Efficacy and safety of insulin degludec/liraglutide (IDegLira) vs. basal–bolus therapy in patients with type 2 diabetes: DUAL VII trial

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Introduction

- The progressive nature of type 2 diabetes (T2D) means that eventually basal insulin alone may not be sufficient to maintain glycaemic control. A study has shown that by the time basal insulin is initiated, patients have had T2D for a mean of 9.2 years, with a mean HbA_{1c} level of 9.5%.[1] Another study demonstrated that only 29% of patients maintained HbA_{1c} levels <7.0% 3 years after basal insulin initiation.[2]
- Current guidelines recommend intensifying basal insulin if HbA_{1c} targets are not reached after 3 to 6 months.[3] However, many patients remain on basal insulin despite the fact that they do not meet glycaemic targets, as a result of concerns about hypoglycaemia, weight gain and treatment complexity.[4,5]
- Many clinical studies have shown that the combination of basal insulin and glucagon-like peptide-1 receptor agonist (GLP-1RA) can improve glycaemic control, with no increase in risks of hypoglycaemia and weight gain.[6]
- The development of the titratable, fixed-ratio combination IDegLira (insulin degludec/liraglutide) provides a simple and convenient alternative intensification option for patients uncontrolled on basal insulin.
- IDegLira is administered subcutaneously once daily at any time of the day, independent of meals.[7]

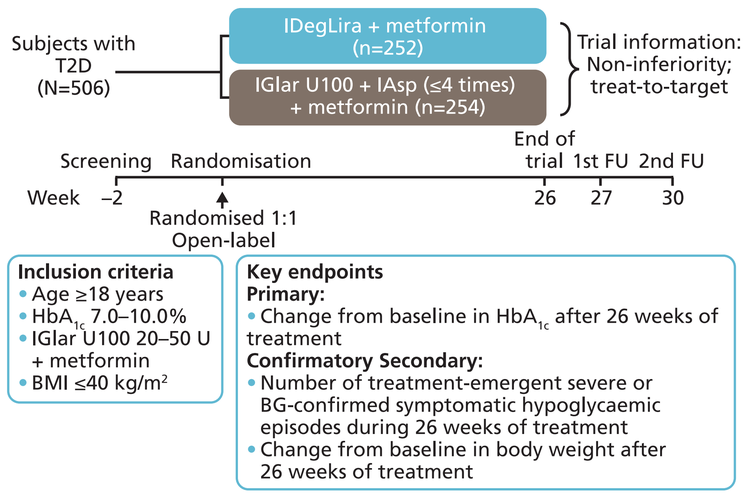
Aim

- To assess the efficacy and safety of once-daily IDegLira compared with basal–bolus therapy for treatment intensification.

Methods

- DUAL VII was a phase 3b, multinational, open-label, two-arm parallel, randomised, treat-to-target trial. The primary objective was to confirm non-inferiority with respect to HbA_{1c} change from baseline. Patients were randomised 1:1 to receive IDegLira once daily or insulin glargine 100 units/mL (IGlar U100) once daily + bolus insulin aspart (IAsp) at each main meal (≤4 times a day), both in combination with metformin, for 26 weeks (Figure 1).
- IDegLira and IGlar U100 were titrated twice weekly, to a fasting glycaemic target of 4 to 5 mmol/L. IAsp was titrated twice weekly to a mean pre-prandial and bedtime self-monitored plasma glucose (SMPG) target range of 4 to 6 mmol/L.

Figure 1 DUAL VII trial design.



BG, blood glucose; BMI, body mass index; FU, follow-up; HbA_{1c}, glycated haemoglobin; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL; T2D, type 2 diabetes.

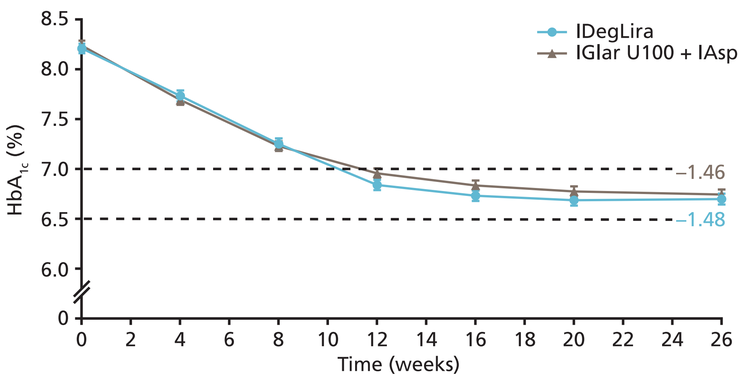
Statistical analyses

- For the primary endpoint, change in HbA_{1c} from baseline to week 26 of treatment, non-inferiority was confirmed if the upper bound of the two-sided 95% confidence interval (CI) for the estimated mean treatment difference in change from baseline in HbA_{1c} was <0.3%.
- A mixed model for repeated measurements (MMRM) with an unstructured covariance matrix was used for the continuous confirmatory and supportive secondary endpoints, including treatment, visit and region as fixed factors and corresponding baseline values as covariates. Interactions between visit and all factors and the covariate were also included in the model.
- A negative binomial model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode is considered treatment-emergent as offset was used to analyse the confirmatory endpoint, number of treatment-emergent severe or blood glucose (BG)-confirmed symptomatic hypoglycaemic episodes, including treatment and region as fixed factors.
- Insulin dose was analysed as the supportive secondary endpoints above with a compound symmetry covariance matrix and included IGlar U100 dose at screening and baseline HbA_{1c} as covariates.
- Responder endpoints were analysed using a logistic regression model with treatment and region as fixed factors and baseline HbA_{1c} and baseline body weight as covariates. Missing response data were imputed from the MMRM analysis of the corresponding continuous endpoints.
- Adverse events (AEs) were summarised descriptively based on the safety analysis set.
- Several sensitivity analyses including reference-based multiple imputation methods were carried out for the confirmatory analyses.

Results

- Treatment groups were well-matched with respect to baseline characteristics (Table 1).
- Similar proportions of patients withdrew from both treatment arms:
  - Two patients (0.8%) in the IDegLira group and five patients (2.0%) in the basal–bolus treatment group.
  - 99.2% of those randomised to IDegLira and 98.0% of those randomised to basal–bolus therapy completed the trial. Additionally, 94.4 and 91.7% completed treatment with IDegLira and basal–bolus insulin, respectively.
- After 26 weeks of treatment, mean HbA_{1c} decreased from 8.2% at baseline to 6.7% with IDegLira, and from 8.2 to 6.7% with basal–bolus insulin. This corresponded to an estimated treatment difference (ETD) of –0.02% [95% CI –0.16; 0.12] $p<0.0001$ (Figure 2), confirming non-inferiority of IDegLira treatment compared with basal–bolus therapy.
- Throughout the trial, 19.8% of patients on IDegLira experienced one or more severe or BG-confirmed symptomatic hypoglycaemic episodes, at a rate of 1.07 episodes per patient-year of exposure (PYE) compared with 52.6% of patients on basal–bolus therapy, at a rate of 8.17 episodes per PYE. This resulted in an 89% lower rate for IDegLira compared with basal–bolus therapy (estimated rate ratio [ERR] 0.11 [95% CI 0.08; 0.17] $p<0.0001$), confirming superiority of IDegLira treatment compared with basal–bolus therapy (Figure 3).
- There was a 92% lower rate of nocturnal hypoglycaemia for IDegLira (0.13 episodes per PYE) compared with basal–bolus therapy (1.66 episodes per PYE); ERR 0.08 [95% CI 0.04; 0.17] $p<0.0001$.
- Body weight decreased with IDegLira from 87.2 to 85.9 kg and increased with basal–bolus therapy from 88.2 kg to 90.7 kg after 26 weeks of treatment (Figure 4); ETD –3.57 kg [95% CI –4.19; –2.95] $p<0.0001$, confirming superiority of IDegLira compared with basal–bolus therapy.
- Mean end of trial total daily insulin dose was 40.4 U with IDegLira and 84.1 U with basal–bolus insulin (52 U basal insulin + 32 U bolus insulin); ETD –44.5 U [95% CI –48.3; –40.7] $p<0.0001$ (Figure 5).
- At the end of trial, 66.5% of patients on basal–bolus insulin required ≥3 bolus injections daily.
- More patients achieved the triple composite endpoints (HbA_{1c} target [<7% or ≤6.5%] without hypoglycaemic episodes during the last 12 weeks of treatment and without weight gain) on IDegLira compared with basal–bolus therapy, odds ratio (OR) 10.39 [95% CI 5.76; 18.75] and 9.23 [95% CI 4.68; 18.20], respectively, both $p<0.0001$.
- AEs occurred in similar proportions of patients in both treatment arms. The most common AE with IDegLira was nausea, with 11.1% of patients reporting one or more event, compared with 1.6% of patients on basal–bolus therapy. The most common AE on basal–bolus therapy was nasopharyngitis, with 11.9% of patients reporting one or more event, compared with 4.8% of patients on IDegLira. There were no fatal events and no confirmed events of pancreatitis, thyroid disease or major cardiovascular events in the trial.
- All sensitivity analyses confirmed the robustness of the results.

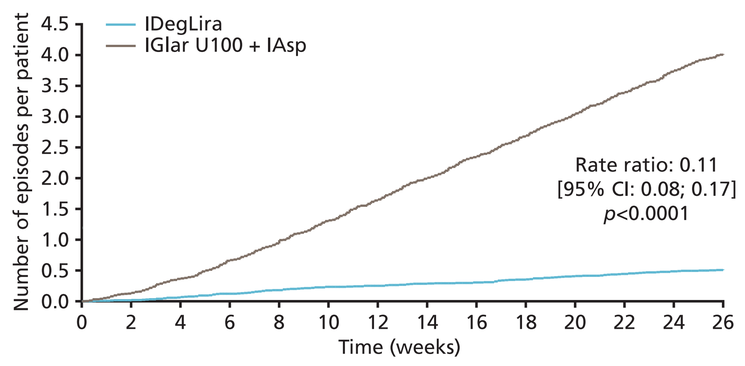
Figure 2 HbA_{1c} over time.



	IDegLira	IGlar U100 + IAsp	ETD [95% CI]
ΔHbA1c (%) LS mean	–1.48	–1.46	–0.02 [–0.16; 0.12], $p<0.0001$ for test of non-inferiority by 0.3%

Mean observed values with error bars (standard error mean) based on full analysis set. ETD is based on LS means from full analysis set, using mixed model for repeated measurement. ---ADA/EASD HbA_{1c} target <7.0% and AACE HbA_{1c} target ≤6.5%. N, number of patients contributing to each data point. AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; CI, confidence interval; EASD, European Association for the Study of Diabetes; ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL; LS, least square.

Figure 3 Severe or BG-confirmed symptomatic hypoglycaemia over time.



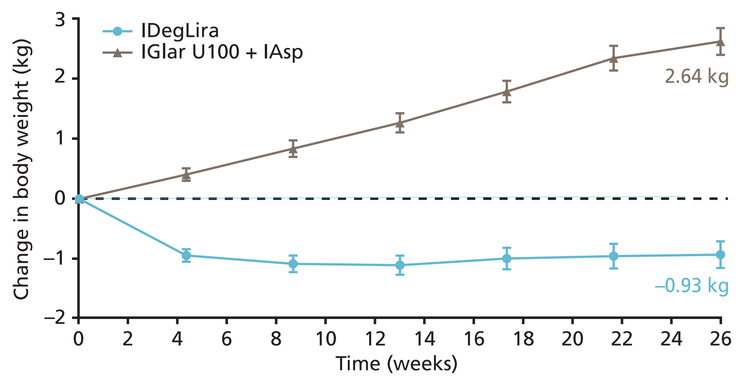
Mean cumulative function based on safety analysis set. Severe or BG-confirmed symptomatic: an episode that is severe according to the ADA classification or BG-confirmed by a plasma glucose value <3.1 mmol/L (<56 mg/dL) with symptoms consistent with hypoglycaemia.
ADA, American Diabetes Association; BG, blood glucose; CI, confidence interval; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL.

Table 1 Baseline characteristics of patients in each treatment arm of the DUAL VII trial.

Characteristic	IDegLira	IGlar U100 + IAsp
Full analysis set, n	252	254
Male, %	43.7	46.1
Age, years	58.6 (9.0)	58.0 (8.6)
Weight, kg	87.2 (16.0)	88.2 (17.2)
BMI, kg/m²	31.7 (4.4)	31.7 (4.5)
Duration of diabetes, years	13.2 (7.0)	13.3 (6.8)
HbA_{1c}, %	8.2 (0.8)	8.2 (0.8)
FPG, mmol/L	8.5 (2.7)	8.3 (2.5)
Daily insulin dose, U	34 (10.7)	33 (10.4)
Daily metformin dose, mg	2049 (456.0)	2091 (458.3)

Values are mean (SD) unless otherwise stated. BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL; SD, standard deviation.

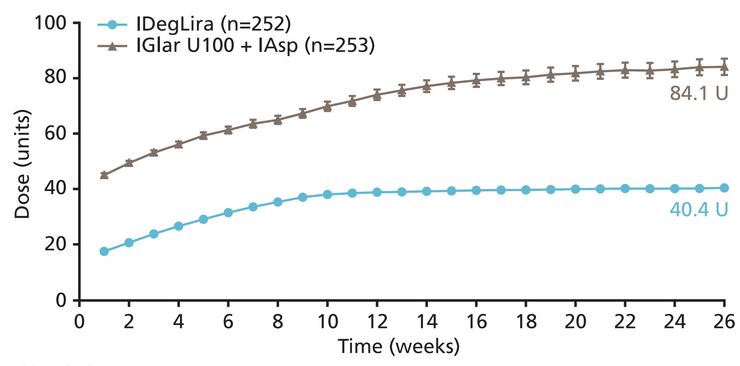
Figure 4 Change from baseline in body weight.



	IDegLira	IGlar U100 + IAsp	ETD [95% CI]
ΔWeight (kg) LS mean	–0.93	2.64	–3.57 [–4.19; –2.95], $p<0.0001$

LS mean values with error bars (standard error mean) based on full analysis set, using MMRM with treatment, region and visit as factors and baseline value as covariate. Interactions between visit and all other factors and covariate are included. CI, confidence interval; ETD, estimated treatment difference; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL; LS, least square; MMRM, mixed model for repeated measurement.

Figure 5 Total daily insulin dose over time.



Mean observed values with error bars (standard error of the mean) based on safety analysis set. N, number of patients contributing to each data point. IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL.

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Conclusions

- Once-daily injection of IDegLira provides an efficacious intensification option that is non-inferior to basal–bolus therapy in terms of glycaemic control in patients with T2D uncontrolled on IGlar U100 and metformin.
- Compared with basal–bolus therapy, IDegLira offers an alternative well-tolerated treatment with fewer injections, taken independently of meals, lower total daily insulin dose, a reduced rate of hypoglycaemic episodes, and improved weight control, which might help overcome the inertia that currently leaves many patients in poor glycaemic control.

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