with the exception of visit) after imputing missing glycated hemoglobin measurements with the use of a mixed model for repeated measures.

Changes from baseline in fasting plasma glucose level, body weight, and the mean of the 9-point patient-measured blood glucose profiles were analyzed with the standard mixed model for repeated measures, with relevant baseline values as the covariates. A linear mixed-effects model was fitted to the 9-point patient-measured blood glucose profile data at week 26. The model included treatment, geographic region, use of a dipeptidyl peptidase 4 inhibitor, time, interaction between treatment and time, interaction between geographic region and time, and interaction between use of dipeptidyl peptidase 4 inhibitor and time as fixed factors and patient as a random effect. The time spent in the tight glycemic range and the logarithmically transformed mean weekly dose during the last 2 weeks of treatment were evaluated by analysis of covariance, including use of a dipeptidyl peptidase 4 inhibitor (yes or no), geographic region, and treatment as fixed factors. Missing end-point values were not imputed.

Adverse events during the treatment exposure period were evaluated descriptively as the num-

ber of patients with at least one event, the percentage of patients with at least one event, the number of events, and the event rate (events per patient-year of exposure). Hypoglycemic events were summarized and analyzed for each category separately with a negative binomial regression model in which treatment, geographic region, and use of a dipeptidyl peptidase 4 inhibitor (yes or no) were used as fixed factors and the logarithm of the time period in which the hypoglycemic events were considered was used as an offset.

RESULTS

PATIENTS

Of the 385 patients who underwent screening, 247 were randomly assigned to one of the two treatment groups; 125 were assigned to receive icodec, and 122 were assigned to receive glargine. All 247 patients were included in the full analysis set and the safety analysis set. Similar numbers of patients in each group completed the week 26 visit without having discontinued treatment (121 [96.8%] in the icodec group and 115 [94.3%] in the glargine group). In total, 4 patients in the icodec group and 7 in the glargine group discontinued treatment, and 1 and 2 patients, respectively, initiated ancillary treatment (Fig. S2). The demographic and baseline characteristics were well balanced between the groups, with the exception of a slightly longer duration of diabetes in the icodec group (Table 1).

EFFICACY END POINTS

The mean (\pm SD) glycated hemoglobin level in the icodec group decreased from $8.09\pm 0.70\%$ at baseline to an estimated mean of 6.69% at week 26; in the glargine group, the level decreased from $7.96\pm 0.65\%$ to 6.87% . The estimated mean change in the glycated hemoglobin level from baseline at week 26 was -1.33 percentage points for icodec and -1.15 percentage points for glargine (Fig. 1A), for an estimated mean treatment difference of -0.18 percentage points (95% confidence interval [CI], -0.38 to 0.02 ; $P=0.08$). The estimated percentages of patients reaching a glycated hemoglobin level of less than 7% at week 26 were 72% in the icodec group and 68% in the glargine group (estimated odds ratio, 1.20; 95% CI, 0.98 to 2.13), and the percentages of patients reaching a glycated hemoglobin level of

Table 1. Demographic and Baseline Characteristics (Full Analysis Set).*

Characteristic	Icodec (N = 125)	Glargine (N = 122)	Total (N = 247)
Male sex — no. (%)	70 (56.0)	69 (56.6)	139 (56.3)
Age — yr	59.7±8.2	59.4±9.5	59.6±8.9
Diabetes duration — yr	10.5±8.4	8.8±6.1	9.7±7.4
Body weight — kg	89.7±16.5	91.3±15.7	90.5±16.1
Body-mass index†	31.1±4.9	31.4±4.4	31.3±4.6
Glycated hemoglobin level — %	8.09±0.70	7.96±0.65	8.02±0.68
Fasting plasma glucose level — mg/dl	182±42	180±42	181±42
Dipeptidyl peptidase 4 inhibitor use — no. (%)	59 (47.2)	56 (45.9)	115 (46.6)
Diabetes complications — no. (%)			
Any complication	27 (21.6)	22 (18.0)	49 (19.8)
Microvascular complication	22 (17.6)	15 (12.3)	37 (15.0)
Diabetic neuropathy	15 (12.0)	8 (6.6)	23 (9.3)
Diabetic retinopathy	4 (3.2)	5 (4.1)	9 (3.6)
Diabetic nephropathy	3 (2.4)	4 (3.3)	7 (2.8)
Other	3 (2.4)	1 (0.8)	4 (1.6)
Atherosclerotic cardiovascular disease	8 (6.4)	5 (4.1)	13 (5.3)
Other	1 (0.8)	3 (2.5)	4 (1.6)

* Plus-minus values are means ±SD. Patients in the trial received either once-weekly insulin icodec or once-daily insulin glargine U100. The full analysis set included all patients who underwent randomization. To convert glucose values to millimoles per liter, multiply by 0.05551.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

6.5% or less were 49% and 39%, respectively (estimated odds ratio, 1.47; 95% CI, 0.85 to 2.52) (Fig. 1B). The results of the analysis of the glycated hemoglobin level with the use of the treatment-policy estimand, which reflects an intention-to-treat analysis, are shown in Table S4.

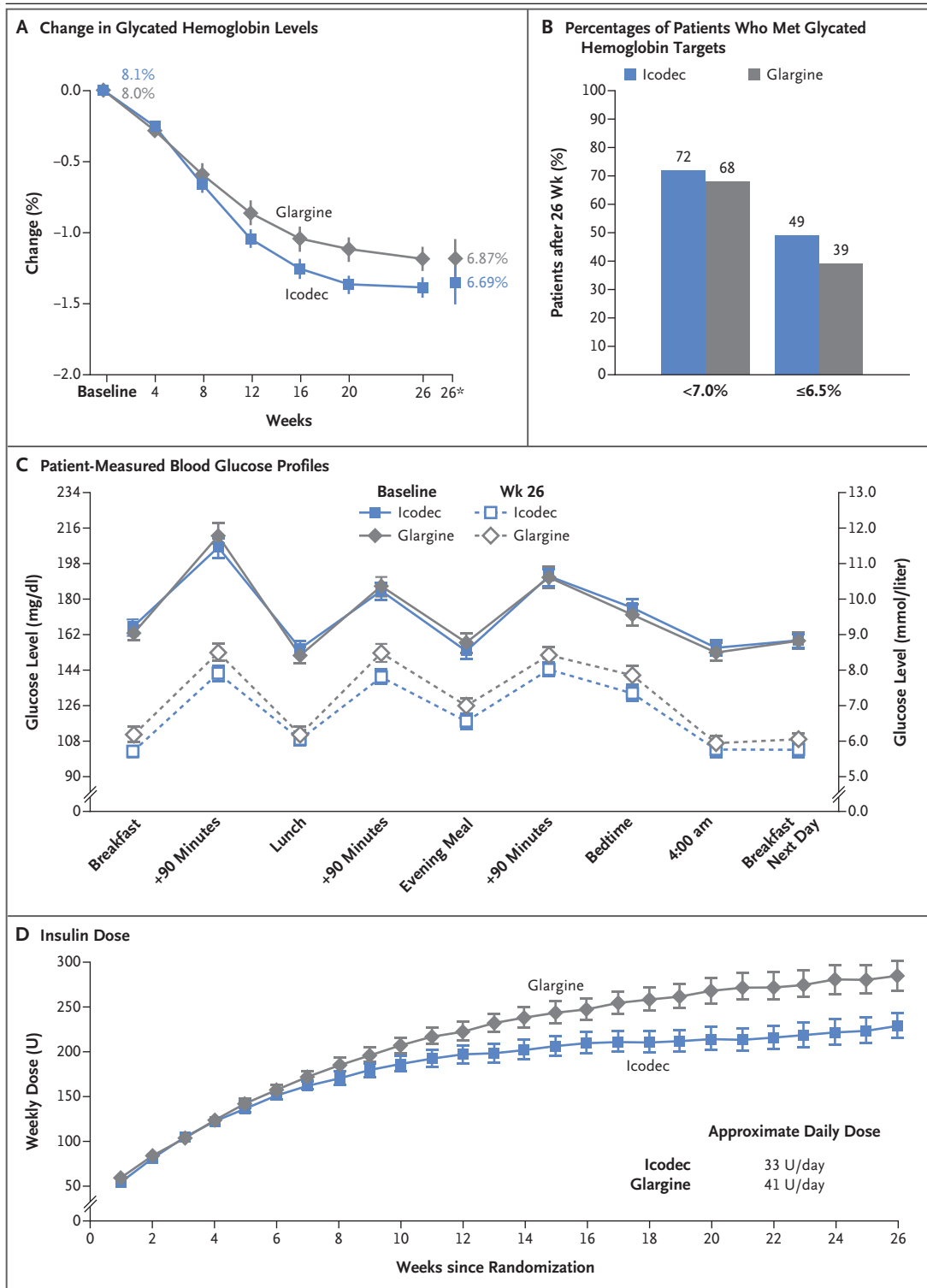
The mean patient-measured blood glucose level was lower in the icodec group than in the glargine group at all time points (Fig. 1C). A greater reduction in the mean 9-point patient-measured blood glucose level from baseline to week 26, a lower insulin dose, and a greater time spent within the tight glycemic range (70 to 140 mg per deciliter) during the last 2 weeks of treatment were also found in the icodec group (Table 2 and Fig. 1D). The change from baseline to week 26 in the fasting plasma glucose level and in body weight were similar in the two groups (Table 2).

SAFETY END POINTS

Approximately 50% of patients in each treatment group had an adverse event (Table 3). Two seri-

ous adverse events were reported in 2 patients receiving icodec, and 12 serious adverse events, including 10 events occurring in 1 patient, were reported in 3 patients treated with glargine (Table S5). None of the serious adverse events were considered by the investigators to be possibly or probably related to the trial medications. Injection-site reactions were reported in 5 patients treated with icodec (28 events, including 20 events of mild erythema reported in 1 patient) and in 3 patients treated with glargine (4 events); all reactions were mild and resolved quickly. None of the confirmed adjudicated hypersensitivity reactions (1 with icodec and 3 with glargine) were considered by the investigators to be related to the trial medications. No deaths occurred during the trial.

The observed incidence of level 1 hypoglycemia alerts was 53.6% in the icodec group and 37.7% in the glargine group, and the observed rates of this end point during the treatment exposure period were 5.09 and 2.11 events per patient-year of exposure for icodec and glargine,



respectively (estimated rate ratio, 2.42; 95% CI, 1.50 to 3.88). For both icodec and glargine, the observed incidence of combined level 2 or level 3 hypoglycemia was low (16.0% and 9.8%, respec-

tively); the observed event rates were 0.53 and 0.46 events per patient-year of exposure, respectively, with an estimated rate ratio of 1.09 (95% CI, 0.45 to 2.65) (Table 3). The odds ratios for a

Figure 1 (facing page). Efficacy End Points.

Panel A shows the mean change from baseline in glycated hemoglobin levels over time among patients who received either once-weekly insulin icodec or once-daily insulin glargine U100. Error bars indicate the standard error. The data shown at week 26* are the estimated mean values and corresponding 95% confidence intervals at week 26 derived on the basis of a mixed model for repeated measures with an unstructured covariance matrix. The model included use of a dipeptidyl peptidase 4 inhibitor (yes or no), geographic region, treatment, and visit as fixed factors and the glycated hemoglobin baseline value as the covariate. Interactions between visit and all factors and covariates were also included in the model. Panel B shows estimated percentages of patients who had reached a glycated hemoglobin level of less than 7% or of 6.5% or lower after 26 weeks. The binary response end points after 26 weeks were analyzed with a logistic-regression model with the same factors and covariates (except for visit) after imputing missing glycated hemoglobin measurements with the use of a mixed model for repeated measures. Panel C shows the 9-point patient-measured blood glucose profiles at baseline and at week 26. Patient-measured blood glucose levels were assessed with a glucose meter as plasma equivalent values of capillary whole-blood glucose. The 9-point profile values after 26 weeks were analyzed with a linear mixed-effects model. The model included treatment, geographic region, use of a dipeptidyl peptidase 4 inhibitor, time (within the 9-point profile), the interaction between treatment and time, the interaction between geographic region and time, and the interaction between use of a dipeptidyl peptidase 4 inhibitor and time as fixed factors and patient as a random effect; measurements within patients were assumed to be correlated with a compound symmetry covariance matrix. Panel D shows the mean weekly insulin dose over time.

affecting rates of clinically relevant hypoglycemia (level 2 or 3) in patients with type 2 diabetes that had been inadequately controlled with metformin with or without a dipeptidyl peptidase 4 inhibitor. During the trial, a similarly robust reduction in the glycated hemoglobin level was observed with both drugs, with more than two thirds of patients reaching a glycated hemoglobin level of less than 7%; the reduction in the fasting plasma glucose level was also similar in the two groups, and greater improvements in the 9-point patient-measured blood glucose profile were observed with once-weekly insulin icodec than with once-daily glargine, which is currently the most commonly used basal insulin analogue. Insulin icodec had a favorable side-effect profile, and no unexpected safety findings occurred. In our trial, the blinded design with a double-dummy strategy provided robustness to the efficacy and safety findings.

The findings in the present trial suggest that once-weekly insulin has the potential to facilitate insulin management, providing clinical benefits and reducing the number of injections per year from 365 to 52. In addition to the improvement in the mean of the 9-point patient-measured blood glucose profile and the better post-breakfast and post-lunch measurements in that profile with icodec than with glargine, patients treated with once-weekly icodec spent a greater amount of time in the tight glycemic range (70 to 140 mg per deciliter) than did those treated with once-daily glargine. The estimated treatment difference was 5.4 percentage points, corresponding approximately to an extra 78 minutes spent in the target glycemic range per day in the icodec group. It is worth noting that the most recent consensus paper on time spent in the glycemic range of 70 to 180 mg per deciliter states that each 5% incremental increase in that measure is associated with clinically significant benefits.⁸⁻¹¹

Once-weekly insulin icodec had a favorable side-effect profile, with rates of level 2 hypoglycemic events similar to those with glargine. The higher number of level 1 hypoglycemic events in the icodec group than in the glargine group may reflect the trial design and suggests that the fasting glucose target may need to be slightly higher and the insulin dose increments smaller to ensure an efficacious initiation and adjustment of insulin icodec with even fewer hypoglycemic events. However, it is reassuring that the

level 1 and a level 2 or 3 hypoglycemic event are shown in Table 3.

The numbers of level 1 and level 2 nocturnal hypoglycemic events were very low in both treatment groups, with no level 3 events occurring (Table S6). One patient in the icodec group had a severe hypoglycemic event that was defined by the investigator as requiring external assistance; however, it was characterized by a blood glucose level of 58 mg per deciliter (3.2 mmol per liter), and the patient had a full recovery with only oral carbohydrate administration.

DISCUSSION

In this 26-week, phase 2 clinical trial investigating a once-weekly basal insulin analogue, the use of icodec resulted in glycemic control similar to that of once-daily glargine without significantly

Table 2. Key Secondary End Points.

End Point	Icodec (N=125)		Glargine (N=122)		Difference or Ratio (95% CI)
	No. of Patients	Change from Baseline	No. of Patients	Change from Baseline	
End points assessed as estimated mean change from baseline to week 26*					
Fasting plasma glucose level — mg/dl	121	-57.74	116	-53.86	-3.9 (-11.9 to 4.2)†
Mean 9-point patient-measured blood glucose level — mg/dl	112	-48.63	111	-40.77	-7.86 (-14.10 to -1.62)†
Body weight — kg	122	1.49	119	1.56	-0.08 (-1.08 to 0.93)†
End points assessed as estimated mean during the last 2 weeks of treatment‡					
Time with glucose level in range of 70–140 mg/dl — %	85	66.11	83	60.71	5.39 (0.69 to 10.09)†
Insulin dose — U/wk	120	229.06§	117	284.05¶	0.81 (0.69 to 0.94)

* Fasting plasma glucose level, mean 9-point patient-measured blood glucose level, and body weight were analyzed with a linear mixed model for repeated measures with an unstructured covariance matrix. The model included use of dipeptidyl peptidase 4 inhibitor (yes or no), geographic region, treatment, and visit as fixed factors and the relevant baseline value as covariate. Interactions between visit and all factors and covariates were also included in the model.

† Value is the estimated difference between the groups (icodec minus glargine).

‡ Time in range and weekly insulin dose were analyzed in an analysis of covariance with dipeptidyl peptidase 4 inhibitor use (yes or no), geographic region, and treatment as fixed factors and with no imputation of missing data. The weekly insulin dose was log-transformed before analysis.

§ Value represents approximately 33 U per day.

¶ Value represents approximately 41 U per day.

|| Value is the estimated ratio (icodec:glargine).

incidence of clinically significant (level 2) and severe (level 3) hypoglycemia was similar with the two types of insulin, with only one case of questionable severe hypoglycemia reported in a patient receiving icodec, which was resolved with oral carbohydrate administration. Moreover, in previous treat-to-target insulin trials in which glargine was evaluated, the overall numbers of events of hypoglycemia per patient-year (using values similar to level 1 and level 2) with glargine were generally higher than what we observed in the current trial in either group, although this comparison should be considered in the context of differences in methods, threshold, and oral antidiabetic treatment.¹²⁻¹⁴

The mean weekly insulin dose was higher in the glargine group than in the icodec group. Given the expected equipotency between the two drugs, this finding awaits further clinical trials to determine whether the difference is observed consistently. Despite the observed difference in dose, no difference in changes in body weight was noted between the two treatment groups.

Published data have indicated that treatment with an injectable once-weekly glucagon-like

peptide 1 (GLP-1) receptor agonist was associated with significantly better treatment adherence and persistence than once-daily treatment,¹⁵ and greater treatment satisfaction without compromising glycemic control was also observed in patients with type 2 diabetes who switched from once-daily to once-weekly therapy with a GLP-1 receptor agonist.¹⁶ Extrapolating these data to our trial results could suggest that once-weekly insulin icodec has the potential to improve treatment satisfaction, adherence, and persistence in patients who are going to receive basal insulin. The smaller number of injections associated with once-weekly icodec than with once-daily basal insulin may facilitate treatment initiation in patients with type 2 diabetes who have not previously taken insulin, by reducing clinical inertia and promoting better acceptance of insulin therapy.

A strength of this study was the double-blind, double-dummy design. The high number of patients who completed therapy during the 26-week treatment period was another strength. However, the results should be interpreted in the context of several limitations. This phase 2 trial

Table 3. Key Safety Measures and Adverse Events during the Treatment Exposure Period (Safety Analysis Set).*

Event	Icodec (N = 125)		Glargine (N = 122)		Rate Ratio (95% CI)†	Odds Ratio (95% CI)‡
	no. of patients (%)	no. of events (events/patient-yr of exposure)	no. of patients (%)	no. of events (events/patient-yr of exposure)		
Any adverse event	65 (52.0)	229 (3.17)	62 (50.8)	158 (2.25)	—	—
Serious adverse event	2 (1.6)	2 (0.03)	3 (2.5)	12 (0.17)	—	—
Severe adverse event	0	0	1 (0.8)	5 (0.07)	—	—
Any adverse event probably or possibly related to basal insulin	8 (6.4)	32 (0.44)	7 (5.7)	7 (0.10)	—	—
Adverse events of special interest						
Injection-site reactions§	5 (4.0)	28 (0.39)	3 (2.5)	4 (0.06)	—	—
Hypersensitivity event¶	1 (0.8)	1 (0.01)	2 (1.6)	3 (0.04)	—	—
Hypoglycemic events						
Hypoglycemia alert	67 (53.6)	368 (5.09)	46 (37.7)	148 (2.11)	2.42 (1.50 to 3.88)	1.84 (1.10 to 3.07)
Clinically significant or severe hypoglycemia**††	20 (16.0)	38 (0.53)	12 (9.8)	32 (0.46)	1.09 (0.45 to 2.65)	1.70 (0.79 to 3.66)
Severe hypoglycemia†††	1 (0.8)	1 (0.01)	0	0	NA	NA

* The total patient-years of exposure were 72.31 for icodec and 70.21 for glargine. One patient-year of exposure is equal to 365.25 days. The treatment exposure period was defined as the period from the date of first dose of icodec or glargine until the last follow-up visit or the day of the last dose of icodec or glargine plus 5 weeks (for glargine) or 6 weeks (for icodec), whichever came first. The safety analysis set included all patients who received at least one dose of trial medication. NA denotes not applicable.

† The rate ratio for hypoglycemia is shown for icodec as compared with glargine. The number of hypoglycemic events was analyzed in a negative binomial regression model in which treatment, geographic region, and use of a dipeptidyl peptidase 4 inhibitor (yes or no) were used as fixed factors and the logarithm of the time period in which the hypoglycemic events were considered was used as an offset.

‡ The odds ratio for the incidence of hypoglycemia is shown for icodec as compared with glargine. The binary response end point of having a hypoglycemic episode was analyzed using a logistic regression model with treatment, geographic region, and use of a dipeptidyl peptidase 4 inhibitor (yes or no) as fixed factors.

§ Injection-site reactions were defined as skin problems at the site where the injection was given; signs at the injection site could include bruising, bleeding, pain and discomfort, and redness or swelling.

¶ Events were confirmed by the event adjudication committee. Hypersensitivity may manifest as local skin problems at the injection site or allergic reactions; signs of mild allergic reaction may include rash, redness, hives, or itching; signs of serious allergic reaction may include swelling of the throat, tongue, or face, trouble breathing, wheezing, fast heartbeat, pale and cold skin, or feeling dizzy or weak.

|| 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.

was not powered to detect significant differences between treatments for any end point, but these data suggest that such a trial design may be worth exploring in the future. In addition, the double-blind, double-dummy design and the requirement to use a treat-to-target approach in regulatory trials necessitated an identical dose-adjustment frequency for both treatments, which meant that insulin adjustment was not tailored for each treatment. Patients treated with sulfonylureas were excluded from the trial, and further investigation will be needed in a larger and more diverse patient population to evaluate the hypoglycemic profile of icodex.

In this trial, the once-weekly basal insulin analogue, insulin icodex, provided glucose-lowering effects and a safety profile similar to those of once-daily glargine.

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