Efficacy and safety of IDegLira vs. basal–bolus insulin in patients with type 2 diabetes: DUAL VII trial

Introduction
- Many patients remain on basal insulin despite the fact that they do not achieve glycaemic targets, as a result of concerns about hypoglycaemia, weight gain and treatment complexity.
- The titratable, fixed-ratio combination IDegLira (insulin degludec/liraglutide) provides a simple and convenient alternative intensification option for patients uncontrolled on basal insulin.
- IDegLira was administered subcutaneously once daily at any time of the day, independent of meals.

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

 Methods
- DUAL VII was a phase 3b, multinational, open-label, treat-to-target trial (Figure 1). The primary objective was to confirm non-inferiority with respect to HbA1c change from baseline. Patients were randomised 1:1 to receive IDegLira once daily or basal insulin glargine U100 (14 U once daily) plus bolus insulin aspart (3 U each meal and 0.4 U at bedtime) in a combination with metformin for 26 weeks (Figure 1).

- IDegLira was titrated twice weekly, to a fasting glycemic target of 4.0–5.5 mmol/L (72–99 mg/dL). Insulin aspart was titrated twice weekly to a mean pre-prandial (BG)-confirmed symptomatic hypoglycaemic episodes during 26 weeks of treatment.


- Non-inferiority for the change in HbA1c from baseline to week 26 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 HbA1c was <0.3%.

- A mixed model for repeated measurement (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 other factors and covariates were included. CI, confidence interval; ETD, estimated treatment difference; HbA1c, glycated haemoglobin; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IDegLira, insulin glargine 100 units/mL; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IDegLira, insulin glargine 100 units/mL; IAsp, insulin aspart.

- After 26 weeks of treatment, mean HbA1c decreased from 8.2% to baseline to 6.7% in both treatment arms (Figure 2), confirming non-inferiority of IDegLira treatment compared with basal–bolus therapy.

- Of the patients on IDegLira, 19.8% experienced ≥1 severe or 45.9% confirmed asymptomatic hypoglycaemic episodes during 26 weeks of treatment. Mean number of treatment-emergent severe or blood glucose <3.1 mmol/L (<56 mg/dL) with symptoms consistent with hypoglycaemia.

- Weight (kg) 87.2 (16.0) 88.2 (17.2)

- Daily metformin dose, mg 2049 (456.0) 2091 (458.3)

- More patients achieved the three composite endpoints (HbA1c target <7.0% and AACE HbA1c target ≤6.5%). N, number of patients contributing to each data point. IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IDegLira, insulin glargine 100 units/mL; IAsp, insulin aspart.

- More end-of-treatment 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 injections daily and 8.0% of patients on basal–bolus insulin required injections daily.

- More patients achieved the triple composite endpoints (HbA1c target <7.0% or ≤6.5%) without hypoglycaemic episodes during the last 12 weeks of treatment and without weight gain on IDegLira versus basal–bolus therapy; odds ratio 10.39 (95% CI 5.7, 18.5) and 9.23 (95% CI 4.6, 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 ≥1 event, versus 1.6% of patients on basal–bolus therapy. The most common AE on basal–bolus therapy was lipodystrophy, with 11.9% of patients reporting ≥1 event, versus 4.8% of patients on IDegLira. There were no fatal events and no new cases of pancreatitis, thyroid disease or major cardiovascular events in the trial.

- The study was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT02420262).

Figure 1 DUAL VII trial design.

Figure 2 HbA1c over time.

Figure 3 Severer or BG confirmed symptomatic hyperglycaemia over time.

Figure 4 Change from baseline in body weight.

Figure 5 Total daily insulin dose over time.

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

<table>
<thead>
<tr>
<th></th>
<th>IDegLira</th>
<th>IDegLira + IAsp</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>58.6 (0.0)</td>
<td>58.0 (0.6)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>87.2 (16.0)</td>
<td>88.2 (17.2)</td>
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<tr>
<td>Duration of diabetes, years</td>
<td>13.2 (7.0)</td>
<td>13.3 (6.8)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.2 (0.8)</td>
<td>8.2 (0.8)</td>
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<tr>
<td>FPG, mg/dL</td>
<td>8.5 (2.7)</td>
<td>8.3 (2.5)</td>
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<tr>
<td>IAsp, mg/dL</td>
<td>153.5 (47.6)</td>
<td>149.3 (46.6)</td>
</tr>
<tr>
<td>Daily insulin dose, U</td>
<td>40.4 (17.0)</td>
<td>33.1 (10.4)</td>
</tr>
<tr>
<td>Daily metformin dose, mg</td>
<td>2049 (456.0)</td>
<td>2091 (458.3)</td>
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Values are mean (SD) unless otherwise stated. IDegLira, insulin degludec/liraglutide combination; IDegLira, insulin glargine 100 units/mL; IAsp, insulin aspart.