



A Randomized, Open-Label Comparison of Once-Weekly Insulin Icodec Titration Strategies Versus Once-Daily Insulin Glargine U100

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OBJECTIVE

Insulin icodec is a novel once-weekly basal insulin analog. This trial investigated the efficacy and safety of icodec using different once-weekly titration algorithms.

RESEARCH DESIGN AND METHODS

This was a phase 2, randomized, open-label, 16-week, treat-to-target study. Insulin-naïve adults ($n = 205$) with type 2 diabetes and HbA_{1c} 7–10% while treated with oral glucose-lowering medications initiated once-weekly icodec titrations A (prebreakfast self-measured blood glucose target 80–130 mg/dL; adjustment ± 21 units/week; $n = 51$), B (80–130 mg/dL; ± 28 units/week; $n = 51$), or C (70–108 mg/dL; ± 28 units/week; $n = 52$), or once-daily insulin glargine 100 units/mL (IGlar U100) (80–130 mg/dL; ± 4 units/day; $n = 51$), all titrated weekly. Percentage of time in range (TIR) (70–180 mg/dL) during weeks 15 and 16 was measured using continuous glucose monitoring.

RESULTS

TIR improved from baseline (means: A, 57.0%; B, 55.2%; C, 51.0%; IGlar U100, 55.3%) to weeks 15 and 16 (estimated mean: A, 76.6%; B, 83.0%; C, 80.9%; IGlar U100, 75.9%). TIR was greater for titration B than for IGlar U100 (estimated treatment difference 7.08%-points; 95% CI 2.12 to 12.04; $P = 0.005$). No unexpected safety signals were observed. Level 2 hypoglycemia (< 54 mg/dL) was low in all groups (0.05, 0.15, 0.38, 0.00 events per patient-year of exposure for icodec titrations A, B, and C and IGlar U100, respectively), with no episodes of severe hypoglycemia.

CONCLUSIONS

Once-weekly icodec was efficacious and well tolerated across all three titration algorithms investigated. The results for icodec titration A (80–130 mg/dL; ± 21 units/week) displayed the best balance between glycemic control and risk of hypoglycemia.

Treatment adherence remains a challenge in patients with type 2 diabetes, and the issue is particularly pronounced in those prescribed insulin (1). Barriers to insulin therapy initiation and adherence include both the reluctance of health care providers to prescribe insulin and the resistance among patients in taking insulin (2).

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Hesitance and fear concerning injections and the additional complexity of timing of insulin administration contribute to these barriers (3–5). In addition, the efficacy and safety of insulin treatments are highly dependent on, among other things, optimal titration, which is often not followed in clinical practice because the resources and support systems are not available to the same extent as in randomized clinical trials. Indeed, insulin dose, timing, and glycemic targets have a greater impact on efficacy and safety profiles of insulin than differences among insulin formulations (6). Reducing the frequency of treatment administration may decrease both provider and patient reluctance to insulin initiation, increase patient adherence and quality of life, and decrease treatment burden, ultimately leading to improved glycemic control. Treatment with an injectable once-weekly glucagon-like peptide 1 receptor agonist has been associated with a significant improvement in glycemic control, treatment adherence, treatment satisfaction, and quality of life compared with once-daily therapies (7–11), and presumably a similar effect may be expected for a once-weekly basal insulin in clinical practice.

Insulin icodec is a novel once-weekly basal insulin analog that strongly but reversibly binds to albumin. The major mode of protraction is due to the formation of an essentially inactive albumin-bound depot, which slowly releases active insulin icodec over time (12). Pharmacokinetic and pharmacodynamic data show that insulin icodec has a half-life of ~1 week with a glucose-lowering effect close to evenly distributed within a 1-week dosing interval (13). Guidance on titration algorithms is needed for the efficacious and safe use of this novel insulin by clinicians and patients. In a recently published 26-week phase 2 study in insulin-naïve patients with type 2 diabetes, insulin icodec displayed glucose-lowering effects and safety profile comparable to those of once-daily insulin glargine 100 units/mL (IGlar U100) (14).

To better inform titration and dosing strategies for this novel once-weekly insulin, we examined three different insulin icodec titration algorithms in comparison with once-daily IGlar U100 in insulin-naïve patients with type 2 diabetes. Glucose-lowering effects were

investigated primarily with continuous glucose monitoring (CGM), an assessment method that is rapidly growing in popularity in clinical practice but novel and rarely used to measure a primary end point in clinical trials.

RESEARCH DESIGN AND METHODS

Research Design

This was a randomized, active-controlled, parallel-group, multicenter, multi-national, open-label, phase 2, treat-to-target trial conducted in seven countries (Croatia, Germany, Hungary, Poland, Slovakia, Spain, and the U.S.). The trial consisted of a 2-week screening period, 16 weeks of treatment, and a 5-week follow-up.

The trial was conducted in accordance with current applicable international and national regulations and ethics requirements and was performed in accordance with the Declaration of Helsinki, applicable recommendation from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use's guidelines for good clinical practice, and the International Organization for Standardization ISO 14155. The protocol, consent form, and other relevant documents were approved by the appropriate independent review boards or independent ethics committees.

Patients

Patients were eligible if they were adults aged 18–75 years who received a diagnosis of type 2 diabetes at least 180 days prior to screening, were treated with metformin with or without dipeptidyl peptidase 4 inhibitor (DPP4i) and/or sodium–glucose cotransporter 2 inhibitors (SGLT2i), and had glycated hemoglobin (HbA_{1c}) of 7.0–10.0% (53.0–85.8 mmol/mol). All inclusion and exclusion criteria are detailed in Supplementary Table 1. Written informed consent was obtained for all participants.

Randomization

Patients were randomized 1:1:1 to receive subcutaneous injections of once-weekly insulin icodec following one of three titration algorithms (icodec titrations A, B, or C, outlined below) or once-daily IGlar U100 (Supplementary Fig. 1A). Randomization was performed centrally with an interactive Web response system, and patients were

stratified based on SGLT2i treatment. The full analysis set (FAS) consisted of all randomized patients. The safety analysis set (SAS) consisted of all patients exposed to at least one dose of trial product.

Procedures

Insulin icodec (Novo Nordisk, Bagsværd, Denmark) was initiated at 70 units weekly and IGlar U100 (Sanofi, Paris, France) at 10 units daily, equivalent to 70 units per week. Prebreakfast self-measured blood glucose (SMBG) target values used for titration were based on the American Diabetes Association (ADA)-recommended preprandial plasma glucose target of 4.4–7.2 mmol/L (80–130 mg/dL) (15) or a tighter target of 3.9–6.0 mmol/L (70–108 mg/dL) that was used in prior treat-to-target studies including a previously published 26-week phase 2 trial (14,16). SMBG was assessed with a blood glucose meter as plasma-equivalent values of capillary whole blood glucose. The titration algorithms were as follows and were based on three prebreakfast SMBG values on the 2 days leading up to titration and on the day of titration: IGlar U100, prebreakfast SMBG target 4.4–7.2 mmol/L (80–130 mg/dL), adjustment ± 4 units/day; insulin icodec titration A, prebreakfast SMBG target 4.4–7.2 mmol/L (80–130 mg/dL), adjustment ± 21 units/week (same SMBG target as for IGlar U100 and smaller dose increments); insulin icodec titration B, prebreakfast SMBG target 4.4–7.2 mmol/L (80–130 mg/dL), adjustment ± 28 units/week (same SMBG target and equivalent dose increments as for IGlar U100); and insulin icodec titration C, prebreakfast SMBG target 3.9–6.0 mmol/L (70–108 mg/dL), adjusted ± 28 units/week (tighter and lower SMBG target than for IGlar U100 and equivalent dose increments).

Insulin doses were adjusted weekly (Supplementary Fig. 1B). If any of the three prebreakfast SMBG values were below the lower limit of the target range, titration was based on the lowest recorded value. If all three SMBG values were above the lower limit of the target range, titration was based on the mean of the three measurements. Both insulin icodec (700 units/mL) and IGlar U100 (100 units/mL) were administered

Table 1—Baseline demographics and characteristics (FAS, N = 205)

	Insulin icodex titration A (n = 51)	Insulin icodex titration B (n = 51)	Insulin icodex titration C (n = 52)	IGlar U100 (n = 51)	Total (N = 205)
Age, years	59.8 (9.1)	61.2 (8.0)	61.4 (8.0)	60.2 (8.1)	60.7 (8.3)
Male, %	52.9	54.9	53.8	52.9	53.7
Duration of type 2 diabetes, years	9.8 (7.2)	9.6 (4.9)	9.2 (4.4)	11.8 (6.8)	10.1 (6.0)
Body weight, kg	91.4 (17.6)	90.4 (18.0)	87.3 (14.0)	86.4 (17.1)	88.9 (16.7)
BMI, kg/m ²	32.3 (4.8)	31.4 (4.7)	30.8 (3.8)	30.6 (4.7)	31.3 (4.5)
TIR, %	57.0 (28.0)	55.2 (26.3)	51.0 (27.4)	55.3 (29.2)	54.6 (27.6)
FPG, mg/dL	174 (33)	180 (38)	177 (41)	168 (42)	175 (39)
HbA _{1c} , %	8.0 (0.7)	8.1 (0.8)	8.2 (0.9)	8.2 (0.8)	8.1 (0.8)
HbA _{1c} , mmol/mol	63.9 (7.8)	64.9 (8.4)	65.6 (10.3)	65.7 (9.1)	65.0 (8.9)
Oral antidiabetic drug, n (%) [*]					
Metformin monotherapy	20 (39.2)	16 (31.4)	25 (48.1)	17 (33.3)	78 (38.0)
Metformin + SGLT2i	12 (23.5)	11 (21.6)	11 (21.2)	10 (19.6)	44 (21.5)
Metformin + DPP4i	14 (27.5)	19 (37.3)	9 (17.3)	16 (31.4)	58 (28.3)
Metformin + SGLT2i + DPP4i	5 (9.8)	5 (9.8)	7 (13.5)	8 (15.7)	25 (12.2)

Data are means (SD) unless otherwise stated. Insulin icodex titration A: titration of insulin icodex to a prebreakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) with dose adjustment of ±21 units. Insulin icodex titration B: titration of insulin icodex to a prebreakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) with dose adjustment of ±28 units. Insulin icodex titration C: titration of insulin icodex to a prebreakfast SMBG target of 3.9–6.0 mmol/L (70–108 mg/dL) with dose adjustment of ±28 units. IGlar U100: titration of IGlar U100 to a prebreakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) with dose adjustment of ±4 units. ^{*}At screening.

subcutaneously in the thigh with the 3-mL FlexTouch and the 3-mL SoloStar prefilled pen injectors, respectively. It was recommended that study drugs be injected at any time of the day but at the same time of the day throughout the trial.

Outcomes

Patients wore a CGM system (Dexcom G6; Dexcom, San Diego, CA) from screening to the end-of-treatment visit. CGM data were uploaded at each site visit. Both patients and investigators

were blinded to CGM data throughout the study and these data were not used for insulin dose titration or reporting of hypoglycemic episodes. Patients performed SMBG assessment once a day (prebreakfast) to inform dose titration decisions and to mitigate hypoglycemic risk. In addition, patients were required to measure SMBG if they suspected having low blood glucose. It was required that at least 70% of the planned CGM measurements, during the last 2 weeks of treatment, be available for end point data to be included in the analysis.

The primary end point was percentage of time in range (TIR) (3.9–10.0 mmol/L [70–180 mg/dL]) during the last 2 weeks of treatment (weeks 15 and 16), measured by CGM (17). Supportive secondary end points were as follows: changes from baseline to week 16 in HbA_{1c}, fasting plasma glucose (FPG), and body weight; weekly insulin dose during the last 2 weeks of treatment (weeks 15 and 16); and number of on-treatment adverse events (AEs) from baseline to week 21 and number of self-reported hypoglycemic episodes documented by SMBG or assessed as the requirement of external assistance for recovery. Hypoglycemic episodes were classified as “alert” values (level 1: blood glucose

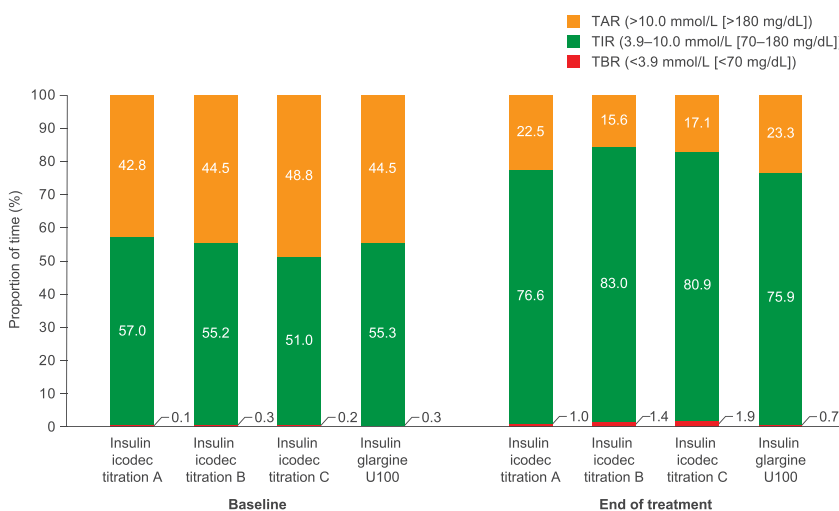


Figure 1—TIR 3.9–10.0 mmol/L (70–180 mg/dL) at baseline and during the last 2 weeks of treatment (weeks 15 and 16) (FAS, N = 205). Baseline values are observed mean values. End-of-treatment values represent estimated mean values. The numbers of patients who had missing or <70% CGM measurements during the last 2 weeks of treatment (weeks 15 and 16) were two for titration A, one for titration B, two for titration C, and one for IGlar U100. Insulin icodex titration A: titration of insulin icodex to a prebreakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) with dose adjustment of ±21 units. Insulin icodex titration B: titration of insulin icodex to a prebreakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) with dose adjustment of ±28 units. Insulin icodex titration C: titration of insulin icodex to a prebreakfast SMBG target of 3.9–6.0 mmol/L (70–108 mg/dL) with dose adjustment of ±28 units. IGlar U100: titration of IGlar U100 to a prebreakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) with dose adjustment of ±4 units. TAR, time above range; TBR, time below range.

<3.9 mmol/L [<70 mg/dL] and ≥ 3.0 mmol/L [≥ 54 mg/dL]), combined clinically significant (level 2: blood glucose < 3.0 mmol/L [< 54 mg/dL]), and severe hypoglycemia (level 3: severe cognitive impairment requiring external assistance) or severe hypoglycemia only (level 3). AEs of interest included major adverse cardiovascular events, hypersensitivity reactions, and deaths; these were reviewed by a blinded, independent adjudication committee.

Statistical Analysis

To achieve a width of the 95% CI for TIR 3.9–10.0 mmol/L (70–180 mg/dL) of 2.5 h (corresponding to a TIR of $\sim 10\%$) for a 24-h period for any pairwise comparison between any insulin icodec treatment group and IGl_{ar} U100 with a probability of 80% and an assumed SD of 3.0 h (corresponding to a TIR of $\sim 12.5\%$), it was required that at least 200 patients be randomized to reach the target sample size of 50 patients per treatment group.

TIR for each individual was calculated as the number of recorded measurements in the range 3.9–10.0 mmol/L (70–180 mg/dL) divided by the total number of recorded measurements over 14 days, multiplied by 100.

The primary estimand, which was the “trial product estimand” (18), was defined as the mean difference in the primary end point measures between each of the three insulin icodec titrations and IGl_{ar} U100 if all patients had adhered to randomized treatment without initiation of rescue medication and had 70% of the planned CGM measurements recorded. A more detailed explanation of the rationale for estimand and of the estimand used in this trial is provided in the Supplementary Material. For TIR, the response during the last 2 weeks of treatment (weeks 15 and 16) was analyzed with an ANCOVA model, with treatment and SGLT2i use as fixed factors and baseline TIR value as a covariate. Missing end point values were imputed with use of multiple imputation based on own treatment group, with baseline TIR as a covariate. Each imputed data set was analyzed separately, and estimates were combined with use of Rubin’s rules (19). Supportive secondary efficacy end points were analyzed in the same way as the primary end point,

with the exception of the mean weekly insulin dose during the last 2 weeks of treatment, which was log transformed and analyzed with an ANOVA model, without baseline value as covariate. Missing data for secondary end points were imputed based on own treatment group with a sequential conditional regression approach, including all postbaseline values whenever intermediate assessments of the end point were available. Interim missing values were imputed with the Markov chain Monte Carlo method. Because this was a phase 2 trial and exploratory in nature, no adjustments were made for multiplicity.

The on-treatment period was defined as the period from the date of first study drug dose until the last follow-up visit or the last dosing day of randomized treatment plus 5 weeks (for IGl_{ar} U100) or 6 weeks (for insulin icodec)—whichever came first—and represents the time period in which patients were considered exposed to trial product.

Data were analyzed with SAS software, version 9.4 (SAS Institute Inc., Cary, NC). No data monitoring committees oversaw the study. This trial was registered on ClinicalTrials.gov (clinical trial reg. no. NCT03951805).

Data and Resource Availability

The data sets generated during or analyzed during the current trial are available from the corresponding author on reasonable request.

RESULTS

Between 9 May and 9 August 2019, 259 patients were screened, of whom 205 were randomized to one of the treatment groups (icodec titration A, $n = 51$; icodec titration B, $n = 51$; icodec titration C, $n = 52$; IGl_{ar} U100, $n = 51$) and received at least one dose of study drug (FAS, $N = 205$; SAS, $N = 205$) (Supplementary Fig. 2). Only one patient in the icodec titration A group withdrew from the trial, and one patient initiated rescue medication in the icodec titration C group. The numbers of patients who had missing or $< 70\%$ CGM measurements during the last 2 weeks of treatment (weeks 15 and 16) were two for icodec titration A, one for icodec titration B, two for icodec titration C, and one for IGl_{ar} U100.

Demographics and baseline characteristics were generally similar across treatment groups (Table 1).

The mean percentages of TIR (3.9–10.0 mmol/L [70–180 mg/dL]) at baseline for icodec titrations A, B, C, and IGl_{ar} U100 were 57.0%, 55.2%, 51.0%, and 55.3%, respectively, and all increased at weeks 15 and 16 to estimated means of 76.6%, 83.0%, 80.9%, and 75.9%, respectively (Fig. 1). In comparison with IGl_{ar} U100, TIR for icodec titration B was longer, with an estimated treatment difference (ETD) of 7.08%-points (95% CI 2.12 to 12.04; $P = 0.005$), corresponding approximately to an extra 102 min spent in target glycemic range daily. In comparison with IGl_{ar} U100, TIR was numerically greater for icodec titration C (ETD 5.01%-points; 95% CI -0.04 to 10.05; $P = 0.05$) and similar for icodec titration A (ETD 0.76%-points; 95% CI -4.28 to 5.80; $P = 0.77$). Data on coefficient of variation are presented in Supplementary Table 2, and time below and time above range are presented in Fig. 1.

End-of-treatment (week 16) results for key secondary end points are presented in Supplementary Table 3. The estimated mean changes from baseline to week 16 in HbA_{1c} for icodec titrations A, B, C, and IGl_{ar} U100 were -1.0% -point (-10.9 mmol/mol), -1.2% -points (-13.4 mmol/mol), -1.4% -points (-15.1 mmol/mol), and -1.0% -point (-11.1 mmol/mol), respectively (Fig. 2A). The ETD for HbA_{1c} was 0.02%-points (95% CI -0.20 to 0.24) for titration A versus IGl_{ar} U100, -0.20% -points (95% CI -0.42 to 0.02) for titration B versus IGl_{ar} U100, and -0.36% -points (95% CI -0.58 to -0.14%) for titration C versus IGl_{ar} U100 (Supplementary Table 3). At week 16, the proportion of patients who achieved HbA_{1c} $< 7.0\%$ (53.0 mmol/mol) was 46.0% for icodec titration A, 64.0% for icodec titration B, 70.6% for icodec titration C, and 51.0% for IGl_{ar} U100 (Supplementary Fig. 3).

The estimated mean change from baseline to week 16 in FPG was -2.2 mmol/L (-40 mg/dL) for icodec titration A, -2.4 mmol/L (-44 mg/dL) for icodec titration B, -3.0 mmol/L (-54 mg/dL) for icodec titration C, and -2.3 mmol/L (-42 mg/dL) for IGl_{ar} U100 (Supplementary Fig. 4).

The estimated mean weekly doses during weeks 15 and 16 were 142.5

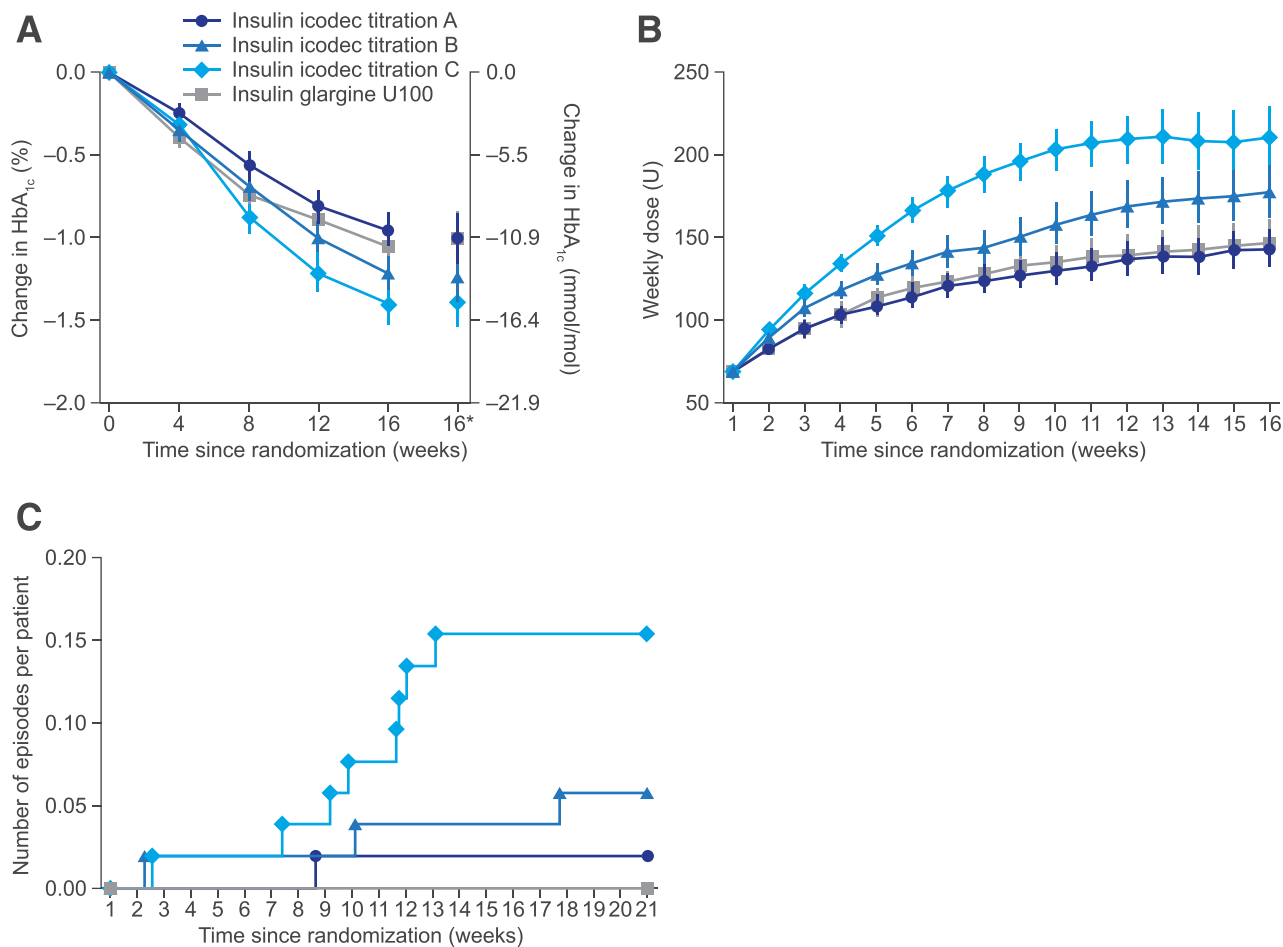


Figure 2—Changes in key parameters during the 16-week study (FAS, $N = 205$). Mean change in HbA_{1c} from baseline to week 16 (A), mean weekly insulin dose over time (B), and mean cumulative function of number of severe (level 3) and clinically significant (level 2) hypoglycemic events when subjects were on treatment (C). Observed data: mean (symbol) \pm SEM (A) and geometric mean (symbol) \pm SEM on log-scale backtransformed (B). Insulin icodec titration A: titration of insulin icodec to a prebreakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) with dose adjustment of ± 21 units. Insulin icodec titration B: titration of insulin icodec to a prebreakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) with dose adjustment of ± 28 units. Insulin icodec titration C: titration of insulin icodec to a prebreakfast SMBG target of 3.9–6.0 mmol/L (70–108 mg/dL) with dose adjustment of ± 28 units. IGlar U100: titration of IGlar U100 to a prebreakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) with dose adjustment of ± 4 units. U, units. *Estimated mean values and the corresponding CIs at week 16 derived based on multiple imputation.

units, 176.4 units, 208.9 units, and 145.6 units for icodec titrations A, B, C, and IGlar U100, respectively (Fig. 2B). There was an estimated increase of 0.9, 1.1, and 1.3 kg in body weight over 16 weeks for icodec titrations A, B, and C, respectively, and of 0.6 kg for IGlar U100 (Supplementary Table 3).

Mean fasting SMBG, used as the basis for titration but not measured as a study end point, decreased in all treatment groups below the upper limits of the respective titration target ranges over the course of the study. The largest change was observed for icodec titration C (prebreakfast SMBG target 3.9–6.0 mmol/L [70–108 mg/dL]) (Supplementary Fig. 5), reflecting the study design.

The incidences and rates of hypoglycemic episodes are presented in Table 2. The rates of on-treatment level 1 hypoglycemic episodes per patient-year of exposure from baseline through follow-up (week 21) were low across treatment groups. Rates of combined clinically significant (level 2) and severe (level 3) hypoglycemic episodes were low for all insulin icodec titrations (0.05, 0.15, and 0.38 events per patient-year of exposure for icodec titrations A, B, and C, respectively) with no clustering of episodes over the on-treatment period (Fig. 2C); none occurred in the IGlar U100 group. No severe (level 3) hypoglycemic episodes occurred in any treatment group (Table 2). During weeks 15 and 16, the estimated mean daily time

spent below range (<3.9 mmol/L) was 1.0% for titration A, 1.4% for titration B, 1.9% for titration C, and 0.7% for IGlar U100, corresponding to ~ 14 , 20, 27, and 10 min per day, respectively (Fig. 1). There was no apparent clustering of level 1 hypoglycemic events in the week following the day of injection for icodec titrations A and B. Clustering of level 2 hypoglycemia in the week following the day of injections could not be assessed because there were too few events. Similar results were observed for the period from baseline to week 16 (data not shown).

The incidences of on-treatment AEs were similar between all four treatment groups (Table 2). Across treatments, most AEs were considered unlikely to

Table 2—On-treatment hypoglycemic episodes and AEs including AEs of special interest (SAS, N = 205)

	Insulin icodec titration A (n = 51; 20.53 PYE)			Insulin icodec titration B (n = 51; 20.66 PYE)			Insulin icodec titration C (n = 52; 21.01 PYE)			IGlar U100 (n = 51; 20.53 PYE)		
	n (%)	Events	Rate*	n (%)	Events	Rate*	n (%)	Events	Rate*	n (%)	Events	Rate*
Hypoglycemic episodes												
Hypoglycemia "alert" value (level 1) [†]	7 (13.7)	15	0.73	10 (19.6)	23	1.11	29 (55.8)	113	5.38	9 (17.6)	12	0.58
Clinically significant (level 2) [‡] and severe (level 3) hypoglycemia	1 (2.0)	1	0.05	3 (5.9)	3	0.15	4 (7.7)	8	0.38	0	—	—
Severe hypoglycemia (level 3) [§]	0	—	—	0	—	—	0	—	—	0	—	—
AEs												
Any AEs	25 (49.0)	44	2.14	28 (54.9)	67	3.24	25 (48.1)	58	2.76	24 (47.1)	45	2.19
Serious AEs	3 (5.9)	4	0.19	1 (2.0)	1	0.05	0	—	—	2 (3.9)	2	0.10
Fatal AEs	0	—	—	0	—	—	0	—	—	0	—	—
Severe AEs	1 (2.0)	2	0.10	0	—	—	0	—	—	2 (3.9)	2	0.10
AEs leading to withdrawal	1 (2.0)	1	0.05	0	—	—	0	—	—	0	—	—
AEs probably related to basal insulin	0	—	—	1 (2.0)	2	0.10	0	—	—	0	—	—
AEs possibly related to basal insulin	1 (2.0)	1	0.05	2 (3.9)	3	0.15	0	—	—	0	—	—
AEs of special interest												
Injection site reaction	0	—	—	1 (2.0)	2	0.10	0	—	—	0	—	—
Hypersensitivity event [¶]	1 (2.0)	1	0.05	0	—	—	2 (3.8)	2	0.10	0	—	—
Cardiovascular event [¶]	0	—	—	0	—	—	0	—	—	0	—	—

Insulin icodec titration A: titration of insulin icodec to a prebreakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) with dose adjustment of ±21 units. Insulin icodec titration B: titration of insulin icodec to a prebreakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) with dose adjustment of ±28 units. Insulin icodec titration C: titration of insulin icodec to a prebreakfast SMBG target of 3.9–6.0 mmol/L (70–108 mg/dL) with dose adjustment of ±28 units. IGlar U100: titration of IGlar U100 to a prebreakfast SMBG target of 70–108 mg/dL with dose adjustment of ±4 units. The on-treatment period was defined as the period from the date of first study drug dose until the last follow-up visit or the last dosing day of randomized treatment plus 5 weeks (for IGlar U100) or 6 weeks (for insulin icodec)—whichever came first—and represents the time period in which patients were considered to be exposed to trial product. %, percentage of all patients; n, number of patients; PYE, patient-years of exposure. *Rate: number of events per patient-years of exposure. [†]Hypoglycemia alert value (level 1): blood glucose value <3.9 mmol/L and ≥3.0 mmol/L (<70 mg/dL and ≥54 mg/dL) confirmed by blood glucose meter. [‡]Clinically significant hypoglycemia (level 2): blood glucose value <3.0 mmol/L (<54 mg/dL). [§]Severe hypoglycemia (level 3): hypoglycemia with severe cognitive impairment requiring external assistance for recovery. [¶]Event adjudication committee–confirmed events.

be related to the trial product and were nonserious and of mild or moderate severity. Serious AEs were reported in three patients receiving icodex titration A, one patient receiving icodex titration B, no patients receiving icodex titration C, and two patients receiving IGlAr U100. All serious AEs were considered unlikely to be related to study drug.

Overall, eight hypersensitivity events were reported in five patients (icodex titration A, two events; icodex titration B, four events; icodex titration C, two events) and three events were confirmed following adjudication (icodex titration A, one event; icodex titration C, two events); all were localized, not at the injection site, and not considered to be related to study drug. Injection site reactions were reported in one patient (icodex titration B, two events, both mild). No cardiovascular events were reported, no AE clusters were observed, and no new safety signals were identified.

CONCLUSIONS

Insulin icodex is a novel once-weekly basal insulin analog with the potential to increase treatment adherence by improving convenience and quality of life of patients with diabetes by reducing the number of injections from 365 to 52 per year. However, there are new aspects inherent to the use of a once-weekly basal insulin analog to consider, such as optimizing titration. A preprandial plasma glucose target of 4.4–7.2 mmol/L (80–130 mg/dL) was investigated because it reflects real-life practice and ADA guidance. Indeed, lower and tighter targets tested in randomized clinical trials are seldom used in clinical practice because primary care practitioners and specialists might have concerns regarding hypoglycemia when using such strict targets. Icodex titration B was intended to provide a direct comparator to IGlAr U100, with the same plasma glucose target and corresponding dose increments, while icodex titration A was included for investigation of the effect of smaller dose increments. The more stringent target used in icodex titration C was included not only to explore the effect of such a stringent target but also to serve as a reference for comparison of the present data with those from the 26-week phase 2 trial (14).

In this phase 2 treat-to-target study, we found that once-weekly insulin icodex effectively lowered glucose levels, similarly to what was seen with once-daily IGlAr U100. Subtle differences were noted across the three icodex titration algorithms evaluated.

In comparison of IGlAr U100 and insulin icodex titrated to the same target with use of the same titration increments (titration B), a greater TIR was achieved with insulin icodex, corresponding approximately to an extra 102 min spent in the target glycemic range daily. HbA_{1c} was lower with insulin icodex, and there was a slightly higher rate of level 2 and level 1 hypoglycemia, albeit the hypoglycemia event rate was very low overall. Titration to attain a more stringent glucose target of 3.9–6.0 mmol/L (70–108 mg/dL), as used in titration algorithm C, was also associated with a higher rate of hypoglycemia in comparison with IGlAr U100 titrated to a target of 4.4–7.2 mmol/L (80–130 mg/dL), while TIR was numerically greater and HbA_{1c} lower with insulin icodex. Lastly, titration algorithm A, which used the same glucose target of 4.4–7.2 mmol/L (80–130 mg/dL) and a smaller titration increment of ± 21 units in comparison with IGlAr U100, which was titrated in ± 4 unit increments (weekly equivalent ± 28 units), led to comparable glucose control, as assessed by both TIR and HbA_{1c}, and comparable hypoglycemia rates. Interestingly, the final daily insulin dose in the titration algorithm B was numerically larger, by $\sim 21\%$, compared with that in the IGlAr U100 group despite the identical titration parameters used in the two groups. This finding contrasts with that in another phase 2 trial that compared insulin icodex with IGlAr U100 and used a double-blind design with 26 weeks of follow-up. In that study, the average daily dose of insulin used during the last 2 weeks of treatment was $\sim 19\%$ lower in the icodex group in comparison with IGlAr U100 while the same weekly titration parameters were used in both groups (pre-breakfast SMBG target 70–108 mg/dL; adjustment ± 14 or 28 units weekly equivalent) (14). Thus, it is prudent to postpone any conclusions regarding dose equivalency between these products until the results of larger ongoing phase 3 studies are available. Interestingly, for icodex titration A, which used

a smaller titration increment than titration B, there was a weekly dose comparable with that of IGlAr U100 and as a likely consequence, icodex titration A showed a profile similar to that of IGlAr U100 with respect to TIR, HbA_{1c}, FPG, and SMBG. Therefore, it is likely that ultimately the daily insulin dose achieved is the primary driver of glucose-lowering efficacy and hypoglycemia risk—rather than a specific titration algorithm.

A modest increase in weight was observed in all groups and was in line with expectations when insulin treatment was initiated in an insulin-naive population. The magnitude of weight gain appeared to be insulin dose dependent, yet the differences between groups were small.

Insulin icodex was well tolerated in this study, with similar incidence of AEs reported in all treatment groups. The rates of hypoglycemia were generally low compared with other treat-to-target trials (16,20,21). It was reassuring that no severe (level 3) hypoglycemic events were reported for any treatment group throughout the entire study duration and that the time spent below range (< 3.9 mmol/L) during the last 2 weeks of treatment (weeks 15 and 16) was below the 4% target recommended by the International Consensus on Time in Range across treatment groups (17).

In summary, titration algorithm A appears to provide the most optimal balance between glycemic control and hypoglycemia across the three titration algorithms tested. These results were very informative for determination of the titration algorithm used in the ongoing phase 3 trials (clinical trial reg. nos. NCT04460885, NCT04795531, and NCT04760626, ClinicalTrials.gov).

The strengths of this study include the following: its randomized, multicenter design; the very low treatment discontinuation rate; and the assessment of glycemic control via TIR with the novel use of CGM in a relatively large clinical trial in patients with type 2 diabetes. While HbA_{1c} is still considered the gold standard in assessment of glycemic control, CGM data are increasingly used in clinical practice and rapidly replacing HbA_{1c} as a more comprehensive tool to assess glycemic control, as they provide a more detailed and granular assessment of various factors that play into

glycemic control beyond an average glucose level. Of these, increased TIR has now been associated with relative risk reductions for various complications of diabetes, including diabetic retinopathy, peripheral neuropathy, cardiovascular autonomic neuropathy, and all-cause and CVD-related mortality (22–27). Previous publications have indicated that a 5% increase in TIR was associated with an estimated 0.3–0.4% decrease in HbA_{1c} (17,28–30); yet, TIR is becoming more clinically relevant. To our knowledge, this is one of the largest studies in patients with type 2 diabetes to use CGM with TIR as a primary end point. In addition, improved glycemic control was achieved in all four treatment groups despite the short duration of the study. The short duration of 16 weeks, which may not be long enough to see the effect of a stable maintenance phase, is an acknowledged limitation of this study, and longer studies will follow in the phase 3 program. However, a plateau was observed in all treatment groups from week 14 for SMBG, suggesting that stability was achieved when TIR was evaluated during weeks 15 and 16. In addition, the study population might not be representative of the typical patient population initiating insulin, among whom there is often a delay in insulin initiation and hereby often a higher HbA_{1c} than what was noted at baseline for the current study population. Finally, it should be noted that, because for icodec titration C there was a lower, more stringent titration target, 3.9–6.0 mmol/L (70–108 mg/dL), than for the other treatment groups, direct comparisons between icodec titration C and IGLar U100 should be cautiously interpreted in the appropriate context.

In conclusion, this study suggests that insulin icodec, a novel, once-weekly basal insulin analog, was efficacious and well tolerated across all three titration algorithms. The titration algorithm with the ADA-recommended preprandial plasma glucose target and the smallest dose increments appears to represent the best balance between glycemic control and risk of hypoglycemia and the profile most comparable with IGLar U100 with regards to TIR, HbA_{1c}, FPG, and SMBG. Insulin icodec has the potential to provide patients and medical teams with a more convenient alternative to once-daily basal insulin and

thus decrease the treatment burden in patients with type 2 diabetes requiring treatment with basal insulin.

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