IDegLira improves glycemic control in subjects with type 2 diabetes uncontrolled on basal insulin without deterioration despite discontinuing pre-trial sulfonylurea

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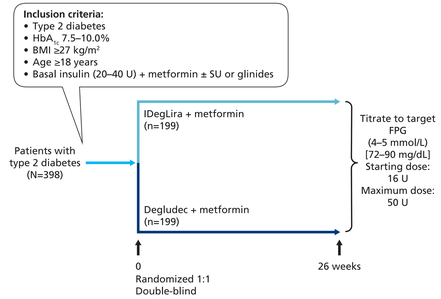
Aim

- In the DUAL II study, the efficacy and safety of insulin degludec/liraglutide (IDegLira) were compared with those of degludec alone, both in combination with metformin, in patients with type 2 diabetes (T2D) uncontrolled on 20–40 U basal insulin + metformin ± sulfonylurea (SU)/glinides.[1]
- This *post-hoc* analysis of DUAL II aimed to investigate glycemic control and other efficacy and safety parameters in the subgroup of patients discontinuing pre-trial SU, compared with patients not previously treated with SU, when initiating IDegLira.

Methods

- Trial design for DUAL II is displayed in Figure 1.[1] Treatment was initiated at 16 U of IDegLira (16 U degludec/0.58 mg liraglutide)/16 U of degludec and titrated to a maximum of 50 U of IDegLira/50 U of degludec and pre-trial treatment with SU or glinides (if applicable), and basal insulin was discontinued at randomisation.
- Change from baseline in HbA_{1c}, fasting plasma glucose (FPG) and body weight, and end of trial (EOT) insulin dose after 26 weeks of treatment were analyzed with an analysis of covariance (ANCOVA) model with region, pre-trial use of SU at screening, randomized treatment and interaction between pre-trial use of SU and randomized treatment as fixed factors, and baseline value as covariate (and baseline HbA_{1c} for insulin dose).

Figure 1: DUAL II trial design



Maximum doses were 50 U for both IDegLira and degludec. Metformin was continued at pre-trial doses.
BMI, body mass index; FPG, fasting plasma glucose, IDegLira, insulin degludec/liraglutide; SU, sulfonylurea; U, units.

- Missing data were imputed using last observation carried forward.
- Number of treatment-emergent hypoglycemic episodes was analyzed using a negative binomial regression model with a log link and the logarithm of the time period in which a hypoglycemic episode is considered treatment-emergent as offset and the same fixed factors as the ANCOVA model.

Results

Patients

- In total, 198 patients were treated with SU at screening (SU group) and 200 patients were not treated with SU (non-SU group) at screening. Baseline characteristics were broadly similar between the two groups.
  - » The mean duration of diabetes was 11.5 years in the SU group and 9.8 years in the non-SU group.
  - » Daily insulin dose at screening was slightly lower in the SU group (27.1 U) than the non-SU group (31.1 U).

Glycemic control

- Treatment with IDegLira resulted in a mean decrease in self-measured blood glucose (SMBG) after 26 weeks in both the SU and non-SU groups (Figure 2). Mean SMBG was lower with IDegLira compared with degludec for both treatment groups throughout the duration of the trial.
- Compared with baseline, there was a non-clinically relevant increase in mean SMBG during the first 3 weeks of trial in the SU group, in both the IDegLira and degludec arms, with continued improvement in mean SMBG levels from Week 4 onwards.
- Mean SMBG decreased from Week 0 until Week 26 with IDegLira in the non-SU group.
- After 26 weeks of treatment, greater reductions in HbA_{1c} and numerically greater reductions in FPG were observed with IDegLira compared with degludec in both the SU and non-SU groups (Figures 3 and 4).
- Safety and efficacy parameters are summarized in Table 1; treatment effect was consistent between arms, with no statistically significant interaction between randomized treatment and SU group for all endpoints.

Body weight

- Treatment with IDegLira resulted in weight loss regardless of pre-trial SU use (Table 1).

EOT daily insulin dose

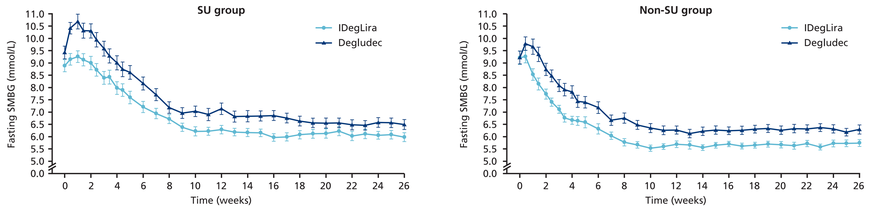
- EOT daily insulin dose was comparable between IDegLira and degludec in both groups (Table 1).

Hypoglycemia

- Hypoglycemia rates were numerically lower with IDegLira compared with degludec in both the SU and non-SU groups (Table 1).

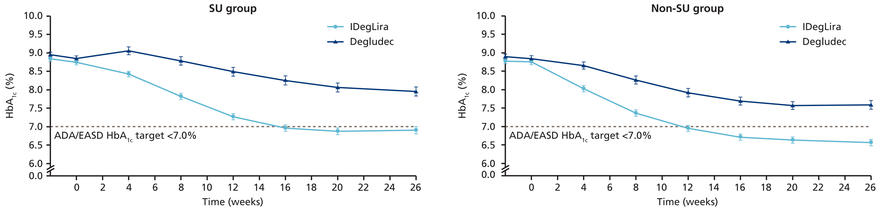
Figure 2: Fasting SMBG over time with IDegLira compared with degludec

Key result



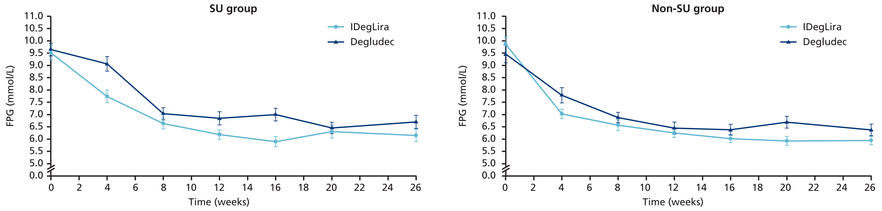
Data are mean (±SEM) and based on the full analysis set. Degludec: insulin degludec U100. IDegLira, insulin degludec/liraglutide; SEM, standard error of the mean; SMBG, self-measured blood glucose; SU, sulfonylurea.

Figure 3: HbA_{1c} over time with IDegLira compared with degludec



Data are mean (±SEM) and based on the full analysis set. Degludec: insulin degludec U100. ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; IDegLira, insulin degludec/liraglutide; SEM, standard error of the mean; SU, sulfonylurea.

Figure 4: FPG over time with IDegLira compared with degludec



Data are mean (±SEM) and based on the full analysis set. Degludec: insulin degludec U100. FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide; SEM, standard error of the mean; SU, sulfonylurea.

Table 1: Outcomes in DUAL II by pre-trial SU use group

Category	SU group			Non-SU group			Test for treatment by subgroup interaction, *p*-value
	IDegLira* (N=99)	Degludec* (N=99)	ETD/ERR [95% CI]	IDegLira* (N=100)	Degludec* (N=100)	ETD/ERR [95% CI]	
Baseline HbA_{1c}, %	8.7 (0.7)	8.9 (0.7)	–	8.8 (0.7)	8.8 (0.8)	–	–
Δ HbA_{1c}, %	–1.7 (1.2)	–0.6 (1.1)	ETD: –1.13 [–1.41; –0.84]	–2.1 (1.0)	–1.2 (1.2)	ETD: –0.94 [–1.23; –0.66]	0.3828
Δ FPG, mmol/L	–3.3 (3.2)	–2.4 (3.3)	ETD: –0.94 [–1.59; –0.30]	–3.7 (2.7)	–2.7 (3.3)	ETD: –0.52 [–1.17; 0.13]	0.3618
Baseline weight, kg	96.5 (22.8)	93.9 (20.2)	–	94.3 (15.4)	93.2 (19.8)	–	–
Δ Body weight, kg	–3.1 (3.6)	–0.3 (2.6)	ETD: –2.77 [–3.75; –1.79]	–2.3 (3.7)	0.3 (4.0)	ETD: –2.41 [–3.39; –1.43]	0.6137
Daily insulin dose at screening†, U	27.5 (7.0)	26.8 (7.1)	–	30.6 (8.1)	31.5 (7.5)	–	–
EOT daily insulin dose*, U	43.8 (10.2)	44.9 (9.3)	ETD: –0.80 [–3.39; 1.79]	45.8 (8.5)	44.9 (9.7)	ETD: 1.09 [–1.52; 3.69]	0.3132
Hypo events/PYE	1.7	3.0	ERR: 0.56 [0.26; 1.22]	1.4	2.3	ERR: 0.88 [0.41; 1.92]	0.4221

Data are mean (SD) unless otherwise stated. *Maximum 50 U IDegLira and degludec; †in total, five patients had missing pre-trial insulin dose at screening; CI, confidence interval; EOT, end of trial; ETD, estimated treatment difference; ERR, estimate rate ratio; FPG, fasting plasma glucose; hypo, unable to self-treat and/or blood glucose <3.1mmol/L; IDegLira, insulin degludec/liraglutide; PYE, patient-year of exposure; SU, sulfonylurea; U, units.

Discussion

- SU doses are often reduced or discontinued upon initiation of insulin due to the increased risk of hypoglycemia associated with their combined use.[2] However, this can lead to a deterioration of glycemic control, which is why many people continue to receive SUs in combination with basal insulin therapy.[3]
- In patients discontinuing SU in DUAL II, there was no clinically relevant deterioration in glycemic control with IDegLira or degludec during the trial despite the discontinuation of SU and the reduction in daily insulin dose from a mean of 27 U to 16 U at randomization.
- Furthermore, IDegLira also provided the benefits of weight loss and low rates of hypoglycemia, irrespective of previous SU use.
- Of note, patients in the SU group did not require a higher dose of IDegLira compared with those in the non-SU group to achieve these outcomes.

Conclusion

- In patients who discontinued SU at IDegLira initiation, no clinically relevant deterioration in glycemic control was observed.
- IDegLira was more favourable compared with degludec in terms of change in HbA_{1c} and body weight. Outcomes were achieved with a comparable EOT insulin dose and low hypoglycemia rates, and findings were consistent between the SU and non-SU groups.

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Presenter Karen Salvesen-Sykes is an employee and shareholder of Novo Nordisk.
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References: (**1**) Buse *et al. Diabetes Care* 2014;37:2926–33; (**2**) Swinnen *et al. Diabetes Obes Metab* 2010;12:923–5; (**3**) Turner *et al. Diabetes Care* 2014;37:985–92.