Similar glycaemic control and less nocturnal hypoglycaemia with intensification of IDegAsp QD or BID vs glargine U100 QD + IAsp 1–3 in adults with type 2 diabetes

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Introduction

- Insulin degludec/insulin aspart (IDegAsp) is the first co-formulation of long-acting, basal insulin (insulin degludec, 70%) and rapid-acting, bolus insulin (insulin aspart, 30%), developed for use without need for resuspension.[1]

Aim

- This phase 3 study aimed to examine the efficacy and safety of two options for the intensification of basal insulin treatment: IDegAsp once (QD) or twice daily (BID) versus glargine U100 QD plus 1–3 injections of insulin aspart (IAsp).

Methods

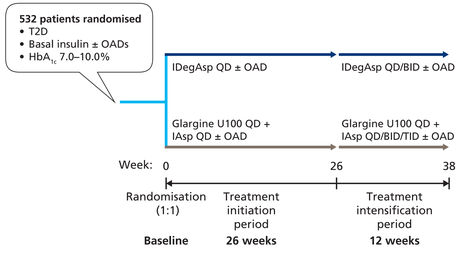
Study design and treatment

- A 38-week, randomised, open-label, treat-to-target trial (NCT02906917), in adults with type 2 diabetes (T2D) for whom basal therapy ± oral antidiabetic drugs (OADs) failed to control blood glucose (Figure 1).
  - » Patients were randomised (1:1) to IDegAsp QD or insulin glargine 100 units/mL (glargine U100) QD + insulin aspart (IAsp) QD, both ± OADs.
  - » Sulphonylureas and glinides were discontinued at randomisation, other OADs continued unchanged.
  - » Treatment intensification was permitted at Week 26 and Week 32, if HbA_{1c} was ≥7% in the previous week.
- Treatment administration:
  - » IDegAsp: administered with the largest meal(s) each day; intensification to BID performed by splitting the total daily QD dose into two doses.
  - » Glargine U100: administered QD throughout.
  - » IAsp: administered with the largest meal(s) each day.

Outcome measures

- Primary endpoint: change in HbA_{1c} (%) from baseline to Week 26 with IDegAsp QD versus glargine U100 QD + IAsp QD, with a non-inferiority margin of 0.4%.

Figure 1: Trial design



BID, twice daily; glargine U100, insulin glargine 100 units/mL; IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart; OAD, oral antidiabetic drug; QD, once daily; TID, three times daily; T2D, type 2 diabetes.

- Additional outcomes assessed included:
  - » Change in HbA_{1c} (%) from baseline to Week 38 with IDegAsp QD/BID versus glargine U100 QD + IAsp QD/BID/TID.
  - » Proportion (%) achieving target HbA_{1c} (<7%) after 26 and 38 weeks.
  - » Daily injections (*post hoc*), insulin dose (*post hoc*), fasting plasma glucose (FPG), and SMBG post-prandial increments.
  - » Incidence of hypoglycaemic episodes, classified as:
    - – Blood glucose-confirmed (<3.1 mmol/L) symptomatic, or severe (American Diabetes Association 2013 definition:[2] requiring assistance of another person).
    - – Nocturnal, occurring 00.01–05.59 (both inclusive).
  - » Incidence of adverse events.

Results

- 532 patients were randomised to IDegAsp (n=267) or glargine U100 + IAsp (n=265).
- Baseline characteristics were comparable between treatment groups (Table 1).
- Treatment groups had similar HbA_{1c} change (%) from baseline to Week 26 (Figure 2).
  - » Mean (standard deviation [SD]): IDegAsp QD, –1.1 (0.9); glargine U100 QD + IAsp QD, –1.1 (0.8).
  - » The estimated treatment difference (ETD) confirmed non-inferiority for IDegAsp: 0.07% (95% CI –0.06; 0.21), p<0.0001 for non-inferiority.

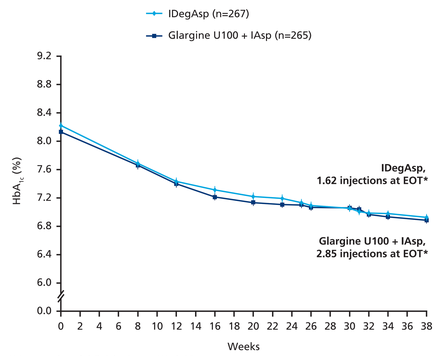
Table 1: Patient demographics

	IDegAsp (n=267)	Glargine U100 + IAsp (n=265)	Total (N=532)
Sex: Male, n (%)	125 (46.8)	137 (51.7)	262 (49.2)
Race: White, n (%)	221 (82.8)	220 (83.0)	441 (82.9)
Mean age, years (SD)	58.2 (8.9)	59.2 (9.1)	58.7 (9.0)
Mean bodyweight, kg (SD)	88.6 (18.5)	88.5 (17.5)	88.6 (18.0)
Mean BMI, kg/m^2 (SD)	31.7 (5.5)	31.7 (5.1)	31.7 (5.3)
Mean duration of diabetes, years (SD)	12.9 (6.9)	13.0 (6.5)	12.9 (6.7)
Mean HbA_{1c} at baseline, % (SD)	8.23 (0.77)	8.13 (0.73)	8.18 (0.75)
Mean FPG at baseline, mmol/L (SD)	9.01 (2.65)	8.75 (2.65)	8.88 (2.66)
Insulin treatment at baseline, n (%)			
Basal therapy OD	217 (81.3)	218 (82.3)	435 (81.8)
Basal therapy BID	50 (18.7)	47 (17.7)	97 (18.2)
OAD treatment at baseline, n (%)			
None	10 (3.7)	20 (7.5)	30 (5.6)
1 OAD	84 (31.5)	82 (30.9)	166 (31.2)
2 OADs	119 (44.6)	116 (43.8)	235 (44.2)
>2 OADs	54 (20.2)	47 (17.7)	101 (19.0)

BID, twice daily; BMI, body mass index; FPG, fasting plasma glucose; glargine U100, insulin glargine 100 units/mL; IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart; n, number of patients; OAD, oral antidiabetic drug; OD, once daily; SD, standard deviation.

Figure 2: Treatment efficacy with number of injections

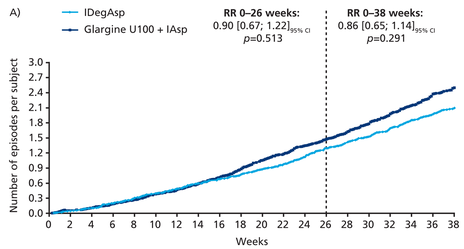
Key result



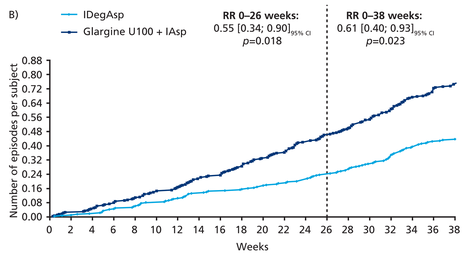
*Mean number of daily injections at Week 38.
EOT, end of trial; Glargine U100, insulin glargine 100 units/mL; IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart.

- Proportions of each treatment group that received treatment intensification:
  - » After the Week 26 visit (to BID): IDegAsp, 57%; glargine U100 + IAsp, 49%.
  - » After the Week 32 visit: IDegAsp BID, 63%; glargine U100 + IAsp BID, 23%; glargine U100 + IAsp TID, 32%.
- Changes in HbA_{1c} (%) from baseline to Week 38 remained similar across both groups:
  - » Mean (SD): IDegAsp QD/BID, –1.3 (0.8); glargine U100 QD + IAsp QD/BID/TID, –1.2 (0.8), ETD: 0.09 (95% CI –0.04; 0.22), p=0.19.
- Hypoglycaemia (Figures 3A and 3B)
  - » Rates of overall severe or blood glucose-confirmed symptomatic hypoglycaemia were similar across treatment groups.
  - » Rates of nocturnal hypoglycaemia associated with IDegAsp were statistically significantly lower than with glargine U100 + IAsp:
    - – Rates of nocturnal hypoglycaemia were 45% lower at Week 26 and 39% lower at Week 38 with IDegAsp versus glargine U100 + IAsp.
- By Week 38, fewer injections per day were required in the IDegAsp group versus glargine U100 + IAsp, mean (SD): 1.62 (0.49) versus 2.85 (0.87) (Figure 2).
- Total actual daily insulin dose was significantly lower with IDegAsp compared with glargine U100 + IAsp at both Week 26 and Week 38 (Figure 4).
- The proportion of individuals that achieved glycaemic targets, and absolute changes in mean FPG and SMBG, were similar across treatment groups, however, a significant difference of 0.28 mmol/L in favour of glargine U100 + IAsp was found in the pre-breakfast SMPG after 26 weeks (p=0.017).
- There were no safety issues identified based on the adverse event reporting or other safety parameters.
- An overview of the key clinical findings is provided in Figure 5.

Figure 3: A) Severe or BG-confirmed symptomatic hypoglycaemic episodes and B) nocturnal severe or BG-confirmed symptomatic hypoglycaemic episodes



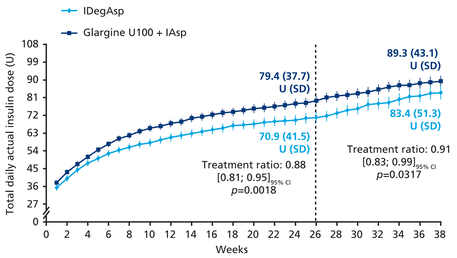
	IDegAsp, N=265				Glargine U100 + IAsp, N=263			
	N	%	E	R	N	%	E	R
Severe or BG-confirmed symptomatic events	128	48.3	537	287.13	147	55.9	640	343.30



	IDegAsp, N=265				Glargine U100 + IAsp, N=263			
	N	%	E	R	N	%	E	R
Nocturnal severe or BG-confirmed symptomatic events	52	19.6	113	60.42	75	28.5	189	101.38

RR = IDegAsp/glargine U100. BG, blood glucose; CI, confidence interval; E, number of events; glargine U100, insulin glargine 100 units/mL; IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart; N, number of patients; R, event rate per 100 patient years of exposure; RR, rate ratio.

Figure 4: Total insulin dose over time



Treatment ratio = IDegAsp/glargine U100. CI, confidence interval; glargine U100, insulin glargine 100 units/mL; IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart; SD, standard deviation; U, units.

Figure 5: Summary of clinical findings

At Week 26 and Week 38		
IDegAsp vs Glargine U100 + IAsp	HbA_{1c}	Similar
	Confirmed hypoglycaemia	Similar
	Nocturnal-confirmed hypoglycaemia	Significantly lower with IDegAsp
	Total daily insulin dose	Significantly lower with IDegAsp
	Total number of injections	Lower with IDegAsp

Glargine U100, insulin glargine 100 units/mL; IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart.

Discussion

- IDegAsp achieved similar glycaemic control to glargine U100 + IAsp, with fewer episodes of nocturnal hypoglycaemia, lower insulin dose and fewer injections.
- IDegAsp QD and BID are simple, effective options for treatment intensification in T2D, compared with the stepwise intensification of basal to basal–bolus therapy used in current clinical practice.
- This study is highly applicable to real-world practice, and can help guide physicians regarding when and how to intensify insulin treatment with fewer injections, in patients with T2D.

Conclusions

- IDegAsp is a simple treatment intensification option in T2D with benefits compared with glargine U100 + IAsp basal–bolus therapy, achieving similar glycaemic control with less nocturnal hypoglycaemia, a lower insulin dose and fewer injections.

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Presenter Yashdeep Gupta has nothing to disclose.
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References: (**1**) FDA 2016 www.accessdata.fda.gov/drugsatfda_docs/label/2016/203313s002lbl.pdf [accessed July 2018]; (**2**) Seaquist, *et al. Diabetes Care* 2013;36:1384–95.