Supplementary Materials

Explanation of the Trial Product Estimand Used in this Trial

The draft addendum from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 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 primary 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 [week 15 and 16]) between each of the 2 different switch approaches of once weekly insulin icodec and once daily insulin glargine 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 that are actually able to take the drug during the intended treatment period.

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.
- Men or women, aged 18–75 years (inclusive) at the time of signing informed consent.
- Received a diagnosis of type 2 diabetes ≥180 days prior to the day of screening.
- HbA_{1c} of 7·0–10·0% (53·0–85·8 mmol/mol) (inclusive) as assessed by the central laboratory.
- Treated with once- or twice-daily basal insulin analogue (insulin degludec, insulin detemir, IGlar U100 or IGlar U300; total daily dose of 10–50 U [inclusive]) ≥90 days prior to the day of screening.
- 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 the patient's medical records).
  - Free or fixed combination therapy of metformin (as outlined above) ± DPP4i ± SGLT2i, including:
    - DPP4i at least half of the maximum approved dose according to local label or maximum tolerated or effective dose
    - SGLT2i at least half of the maximum approved dose according to local label or maximum tolerated or effective dose.
- 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 providing signed informed consent.
- Any woman who is pregnant or breast-feeding, intends to become pregnant, or is of childbearing potential and not using an adequate contraceptive method.
- Participation in any clinical trial of an approved or non-approved investigational medicinal product in the 90 days before screening.
- Any disorder, except for conditions associated with type 2 diabetes, that might jeopardize the patient's safety or compliance with the protocol (in the investigator's opinion).
- Any episodes of diabetic ketoacidosis in the 90 days prior to the day of screening and between screening and randomization.
- Known hypoglycaemic unawareness as indicated by the investigator according to question 8 of Clarke's questionnaire.
- Recurrent severe hypoglycaemic episodes in the past year as judged by the investigator.
- Myocardial infarction, stroke, hospitalization for unstable angina pectoris, or transient ischaemic attack in the 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 of <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, the upper normal limit at screening.
- Inadequately treated blood pressure, defined as Grade 3 or higher hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg) at screening.
- Treatment with any medication for the indication of diabetes or obesity, other than those stated in the inclusion criteria, in the 90 days prior to the day of screening.
- Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed in the 90 days prior to screening or 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 in the 5 years prior to the day of screening. Basal- and squamous-cell skin cancer and any carcinoma *in situ* are allowed.

Supplementary Table S1–Inclusion and exclusion criteria
ALT, alanine aminotransferase; DPP4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; IGlar, insulin glargine; KDIGO, Kidney Disease Improving Global Outcomes; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter 2 inhibitor; U, unit.

	Icodec LD (*n* = 54)	**Icodec NLD (*n* = 50)**	**IGlar U100 (*n* = 50)**	**Total (*N* = 154)**
OAD at screening, n (%)				
One OAD	28 (51.9%)	19 (38.0%)	18 (36.0%)	65 (42.2%)
Metformin	27 (50.0%)	19 (38.0%)	18 (36.0%)	64 (41.6%)
SGLT2i	1 (1.9%)	0		1 (0.6%)
Two OADs	17 (31.5%)	22 (44.0%)	25 (50.0%)	64 (41.6%)
Metformin + SGLT2i	10 (18.5%)	9 (18.0%)	11 (22.0%)	30 (19.5%)
Metformin + DPP4i	7 (13.0%)	13 (26.0%)	14 (28.0%)	34 (22.1%)
Three OADs	9 (16.7%)	9 (18.0%)	7 (14.0%)	25 (16.2%)
Metformin + SGLT2i + DPP4i	9 (16.7%)	9 (18.0%)	7 (14.0%)	25 (16.2%)
Daily dose of basal insulin at screening, U, geometric mean (CV%)				
Insulin degludec	24.8 (69.7)	23.5 (50.3)	23.7 (45.2)	23.8 (49.4)
Insulin detemir	24.4 (63.2)	15.2 (41.3)	50.0 (..)	23.1 (64.3)
Insulin glargine U100	20.7 (57.8)	27.9 (44.1)	24.2 (50.1)	23.7 (52.5)
Insulin glargine U300	26.7 (72.3)	20.1 (34.8)	19.9 (45.1)	22.5 (53.8)
NPH (isophane) insulin	--	48.0 (..)	--	--
Antidiabetic drug strata, n (%)				
Once-daily basal insulin* and SGLT2i	16 (29.6%)	16 (32.0%)	16 (32.0%)	48 (31.2%)
Once-daily basal insulin* and no SGLT2i	27 (50.0%)	26 (52.0%)	26 (52.0%)	79 (51.3%)
Twice-daily basal insulin† and SGLT2i	4 (7.4%)	2 (4.0%)	2 (4.0%)	8 (5.2%)
Twice-daily basal insulin† and no SGLT2i	7 (13.0%)	6 (12.0%)	6 (12.0%)	19 (12.3%)

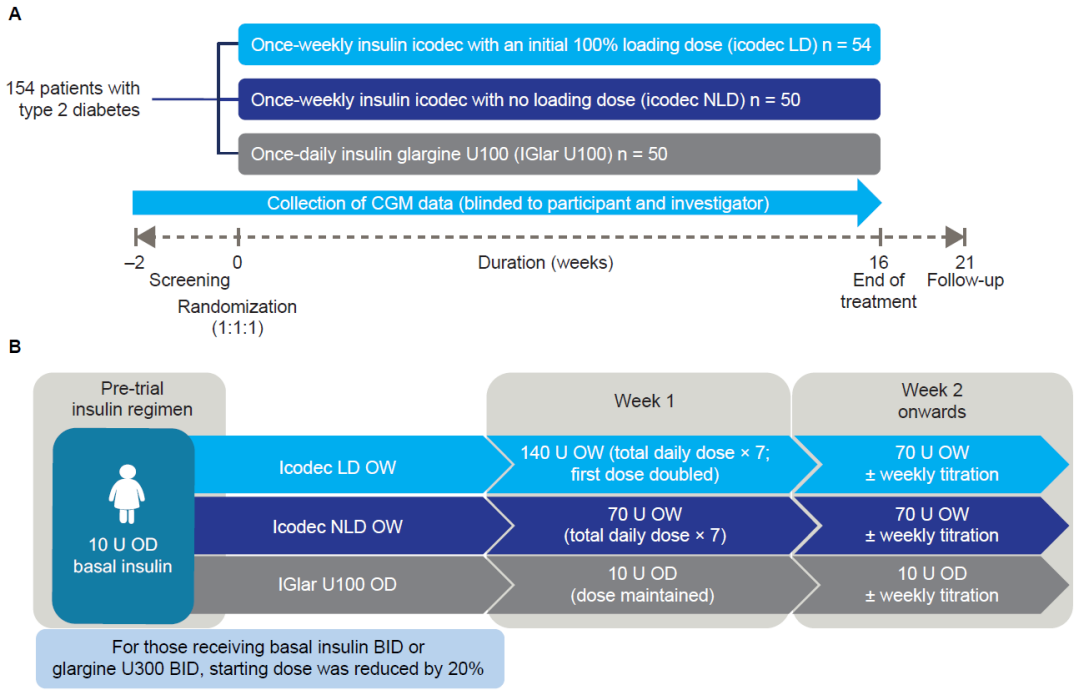
Supplementary Table S2–Baseline treatment for diabetes

All data are mean (SD) unless otherwise stated. CV%, coefficient of variation; DPP4i, dipeptidyl peptidase 4 inhibitor; icodec LD, insulin icodec with an initial 100% loading dose; icodec NLD, insulin icodec with no loading dose; Insulin glargine U100, insulin glargine 100 U/mL; Insulin glargine U300, insulin glargine 300 U/mL; NPH, neutral protamine Hagedorn; OAD, oral antidiabetic drug; SD, standard deviation; SGLT2i, sodium–glucose cotransporter 2 inhibitor; U, unit. *Except IGlar U300. †And IGlar U300.

	Icodec LD (*n* = 54, 21.8 PYE)			**Icodec NLD (*n* = 50, 20.3 PYE)**			**IGlar U100 (*n* = 50, 20.2 PYE)**		
	N (%)	E	R	*N* (%)	E	R	*N* (%)	E	R
Infections and infestations									
Nasopharyngitis	8 (14.8)	9	0.41	7 (14.0)	8	0.39	2 (4.0)	3	0.15
Influenza	1 (1.9)	1	0.05	3 (6.0)	3	0.15	0	--	--
Upper respiratory tract infection	2 (3.7)	2	0.09	1 (2.0)	1	0.05	4 (8.0)	4	0.20
Musculoskeletal and connective tissue disorders									
Pain in extremity	1 (1.9)	1	0.05	3 (6.0)	4	0.20	1 (2.0)	2	0.10
Vascular disorders									
Hypertension	1 (1.9)	1	0.05	3 (6.0)	3	0.15	1 (2.0)	1	0.05
Eye disorders									
Diabetic retinopathy	2 (3.7)	2	0.09	2 (4.0)	2	0.10	3 (6.0)	3	0.15

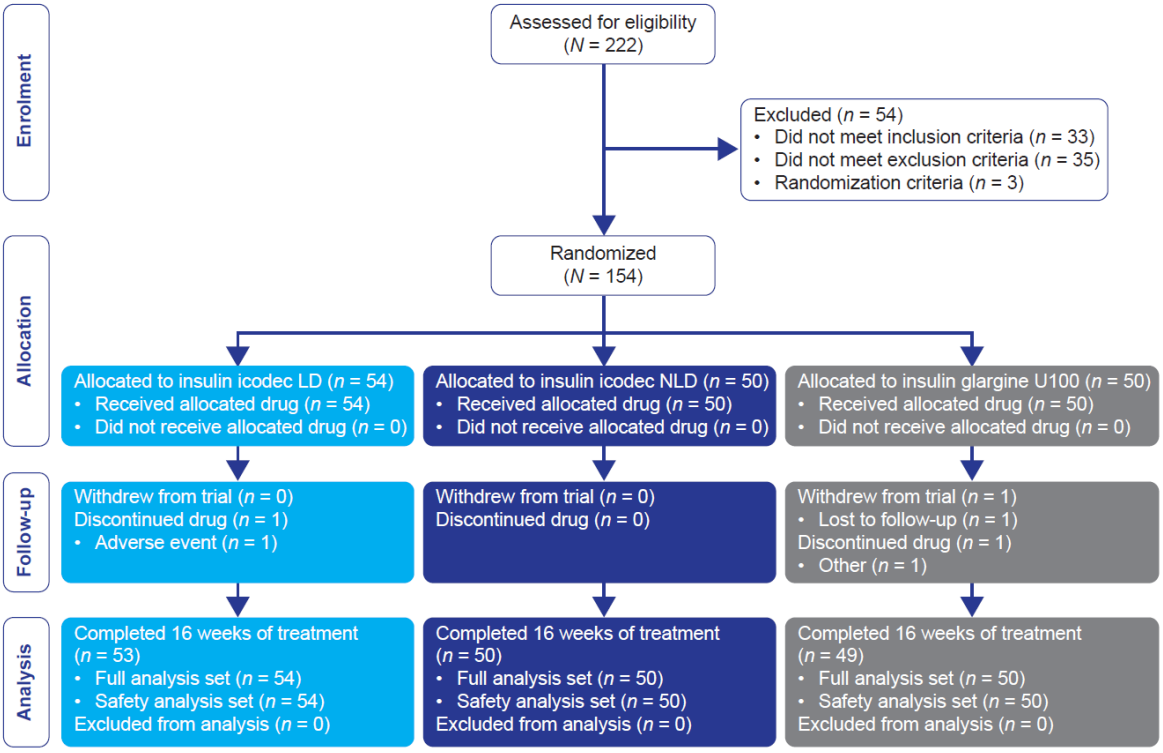
Supplementary Table S3–Most frequent (>5%) adverse events by system organ class and preferred term (SAS; *N* = 154)

The on-treatment period represents the time period during which participants are considered to be exposed to trial product. E, events; icodec LD, insulin icodec with an initial 100% loading dose; icodec NLD, insulin icodec with no loading dose; IGlar U100, insulin glargine 100 U/mL; PYE, patient-years of exposure; R, rate; SAS, safety analysis set. *Rate: number of events per patient-year of exposure.



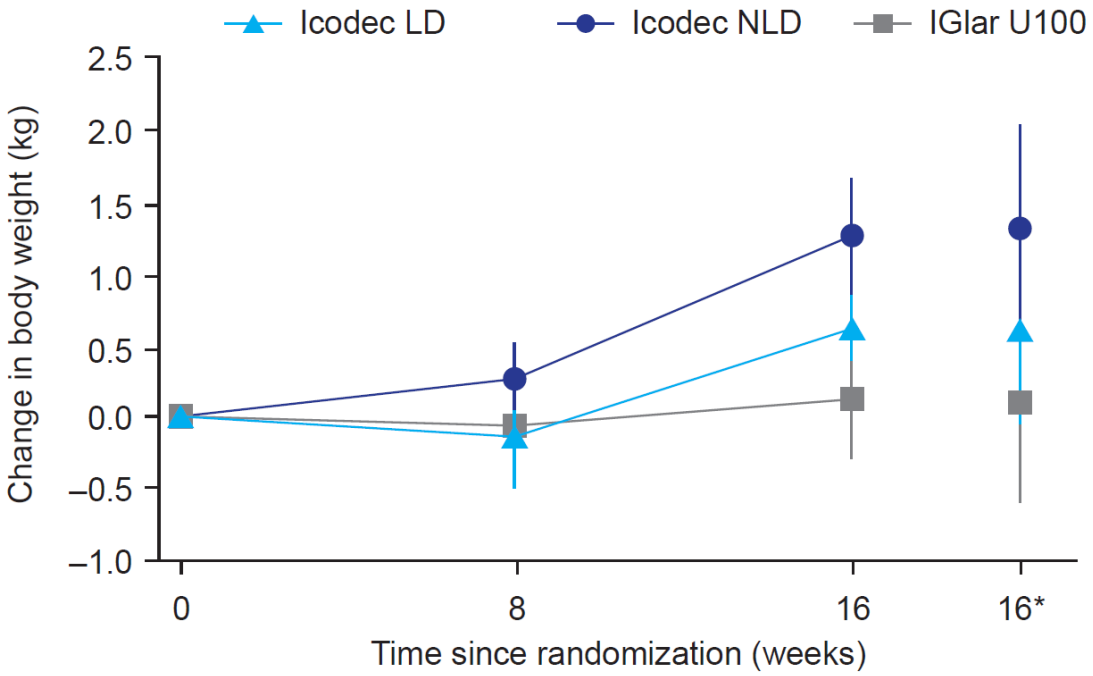
Supplementary Figure S1– Study design schematic (A) and example of switching protocol (B)

BID, twice daily; CGM, continuous glucose monitoring; icodec LD, insulin icodec with an initial 100% loading dose; icodec NLD, insulin icodec with no loading dose; IGlar U100, insulin glargine 100 U/mL; IGlar U300, insulin glarine 300 U/mL; OD, once daily; OW, once weekly; TIR, time in range; U, unit.



Supplementary Figure S2–Trial profile

Insulin icodec LD, insulin icodec with an initial 100% loading dose; Insulin icodec NLD, insulin icodec with no loading dose; Insulin glargine U100, insulin glargine 100 U/mL.



Supplementary Figure S3–Mean change in body weight from baseline to week 16

Observed data: mean (symbol) ± standard error of the mean. FAS, full analysis set; icodec LD, insulin icodec with an initial 100% loading dose; icodec NLD, insulin icodec with no loading dose; IGlar U100, insulin glargine 100 U/mL; *Estimated mean values and the corresponding CI at week 16 derived based on multiple imputation.