Patients with T2D treated with IDegLira have a greater chance of reaching glycaemic targets without hypoglycaemia and weight gain than with insulin glargine U100 (IGlar U100)

1. **Ildiko Lingvay**
University of Texas Southwestern Medical Center, Dallas, TX, USA
2. **Paul C Norwood**
Valley Research, Fresno, CA, USA
3. **Kamilla Begtrup**
Novo Nordisk A/S, Søborg, Denmark
4. **Irene H Langbakke**
Novo Nordisk A/S, Søborg, Denmark
5. **Federico C Pérez Manghi**
CINME, Buenos Aires, Argentina

Introduction

- IDegLira is a once-daily, fixed-ratio combination of insulin degludec and liraglutide that has been investigated in the DUAL clinical trial programme.
- Results from DUAL V, in which IDegLira was titrated twice weekly to a fasting plasma glucose (FPG) target of 4.0–5.0 mmol/L, demonstrated that IDegLira was superior to IGlar U100 in terms of HbA_{1c} reduction (estimated treatment difference [ETD]: –0.59%), rate of confirmed hypoglycaemia (estimated rate ratio [ERR]: 0.43) and weight change (ETD: –3.20 kg) after 26 weeks of treatment (all $p<0.001$). This was achieved at a statistically significantly lower mean daily insulin dose for IDegLira versus IGlar U100 (ETD: –25.5 units).[1]
- The use of composite endpoints in diabetes trials is important to assess the clinical benefit of a therapy,[2] particularly with respect to weight gain and hypoglycaemia, as these are often cited as barriers to insulin initiation.[2,3]
  - In DUAL V, more patients achieved HbA_{1c} <7% (72% vs. 47%), HbA_{1c} <7% without hypoglycaemia (54% vs. 30%), HbA_{1c} <7% without weight gain (50% vs. 20%) and HbA_{1c} <7% without hypoglycaemia and weight gain (39% vs. 12%) with IDegLira vs. IGlar U100.[1]
- The glycaemic targets used in clinical trials may vary from those used in clinical practice[4] and achieving timely glycaemic control is important to improve patient adherence to therapies.[5]
  - Therefore, we have performed additional analyses of DUAL V to explore further the applicability of the findings to clinical practice.

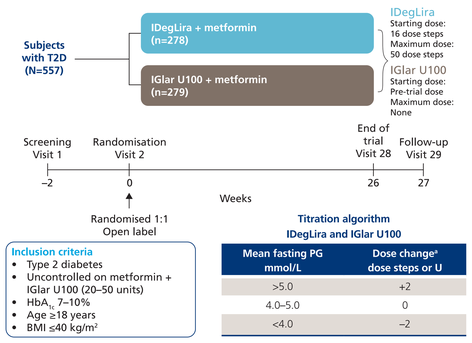
Aim

- This *post hoc* analysis of DUAL V investigated (i) whether patients who achieved FPG ≤7.2 mmol/L did so without hypoglycaemia and/or without weight gain, (ii) the effect of baseline HbA_{1c} on achievement of HbA_{1c}-based composite endpoints, and (iii) the time course of FPG and HbA_{1c} reductions in the first 12 weeks of the trial.

Methods

- The DUAL V trial design is summarised in Figure 1.
  - Adults uncontrolled (HbA_{1c} 7–10%) on IGlar U100 (20–50 units) and with a BMI ≤40 kg/m² were randomised 1:1 to receive IDegLira or continued IGlar U100 titration, both with pre-trial metformin dose, for 26 weeks.
  - IDegLira was adjusted twice weekly, with titration to a fasting glycaemic target of 4.0–5.0 mmol/L.
- As part of this analysis:
  - The FPG target of 7.2 mmol/L was selected to reflect the upper range of the recommended pre-prandial target[2]
  - Patients were grouped into HbA_{1c} categories of ≤7.5%, >7.5–≤8.5% and >8.5% according to HbA_{1c} at baseline
  - Change from baseline in HbA_{1c} and FPG were assessed after 4, 8 and 12 weeks of treatment.

Figure 1 DUAL V trial design.



[a]Titration performed twice weekly based on the mean of three preceding fasting self-measured blood glucose values obtained prior to dosing adjustment days.
One IDegLira dose step = 1 unit IDeg/0.036 mg liraglutide.
BMI, body mass index; IDeg, insulin degludec; IDegLira, insulin degludec/insulin liraglutide combination; IGlar U100, insulin glargine 100 units/mL; PG, plasma glucose; T2D, type 2 diabetes.

Statistical analyses

- Proportion of patients achieving HbA_{1c} <7% or FPG ≤7.2 mmol/L and composite endpoints of HbA_{1c} or FPG targets with no hypoglycaemia and/or without weight gain were analysed using a logistic regression model based on full analysis set (FAS) with treatment and region as fixed effects and corresponding baseline value as covariate. Missing data were imputed using last observation carried forward (LOCF).
- Hypoglycaemia was defined as severe hypoglycaemia or plasma glucose <3.1 mmol/L in the last 12 weeks of treatment.
- Change from baseline in HbA_{1c} and FPG were analysed using an ANCOVA model based on the FAS and LOCF-imputed data with treatment and region as fixed effects and baseline response as covariate.
- The models were consistent with the pre-specified models for DUAL V.

Results

- Treatment groups were well matched with respect to baseline characteristics (Table 1).[1]
- In DUAL V, no apparent or unexpected safety and tolerability issues for IDegLira were identified.[1]

FPG targets and composite endpoints

- The odds of reaching an FPG target of ≤7.2 mmol/L without hypoglycaemia and/or weight gain were statistically significantly higher for patients treated with IDegLira versus IGlar U100 (Figure 2).

Table 1 Baseline characteristics.[1]

	DUAL V	
	IDegLira	IGlar U100
FAS, n	278	279
Female, %	48.6	50.9
Age, years	58.4 (9.8)	59.1 (9.3)
Body weight, kg	88.3 (17.5)	87.3 (15.8)
BMI, kg/m²	31.7 (4.4)	31.7 (4.5)
Duration of diabetes, years	11.6 (7.4)	11.3 (6.6)
HbA_{1c}, %	8.4 (0.9)	8.2 (0.9)
FPG, mmol/L	8.9 (2.6)	8.9 (2.9)
Pre-trial insulin dose	31 (10)	32 (10)

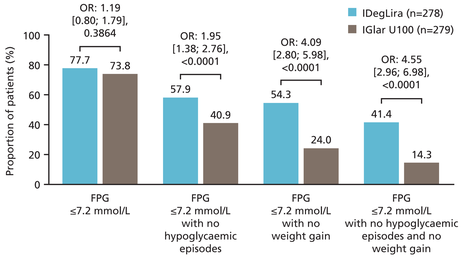
Values are mean (SD) unless otherwise stated. BMI, body mass index; FAS, full analysis set; FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/mL.

- Similar proportions of patients achieved FPG ≤7.2 mmol/L as expected, since both treatment arms were titrated to the same target.
- 57.9% vs. 40.9% of IDegLira- vs. IGlar U100-treated patients achieved FPG ≤7.2 mmol/L without hypoglycaemia.

Composite endpoints by baseline HbA_{1c} category

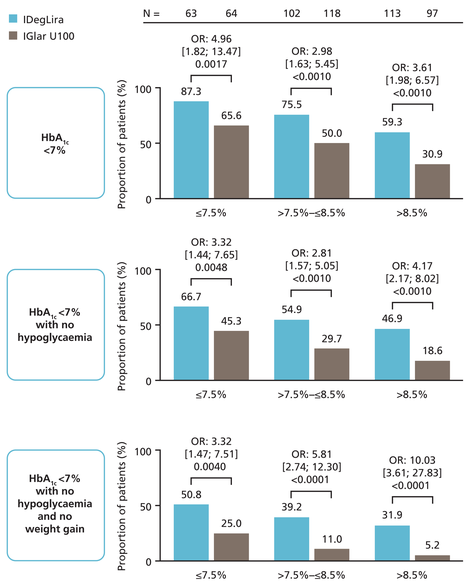
- The odds of reaching HbA_{1c} <7% and composite endpoints of HbA_{1c} <7% without hypoglycaemia and/or without weight gain were statistically significantly higher for patients treated with IDegLira versus IGlar U100 regardless of baseline HbA_{1c} category (Figure 3).

Figure 2 Proportion of patients achieving FPG targets and composite endpoints.



Odds ratios (IDegLira/IGlar U100) are from a logistic regression model based on FAS and LOCF-imputed data. Odds ratios [95% CI], *p*-values are presented.
CI, confidence interval; FAS, full analysis set; FPG, fasting plasma glucose, IDegLira, insulin degludec/insulin liraglutide combination; IGlar U100, insulin glargine 100 units/mL; LOCF, last observation carried forward; OR, odds ratio.

Figure 3 Proportion of patients achieving HbA_{1c} targets and composite endpoints by baseline HbA_{1c} category.

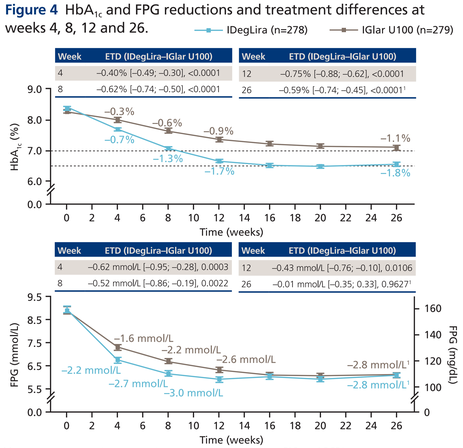


Proportion of patients achieving HbA_{1c} targets and composite endpoints analysed using a logistic regression model based on FAS and LOCF-imputed data with treatment and region as fixed effects and baseline HbA_{1c} as covariate. Hypoglycaemia was defined as severe hypoglycaemia or plasma glucose <3.1 mmol/L in the last 12 weeks of treatment. Odds ratios [95% CI], *p*-values are presented.
CI, confidence interval; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; FAS, full analysis set; LOCF, last observation carried forward.

Glycaemic control at initiation of IDegLira

- Statistically significantly greater HbA_{1c} and FPG reductions were observed at weeks 4, 8 and 12 with IDegLira versus IGlar U100 (Figure 4)
  - Mean change in HbA_{1c} from baseline to week 4 was –0.7% vs. –0.3% for patients treated with IDegLira versus IGlar U100.
  - Mean change in FPG from baseline to week 4 was –2.2 vs. –1.6 mmol/L for patients treated with IDegLira versus IGlar U100.

Figure 4 HbA_{1c} and FPG reductions and treatment differences at weeks 4, 8, 12 and 26.



Mean observed values with error bars (standard error mean) based on FAS and LOCF imputed data.
ETD (IDegLira–IGlar U100) is estimated from an ANCOVA analysis while Δ values are observed LOCF. ETD [95% CI], *p* values are presented in table.
— ADA/EASD HbA_{1c} target <7.0%; AACE HbA_{1c} target ≤6.5%.
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; FAS, full analysis set; FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; LOCF, last observation carried forward.

References

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Conclusions

- These analyses suggest that the clinical advantages of IDegLira over IGlar U100:
  - Would also be observed in clinical practice, at titration targets closer to a real-world setting, allowing patients to experience improvements in glycaemic control without the detrimental effects of hypoglycaemia and weight gain
  - Are observed regardless of baseline HbA_{1c}
  - Are observed early after treatment initiation, despite the reduction in insulin dose when switching to IDegLira.

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The DUAL V study (NCT01952145) was sponsored by Novo Nordisk A/S.
The authors take full responsibility for the content of the poster but are grateful to Watermeadow Medical (supported by Novo Nordisk) for writing assistance.
Presented at the European Association for the Study of Diabetes, 52nd Annual Meeting, 12–16 September 2016, Munich, Germany.