Efficacy and safety of a fixed combination of insulin degludec/insulin aspart in children and adolescents with type 1 diabetes

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Introduction

- The importance of establishing good glycaemic control in type 1 diabetes to prevent diabetic ketoacidosis and to avoid prolonged hypoglycaemic episodes and the development of long-term complications has previously been demonstrated.[1]
- Achieving good glycaemic control in children and adolescents can be challenging due to lifestyle factors and the physiological and developmental changes that occur as they grow into adulthood.[2]
- Achievement of glycaemic targets may also be negatively impacted by attempts to minimise hypoglycaemic events.[3]
- Insulin degludec/insulin aspart (IDegAsp) is the first soluble co-formulation of two insulin analogues (insulin degludec [IDeg] and insulin aspart [IAsp]).[4]
- This study aimed to assess the efficacy and safety of IDegAsp administered once daily (OD) plus mealtime IAsp for remaining meals in controlling glycaemia in a paediatric population.

Methods

- This was a 16-week, randomised, parallel-group, open-label, treat-to-target, phase 3b non-inferiority trial conducted in 63 sites across 14 countries.
- The efficacy and safety of IDegAsp OD + IAsp (1–3 injections), versus insulin detemir (IDet) once or twice daily plus mealtime IAsp (2–4 injections), was assessed in children and adolescents with type 1 diabetes.
- The primary endpoint was change from baseline in HbA_{1c} (%) after 16 weeks of treatment.
- Eligible patients (aged 1 to <18 years, treated for ≥3 months on any insulin regimen, with a total daily insulin dose ≤2 U/kg and with HbA_{1c} ≤11%) were randomised 1:1 to the treatment groups and stratified by age (1–5 years, 6–11 years and 12–17 years).
- At randomisation, investigators were recommended to reduce the daily total insulin dose by 20% and aim to adjust the basal–bolus ratio to between 50:50 and 30:70.

Results

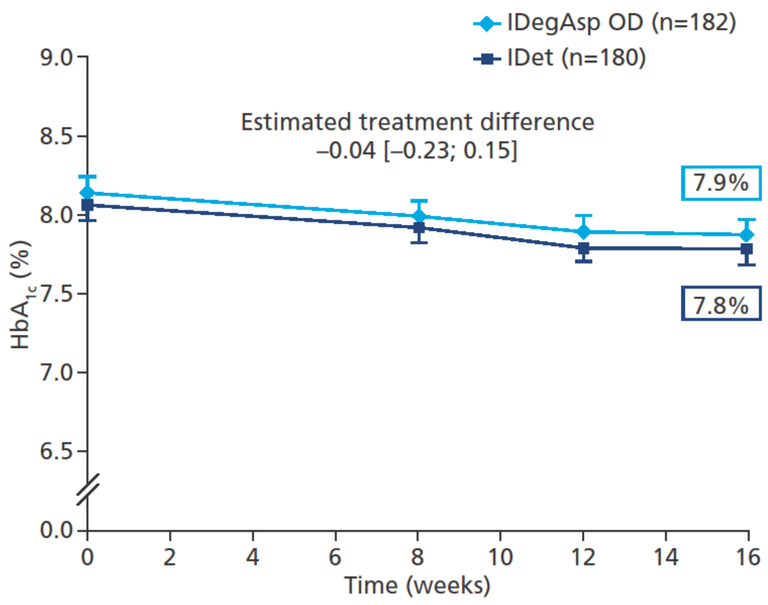
- A total of 362 children aged 1–5 years (n=82), 6–11 years (n=122) and 12–17 years (n=158) were randomised to receive IDegAsp OD or IDet.
- Baseline characteristics were generally comparable between the two treatment groups (Table 1), with some difference in the mean duration of diabetes and fasting plasma glucose (FPG).

Table 1. Demographics and baseline characteristics.

Characteristic	IDegAsp OD	IDet
Full analysis set (FAS), n	182	180
Female/Male, %	51.1/48.9	52.2/47.8
Race: White/Black/ Asian/Other, %	92.9/4.4/ 0.0/2.7	93.3/2.2/ 0.6/3.9
Age, years	10.5 (±4.3)	10.8 (±4.6)
Weight, kg	41.1 (±20.7)	42.9 (±21.2)
BMI, kg/m²	19.2 (±4.2)	19.6 (±4.0)
Duration of diabetes, years	4.4 (±3.7)	3.8 (±3.2)
HbA_{1c}, %	8.1 (±1.2)	8.1 (±1.2)
HbA_{1c}, mmol/mol[a]	65.4 (±13.6)	64.6 (±13.6)
FPG, mmol/L	8.6 (±4.4)	8.1 (±4.2)

Values are mean ±SD unless otherwise indicated. BMI, body mass index; FPG, fasting plasma glucose; IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart; IDet, insulin detemir; OD, once daily; SD, standard deviation.

Figure 1. HbA_{1c} over time.



Mean ± SEM; FAS; observed data. Estimated treatment difference [95% confidence interval]. Change from baseline in HbA_{1c} after 16 weeks of treatment was analysed using an ANCOVA method with treatment, sex, region and age group as fixed factors and baseline HbA_{1c} as covariate, and where the missing values were imputed using the LOCF method. ANCOVA, analysis of covariance; FAS, full analysis set; IDegAsp, insulin degludec/insulin aspart; IDet, insulin detemir; LOCF, last observation carried forward; OD, once daily; SEM, standard error of the mean.

- IDegAsp OD was non-inferior to IDet for change in HbA_{1c}, with a change of –0.27% and –0.23%, respectively, and an estimated treatment difference (ETD) of –0.04 $[–0.23; 0.15]_{95\% \text{ confidence interval (CI)}}$ (Figure 1).
- After 16 weeks of treatment, mean (SD) HbA_{1c} was 7.9% (1.2) with IDegAsp OD and 7.8% (1.3) with IDet.
- On average, the daily basal insulin dose was numerically lower with IDegAsp OD than IDet (0.36 U/kg and 0.49 U/kg, respectively), representing a 28% reduction in daily basal insulin dose.
- The mean daily total (basal plus bolus) insulin dose after 16 weeks of treatment was 14% lower in the IDegAsp OD group (0.88 U/kg) than in the IDet group (1.01 U/kg).
- At 16 weeks, there was no statistically significant difference in FPG between treatment groups (8.4 mmol/L with IDegAsp OD and 8.3 mmol/L with IDet). ETD for FPG was 0.31 mmol/L $[–0.70; 1.33]_{95\% \text{ CI}}$.
- There were no statistically significant differences in 8-point or 4-point self-monitored plasma glucose (SMPG) measurements between the treatment groups.
- Rates of confirmed, nocturnal confirmed and severe hypoglycaemia are shown in Table 2. There was a numerical difference in the incidence of severe hypoglycaemia in favour of IDet: IDegAsp OD 0.26 episodes per patient-year of exposure (PYE), IDet 0.07 episodes PYE; estimated rate ratio 3.20, not significant (NS).
- There was a numerical difference in the number of hyperglycaemic episodes with ketosis in favour of IDegAsp OD: IDegAsp OD 0.11 episodes PYE, IDet 0.22 episodes PYE; estimated rate ratio 0.44, NS (Table 2).
- There was a small, statistically significant difference in the SD score for weight with IDegAsp OD compared with IDet (+0.06 and –0.02, respectively); ETD 0.07 $[0.02; 0.12]_{95\% \text{ CI}}$.
  - Based on reference data,[5] this SD score difference would correspond to a difference of about 0.17 kg (girls) and 0.14 kg (boys) in 4-year-olds, 0.50 kg (girls) and 0.44 kg (boys) in 11-year-olds, and 0.45 kg (girls) and 0.73 kg (boys) in 17-year-olds.
- After 16 weeks, 54.2% of patients in the IDet + IAsp arm received IDet twice daily.
- The mean number of injections per day was 3.6 in the IDegAsp OD + IAsp group, and 4.9 in the IDet + IAsp group.
- The overall adverse event profile was similar between the treatment groups, and no new safety issues were identified.

Table 2. Rates of confirmed, nocturnal confirmed and severe hypoglycaemia per patient-year, and rates of hyperglycaemic episodes with ketosis per patient-year.

	IDegAsp OD	IDet	Estimated ratio (95% CI)
Confirmed hypoglycaemia	46.23	49.55	0.95 (0.76; 1.17); NS
Nocturnal confirmed hypoglycaemia	5.77	5.40	1.09 (0.81; 1.48); NS
Severe hypoglycaemia	0.26	0.07	3.20 (0.88; 11.66); NS
Hyperglycaemic episodes with ketosis	0.11	0.22	0.44 (0.11; 1.74); NS

Confirmed hypoglycaemia: severe (as defined by the International Society for Pediatric and Adolescent Diabetes [ISPAD] 2009), or an episode biochemically confirmed by plasma glucose value of <3.1 mmol/L, with or without symptoms consistent with hypoglycaemia.
Nocturnal confirmed hypoglycaemia: any episode of confirmed hypoglycaemia where the time of onset was 23:00–07:00 inclusive.
Severe hypoglycaemia (as defined by ISPAD 2009): any episode where the child has altered mental status and cannot assist in their own care, is semiconscious or unconscious, or in coma ± convulsions and may require parenteral therapy (glucagon or intravenous glucose).
Hyperglycaemia with ketosis: self-monitored blood ketones >1.5 mmol/L (capillary blood ketone measurement performed if SMPG exceeded 14.0 mmol/L and the patient looked/felt ill).
CI, confidence interval; IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart; IDet, insulin detemir; NS, not significant; OD, once daily; SMPG, self-monitored plasma glucose.

References

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Conclusions

- IDegAsp OD + IAsp effectively maintained glycaemic control and was non-inferior to IDet + IAsp in terms of reducing HbA_{1c}.
- No differences were observed in FPG or SMPG parameters between the treatment groups.
- On average, patients in the IDegAsp OD group had a numerically lower daily basal and total insulin dose than those in the IDet group.
- The rates of confirmed, nocturnal confirmed and severe hypoglycaemic episodes were not statistically significantly different between the treatment groups, although there was a numerically higher rate of severe hypoglycaemia in the IDegAsp OD group versus the IDet group.
- There were no statistically significant differences between treatment groups in the rates of hyperglycaemic episodes with ketosis, although there were numerically fewer in the IDegAsp OD group versus the IDet group.
- There was a small, statistically significant increase in weight with IDegAsp OD versus IDet.
- IDegAsp, as the first combination insulin, may provide an alternative treatment for some children and adolescents, particularly to replace suboptimal injection regimens and/or improve compliance.

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