SUPPLEMENTARY DATA

Statistical analyses

Hierarchical testing procedure

Hierarchical testing was used to control the type I error rate (false positive results) for the confirmatory secondary endpoints. This scheme included a fixed ordering of the confirmatory secondary endpoints (Number of confirmed hypoglycemic episodes; Change in FPG after 52 weeks of treatment; Within-subject variability in pre-breakfast PG; and Responders for A1C <7% at end of trial without confirmed hypoglycemia who had been exposed to trial drug for at least 12 treatment weeks) to be tested for the superiority of insulin degludec to insulin glargine, if insulin degludec was shown to be non-inferior to insulin glargine in changing A1C from baseline to a non-inferiority limit of 0.4%. The non-inferiority criteria was determined as per recommendation in the 2008 FDA guidance (22) which states, "*Typically, we accept a noninferiority margin of 0.3 or 0.4 HbA1c percentage units provided this is no greater than a suitably conservative estimate of the magnitude of the treatment effect of the active control in previous placebo-controlled trials*." Superiority could only be confirmed for endpoints when all previous hypotheses were confirmed.

Sensitivity Analyses

Sensitivity analyses were performed using the full analysis set. All observed HbA_{1c} measurements available for randomized subjects at scheduled times of measurement were analyzed in a linear mixed model (repeated measure model) using an unstructured residual covariance matrix (if possible). This approach relies on the assumption that data were missing at random according to the taxonomy defined by Rubin (1). The results were compared to the results of the last-observation-carried-forward (LOCF) method for dealing with missing data.

Change in HbA_{1c} from baseline was also analyzed using a model (simple model) with only treatment as fixed factor and baseline HbA_{1c} as covariate to assess the sensitivity of the results to inclusion/exclusion of fixed factors and covariates.

9-point SMBG Analyses

Participants measured blood glucose with a glucose meter (Abbott Diabetes Care, Abbot Park, IL, USA) with test strips calibrated to plasma values, to obtain plasma glucose readings. The 9-point profile included measurements before and 90 minutes after breakfast, lunch and main evening meal, measurements prior to bedtime and at 4 am, and before breakfast the following day.

A mixed effect model was fitted to the 9-point profile data. The model included treatment, time, interaction between treatment and time, antidiabetic therapy at screening, sex and region as fixed factors, age and relevant baseline value as covariate and subject as random effect. From the model, mean profile by treatment and relevant treatment differences were estimated.

Methodology for plotting graphs on confirmed hypoglycemia

The graphs plotting the mean cumulative number of episodes per participant against the study timeline (shown in Fig. 2) were constructed using a Kaplan-Meier technique, calculating the number of events per patient under risk at small intervals and accumulating over time.

The rate of hypoglycemia (expressed as episodes per PYE) can be read at 52 weeks i.e. cumulative across all 52 weeks. The slope of the curve depicts the change in hypoglycemic rate over time. The nocturnal confirmed hypoglycemic episodes constitute a subset of all episodes and are reported at a lower rate. The Y-axis scale is adapted to the total number of episodes for overall and nocturnal confirmed hypoglycemia to allow easy assessment of the absolute rate across the study timelines.

SUPPLEMENTARY DATA

Reasons for withdrawal of participants

Adverse events leading to withdrawal

Twenty (2·6%) participants in the insulin degludec group and five (1·9%) participants in the insulin glargine group were withdrawn due to adverse events (AEs). Interpretation of these data must consider the 3:1 randomization of participants to the insulin degludec and insulin glargine treatment groups.

Twenty participants in the insulin degludec group were withdrawn for 25 AEs. Of these, 12 were non-serious events of mild severity: injection site pain, nausea (two events), vomiting, headache (two events), eczema, Type 1 diabetes mellitus, nephropathy, weight gain, dizziness and urticaria. Three were non-serious events of moderate severity: diarrhea, renal impairment and abdominal pain. Two were serious events of moderate severity: ischemic stroke and thyroid cancer. Eight were serious, severe events: unstable angina, primary atypical pneumonia, abdominal pain, chest pain, hypersensitivity, colon cancer, cerebral infarction and diabetic ketoacidosis.

Five participants in the insulin glargine group were withdrawn for six AEs. Of these, two were non-serious events of moderate severity: macular degeneration and dizziness. Four were serious, severe events: hypoglycaemia, urosepsis, fibula fracture and colitis.

Participants withdrawn for ineffective therapy

Seven (0·9%) participants in the insulin degludec group and two (0·8%) participants in the insulin glargine group were withdrawn due to ineffective therapy as judged by the Investigator. Per protocol, the withdrawal criterion (WC) for lack of effect was defined as follows: After week 12, if the subject had not had a reduction in A1C and had a pre-breakfast SMBG reading corresponding to plasma glucose of > 13·3 mmol/l (> 240 mg/dl) on three consecutive days despite appropriate dose adjustments, the subject was to contact the Investigator and come in for an unscheduled visit as soon as possible (within 2 weeks). The next scheduled visit was not to be awaited. A fasting plasma glucose (FPG) would have to be obtained and analyzed by the central laboratory. If this FPG exceeded 13·3 mmol/l (>240 mg/dl) and no treatable cause for the hyperglycemia had been diagnosed, the subject had be withdrawn. Of the seven participants withdrawn in the insulin degludec group only one participant met the WC completely; five participants met the WC partially; and one participant was withdrawn in error. Of the two participants withdrawn in the insulin glargine group, one participant met the WC completely and one met the WC partially.

'Other' reasons for withdrawal in participants who received treatment

Seventy-seven (10·0%) participants in the insulin degludec group and 30 participants (11·7%) in the insulin glargine group were withdrawn due to 'other' reasons after receiving treatment. Interpretation of these data must consider the 3:1 randomization of participants to the insulin degludec and insulin glargine treatment groups.

The most common 'other' reasons for withdrawal included randomization in error (degludec: 30; glargine: 12) and withdrawal of informed consent (degludec: 25; glargine: 10). Of the participants who withdrew informed consent, one (glargine) was withdrawn due to generally weak condition after the treatment of coronary atherosclerosis and was unable to attend further visits and one (degludec) stopped insulin because her SMPG readings were 80─90 mg/dL without insulin after she lost weight. Additional 'other' reasons for withdrawal included lost to follow-up (degludec: 6; glargine: 4); protocol deviations (degludec: 8; glargine: 4); and treatment-related patient-initiated withdrawal (degludec: 2). One patient who withdrew in relation to treatment did so because of "feeling no effect of treatment anymore" and the other had not met FPG target and was not willing to increase dose beyond 160 units because increased dose would mean three injections. One patient (degludec) was withdrawn due to study site closure. Additionally, five participants (degludec) were withdrawn at the discretion of the investigator

(one withdrawn due to safety concerns described as hyperglycemia experienced in the evenings and risk of hypoglycaemia with higher insulin dose; one due to high A1C of 10·6% at Visit 35; one due to hypoglycaemia with very low insulin dose; one due to 'primary investigator decision to discontinue' and one due to 'primary endocrinologist opinion'.

List of investigators:

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SUPPLEMENTARY DATA

Supplementary Table 1A. *Statistical comparison of various parameters assessed in trial*					
Parameter		**N[a]**	**Baseline Mean (SD)**	**Change from baseline Mean (SD)**	**ETD [95% CI]**
Reduction in A1C from baseline after 52 weeks (FAS)	IDeg	773	8.2 (0.8)%	−1.06 (1.01) %	0.09 % [−0.04; 0·22]
	IGlar	257	8.2 (0.8)%	−1.19 (0.97) %	
Reduction in A1C from baseline after 52 weeks (PP set)[b]	IDeg	665	8.2 (0.8)%	−1.14 (0.04) %[c]	0.13 % [−0.01; 0.26]
	IGlar	221	8·2 (0·8)%	−1.27 (0.06) %[c]	
Sensitivity analyses (Simple Model) - Reduction in A1C from baseline after 52 weeks (FAS)[d]	IDeg	773	8.2 (0.8)%	−1.07 (0.03) %[c]	0.10 % [−0.03; 0.22]
	IGlar	257	8.2 (0.8)%	−1·17 (0·06) %[c]	
Sensitivity analyses (Repeated Measures Model) - Reduction in A1C from baseline after 52 weeks (FAS)[e]	IDeg	701	8.2 (0.8)%	-	0.10 % [−0.04; 0.23]
	IGlar	231	8.2 (0.8)%	-	
Reduction in FPG from baseline after 52 weeks (FAS)	IDeg	762	9.6 (2.6) mmol/l	−3.76 (3.04) mmol/l	-0.43 mmol/L [−0.74; −0.13]
	IGlar	256	9.7 (2.6) mmol/l	−3.30 (2.87) mmol/l	
Weight change from baseline after 52 weeks (FAS)	IDeg	766	89.5 (17.7) kg	2.4 (4.3) kg	0.28 kg [−0.32; 0.88]
	IGlar	257	91.8 (15.8) kg	2.1 (4.1) kg	

SUPPLEMENTARY DATA

Supplementary Table 1B. *Statistical comparison of various parameters assessed in trial*				
		N[a]	**Responders, n (%)**	**Treatment odds ratio [95% CI]**
A1C < 7.0% after 52 wks[f]	IDeg	773	400 (51.7)	0.88 [0.65; 1.19]
	IGlar	257	139 (54.1)	
A1C < 7.0% at end of trial without confirmed hypoglycaemia in the last 12 weeks of treatment[f]	IDeg	703	296 (42.1)	0.86 [0.63; 1.17]
	IGlar	232	106 (45.7)	
A1C < 7.0% at end of trial without nocturnal confirmed hypoglycaemia in the last 12 weeks of treatment[f]	IDeg	703	373 (53.1)	0.94 [0.68; 1.28]
	IGlar	232	126 (54.3)	
			Coefficient of variation (%)	**Treatment ratio [95% CI]**
Within-subject variation in pre-breakfast SMBG (calibrated to plasma glucose) for dose adjustment after 52 weeks	IDeg	770	16.6	0.99 [0.92; 1.06]
	IGlar	255	16.7	

Supplementary Table 1C. *Descriptive statistics*				
Parameter		**N[a]**	**Baseline Mean (SD)**	**Change from baseline Mean (SD)**
Total cholesterol change from baseline after 52 weeks	IDeg	762	4.5 (1.1) mmol/l	−0.0 (0.8) mmol/l
	IGlar	257	4.5 (1.1) mmol/l	−0.1 (0.8) mmol/l
HDL cholesterol change from baseline after 52 weeks	IDeg	762	1.2 (0.3) mmol/l	0.1 (0.2) mmol/l
	IGlar	257	1.1 (0.3) mmol/l	0.1 (0.2) mmol/l
LDL cholesterol change from baseline after 52 weeks[g]	IDeg	762	2.4 (0.9) mmol/l	−0.0 (0.7) mmol/l
	IGlar	257	2.4 (0.9) mmol/l	−0.1 (0.6) mmol/l
Triglycerides change from baseline after 52 weeks	IDeg	762	2.1 (1.6) mmol/l	−0·4 (1.3) mmol/l
	IGlar	257	2.2 (1.9) mmol/l	−0·3 (1.6) mmol/l

SUPPLEMENTARY DATA

Change from baseline in NT-proBNP after 52 weeks	IDeg	748	14.6 (35.3) pmol/l	3·8 (49.2) pmol/l
	IGlar	253	13.1 (19.7) pmol/l	5·7 (59.7) pmol/l
Change from baseline in hsCRP after 52 weeks	IDeg	762	4.2 (7.7) mg/l	0·5 (8.6) mg/l
	IGlar	257	4.8 (8.1) mg/l	0·3 (8.2) mg/l
Change from baseline in QTcB interval after 52 weeks	IDeg	736	415.2 (29.1) msec	0·1 (20.8) msec
	IGlar	241	415.8 (25.1) msec	1.1 (23.1) msec
Change from baseline in QTcF interval after 52 weeks	IDeg	736	403.0 (25.4) msec	1.0 (18.1) msec
	IGlar	241	404.4 (22.4) msec	0.7 (19.5) msec

Supplementary Table 1D. *Additional analyses of nocturnal confirmed and severe hypoglycemia*

	N	PYE	Patients with episodes n (%)	Episodes	Rate	Number of patients needed to be treated for 1 year to avoid 1 hypoglycemic episode with IDeg	Number of hypoglycemic events avoided if 100 patients are treated with IDeg for 1 year
Nocturnal confirmed hypoglycemia							
IDeg	766	667.2	106 (13.8%)	169	0.25	8	13
IGlar	257	217.9	39 (15.2%)	84	0.39		
Severe hypoglycemia							
IDeg	766	667.2	2 (0.3%)	2	0.003	50	2
IGlar	257	217.9	5 (1.9%)	5	0.023		

[a]N=participants contributing to analyses.
[b]Per protocol (PP) analysis set included participants who complied with all recruitment criteria (i.e. inclusion and exclusion criteria); had at least 12 weeks of exposure; and had a valid A1C assessment at baseline and at or after 12 weeks of treatment.
[c]LSMean change from baseline (SE) reported.
[d]Statistical sensitivity analyses using Simple Model: Response and change from baseline in the response after 52 wks of treatment was analyzed using an ANOVA method with treatment as fixed effect, and baseline response as covariate.
[e]Statistical sensitivity analyses using Repeated Measures Model: A1C (%) at scheduled time points after randomization were jointly analyzed in a linear mixed model with an unstructured residual covariance matrix, and with treatment, time, interaction between treatment and time, region, anti-diabetic treatment at screening and sex as fixed effects and age and baseline A1C (%) as covariates.

SUPPLEMENTARY DATA

[f]Dichotomous endpoints (responder/non-responder for A1C <7%) were analyzed based on a logistic regression model.
[g]The treatment difference (IDeg−IGlar) for change in LDL cholesterol from baseline after 52 weeks was statistically significant. ETD: 0.12 mmol/L [0.03; 0.21]. Statistical analysis was based on the FAS. Proportion of participants using statins at randomization (degludec: 53.9% [417/773]; glargine: 56.4% [145/257]) and initiating use during treatment (degludec: 1.7% [13/773]; glargine: 1.9% [5/257]) and proportion of participants using lipid modifying agents at randomization (degludec: 61.6% [476/773]; glargine: 63.8% [164/257]) and initiating use during treatment (degludec: 1.8% [14/773]; glargine: 2.3% [6/257]) were similar between the treatment groups.
Estimated treatment difference (ETD)=IDeg−IGlar; Treatment odds ratio=IDeg/IGlar; Treatment ratio=IDeg/IGlar
IDeg=insulin degludec; IGlar=insulin glargine; FPG=fasting plasma glucose; SMBG=self-measured blood glucose; NT-proBNP=B-type natriuretic peptide; hsCRP=high sensitive C-reactive protein; QT interval=measure of the time between the start of the Q wave and the end of the T-wave; QTcB=QT interval corrected for heart rate using Bazett's formula; QTcF= QT interval corrected for heart rate using Fridericia's formula; ANOVA=analysis of variance; PYE=patient-years of exposure; Rate=rate of hypoglycemia in episodes per PYE

Supplementary Table 2. *Mean daily insulin dose*

Mean Daily Insulin Dose	**IDeg *od* (U/kg)**	**IGlar *od* (U/kg)**	**Mean ratio[a] IDeg/IGlar**	**Estimated Treatment Ratio[b] IDeg/IGlar [95% CI]**
Participants, n	766	257		
Basal				
Week 1	0.12 (0.03)	0.11 (0.02)	-	
Week 52	0.59 (0.35)	0.60 (0.32)	0.98	0.97 [0.89; 1.05]

[a]Mean ratio is the unadjusted ratio between mean doses at last treatment visit, where missing data are imputed using LOCF.
[b]Estimated treatment ratios were adjusted using ANOVA with treatment, sex, antidiabetic therapy at screening, age and Week 1 dose as covariates. Values are observed mean (SD) for the safety analysis set.
IDeg *od*=insulin degludec once-daily; IGlar *od*=insulin glargine once-daily.
SD=standard deviation; ANOVA=Analysis of Variance; LOCF=last observation carried forward; CI=confidence interval

SUPPLEMENTARY DATA

Supplementary Table 3. *Summary of adverse events*						
	IDeg *od* (N=766)			**IGlar *od* (N=257)**		
	n	**%**	**R**	**n**	%	**R**
AEs	572	74.7	403	182	70.8	384
SAEs	62	8.1	12	26	10.1	15
Severity						
Severe	62	8.1	13	26	10.1	18
Moderate	271	35.4	99	87	33.9	95
Mild	513	67.0	291	162	63.0	270
AEs possibly/probably related to basal insulin	94	12.3	26	35	13.6	29
Injection-site reactions	45	5.9	10	18	7.0	13
	n	**%**	**E**	**n**	%	**E**
EAC evaluated events	32†	4.2†	37†	8	3.1	10
Adjudicated MACE	12†	1.6†	13†	2	0.8	2

Treatment-emergent adverse events (adverse events occurring on or after the first day of exposure to treatment and no later than 7 days after the last day of treatment with insulin degludec or insulin glargine). N=number of participants exposed to treatment; n=number of participants with events; %=proportion of participants; R=number of events per 100 patient-years of exposure; E=Number of events; EAC=Event Adjudication Committe; MACE=Major Adverse Cardiovascular Event; Interpretation of 'n' must take the 3:1 (IDeg:IGlar) randomization of participants into consideration.
IDeg *od*=insulin degludec once-daily; IGlar *od*=insulin glargine once-daily; AE=adverse event; SAE=serious adverse event; †Includes two non-treatment emergent events in two participants

SUPPLEMENTARY DATA

Supplementary Table 4. *Serious adverse events possibly/probably related to the trial product*

	IDeg *od* n=766				**IGlar *od* n=257**			
	n	**%**	**e**	**R**	**n**	**%**	**e**	**R**
Events	5	0.7	5	1	2	0.8	2	1
Metabolism and nutrition disorders								
Hypoglycaemia	1	0.1	1	0	2	0.8	2	1
Diabetic ketoacidosis	1	0.1	1	0	–	–	–	–
Hypoglycemic unconsciousness	1	0.1	1	0	–	–	–	–
Gastrointestinal disorders								
Abdominal pain	1	0.1	1	0	–	–	–	–
Immune system disorders								
Hypersensitivity	1	0.1	1	0	–	–	–	–

Treatment-emergent serious adverse events possibly/probably related to the trial product by system organ class and preferred term. Data are from the safety analysis set.
Interpretation of n and e must take the 3:1 randomization (IDeg:IGlar) into consideration.
n=number of participants with events; %=proportion of participants with episodes; e=number of events; R=rate per 100 patient-years of exposure; IDeg *od*=insulin degludec once-daily; IGlar *od*=insulin glargine once-daily

Supplementary Table 5. *Antibodies*

	n	**IDeg-specific antibodies (%B/T) Median [min; max]**	**Cross-reacting antibodies[a] (%B/T) Median [min; max]**	**Participants with change in IDeg specific antibodies (≥10 %B/T from baseline to Week 53)[b] n (%)**	**Participants with change in cross-reacting antibodies (≥10 %B/T from baseline to Week 53)[a,b] n (%)**
Baseline					
IDeg	763	0·0 [−2.0; 2.0]	0·0 [−2.0; 59.0]	–	–
Week 53					
IDeg	602	0·0 [−1.0; 3.0]	0·0 [−3.0; 62.0]	0 (0.0)	12 (1.6%)
	n	**IGlar-specific antibodies (%B/T) Median [min; max]**	**Cross-reacting antibodies[c] (%B/T) Median [min; max]**	**Participants with change in IGlar specific antibodies (≥10 %B/T from baseline to Week 53)[b]**	**Participants with change in cross-reacting antibodies (≥10 %B/T from baseline to Week 53)[b,c]**

SUPPLEMENTARY DATA

				n (%)	n (%)
Baseline					
IGlar	255	−1·0 [−7.0; 2.0]	0·0 [−1.0; 26.0]	–	–
Week 53					
IGlar	193	−1·0 [−6.0; 5.0]	0·0 [−1.0; 57.0]	0 (0.0)	14 (5.4%)

Data represent all exposed patients with antibodies measured. The antibodies are measured by a subtraction radioimmunoassay method (see references 23 and 24 in the manuscript). The reported result represents the %B/T (%bound/total) values after subtraction of background. Due to the assay variation, the resulting difference can be negative. Samples that do not contain insulin antibodies will therefore give values that vary around zero.

%=Proportion of exposed participants (degludec=766; glargine=257) with ≥ 10 %B/T change in antibodies

[a]Antibodies cross-reacting between insulin degludec and human insulin

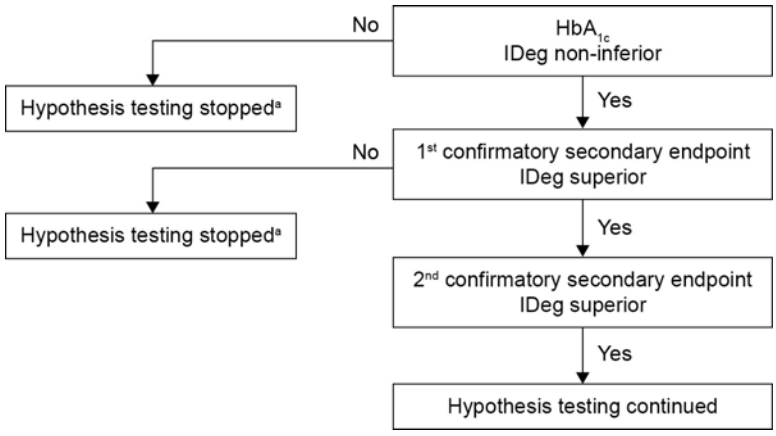
[b]10% B/T is an arbitrary cut-off based on the assay-to-assay uncertainty

[c]Antibodies cross-reacting between insulin glargine and human insulin

% B/T=% bound over total radioactivity

IDeg=insulin degludec; IGlar=insulin glargine

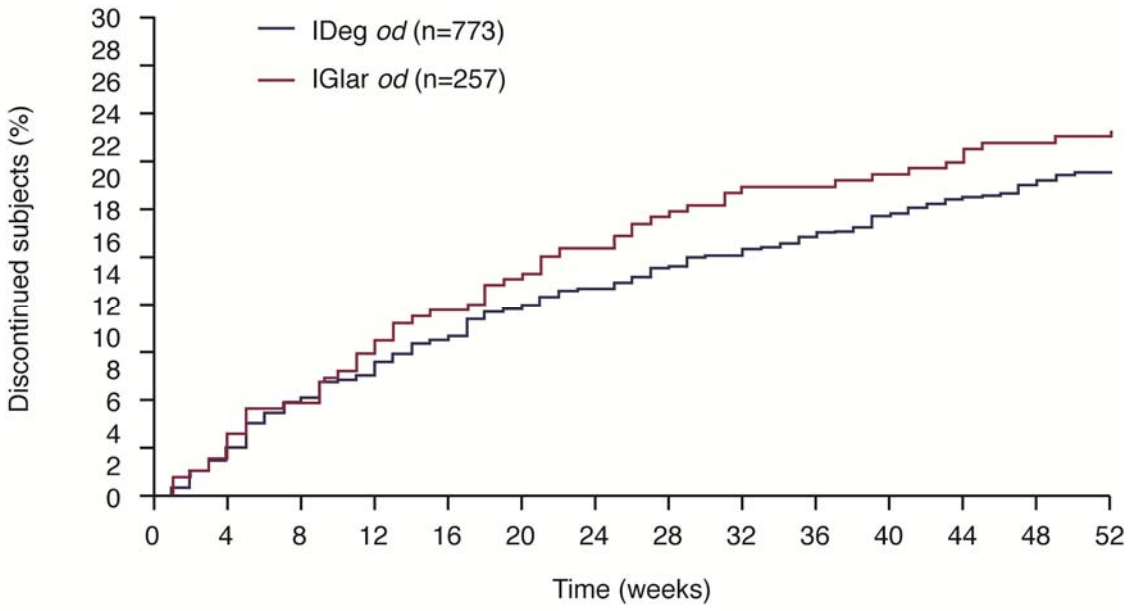
Supplementary Figure 1. *Hierarchical testing scheme.*



[a]Analysis performed, but no formal hypothesis testing is performed.

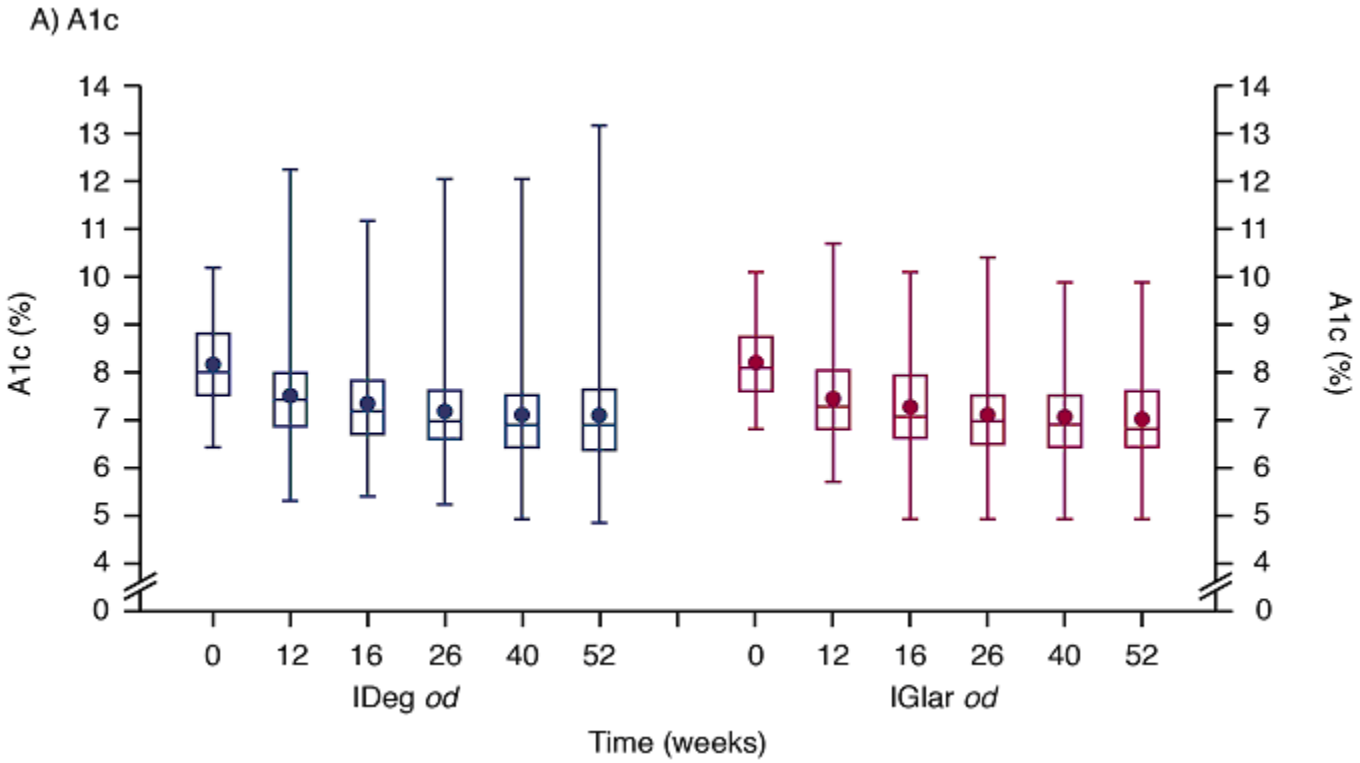
SUPPLEMENTARY DATA

Supplementary Figure 2. *Discontinuation of randomized participants over time.*

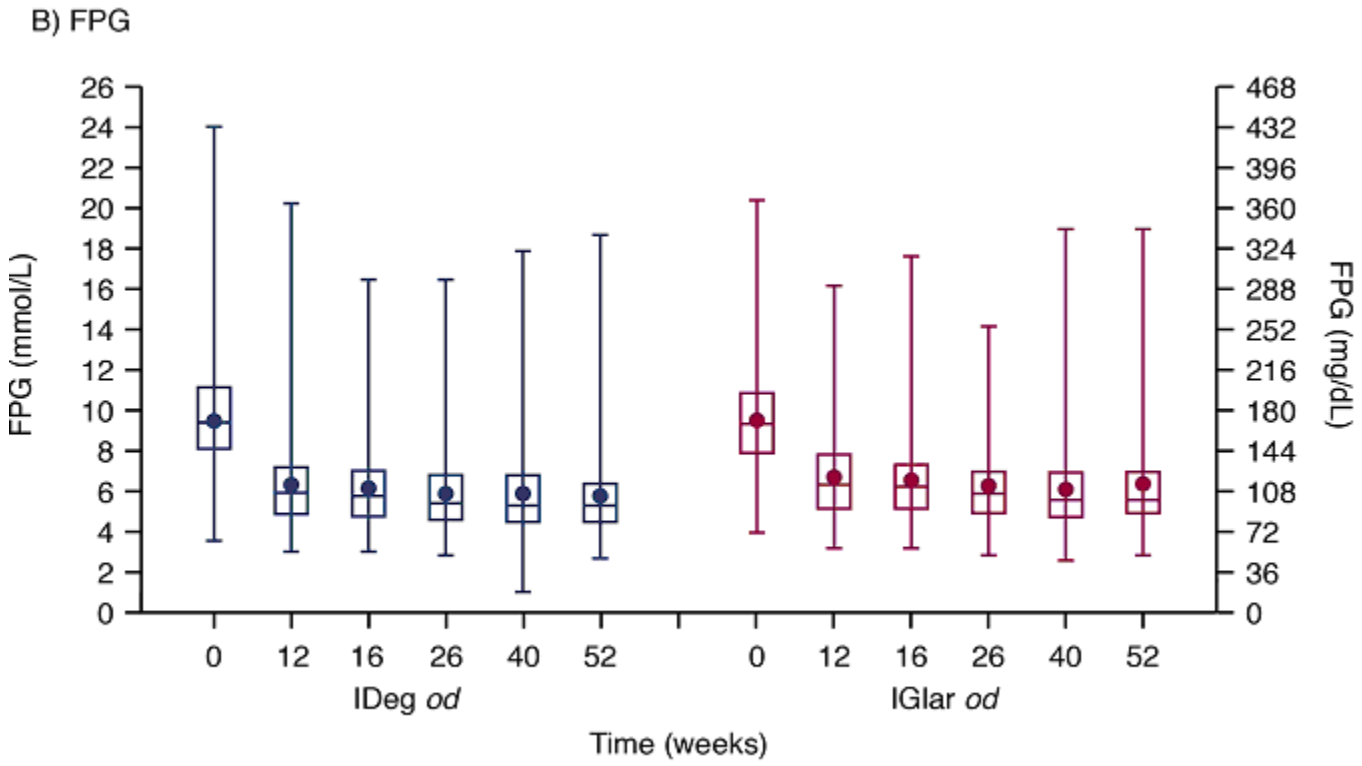


IDeg *od*=insulin degludec once-daily; IGlar *od*=insulin glargine once-daily

Supplementary Figure 3. *Box and whisker plots of A) A1C and B) FPG.*

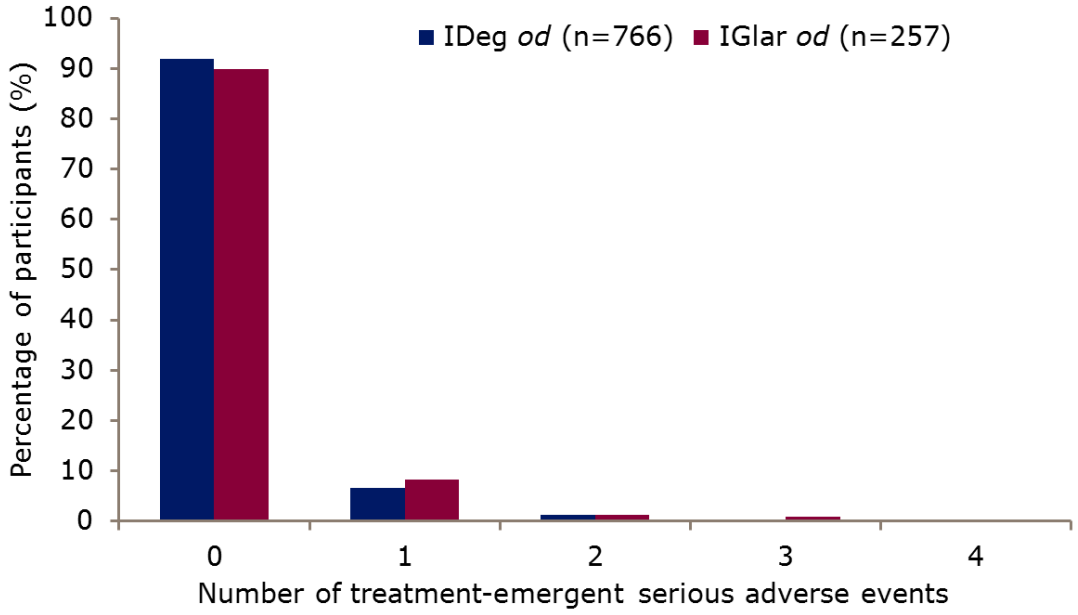


SUPPLEMENTARY DATA



Mean (dot), Median (center line), 25 and 75 percentiles (box), Maximum and minimum (top and bottom bars); A1C=glycated hemoglobin; FPG=fasting plasma glucose; IDeg *od*=insulin degludec once-daily; IGlar *od*=insulin glargine once-daily

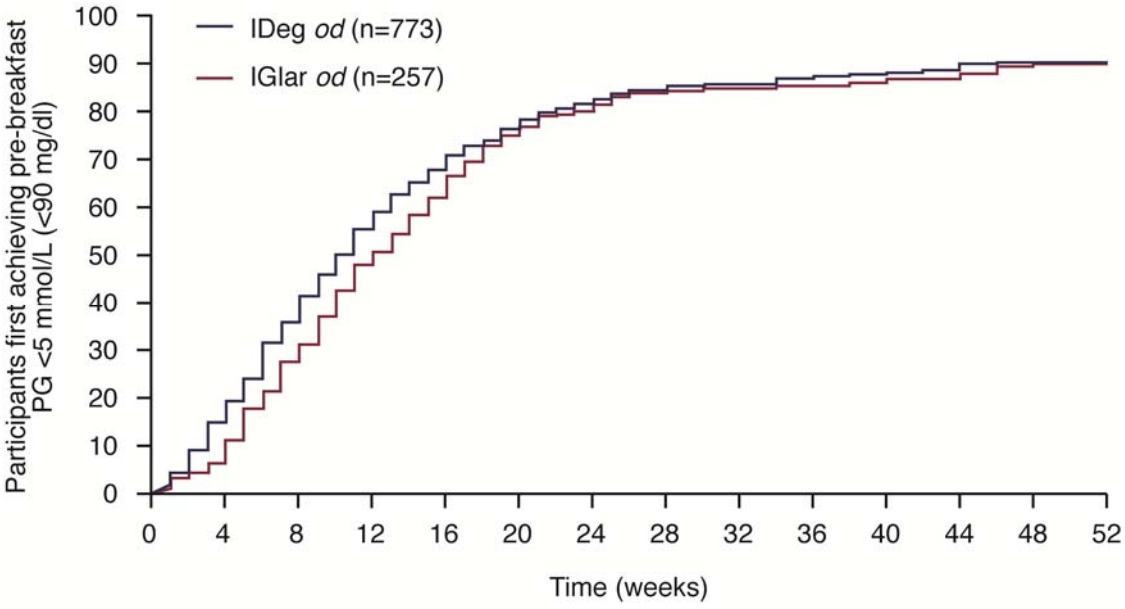
Supplementary Figure 4. *Distribution of treatment emergent serious adverse events.*



IDeg *od*=insulin degludec once daily; IGlar *od*=insulin glargine once daily

SUPPLEMENTARY DATA

Supplementary Figure 5. *Time to first reach titration target.*



Shown by inverted Kaplan-Meier plot for all randomized participants (observed data).

References

Rubin DB. Inference and missing data. *Biometrika* 63:581-592, 1976