Electronic Supplementary Material

A multinational, randomized, open-label, treat-to-target trial comparing insulin degludec and insulin glargine in insulin-naïve patients with type 2 diabetes.

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Table S1   Titration algorithm.

| Mean pre-breakfast PG[a] | | Dose adjustment of IDeg or IGlar |
mmol/L	mg/dL	
< 3.1[b]	< 56[b]	Decrease by 4 U[c]
≤ 3.9[b]	≤ 70[b]	Decrease by 2 U[d]
< 5.0	< 90	No adjustment
< 7.0	< 126	Increase by 2 U
< 8.0	< 144	Increase by 4 U
< 9.0	< 162	Increase by 6 U
≥ 9.0	≥ 162	Increase by 8 U

PG plasma glucose, *IDeg* insulin degludec, *IGlar* insulin glargine, *U* units,

[a] Mean from 3 consecutive days prior to a site visit or telephone contact.

[b] If low PG values occurred without obvious explanation.

[c] For a dose of >45 U, a 10% dose reduction was recommended.

[d] For a dose of >45 U, a dose reduction of 5% was recommended.

The starting dose was 10 U for all subjects. Insulin dose was titrated once weekly throughout the trial based on the mean pre-breakfast self-measured plasma glucose (SMPG) from the last 3 days prior to site visits or telephone contacts. It was recommended that the titration algorithm was followed at all visits/phone contacts. However, the investigators based the decision to adjust the insulin dose on all available information, such as symptoms of hypo-/hyperglycemia, previous responses to dose adjustments as well as blood glucose measurements other than the mandatory ones. A blinded titration committee reviewed deviations weekly. The difference between the recommended dose according to the titration algorithm and the prescribed dose was close to zero for both groups suggesting a close adherence to the titration algorithm.

SMPG was measured using a blood glucose meter (Precision Xtra®/FreeStyle Optimum®; Abbott Diabetes Care Inc., Illinois, USA) with test strips calibrated to plasma values.

Table S2   Sensitivity analyses of the primary analysis, change from baseline in HbA$_{1c}$ (%) after 26 weeks of treatment.

| Analysis | N | | Estimated treatment difference |
	IDeg	IGlar	IDeg-IGlar Mean [95% CI]
Per protocol[a,b]	538	266	-0.05 [-0.17; 0.08]
Simple model[b,c]	555	278	-0.06 [-0.19; 0.07]
Repeated measurements model[d]	538	268	-0.03 [-0.15; 0.10]

CI confidence interval, *HbA$_{1c}$* glycosylated hemoglobin, *IDeg* insulin degludec, *IGlar* insulin glargine

[a] Per protocol (PP) analysis was performed on the PP set, including subjects who complied with all inclusion/exclusion criteria, who had at least 12 weeks of exposure, and who had a non-missing HbA$_{1c}$ at screening or randomization, and at least one non-missing HbA$_{1c}$ at or after 12 weeks of treatment.

[b] Missing values imputed using last observation carried forward method

[c] Change from baseline analyzed with an analysis of variance (ANOVA) including treatment as fixed factor and baseline HbA$_{1c}$ as covariate.

[d] HbA$_{1c}$ values available at scheduled time points after randomization were jointly analyzed using 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 HbA$_{1c}$ as covariates.

Table S3 Summary of treatment emergent adverse events[a] (safety analysis set).

	IDeg OD (n=553)			IGlar OD (n=278)		
	N (%)	Episodes	Rate[b]	N (%)	Episodes	Rate[b]
AEs	293 (53.0)	612	228.3	161 (57.9)	387	289.6
SAEs	16 (2.9)	18	6.7	10 (3.6)	12	9.0
Severity						
Mild	243 (43.9)	448	167.1	140 (50.4)	299	223.8
Moderate	81 (14.6)	148	55.2	44 (15.8)	76	56.9
Severe	16 (2.9)	16	6.0	10 (3.6)	12	9.0
Related to insulin[c]						
Probably	17 (3.1)	19	7.1	9 (3.2)	12	9.0
Possibly	51 (9.2)	71	26.5	24 (8.6)	32	23.9
Unlikely	257 (46.5)	519	193.6	153 (55.0)	342	255.9
Missing	3 (0.5)	3	1.1	1 (0.4)	1	0.7
Most frequent AEs[d]						
URTI	60 (10.8)	77	28.7	32 (11.5)	40	29.9
Nasopharyngitis	41 (7.4)	49	18.3	27 (9.7)	40	29.9
Injection site reactions	9 (1.6)	9	3	2 (0.7)	3	2
Confirmed MACE[e]	4 (0.7)	4	1.5	2 (0.7)	2	1.5

IDeg insulin degludec, *IGlar* insulin glargine, *OD* once daily, *N* number of subjects with events, *%* proportion of subjects with events, *AE* adverse event, *SAE* serious adverse event, *URTI* upper respiratory tract infection, *MACE* major adverse cardiovascular events

[a] Treatment emergent adverse events are events occurring on or after the first day of exposure and no later than 7 days after the last day of treatment

[b] Event rate per 100 years of patient exposure

[c] Relationship based on Investigator's assessment

[d] Adverse events with a frequency ≥5%

[e] Events confirmed by an external event adjudication committee

Fig. S1   Mean insulin dose over the 26-week treatment period (full analysis set).
IDeg insulin degludec, *IGlar* insulin glargine, *U* units