SUPPLEMENTARY DATA

Supplementary Material for Efficacy and Safety of IDegLira versus Basal–bolus Insulin Therapy in Patients with Type 2 Diabetes Uncontrolled on Metformin and Basal Insulin; DUAL VII randomized clinical Trial.

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Statistical Analyses Detail:

1. To control the overall type 1 error for primary and confirmatory secondary endpoints, a hierarchical testing was applied: The tests for superiority with respect to number of treatment emergent severe or blood glucose (BG) confirmed symptomatic hypoglycemic episodes during

26 weeks of treatment was carried out only if non-inferiority of IDegLira versus basal–bolus therapy with regards to the primary endpoint was confirmed. The test for superiority with respect to change in body weight after 26 weeks of treatment was carried out only if non-inferiority of IDegLira versus basal–bolus therapy with regards to the primary endpoint and superiority in terms of BG-confirmed symptomatic hypoglycemic episodes was confirmed.

2. The primary analysis was repeated on the per protocol (PP) analysis set, the completer analysis set (CAS) and based on all data recorded after randomization at scheduled visits, including week 26 HbA_{1c} values for patients who discontinued randomized treatment as sensitivity analysis, plus a tipping point analysis (Supplementary Figure 3) and multiple imputation sensitivity analyses (Supplementary Table 5) with two reference-based methods with retrieved data values at week 26 included for patients who prematurely discontinued treatment (Supplementary Table 6). Sensitivity analysis was also performed on the full analysis set (FAS) using an analysis of covariance (ANCOVA) model with missing data imputed using last observation carried forward (LOCF).
3. Sensitivity analyses for body weight included a tipping point analysis and two reference-based multiple imputation methods (Supplementary Table 5).
4. Sensitivity analyses for the number of severe or BG-confirmed symptomatic hypoglycemic episodes using two pattern mixture approaches based on multiple imputation methods (Supplementary Table 5).

Composite Responders Results for HbA_{1c} ≤6.5%, with No Weight Gain and No Hypoglycemia.

- More patients reached the triple composite HbA_{1c} target ≤6.5% [≤48 mmol/mol]) without hypoglycemic episodes in the last 12 weeks of treatment and without weight gain on IDegLira versus basal–bolus, OR 9.23 [95% CI 4.68; 18.20] respectively, $P < 0.0001$ (Supplementary Fig 4).
- The odds for HbA_{1c} target ≤6.5% (48 mmol/mol) without hypoglycemic episodes in 26 weeks of treatment and without weight gain were higher with IDegLira versus basal–bolus, OR 11.76 [95% CI 5.44; 25.40] respectively, $P < 0.0001$ (Supplementary Fig 4).

Supplementary Table 1. Patient disposition by country

Country	Number of patients randomized (n)	Proportion of patients completing treatment (%)
Argentina	45	97.8
Czech republic	37	100.0
France	16	81.3
Greece	44	90.9
Hungary	37	100.0
Israel	30	83.3
Mexico	46	97.8
Russian Federation	50	100.0

Slovakia	36	94.4
Spain	45	82.2
Turkey	40	92.5
United States	80	90.0

Supplementary Table 2. Inclusion and exclusion criteria

Inclusion Criteria (for an eligible patient, all must be answered 'yes')	Exclusion Criteria (for an eligible patient, all must be answered 'no')
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.	Known or suspected hypersensitivity to trial product(s) or related products.
Male or female, age ≥18 years at the time of signing informed consent.	Previous participation in this trial. Participation is defined as signed informed consent.
Patients with type 2 diabetes patients (diagnosed clinically) ≥6 months prior to screening.	Female who is pregnant, breast-feeding or intend to become pregnant or is of child-bearing potential not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice).
HbA_{1c} 7.0 to 10.0% [53–86 mmol/mol] (both inclusive) by central laboratory analysis.	Receipt of any investigational medicinal product within 30 calendar days before screening.
Current treatment with IGlar U100 for at least 90 calendar days prior to screening.	Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 calendar days before screening.
Stable daily dose of IGlar U100 between 20 units and 50 units (both inclusive) for at least 56 calendar days prior to screening. Individual fluctuations of ± 10% within the 56 calendar days prior to screening are acceptable; however, on the day of screening total daily dose should be within the range of 20 units to 50 units both inclusive.	Anticipated initiation or change in concomitant medications in excess of 14 calendar days known to affect weight or glucose metabolism, such as weight loss/modifying (e.g. sibutramine, orlistat, thyroid hormones, corticosteroids).
Stable daily dose of metformin (≥1500 mg or max tolerated dose) for at least 90 calendar days prior to screening.	Impaired liver function, defined as alanine transaminase ≥2.5 times upper limit of normal.
Body mass index ≤ 40 kg/m^2.	Renal impairment eGFR (estimated glomerular filtration rate) <60 mL/min/1.73 m^2 as per Chronic Kidney Disease Epidemiology Collaboration guidelines.

Able and willing to adhere to the protocol including performing self-measured plasma glucose profiles, to keep a trial diary and to use pre-filled pen device.	Screening calcitonin ≥50 ng/L.
	History of pancreatitis (acute or chronic).
	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.
	Patients presently classified as being in New York Heart Association Class IV.
	Within the past 180 calendar days any of the following: myocardial infarction, stroke or hospitalization for unstable angina and/or transient ischemic attack.
	Currently planned coronary, carotid or peripheral artery revascularization.
	Inadequately treated blood pressure defined as Class 2 hypertension or higher (systolic≥160 mmHg or diastolic ≥100 mmHg) in accordance with National High Blood Pressure Education Program, 7th Joint National Committee and European Society of Hypertension/European Society of Cardiology 2013 guidelines.
	Proliferative retinopathy or maculopathy requiring acute treatment. Verified by Fundus photography.
	Diagnosis of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer, polyps and *in-situ* carcinomas).
	Any condition which, in the opinion of the investigator might jeopardize patient's safety or compliance with the protocol.

HbA_{1c}, glycated hemoglobin; IGlar U100, insulin glargine 100 units/mL

Supplementary Table 3.a) Titration algorithm for IDegLira and IGlar U100 and b) Titration algorithm for prandial insulin

a

Mean pre-breakfast (fasting) SMPG		**Dose change**
mmol/L	**mg/dL**	**Dose steps or units of insulin**

<4.0	<72	–2
4.0–5.0	72–90	0
>5.0	>90	+2

b

Mean pre-prandial and bedtime SMPG		Dose change	Rules for dose adjustment
mmol/L	mg/dL	Units	
<4.0	<72	–1	≥1 SMPGs below target
4.0–6.0	72–108	0	0–1 SMPG above target, no SMPGs below target
>6.0	>108	+1	≥2 SMPGs above target, no SMPGs below target

SMPG, self-monitored plasma glucose; IGlar U100, insulin glargine 100 units/mL; IDegLira, insulin degludec/liraglutide fixed-ratio combination

Supplementary Table 4. Analysis set definitions

Analysis Set	Definition
FAS	All randomized patients
PP	All patients in the FAS who did not violate any inclusion criteria, did not meet any exclusion criteria, who's HbA_{1c} was known at screening or randomization, had at least 12 weeks of treatment and afterwards had at least one documented HbA_{1c} measurement.
CAS	All randomized patients who completed the trial without discontinuation of the randomized treatment.
SAS	All patients receiving at least one dose of either IDegLira or basal–bolus therapy.

FAS, full analysis set; PP, per protocol; SAS, safety analysis set; CAS, completer analysis set; HbA_{1c}, glycated hemoglobin

SUPPLEMENTARY DATA

Supplementary Table 5. Algorithm for multiple imputation based sensitivity analyses.

HbA_{1c}

Conditional MI

A pattern mixture model approach, mimicking an ITT scenario where patients withdrawn from the IDegLira arm were assumed to be switched to a treatment inferior to basal–bolus treatment after discontinuation with a gradual loss of the treatment effect obtained up until withdrawal was performed for evaluation of non-inferiority for the primary endpoint (conditional approach). The analysis was based on the FAS using all post-baseline HbA_{1c} measurements obtained up until week 26, especially including measurements retrieved at week 26 from patients who had discontinued their randomized treatment. The imputation was based on the conditional sequential modelling described in the book by O' Kelly and Ratitch (1). The model was estimated as follows:

- In the first step, intermittent missing values were imputed using a Markov Chain Monte Carlo method, in order to obtain a monotone missing data pattern. This imputation was done for each treatment arm separately and 1000 copies of the dataset were generated.
- In the second step, for each of the 1000 copies of the dataset, an analysis of variance model with treatment and region as fixed factors, and baseline HbA_{1c} as covariate was fitted to the change in HbA_{1c} from baseline to 4 weeks for the basal–bolus arm only. The estimated parameters, and their variances, from this model were used to impute missing values at 4 weeks for patients in all treatment arms, based on region and HbA_{1c} at baseline.
- In the third step, for each of the 1000 copies of the dataset, an analysis of variance model with treatment and region as fixed factors, and baseline HbA_{1c} and HbA_{1c} at 4 weeks (visit 6) as covariates was fitted to the change in HbA_{1c} from baseline to 8 weeks for the basal–bolus arm only. The estimated parameters, and their variances, from this model were used to impute missing values at 8 weeks for patients in all treatment arms, based on region and HbA_{1c} at baseline and 4 weeks.
- In the fourth step, for each of the 1000 copies of the dataset, missing HbA_{1c} values at 12 weeks were imputed in the same way as for 8 weeks. Now the imputations were based on an analysis of variance model with the same factors and the HbA_{1c} values at baseline, 4 weeks and 8 weeks as covariates, fitted to the basal–bolus arm.
- This stepwise procedure was then repeated sequentially over the available planned visits, adding one visit in each step until the last planned visit at 26 weeks.
- For each withdrawn patient or patient discontinued from treatment in the IDegLira treatment arm, a value of 0.3% (the non-inferiority limit) was added to the change in HbA_{1c} at 26 weeks.
- For each of the complete data sets, the change from baseline to 26 weeks was analyzed using an analysis of variance model with treatment and region as fixed factors and baseline HbA_{1c} value as a covariate.
- The estimates and standard deviations for the 1000 data sets were pooled to one estimate and associated standard deviation using Rubin's rule. From

these pooled estimates the confidence interval for the treatment differences and the associated *P*-value were calculated.

Unconditional MI

A pattern mixture model approach, mimicking an ITT scenario where patients withdrawn from the IDegLira arm are assumed to be switched to a treatment inferior to basal–bolus treatment after discontinuation with an immediate loss of the treatment effect obtained up until withdrawal was also performed (unconditional approach). As a first step, all post-baseline HbA_{1c} measurements were set to missing for withdrawn patients in the IDegLira arm not having a retrieved HbA_{1c} measurement at 26 weeks. Thereafter, the steps conducted in the conditional approach described above were followed. This imputation was based on the unconditional sequential modelling described in the book by O'Kelly and Ratitch (1).

Tipping point analysis

A tipping point analysis was carried out where patients withdrawn from the IDegLira arm were assumed to receive treatment inferior to basal–bolus treatment. The analysis followed the steps above for the un-conditional pattern mixture approach with the non-inferiority step replaced by a gradual increase in inferiority. The extent of the inferiority was gradually increased to evaluate at which point IDegLira is no longer statistically significantly better than basal–bolus treatment.

Body weight

As sensitivity analyses for body weight the pattern mixture models and tipping point analysis specified for HbA_{1c} was repeated substituting body weight for HbA_{1c} as response and leaving out the non-inferiority penalty. The analyses was based on the FAS using all post-baseline body weight measurements obtained on visits up until week 26. Imputations were made for both withdrawn and prematurely discontinued patients as body weight is not measured at week 26 in patients discontinuing their randomized treatment.

Hypoglycemia

Two pattern mixture approaches were applied as sensitivity analyses for the number of treatment emergent severe or BG confirmed symptomatic hypoglycemic episodes.

Method 1 MI

In the first sensitivity analysis, for withdrawn or prematurely discontinued patients, the number of events in the missing period (time of premature discontinuation to planned treatment emergent period [max of 27 weeks and longest treatment emergent exposure time observed in the trial]) were imputed using a multiple imputation technique, and assuming that all patients had an event rate in the period before and after premature discontinuation corresponding to the event rate in the basal–bolus arm.

This was done as follows:

1. As a first step, a Bayes negative binomial model was fitted to the event rate data to obtain the posterior distribution of model parameters.
2. In the second step, based on the estimated parameters for basal–bolus arm in this model, the number of events in the missing period was imputed for all withdrawn or prematurely discontinued patients (i.e. pre- and post-

discontinuation event rates in the conditional distribution used for imputation were as for basal–bolus treatment). Multiple copies (1000 copies) of a complete data set were generated by sampling from the estimated distribution.

3. In the third step, for each of the complete data sets, the number of events was analyzed using a negative binomial model with a log-link function and the logarithm of the time period in which a hypoglycemic episode is considered treatment emergent as offset. The model included treatment and region as fixed factors.
4. In the fourth step, the estimates and standard deviations for the 1000 data sets were pooled to one estimate and associated standard deviation using Rubin's rule 2. From these pooled estimates the confidence interval for the treatment ratio and the associated P-value were calculated.

Method 2 MI

In the second analysis, patients on IDegLira were assumed to have the event rate of the IDegLira arm prior to withdrawal or premature discontinuation and the event rate of the basal–bolus arm after withdrawal or premature discontinuation. The method followed the multiple imputation above, but in the second step pre-discontinuation rates were the respective arms rates while post-discontinuation rate was the rate of basal–bolus arm.

FAS, full analysis set; HbA_{1c}, glycated hemoglobin; IDegLira, insulin degludec/liraglutide combination; ITT, intent-to-treat; TE, treatment exposure

Supplementary Table 6. HbA_{1c}, body weight and hypoglycemia statistical sensitivity analyses.

HbA_{1c} (%) Model (analysis set)	**Treatment difference IDegLira – IGlar U100 + IAsp**	
	Estimate	**[95% CI]**
MMRM (primary, full analysis set)	–0.02	[–0.16;0.12]
LOCF (full analysis set)	0.00	[–0.15; 0.16]
Unconditional MI* (full analysis set)	0.00	[–0.15; 0.15]
Conditional MI* (full analysis set)	0.00	[–0.15; 0.15]
MMRM* (full analysis set)	–0.01	[–0.16; 0.13]
MMRM (completer analysis set)	–0.04	[–0.17; 0.10]
MMRM (per protocol analysis set)	–0.04	[–0.17; 0.10]
HbA_{1c} (mmol/mol) Model (analysis set)	**Treatment difference IDegLira – IGlar U100 + IAsp**	
	Estimate	**[95% CI]**

MMRM (primary, full analysis set)	–0.2	[–-1.7;1.3]
LOCF (full analysis set)	0.1	[–1.7; 1.8]
Unconditional MI* (full analysis set)	0.0	[–1.6; 1.7]
Conditional MI* (full analysis set)	0.0	[–1.6; 1.7]
MMRM* (full analysis set)	–0.1	[–1.8; 1.5]
MMRM (completer analysis set)	–0.4	[–1.9; 1.1]
MMRM (per protocol analysis set)	–0.4	[–1.9; 1.1]

Body weight (kg) **Model (analysis set)**	**Treatment difference** **IDegLira – IGlar U100 + IAsp**	
	Estimate	**[95% CI]**
MMRM (confirmatory, full analysis set)	–3.6	[–4.2; –2.9]
Unconditional MI (full analysis set)	–3.3	[–4.0; –2.7]
Conditional MI (full analysis set)	–3.4	[–4.1; –2.8]

Severe or BG-confirmed symptomatic hypoglycemic episodes **Model (analysis set)**	**Statistical analysis**			
	N	**%**	**E**	**Estimated number of events per 100 PYE**
Confirmatory analysis (full analysis set) IDegLira	252	19.8	129	90.16
IGlar U100 + IAsp	253	52.6	975	784.43
Method 1 MI (full analysis set)				
IDegLira	252	-	-	100.87
IGlar U100 + IAsp	253	-	-	780.53
Method 2 MI (full analysis set)				
IDegLira	252	-	-	122.66
IGlar U100 + IAsp	253	-	-	779.94

Severe or BG-confirmed symptomatic hypoglycemic episodes **Model (analysis set)**	**Rate ratio** **IDegLira/IGlar U100 + IAsp**	
	Estimate	**[95% CI]**
Confirmatory analysis (full analysis set)	0.11	[0.08; 0.17]

Method 1 MI (full analysis set)	0.13	[0.08; 0.20]
Method 2 MI (full analysis set)	0.16	[0.10; 0.26]

Sensitivity analyses were in agreement with confirmatory analysis.

Hypoglycemia analysis - Negative binomial regression model with log link and log of exposure + 7 days as offset. The model included region and treatment as factors. HbA_{1c} and body weight analyses – the model included region and treatment as factors and baseline response as covariate.

*Including retrieved data at week 26 from patients who prematurely discontinued treatment

BG, blood glucose; CI, confidence interval; HbA_{1c}, glycated hemoglobin; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL; LOCF, last observation carried forward; MI, multiple imputation; MMRM, mixed model for repeated measurement; N, number or patients contributing to the analysis; %, proportion of patients with one or more hypoglycemic events, E, number of events, PYE, patient year of exposure

SUPPLEMENTARY DATA

Supplementary Table 7. Treatment-emergent adverse events.

Event	IDegLira				IGlar U100 + IAsp			
	n	%	E	R	n	%	E	R
Adverse events	149	59.1	494	4.10	144	56.9	414	3.47
Serious	12	4.8	13	0.11	10	4.0	11	0.09
Cardiac disorders	4	1.6	4	0.03	1	0.4	1	0.01
Angina unstable	1	0.4	1	0.01	0	–	–	–
Atrial fibrillation	1	0.4	1	0.01	0	–	–	–
Atrial flutter	1	0.4	1	0.01	0	–	–	–
Cardiac failure	1	0.4	1	0.01	0	–	–	–
Silent myocardial infarction	0	–	–	–	1	0.4	1	0.01
Gastrointestinal disorders	0	–	–	–	2	0.8	2	0.02
Anal fistula	0	–	–	–	1	0.4	1	0.01
Gastritis	0	–	–	–	1	0.4	1	0.01
Infections and Infestations	3	1.2	4	0.03	2	0.8	2	0.02
Postoperative wound infection	1	0.4	1	0.01	1	0,4	1	0.01
Diabetic foot infection	1	0.4	1	0.01	0	–	–	–
Gastroenteritis	1	0.4	1	0.01	0	–	–	–
Pneumonia	0	–	–	–	1	0.4	1	0.01
Staphylococcal bacteremia	1	0.4	1	0.01	0	–	–	–
Musculoskeletal and connective tissue disorders	0	–	–	–	2	0.8	2	0.02
Musculoskeletal chest pain	0	–	–	–	1	0.4	1	0.01
Osteoarthritis	0	–	–	–	1	0.4	1	0.01
Eye disorders	1	0.4	1	0.01	0	–	–	–
Retinal detachment	1	0.4	1	0.01	0	–	–	–
Generals disorders and administration site conditions	1	0.4	1	0.01	0	–	–	–

Chest pain	1	0.4	1	0.01	0	–	–	–
Hepatobiliary disorders	1	0.4	1	0.01	0	–	–	–
Hepatic cyst	1	0.4	1	0.01	0	–	–	–
Metabolism and nutrition disorders	1	0.4	1	0.01	0	–	–	–
Hypoglycemia	1	0.4	1	0.01	0	–	–	–
Renal and urinary disorders	1	0.4	1	0.01	0	–	–	–
Staghorn calculus	1	0.4	1	0.01	0	–	–	–
Neoplasms benign, malignant and unspecified	0	–	–	–	1	0.4	1	0.01
Breast cancer	0	–	–	–	1	0.4	1	0.01
Vascular disorders	0	–	–	–	1	0.4	1	0.01
Embolism arterial	0	–	–	–	1	0.4	1	0.01
Reproductive system and breast disorders	0	–	–	–	1	0.4	1	0.01
Metrorrhagia	0	–	–	–	1	0.4	1	0.01
Skin and subcutaneous tissue disorders	0	–	–	–	1	0.4	1	0.01
Diabetic foot	0	–	–	–	1	0.4	1	0.01
Fatal	0	–	–	–	0	–	–	–
Severe	7	2.8	10	0.08	2	0.8	2	0.02
Cardiac disorders	2	0.8	2	0.02	0	–	–	–
Gastrointestinal disorders	2	0.8	4	0.03	0	–	–	–
Infections and Infestations	2	0.8	3	0.03	0	–	–	–
Metabolism and nutrition disorders	1	0.4	1	0.01	0	–	–	–
Neoplasms benign, malignant and unspecified	0	–	–	–	1	0.4	1	0.01
Vascular disorders	0	–	–	–	1	0.4	1	0.01
Probably related to IDegLira/IGlar U100	47	18.7	118	0.98	13	5.1	37	0.31

Probably related to bolus insulin	NA	NA	NA	NA	14	5.5	38	0.32
EAC confirmed Cardiovascular AE	1[†]	0.4	1	0.01	0	–	–	–
EAC confirmed Neoplasm AE	1[‡]	0.4	1	0.01	0	–	–	–

[†]angina pectoris, unstable [‡]large intestine polyp, benign. Data based on safety analysis set. One breast cancer event in the basal–bolus arm was deemed non-treatment emergent by a blinded EAC. Serious = death, life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, persistent/significant disability/incapacity, congenital anomaly, event that jeopardizes the patient and requires medical/surgical intervention, suspicion of transmission of infectious agents via trial product. Severe = considerable interference with patient's daily activities. The severity of AEs was evaluated by the investigator.
n, number of patients with one or more events; (%), percentage of patients with one or more events; E, Number of events; R, Events per year of exposure
AE, adverse event; EAC, event adjudication committee; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL

Supplementary Table 8. Fasting lipids

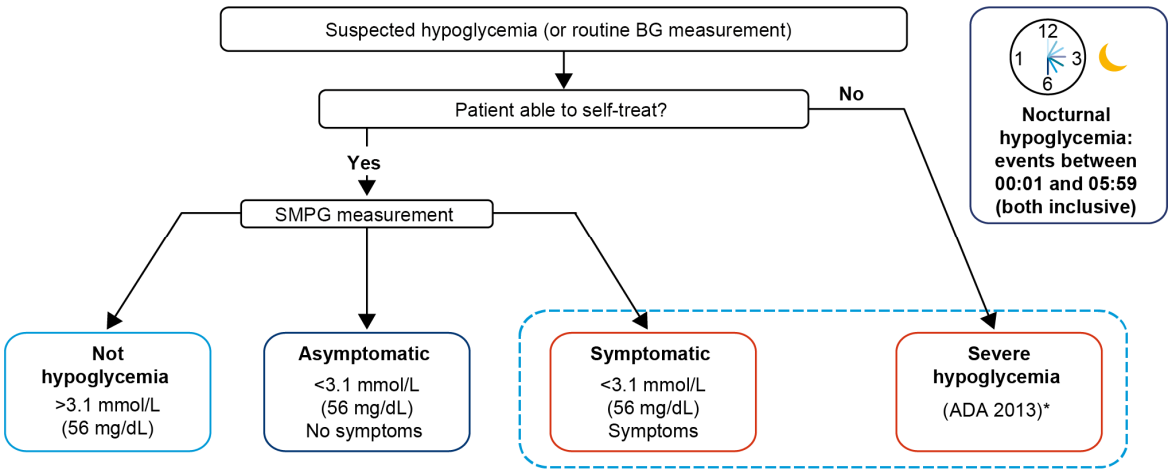
Event	IDegLira		IGlar U100 + IAsp		Estimated Treatment Ratio (95% CI)
	Week 0	Week 26	Week 0	Week 26	
Total cholesterol, mmol/L	4.43	4.25	4.29	4.35	0.96 [0.92; 0.99], *P* = 0.0120
LDL cholesterol, mmol/L	2.30	2.25	2.26	2.32	0.96 [0.91; 1.02], *P* = 0.1600
HDL cholesterol, mmol/L	1.17	1.17	1.16	1.21	0.97 [0.94; 0.99], *P* = 0.0133
VLDL cholesterol, mmol/L	0.74	0.66	0.71	0.66	0.97 [0.91; 1.03], *P* = 0.3119
Triglycerides, mmol/L	1.64	1.43	1.56	1.44	0.97 [0.91; 1.03], *P* = 0.2764
Free fatty acids, mmol/L	0.44	0.33	0.42	0.38	0.84 [0.77; 0.92], *P* < 0.0001

The log-transformed response after 26 weeks of treatment is analyzed using a MMRM model with unstructured covariance matrix. The model includes treatment, visit and region as fixed factors and the log-transformed baseline response as covariate. CI, confidence interval; HDL, high-density lipoprotein; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination;

SUPPLEMENTARY DATA

IGlar U100, insulin glargine 100 units/mL; MMRM, mixed model of repeated measurements; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein

Supplementary Figure 1. Hypoglycemia classification

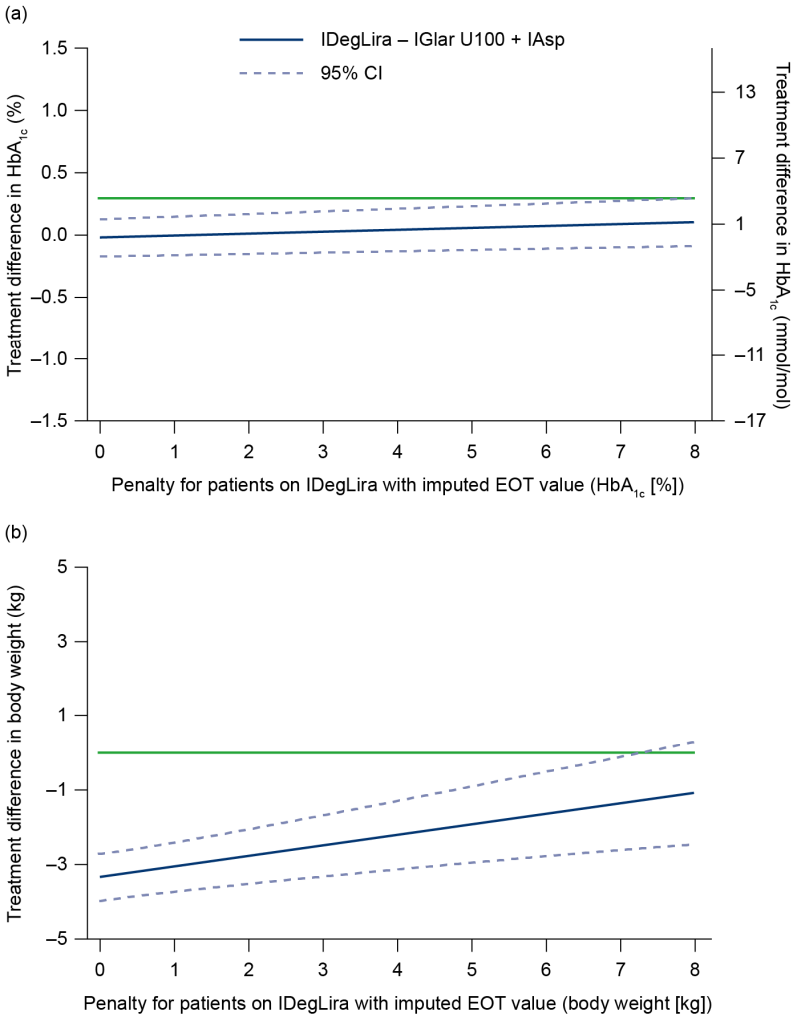


*An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions and/or neurological recovery following the return of plasma glucose to normal.

BG, blood glucose; SMPG, self-measured plasma glucose

SUPPLEMENTARY DATA

Supplementary Figure 2. (a) HbA_{1c} full analysis set and (b) body weight tipping point analyses



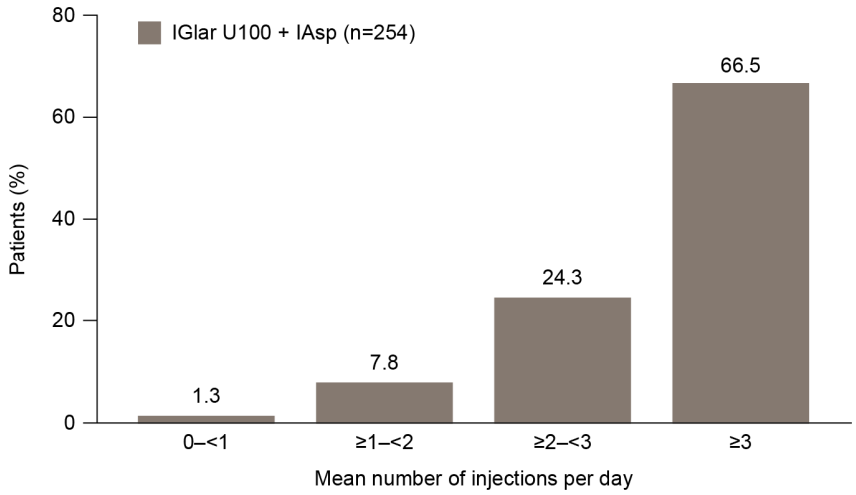
(a) Unconditional referenced-based multiple imputation tipping point analysis. Observed data including retrieved data at week 26. 4 IDegLira patients and 9 IGlar U100 + IAsp patients had imputed end-of-trial values. Horizontal green line: Non-inferiority margin 0.3%. The tipping point analysis found that it was necessary to add a penalty of more than 7.0% (53 mmol/mol) increase in HbA_{1c} for patients withdrawn from the IDegLira arm to abolish the conclusion of non-inferiority (meaning these patients would have to have HbA_{1c} at week 26 averaging approximately 14% [130 mmol/mol]); this tipping point is outside the range of clinically plausible values, confirming the robustness of the analysis results.

(b) ANCOVA model, multiple imputation (un-conditional) – full analysis set. Horizontal green line indicates no weight change (0 kg). This tipping point analysis found that it was necessary to add a penalty of approximately 36 kg weight gain to the imputed body weight change from baseline values for patients withdrawn from the IDegLira arm to abolish the conclusion of statistical superiority; this tipping point is outside the range of clinically plausible values, confirming the robustness of the analysis results.

ANCOVA, analysis of covariance. HbA_{1c}, glycated hemoglobin.

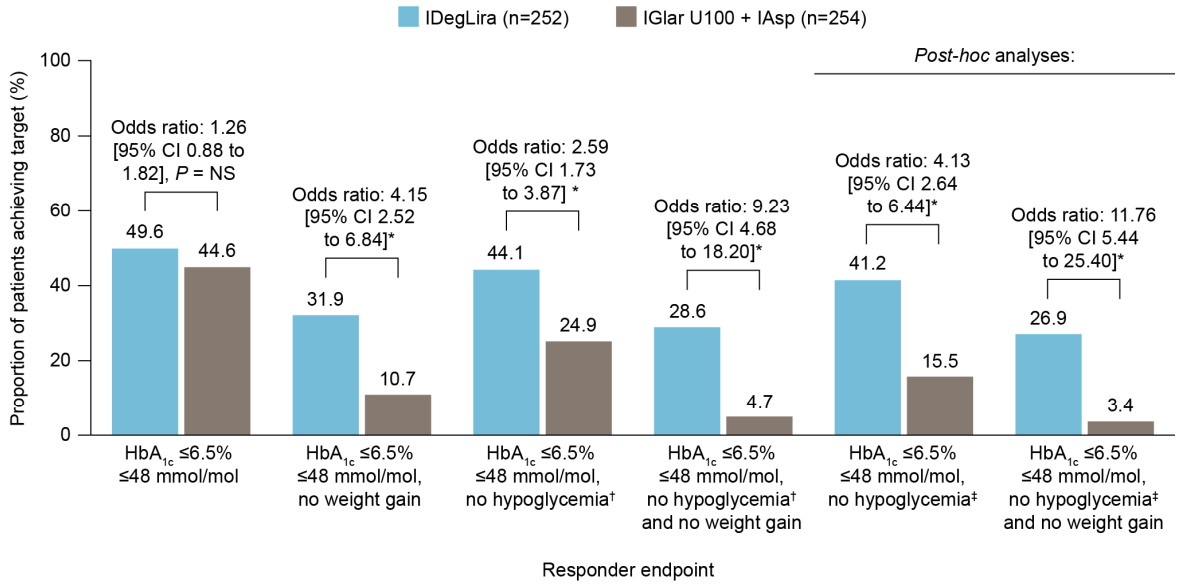
SUPPLEMENTARY DATA

Supplementary Figure 3. Mean number of bolus injections per day at week 26.



Mean observed values based on patients in the IGlar U100 + IAsp arm who completed treatment without premature discontinuation of randomized treatment. IAsp, insulin aspart; IGlar U100, insulin glargine 100 units/mL

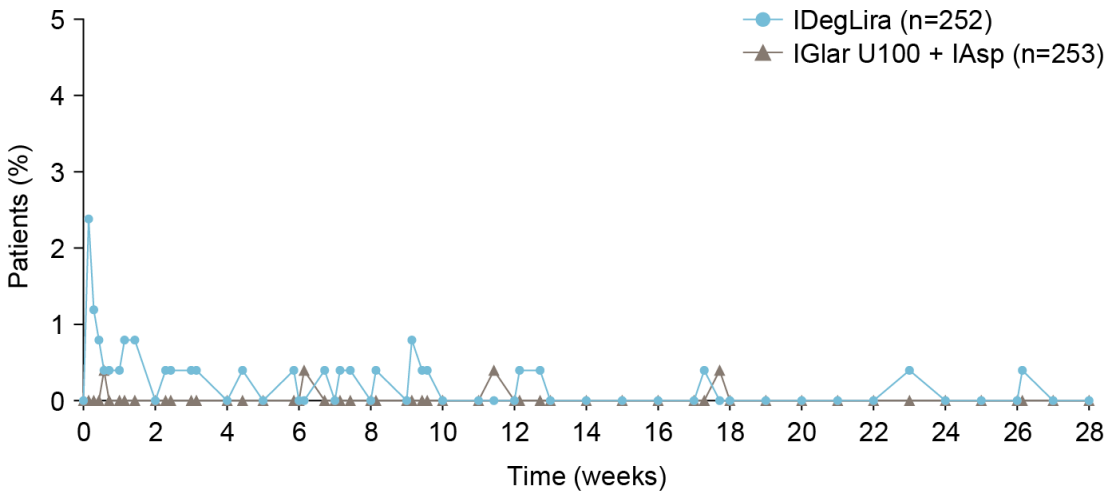
Supplementary Figure 4. Patients achieving composite outcomes with HbA_{1c} ≤6.5% (48 mmol/mol) at week 26



*statistically significant in favor of IDegLira. Odds ratios and *P*-values are based on logistic regression. †Severe or BG-confirmed symptomatic hypoglycemia based on episodes during the last 12 weeks of treatment. ‡Severe or BG-confirmed symptomatic hypoglycemia based on hypoglycemic episodes during a patient's entire 26 weeks of treatment (*post hoc* analysis).
BG, blood glucose; CI, confidence interval; HbA_{1c}, glycated hemoglobin; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL.

SUPPLEMENTARY DATA

Supplementary Figure 5. Percentage of patients with nausea over time.



Data are for the safety analysis set. ; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL.

Reference

1. O'Kelly M, Ratitch B. Clinical Trials with Missing Data: A Guide for Practitioners. 2014. Wiley Publishing.