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

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Clinical trial ref. no. NCT03951805, ClinicalTrials.gov

SUPPLEMENTARY MATERIAL

Explanation of the Trial Product Estimand Used in this Trial

The draft addendum from the International Council for Harmonisation was developed in consultation with regulators in response to concerns regarding the limitations of statistical constructs such as 'last observation carried forward' to fully account for potential bias due to the occurrence of intercurrent events, such as the use of rescue medication or premature discontinuation.

The aim of the estimand is to provide a detailed description of the type of treatment effect that is to be estimated in order to address a particular hypothesis and should include the population of interest, the variable endpoint to be studied, the method for handling intercurrent events, and a population level summary, such as the difference between two treatment groups.

In this trial, the analysis was based on the 'trial product estimand'. The 'trial product estimand' evaluates the treatment effect (difference in time in target range 3.9-10.0 mmol/L [70–180 mg/dL] during the last 2 weeks of treatment [weeks 15 and 16]) between each of the three different titration algorithms for once-weekly insulin icodec and once-daily IGlar U100 for all randomized participants, under the assumption that all participants had adhered to treatment for the entire planned duration of the trial, did not receive rescue medication, and had 70% of the planned continuous glucose monitoring (CGM) measurements recorded. This is a 'hypothetical' estimand intended to provide an estimation of the achievable treatment effect of insulin icodec without any confounding effect of rescue medication for participants who are actually able to take the drug during the intended treatment period.

Supplemental Table S1—Inclusion and exclusion criteria

Inclusion criteria

• Informed consent obtained before any trial-related activities
  ○ Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
• Male or female, aged 18–75 years (both inclusive) at the time of signing informed consent
• Diagnosed with type 2 diabetes ≥180 days prior to the day of screening
• HbA_{1c} of 7·0–10·0% (53·0–85·8 mmol/mol) (both inclusive) as assessed by central laboratory
• Stable daily dose(s) for 90 days prior to the day of screening of any of the following antidiabetic drug(s) or combination regimen(s)
  ○ Any metformin formulations ≥1500 mg or maximum tolerated or effective dose (as documented in patient's medical records)
  ○ Free or fixed combination therapy: metformin as outlined above ± DPP4i ± SGLT2i is allowed
  ▪ DPP4i (≥half of the maximum approved dose according to local label or maximum tolerated or effective dose)
  ▪ SGLT2i (≥half of the maximum approved dose according to local label or maximum tolerated or effective dose)
• Insulin-naïve; however, short-term insulin treatment for ≤14 days prior to the day of screening is allowed, as is prior insulin treatment for gestational diabetes
• BMI ≤40·0 kg/m^2

Exclusion criteria
• Known or suspected hypersensitivity to trial product(s) or related products • Previous participation in this trial. Participation is defined as signed informed consent • Female who is pregnant, breast-feeding, or intends to become pregnant, or is of child-bearing potential and not using an adequate contraceptive method • Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening • Any disorder, except for conditions associated with type 2 diabetes, which in the investigator's opinion might jeopardize the patient's safety or compliance with the protocol • Any episodes of diabetic ketoacidosis within the past 90 days, prior to the day of screening and between screening and randomization • Myocardial infarction, stroke, hospitalization for unstable angina pectoris, or transient ischemic attack within 180 days prior to the day of screening and between screening and randomization • Presently classified as being in NYHA Class IV • Planned coronary, carotid, or peripheral artery revascularization between screening and randomization • Renal impairment measured as eGFR <60 mL/min/1·73 m^2 as defined by KDIGO 2012

- Impaired liver function, defined as ALT ≥2·5 times or bilirubin >1·5 times upper normal limit at screening
- Inadequately treated blood pressure, defined as grade 3 hypertension or higher (systolic ≥180 mmHg or diastolic ≥110 mmHg) at screening
- Treatment with any medication for the indication of diabetes, or obesity other than stated in the inclusion criteria within the past 90 days, prior to the day of screening. However, short-term insulin treatment for ≤14 days prior to the day of screening is allowed, as is prior insulin treatment for gestational diabetes
- Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening or in the period between screening and randomization. Pharmacological pupil dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination
- Presence or history of malignant neoplasms within 5 years prior to the day of screening. Basal and squamous cell skin cancer and any carcinoma *in situ* are allowed

ALT, alanine aminotransferase; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; KDIGO, Kidney Disease Improving Global Outcomes; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Supplemental Table S2—Within-patient variability in CGM measured by CV (%)

	Insulin icodec titration A	Insulin icodec titration B	Insulin icodec titration C	Insulin glargine U100
CV, geometric mean (CV%)				
At baseline	20.64 (18.6)	20.99 (19.1)	21.72 (19.9)	21.33 (20.0)
At weeks 15/16	24.75 (19.5)	25.31 (18.9)	28.33 (17.8)	25.25 (17.4)
Relative to baseline at weeks 15/16	1.21 (17.4)	1.22 (19.3)	1.30 (17.7)	1.19 (18.7)

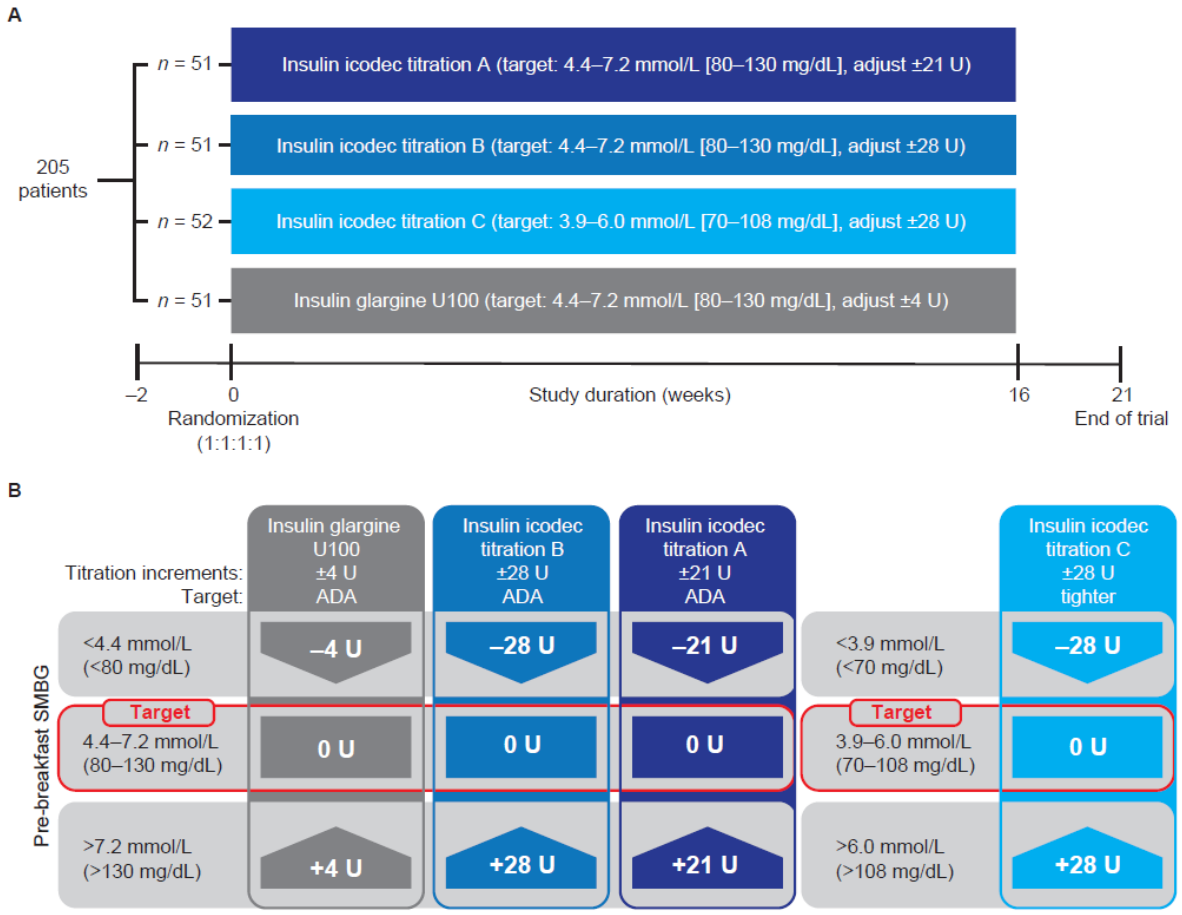
Insulin icodec titration A: titration of insulin icodec to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±21 U. Insulin icodec titration B: titration of insulin icodec to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±28 U. Insulin icodec titration C: titration of insulin icodec to a pre-breakfast SMBG target of 3.9–6.0 mmol/L (70–108 mg/dL) using dose adjustment of ±28 U. Insulin glargine U100: titration of insulin glargine U100 to a pre-breakfast SMBG target of 70–108 mg/dL using dose adjustment of ±4 U. CGM, continuous glucose monitoring; CV, coefficient of variation; SMBG, self-measured blood glucose; U, unit.

Supplemental Table S3—Key secondary endpoints (FAS, *N* = 205)

	Insulin icodec titration A	Insulin icodec titration B	Insulin icodec titration C	Insulin glargine U100
Estimated mean HbA_{1c} (%)				
Week 16, %	7.1	6.9	6.7	7.1
Change from baseline, %-point	–1.0	–1.2	–1.4	–1.0
ETD vs IGlar U100, %-point (95% CI)	0.02 (–0.20 to 0.24)	–0.20 (–0.42 to 0.02)	–0.36* (–0.58 to –0.14)	..
Estimated mean HbA_{1c} (mmol/mol)				
Week 16	54.1	51.7	50.0	53.9
Change from baseline	–10.9	–13.4	–15.1	–11.1
ETD vs IGlar U100 (95% CI)	0.2 (–2.2 to 2.6)	–2.2 (–4.6 to 0.2)	–3.9 (–6.3 to –1.5)	..
Estimated mean FPG, mg/dL				
Week 16	135	131	121	133
Change from baseline	–40	–44	–54	–42
ETD vs IGlar U100, mg/dL (95% CI)	2.09 (–6.44 to 11.62)	–1.43 (–10.01 to 7.15)	–12.02* (–20.52 to –3.51)	..
Estimated mean weekly dose, U†				
Week 15 and 16	142.5	176.4	208.9	145.6
ETR vs IGlar U100 (95% CI)	0.98 (0.77 to 1.25)	1.21 (0.95 to 1.55)	1.44* (1.12 to 1.83)	..
Estimated mean body weight, kg				
Week 16	89.7	90.0	90.1	89.5
Change from baseline	0.9	1.1	1.3	0.6
ETD vs IGlar U100 (95% CI)	0.24 (–0.74 to 1.22)	0.48 (–0.49 to 1.44)	0.62 (–0.34 to 1.58)	..

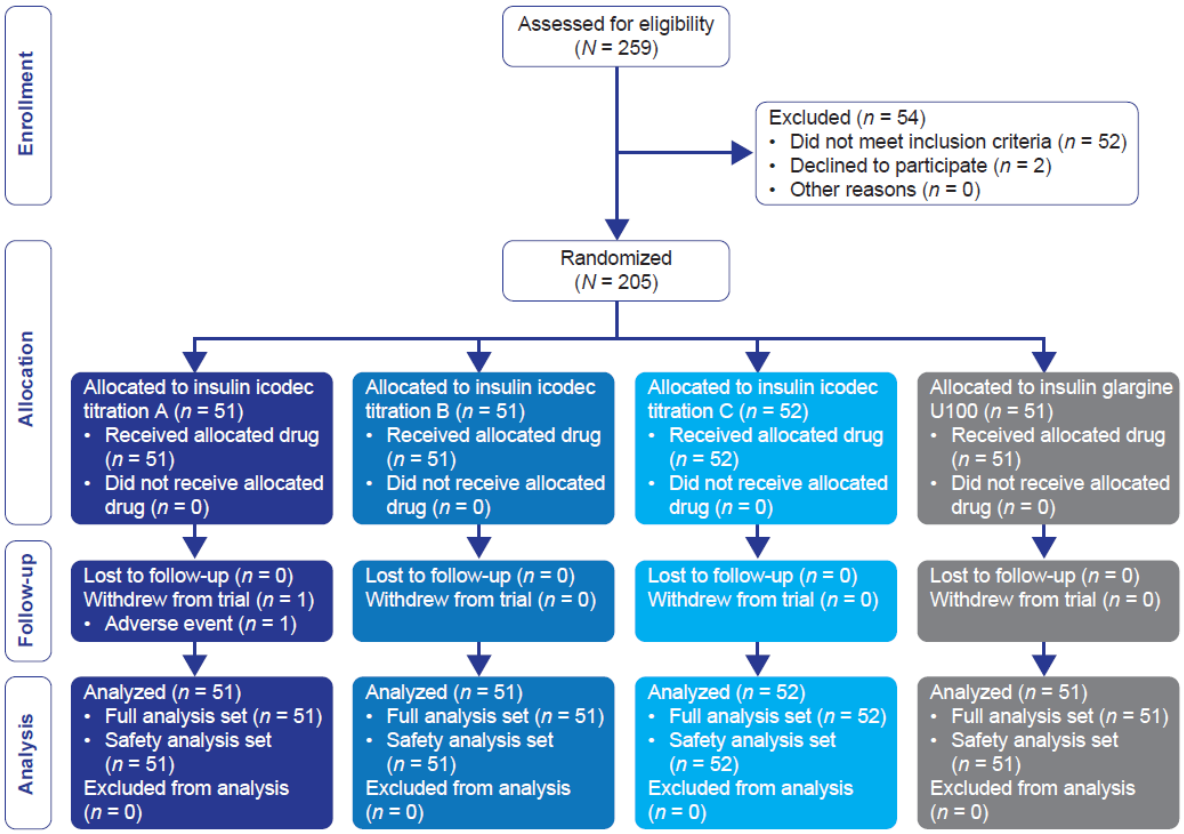
Insulin icodec titration A: titration of insulin icodec to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±21 U. Insulin icodec titration B: titration of insulin icodec to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±28 U. Insulin icodec titration C: titration of insulin icodec to a pre-breakfast SMBG target of 3.9–6.0 mmol/L (70–108 mg/dL) using dose adjustment of ±28 U. Insulin glargine U100: titration of insulin glargine U100 to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±4 U. ETD, estimated treatment difference; ETR, estimated treatment ratio; FAS, full analysis set; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; IGlar U100, insulin glargine U100; SMBG, self-measured blood glucose; U, unit. *$P < 0.05$ versus IGlar U100. †Corresponding to estimated daily doses of approximately 20.4 U, 25.2 U, 29.8 U, and 20.8 U for insulin icodec titrations A, B, C, and IGlar U100, respectively.

Supplemental Figure S1—Study design (*A*) and titration algorithms (*B*)



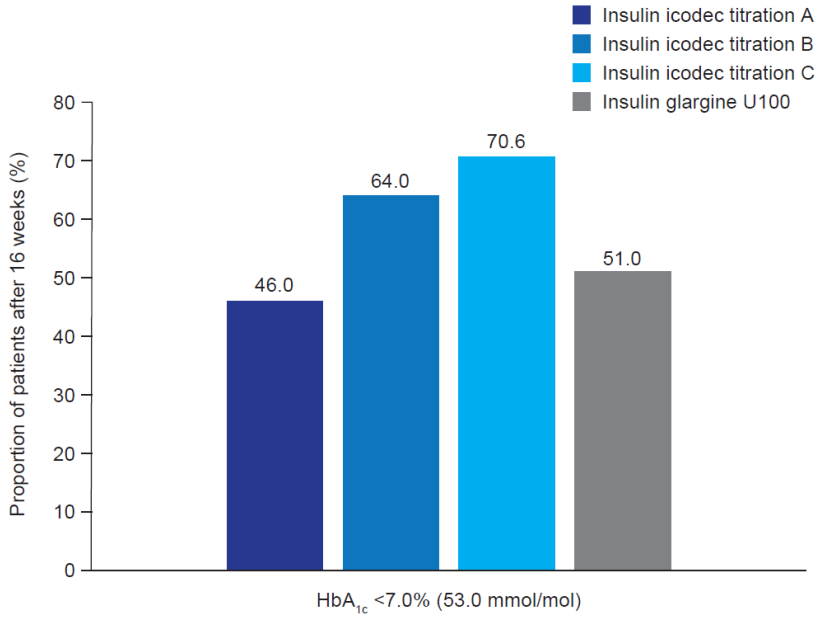
Titration was based on three pre-breakfast SMBG measurements. All arms consisted of the specified treatment regimen on a background of metformin with or without DPP4is and/or SGLT2is. If any of the three pre-breakfast SMBG values on the days leading up to titration and on the day of titration were below the lower limit of the target range, the insulin dose was reduced. If all three SMBG values were above the lower limit of the respective target ranges, dose adjustment was based on the mean of the three pre-breakfast SMBG measurements. ADA, American Diabetes Association; DPP4i, dipeptidyl peptidase 4 inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SMBG, self-measured blood glucose; U, unit.

Supplemental Figure S2—Patient disposition



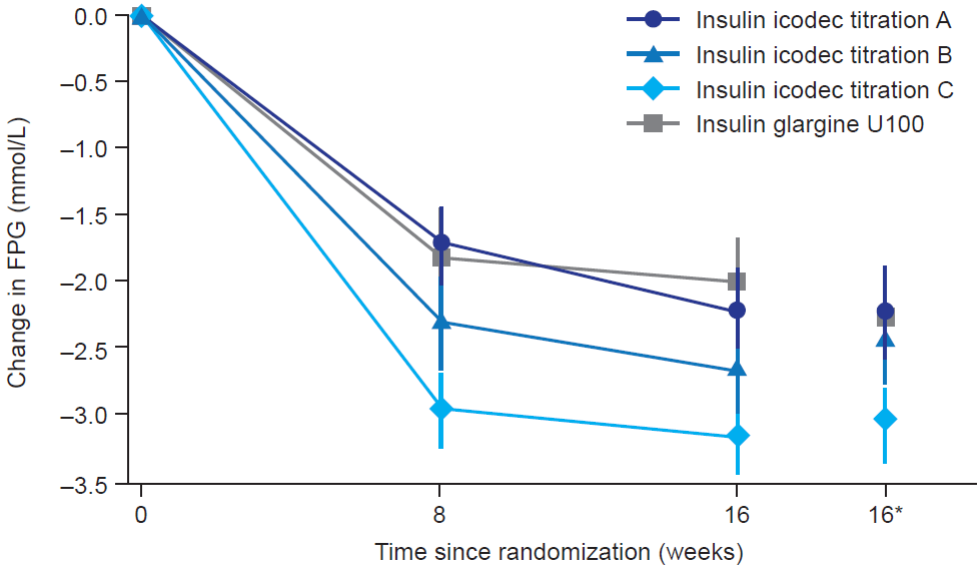
One patient in the insulin icodec titration A group withdrew from the study, owing to a severe adverse event that was considered unlikely to be related to study drug (transitional cell carcinoma).
Insulin icodec titration A: titration of insulin icodec to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±21 U. Insulin icodec titration B: titration of insulin icodec to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±28 U. Insulin icodec titration C: titration of insulin icodec to a pre-breakfast SMBG target of 3.9–6.0 mmol/L (70–108 mg/dL) using dose adjustment of ±28 U. Insulin glargine U100: titration of insulin glargine U100 to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±4 U. SMBG, self-measured blood glucose.

Supplemental Figure S3—Proportion of patients achieving HbA_{1c} <7.0% (53.0 mmol/mol) after 16 weeks



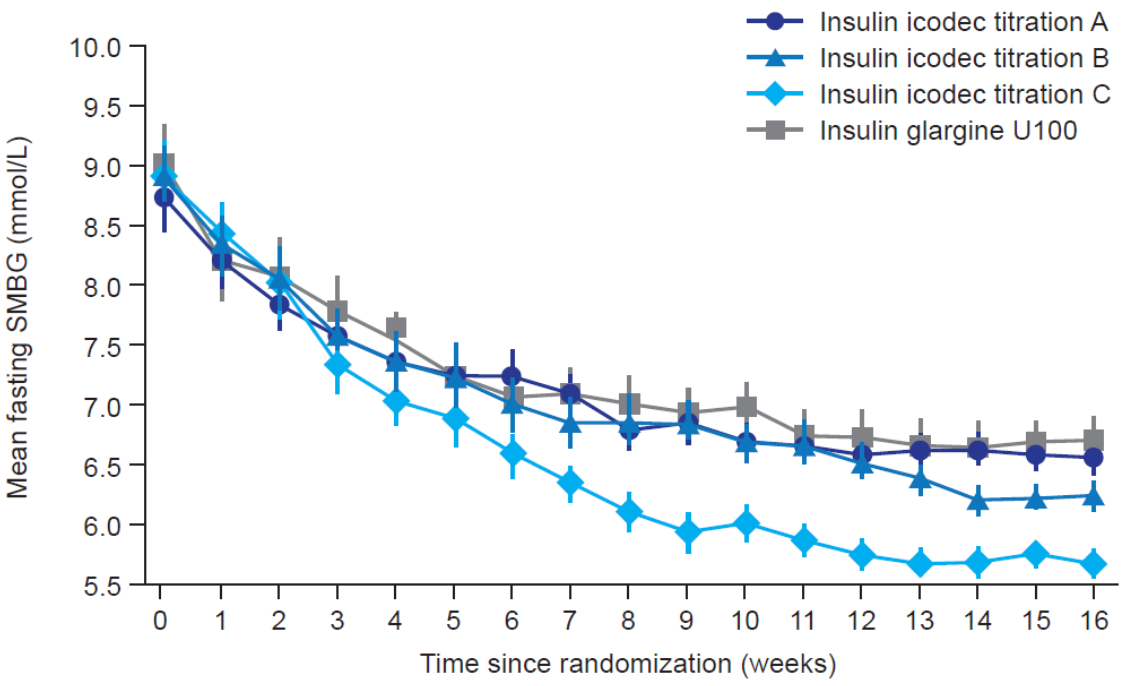
Insulin icodec titration A: titration of insulin icodec to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±21 U. Insulin icodec titration B: titration of insulin icodec to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±28 U. Insulin icodec titration C: titration of insulin icodec to a pre-breakfast SMBG target of 3.9–6.0 mmol/L (70–108 mg/dL) using dose adjustment of ±28 U. Insulin glargine U100: titration of insulin glargine U100 to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±4 U. HbA_{1c}, glycated hemoglobin; SMBG, self-measured blood glucose; U, unit.

Supplemental Figure S4—Mean change in FPG from baseline to week 16 (FAS, *N* = 205)



Observed data: mean (symbol) ± standard error of the mean. *Estimated mean values and the corresponding confidence intervals at week 16 derived based on multiple imputation.
Insulin icodec titration A: titration of insulin icodec to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±21 U. Insulin icodec titration B: titration of insulin icodec to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±28 U. Insulin icodec titration C: titration of insulin icodec to a pre-breakfast SMBG target of 3.9–6.0 mmol/L (70–108 mg/dL) using dose adjustment of ±28 U. Insulin glargine U100: titration of insulin glargine U100 to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±4 U.
FAS, full analysis set; FPG, fasting plasma glucose; SMBG, self-measured blood glucose; U, unit.

Supplemental Figure S5—Changes in mean fasting SMBG during the 16-week study (FAS, *N* = 205)



Incorrect values reported in mmol/L instead of mg/dL at week 10 for one patient in insulin icodec titration B were removed before calculating the mean SMBG. Insulin icodec titration A: titration of insulin icodec to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±21 U. Insulin icodec titration B: titration of insulin icodec to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±28 U. Insulin icodec titration C: titration of insulin icodec to a pre-breakfast SMBG target of 3.9–6.0 mmol/L (70–108 mg/dL) using dose adjustment of ±28 U. Insulin glargine U100: titration of insulin glargine U100 to a pre-breakfast SMBG target of 4.4–7.2 mmol/L (80–130 mg/dL) using dose adjustment of ±4 U.

FAS, full analysis set; SMBG, self-measured blood glucose; U, unit.