Insulin degludec/insulin aspart (IDegAsp) twice daily (BID) vs biphasic insulin aspart 30 (BIAsp 30) BID: a randomised trial in Chinese patients with type 2 diabetes

qrs.ly/nn7f3p0

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Aim

- IDegAsp is the first co-formulation of long-acting basal (insulin degludec [IDeg]) and rapid-acting bolus (insulin aspart [IAsp]) insulin with no need for resuspension.[1]
- Biphasic insulin aspart 30 (BIAsp 30) is a mixture of intermediate-acting and rapid-acting IAsp that requires resuspension.[2]
- In two multinational phase 3 trials, IDegAsp twice daily (BID) demonstrated non-inferiority to BIAsp 30 BID for change in HbA_{1c} from baseline to end of trial, in patients with type 2 diabetes (T2D).[3–4]
- This confirmatory phase 3 trial (ClinicalTrials.gov NCT02762578) assessed the efficacy and safety of IDegAsp BID vs. BIAsp 30 BID ± metformin in Chinese adults with T2D inadequately controlled on pre-/self-mix or basal insulin ± metformin.

Methods

Patients

- Adults being treated for T2D with a basal insulin, premix insulin or self-mix insulin regimen administered once daily or BID, ± metformin, and with an HbA_{1c} of 7–10% (both inclusive), were eligible.

Study design and treatment

- This was a 26-week, open-label, 2:1 (IDegAsp:BIAsp 30) randomised, treat-to-target trial (pre-breakfast/pre-dinner self-measured blood glucose [SMBG] targets of 4.0–5.0 mmol/L [71–90 mg/dL].
- Insulin was administered with breakfast and dinner. A stepwise titration algorithm was used to determine insulin dose based on pre-breakfast and pre-dinner SMBG values.[4]
- A hierarchical statistical testing structure was employed with non-inferiority of HbA_{1c} change from baseline to Week 26 as the primary endpoint, and superiority of IDegAsp BID vs. BIAsp 30 BID assessed for sequential secondary endpoints: change from baseline in fasting plasma glucose (FPG); number of nocturnal confirmed hypoglycaemic episodes; number of confirmed hypoglycaemic episodes; change from baseline in body weight; and HbA_{1c} <7% without confirmed hypoglycaemic episodes.
  - » Confirmed hypoglycaemic episodes were defined as severe (requiring third-party assistance) or having an SMBG of <3.1 mmol/L (<56 mg/dL) with or without symptoms.
  - » Nocturnal confirmed hypoglycaemic episodes occurred between 00:01 and 05:59 h (both inclusive).

Results

Patients

- A total of 543 patients were randomised; 541 patients were exposed to treatment (IDegAsp BID n=360; BIAsp 30 BID n=181).
- Baseline characteristics were similar between the two treatment arms (Table 1).

Efficacy and safety

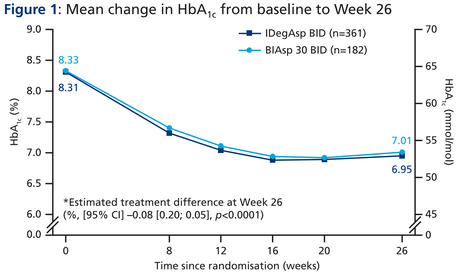
- Non-inferiority of IDegAsp BID versus BIAsp 30 BID was confirmed for HbA_{1c} observed change (mean % [SD]) from baseline to Week 26 (–1.37 [0.94] vs. –1.32 [0.81]; Figure 1).
- Superiority of IDegAsp BID versus BIAsp 30 BID was confirmed for the following secondary endpoints:
  - » FPG, observed change (mean mmol/mol [SD]) from baseline to Week 26 (–2.99 [2.59] vs. –1.57 [2.58]; Figure 2).
  - » Rate (episodes per 100 patient-years of exposure [PYE]) of nocturnal confirmed hypoglycaemia (34.86 vs. 61.02; Figure 3).
  - » Rate (episodes per 100 PYE) of confirmed hypoglycaemia (237.16 vs. 412.16; Figure 4).

Table 1: Baseline characteristics

	IDegAsp BID (N=361)	BIAsp 30 BID (N=182)	Total (N=543)
Age, years (SD)	59.6 (9.0)	58.8 (9.4)	59.4 (9.2)
Male, %	54.8	54.4	54.7
Body weight (SD), kg	68.5 (11.6)	69.4 (12.4)	68.8 (11.9)
BMI, kg/m² (SD)	25.5 (3.3)	25.7 (3.4)	25.5 (3.3)
Duration of diabetes, years (SD)	12.7 (6.2)	13.1 (6.9)	12.8 (6.4)
HbA_{1c}, % (SD)	8.3 (0.8)	8.3 (0.8)	8.3 (0.8)
FPG (SD), mmol/L mg/dL	9.1 (2.2) 163.4 (39.9)	9.1 (2.5) 163.4 (44.8)	9.1 (2.3) 163.4 (41.6)
Anti-diabetic treatment at screening, %			
Basal insulin only	4.4	6.6	5.2
Basal insulin + metformin	13.9	15.4	14.4
Premix/self-mix only	38.8	35.2	37.6
Premix/self-mix + metformin	42.4	42.9	42.5

Data are shown for number of randomised patients. BIAsp 30, biphasic insulin aspart 30; BID, twice daily; BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; IDegAsp, insulin degludec/aspart; N, number of patients.

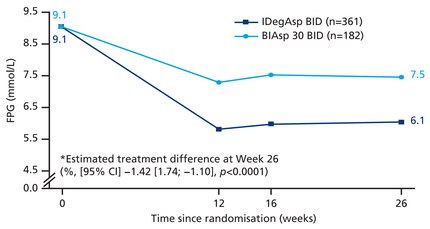
Figure 1: Mean change in HbA_{1c} from baseline to Week 26



*Confirmatory ANOVA analysis (LS mean, %) with treatment, anti-diabetic therapy at screening and sex as fixed factors, age and baseline response as covariates, and one-sided *p* value. Data are shown for patients who were exposed to treatment for at least 12 weeks. Data at Week 26 are last observed values. ANOVA, analysis of variance; BIAsp 30, biphasic insulin aspart 30; BID, twice daily; CI, confidence interval; IDegAsp, insulin degludec/aspart; LS, least squares; n, number of patients.

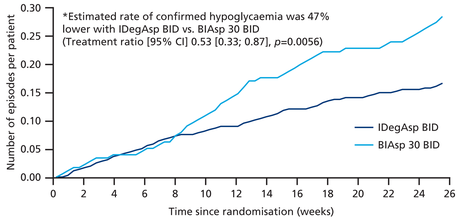
- Superiority of IDegAsp BID versus BIAsp 30 BID was not confirmed for body weight observed change from baseline (mean kg [SD]: 2.81 [2.56] vs. 2.26 [2.70], LS mean treatment contrast [95% confidence interval, CI], 0.61 [0.15; 1.08], p=0.9954).
- Superiority could not be confirmed for IDegAsp BID versus BIAsp 30 BID for percentage of patients reaching HbA_{1c} <7% without confirmed hypoglycaemic episodes by Week 26, because the hierarchical testing process was stopped at the previous confirmatory endpoint (body weight).
  - » Patients (%, estimated treatment ratio [95% CI]) in the IDegAsp BID arm were statistically more likely to reach this target versus those in the BIAsp 30 BID arm (42.4 vs. 26.4, 2.22 [1.47; 3.35], p<0.0001).

Figure 2: Mean fasting plasma glucose from baseline to Week 26



*Confirmatory ANOVA analysis (LS mean, mmol/L) with treatment, anti-diabetic therapy at screening and sex as fixed factors, age and baseline response as covariates and one-sided *p* value. Data are shown for patients who were exposed to treatment for at least 12 weeks. ANOVA, analysis of variance; BIAsp 30, biphasic insulin aspart 30; BID, twice daily; CI, confidence interval; FPG, fasting plasma glucose; IDegAsp, insulin degludec/aspart; LS, least squares; n, number of patients.

Figure 3: Nocturnal confirmed hypoglycaemia

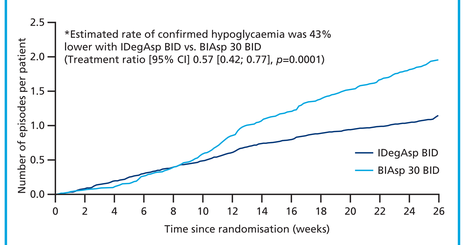


*Confirmatory analysis (LS mean) using a negative binominal regression model with a log-link function and the logarithm of the exposure time (100 years) as offset. The model included, treatment, anti-diabetic therapy at screening and sex as fixed factors, and age as covariate, with one-sided *p* value. BIAsp 30, biphasic insulin aspart 30; BID, twice daily; CI, confidence interval; estimated rate, number of episodes per 100 patient-years of exposure; IDegAsp, insulin degludec/aspart; LS, least squares.

- There was a significantly lower mean pre-breakfast and pre-dinner SMBG at Week 26 for IDegAsp BID compared with BIAsp 30 BID (estimated difference mmol/L [95% CI]: pre-breakfast: –1.1 [–1.3: –0.8], p<0.0001; pre-dinner: –0.8 [–1.1; –0.4], p<0.0001).
- The mean of the 9-point SMBG profile was significantly lower for IDegAsp BID compared with BIAsp 30 BID by Week 26 (estimated difference mmol/L [95% CI]: –0.40 [–0.69; –0.11], p=0.0070) (Figure 5).

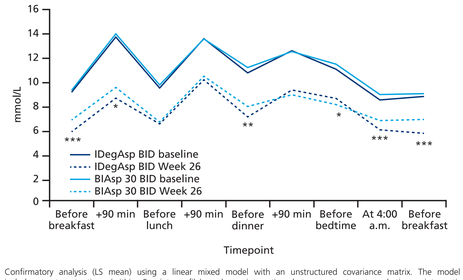
Figure 4: Confirmed hypoglycaemia

Key result



*Confirmatory analysis (LS mean) using a negative binominal regression model with a log-link function and the logarithm of the exposure time (100 years) as offset. The model included, treatment, anti-diabetic therapy at screening and sex as fixed factors, and age as covariate, with one-sided *p* value. BIAsp 30, biphasic insulin aspart 30; BID, twice daily; CI, confidence interval; estimated rate, number of episodes per 100 patient-years of exposure; IDegAsp, insulin degludec/aspart; LS, least squares.

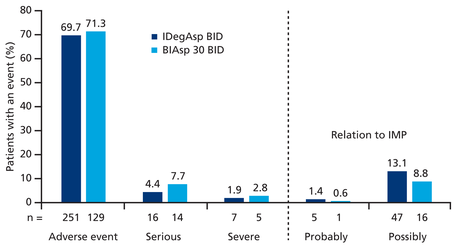
Figure 5: 9-point SMBG profiles at baseline and Week 26



Confirmatory analysis (LS mean) using a linear mixed model with an unstructured covariance matrix. The model includes treatment, time (within 9-point profile) and an interaction between treatment and time-point, anti-diabetic treatment at screening and sex as fixed effects, and age as covariates and subject as random effect. *p<0.05, **p<0.001, ***p<0.0001. BIAsp 30, biphasic insulin aspart 30; BID, twice daily; IDegAsp, insulin degludec/aspart; SMBG, self-measured blood glucose.

- Daily insulin dose (mean U/kg [SD]; dose ratio) was numerically lower by 20% in patients receiving IDegAsp BID versus BIAsp 30 BID at Week 26 (0.78 [0.35] vs. 0.95 [0.35]; 0.80).
- Similar percentages of adverse events and serious adverse events were recorded between treatment arms (Figure 6).
- No safety issues with IDegAsp were identified, and no difference in standard safety parameters were observed between treatment groups.

Figure 6: Treatment-emergent adverse events



Data is shown for patients with at least one adverse event. A serious adverse event was defined as any event resulting in death, a life-threatening experience, hospitalization, a persistent or significant disability or incapacity, congenital anomaly or birth defect, or an important medical event based on clinical judgment. An event was considered severe if it interfered considerably or unacceptably with the patients' daily activities. BIAsp 30, biphasic insulin aspart 30; BID, twice daily; IDegAsp, insulin degludec/aspart; IMP, investigational medicinal product; n, number of patients.

Discussion

- IDegAsp BID demonstrated non-inferiority versus BIAsp 30 BID with respect to change in HbA_{1c} from baseline to Week 26, and superiority versus BIAsp 30 BID with respect to change in FPG from baseline to Week 26, rate of nocturnal confirmed hypoglycaemic episodes and rate of confirmed hypoglycaemic episodes.
- Improved nocturnal glycaemic control was further indicated by lower SMBG levels before breakfast with IDegAsp BID versus BIAsp 30 BID, most likely due to the long-acting IDeg component of IDegAsp BID.
- Daily insulin dose was lower by end of trial in patients in the IDegAsp BID arm than in the BIAsp 30 BID arm, which may indicate economic benefits.
- No difference in safety events was observed between the two treatment modalities.

Conclusion

- These results demonstrate the efficacy and safety of IDegAsp compared with BIAsp 30 in Chinese patients with T2D, confirming results from other international trials.[3–4]

The trial was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT02762578).
The authors are grateful to Edmond Gabriel Fita and Jing Catherine Zhu, Novo Nordisk, for review of and input to the poster, and to Nicola Winstone, Watermeadow Medical (supported by Novo Nordisk), for writing assistance.
Presenter Jianhua Ma has nothing to disclose.
Presented at the European Association for the Study of Diabetes, 54th Annual Meeting.
1–5 October 2018, Berlin, Germany.

References: (**1**) FDA 2016 https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/203313s002lbl.pdf; (**2**) FDA 2017 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021172s062lbl.pdf; (**3**) Fulcher *et al. Diabetes Care* 2014;37:2084–90; (**4**) Kaneko *et al. Diabetes Res Clin Pract* 2015;107:139–47