DUAL II China: superior HbA_{1c} reductions and weight loss with insulin degludec/liraglutide (IDegLira) versus insulin degludec in a randomized trial of Chinese people with type 2 diabetes inadequately controlled on basal insulin

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Supplementary material

Supplementary Table 1. Inclusion and exclusion criteria

Inclusion criteria
1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures carried out as part of the trial, including activities to determine suitability for the trial.
2. Male or female, age ≥18 years at the time of signing inform consent.
3. Type 2 diabetes mellitus (clinically diagnosed).
4. HbA_{1c} ≥7.5% by central laboratory analysis, with the aim of a median of 8.5%. When approximately 50% of the randomized subjects have an HbA_{1c} above 8.5%, the remaining subjects must have an HbA_{1c} less than or equal to 8.5% or when approximately 50% of the randomized subjects have an HbA_{1c} less than or equal to 8.5%, the remaining subjects randomized must have a HbA_{1c} above 8.5%.
5. Current treatment for at least 90 calendar days prior to screening with basal insulin + metformin ± AGI, SU, glinides and TZD. Participants should be on a stable dose for at least 60 calendar days prior to screening of: Basal insulin 20−50 U/day (both inclusive) on the day of screening in combination with: a) Metformin (≥1500 mg or max tolerated dose) or b) Metformin (≥1500 mg or max tolerated dose) and SU (≥ half of the max approved dose according to local label) or c) Metformin (≥1500 mg or max tolerated dose) and glinide (≥ half of the max approved dose according to local label) or d) Metformin (≥1500 mg or max tolerated dose) and AGI (≥ half of the max approved dose according to local label) or e) Metformin (≥1500 mg or max tolerated dose) and TZD (≥ half of the max approved dose according to local label)
6. BMI ≥24 kg/m^2.
7. Able and willing to adhere to the protocol, including performing self-monitoring of plasma glucose profiles, keeping a trial diary and using a pre-filled pen device.
Exclusion criteria
1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (sterilization, intrauterine device, oral contraceptives or barrier methods).

4. Receipt of any investigational medicinal product within 30 calendar days before Visit 1.
5. Current use of any antidiabetic drug (except for basal insulin, AGI, SU, glinides and TZD) or anticipated change in concomitant medication that, in the investigator's opinion, could interfere with glucose level (e.g. systemic corticosteroids).
6. Use of non-herbal Chinese medicine or other non-herbal local medicine with unknown/unspecified content within 90 calendar days prior to screening. Herbal traditional Chinese medicine or other local herbal medicines may, at the investigator's discretion, be continued throughout the trial.
7. Treatment with GLP-1 RAs or DPP-4is or insulin (except for basal insulin) within 90 days prior to Visit 1.
8. Impaired liver function defined as alanine aminotransferase ≥2.5 times the upper normal range.
9. Impaired renal function defined as serum-creatinine ≥133 µmol/L for males and ≥125 µmol/L for females, or as defined according to local contraindications for metformin.
10. Screening calcitonin ≥50 ng/L.
11. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.
12. Cardiac disorder defined as: congestive heart failure (New York Heart Association class III-IV), diagnosis of unstable angina pectoris, cerebral stroke and/or myocardial infarction within the last 12 months period to screening and/or planned coronary, carotid or peripheral artery revascularization procedures.
13. Severe uncontrolled treated or untreated hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg).
14. Proliferative retinopathy or maculopathy (macular oedema) requiring acute treatment.
15. Subject with a clinically significant, active (during the past 12 months) disease of the gastrointestinal, pulmonary, neurological, genito-urinary or haematological system (except for conditions associated with T2D) that, in the opinion of the investigator, may confound compliance and the results of the trial or pose additional risk in administering trial drug.
16. Mental incapacity, unwillingness or language barrier precluding adequate understanding of the trial procedure or cooperation with the trial site personnel.
17. Known or suspected abuse of alcohol or narcotics.
18. History of pancreatitis (acute or chronic).
19. Suffer from a life-threatening disease, including malignant neoplasms, and medical history of malignant neoplasms and medical history of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer).

AGI, α-glucosidase inhibitor; DPP4i, dipeptidyl-peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; SU, sulphonylurea; TZD, thiazolidinedione; T2D, type 2 diabetes.

Supplementary Table 2. Insulin titration algorithm

Mean of three pre-breakfast SMPG (fasting)		Twice-weekly dose adjustments for either IDegLira or degludec†
mmol/L	**mg/dL**	**Units**
<4.0	<72	–2
4.0–5.0	72–90	0
>5.0	>90	+2

†Calculated using the insulin titration algorithm used in the DUAL VI trial.[1]
Degludec, insulin degludec; IDegLira, insulin degludec/liraglutide; SMPG, self-measured plasma glucose.

Reference:

1. Harris SB, Kocsis G, Prager R, et al. Safety and efficacy of IDegLira titrated once weekly versus twice weekly in patients with type 2 diabetes uncontrolled on oral antidiabetic drugs: DUAL VI randomized clinical trial. *Diabetes Obes Metab* 2017;19:858-65.

Supplementary Table 3. Hypoglycaemia definitions

	Definition
Severe or BG-confirmed symptomatic hypoglycaemia	An episode that is severe according to the ADA classification or BG-confirmed by a plasma glucose value <3.1 mmol/L with symptoms consistent with hypoglycaemia.
Nocturnal severe or BG-confirmed symptomatic hypoglycaemia	An episode of severe or BG-confirmed hypoglycaemia occurring between 00:01 and 05:59 hs (both inclusive).
ADA-defined severe hypoglycaemia	An episode requiring assistance of another person to actively administer carbohydrate, glucagon or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
ADA-classified symptomatic hypoglycaemia	An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤3.9 mmol/L.
ADA-classified documented symptomatic hypoglycaemia	An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤3.9 mmol/L.
ADA-classified pseudo-hypoglycaemia	An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration >3.9 mmol/L but approaching that level.
ADA-classified probable symptomatic hypoglycaemia	An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤3.9 mmol/L.

ADA, American Diabetes Association; BG, blood glucose.

Supplementary Table 4. Adverse events undergoing independent external adjudication

Adverse events for adjudication
Fatal events CV death Non-CV death Undetermined cause of death
ACS Acute MI Silent MI UAP requiring hospitalization
Cerebrovascular event Stroke Transient ischaemic attack
Neoplasm Benign Malignant Pre-malignant/carcinoma in situ/borderline Unclassified
Thyroid disease requiring thyroidectomy and/or thyroid neoplasm
Pancreatitis or clinical symptoms leading to suspicion of pancreatitis Acute pancreatitis Chronic pancreatitis

ACS, acute coronary syndrome; CV, cardiovascular; MI, myocardial infarction; UAP, unstable angina pectoris.

Supplementary Table 5. Change from baseline to week 26 in HbA_{1c} (primary endpoint) sensitivity analyses

Model (analysis set)	**ETD [95% CI] IDegLira–degludec**	**p-value**
ANCOVA with LOCF (FAS)†	−0.92 [−1.09; −0.75]	<0.0001
ANCOVA with LOCF (PP analysis set)	−0.91 [−1.08; −0.73]	<0.0001
ANCOVA with LOCF (CAS)	−0.88 [−1.06; −0.71]	<0.0001
MMRM (FAS)	−0.92 [−1.09; −0.75]	<0.0001
ANCOVA with conditional multiple imputation (FAS)	−0.88 [−1.06; −0.71]	<0.0001

†Primary endpoint.

ANCOVA, analysis of covariance; CAS, completer analysis set; CI, confidence interval; degludec, insulin degludec; ETD, estimated treatment difference; FAS, full analysis set; HbA_{1c}, glycated haemoglobin; IDegLira, insulin degludec/liraglutide; LOCF, last observation carried forward; MMRM, mixed model for repeated measurements; PP, per protocol.

Supplementary Table 6. Treatment-emergent hypoglycaemic episodes over 26 weeks' treatment with IDegLira versus degludec

	IDegLira				Degludec			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Number of participants	301				151			
PYE (years)	151.9				74.5			
Severe or BG-confirmed symptomatic hypoglycaemia	22	7.3	23	15.1	16	10.6	21	28.2
Severe or BG-confirmed hypoglycaemia	34	11.3	38	25.0	22	14.6	36	48.3
Nocturnal severe or BG-confirmed hypoglycaemia	9	3.0	9	5.9	7	4.6	8	10.7
ADA-classified hypoglycaemia	199	66.1	1099	723.6	103	68.2	680	912.6
Severe hypoglycaemia	2	0.7	2	1.3	0	0	0	0
Documented symptomatic hypoglycaemia	105	34.9	332	218.6	74	49.0	315	422.7
Asymptomatic hypoglycaemia	159	52.8	708	466.2	65	43.0	327	438.9
Probably symptomatic hypoglycaemia	11	3.7	13	8.6	5	3.3	7	9.4
Pseudo-hypoglycaemia	28	9.3	44	29.0	13	8.6	31	41.6

Episodes were defined as per Supplementary Table 3.

ADA, American Diabetes Association; BG, blood glucose; degludec, insulin degludec; E, number of events; IDegLira, insulin degludec/liraglutide; N, number of participants; PYE, participant-years of exposure; R, event rate per 100-PYE.

Supplementary Table 7. Geometric mean fasting lipid profiles at baseline and after 26 weeks' treatment with IDegLira or degludec

Fasting lipids, mmol/L	IDegLira		Degludec		ETR [95% CI] IDegLira vs degludec	p-value
	Week 0	Week 26	Week 0	Week 26		
Total cholesterol	4.54	4.20	4.50	4.34	0.96 [0.93; 1.00]	0.0281
HDL cholesterol	1.11	1.11	1.10	1.13	0.97 [0.94; 1.00]	>0.05
LDL cholesterol	2.40	2.14	2.36	2.25	0.95 [0.89; 1.01]	>0.05
VLDL cholesterol	0.81	0.74	0.82	0.76	0.99 [0.91; 1.08]	>0.05
Triglycerides	1.84	1.68	1.86	1.72	0.99 [0.90; 1.09]	>0.05
Free fatty acids	0.38	0.26	0.40	0.26	0.99 [0.89; 1.09]	>0.05

p-value was two-sided p-value for test of no difference. No correction for multiplicity. The log-transformed response after 26 weeks is analysed using an ANCOVA model with treatment and previous OAD treatment as fixed factors, and corresponding log-transformed baseline value as covariate. Missing values are imputed by LOCF.

ANCOVA, analysis of covariance; CI, confidence interval; degludec, insulin degludec; ETR, estimated treatment ratio; HDL, high-density lipoprotein; IDegLira, insulin degludec/liraglutide; LDL, low-density lipoprotein; LOCF, last observation carried forward; OAD, oral antidiabetic drug; VLDL, very-low-density lipoprotein.

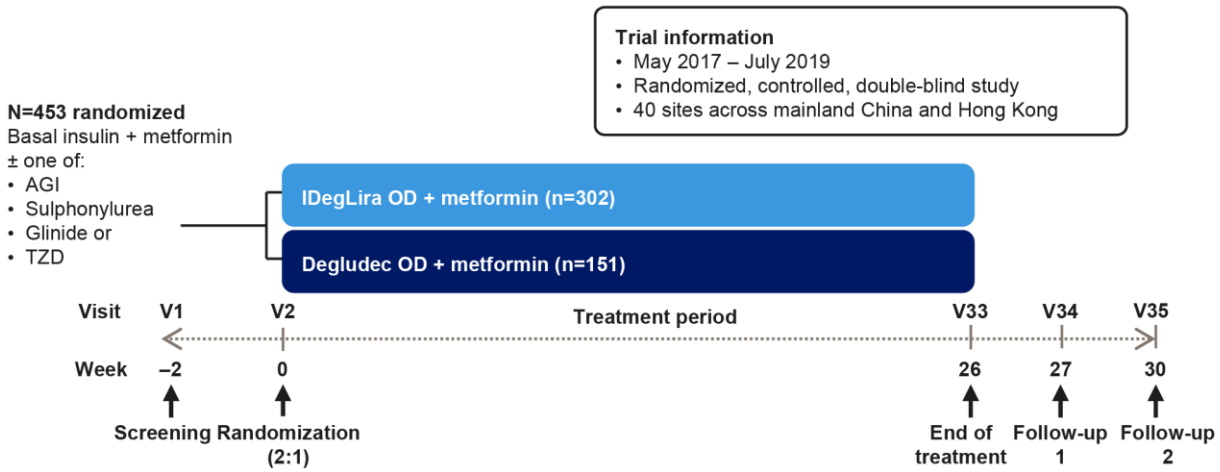
Supplementary Table 8. Change from baseline to week 26 in blood pressure and pulse

Vital sign	Change from baseline		ETD [95% CI] IDegLira–degludec	p-value
	IDegLira	Degludec		
Blood pressure, mmHg				
Systolic blood pressure	−3.5	–0.1	−3.13 [−5.33; −0.93]	0.0053
Diastolic blood pressure	+0.1	−0.3	0.32 [−1.06; 1.70]	>0.05
Heart rate, bpm	+5.8	+1.4	4.41 [2.83; 5.99]	<0.0001

Full analysis set. The change from baseline after 26 weeks was analysed using an ANCOVA model with treatment and previous antidiabetic medication as fixed factors and corresponding baseline value as covariate. p-values were based on a two-sided test of no difference, without correction for multiplicity.

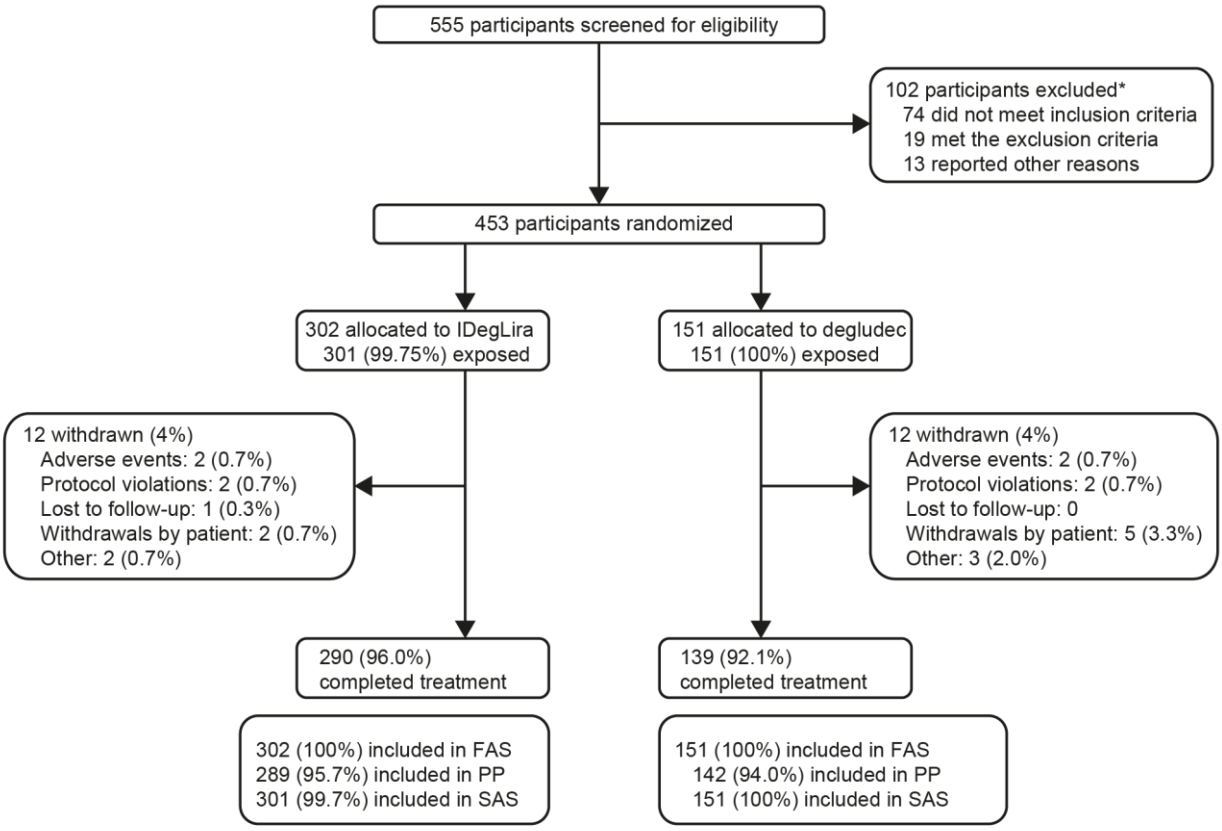
ANCOVA, analysis of covariance; CI, confidence interval; degludec, insulin degludec, ETD, estimated treatment difference; IDegLira, insulin degludec/liraglutide.

Supplementary Figure 1. Trial design



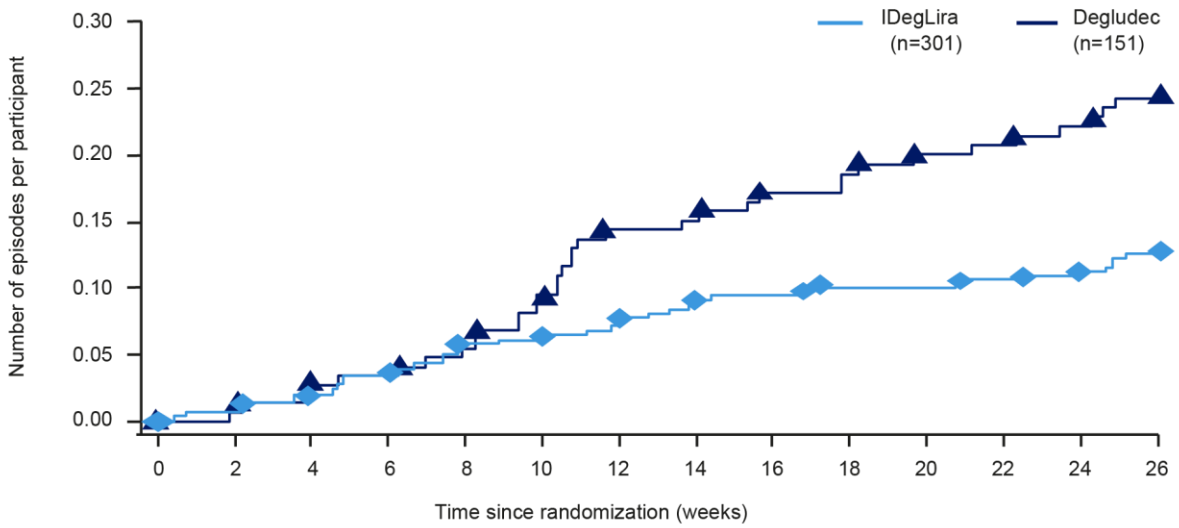
AGI, α-glucosidase inhibitor; IDegLira, insulin degludec/liraglutide; OD, once daily; TZD, thiazolidinedione.

Supplementary Figure 2. Participant disposition



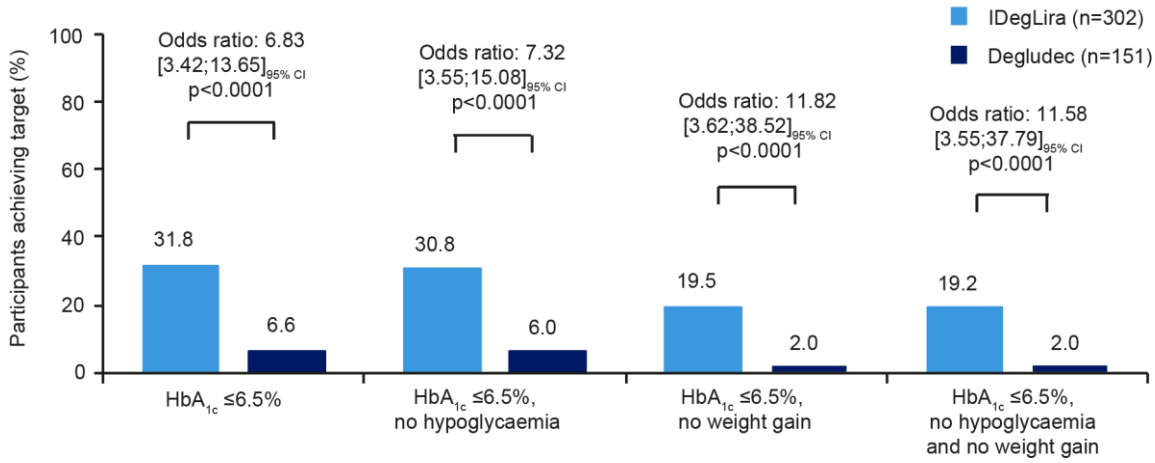
*A participant may meet more than one inclusion or exclusion criteria.
FAS, full analysis set; IDegLira, insulin degludec/liraglutide; PP, per protocol; SAS, safety analysis set.

Supplementary Figure 3. Cumulative incidence of severe or BG-confirmed hypoglycaemia over 26 weeks' treatment



Safety analysis set. Episodes were defined as per Supplementary Table 3.
BG, blood glucose; degludec, insulin degludec; IDegLira, insulin degludec/liraglutide.

Supplementary Figure 4. Responder endpoints for HbA_{1c} ≤6.5%, with composite endpoints of reaching HbA_{1c} targets without weight gain and/or without treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes



Full analysis set. Treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment.
BG, blood glucose; CI, confidence interval; degludec, insulin degludec; HbA_{1c}, glycated haemoglobin; IDegLira, insulin degludec/liraglutide.