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# Efficacy and safety of insulin degludec/insulin aspart versus biphasic insulin aspart 30 in Chinese adults with type 2 diabetes: A phase III, open-label, 2:1 randomized, treat-to-target trial

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**Aims:** To assess the efficacy and safety of twice-daily insulin degludec/insulin aspart (IDegAsp) versus biphasic insulin aspart 30 (BIAsp 30) twice daily, both ± metformin, in Chinese adults (*N* = 543) with type 2 diabetes (T2D) inadequately controlled on premixed/self-mixed or basal insulin ± metformin.

**Materials and methods:** We conducted a 26-week, phase III, open-label, treat-to-target, 2:1 randomized trial. Hierarchical testing was used with non-inferiority of glycated haemoglobin (HbA1c) change from baseline to week 26 as the primary endpoint and superiority for the confirmatory secondary endpoints which were as follows: change from baseline in fasting plasma glucose (FPG); nocturnal confirmed hypoglycaemic episodes (12:01–5:59 AM, inclusive); total confirmed hypoglycaemic episodes (severe or plasma glucose <3.1 mmol/L with/without symptoms); body weight; and percentage of responders (HbA1c <53 mmol/mol [<7.0%]) without confirmed hypoglycaemic episodes.

**Results:** Non-inferiority for change from baseline to week 26 in HbA1c and superiority of IDegAsp twice daily versus BIAsp 30 twice daily for change in FPG, nocturnal confirmed and total confirmed hypoglycaemic episodes, was demonstrated. Estimated rates of nocturnal confirmed and total confirmed hypoglycaemic episodes were 47% and 43% lower, respectively, with IDegAsp twice daily versus BIAsp 30 twice daily. Superiority for change in body weight was not confirmed. Participants were more likely to reach the HbA1c goal of <53 mmol/mol (<7.0%) without confirmed hypoglycaemia with IDegAsp twice daily versus BIAsp 30 twice daily by trial end. No new safety signals were identified.

**Conclusions:** The efficacy and safety of IDegAsp in Chinese patients with T2D was demonstrated, confirming results from international trials.

W.Y. and J.M. should be considered joint first authors.

**Peer Review**
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**KEYWORDS**
biphasic insulin aspart, insulin aspart, insulin degludec, insulin treatment, intensive insulin therapy, type 2 diabetes

## 1 | INTRODUCTION

Type 2 diabetes (T2D) is a progressive disorder characterized by increasing deficiency in insulin secretion and insulin resistance. In China, the disease burden of diabetes is high and increasing.[1] A survey of >170 000 Chinese people, undertaken in 2013 (when the population of China numbered 1.36 billion), estimated an overall prevalence of 10.9% for diabetes and 35.7% for prediabetes.[2,3] It is estimated that diabetes prevalence in China will increase to 11.6% (119 753 800 people) by the year 2045.[4] Diabetes currently accounts for 34% of deaths among Chinese people under the age of 60 years.[1]

Type 2 diabetes is treated using a stepwise approach, starting with lifestyle management and progressing to oral antidiabetic treatments and injectable glucagon-like peptide-1 receptor agonists (GLP-1RAs) or insulin, to prevent micro- and macrovascular tissue damage caused by chronic hyperglycaemia.[5–7] Insulin therapy is required for patients with T2D who are unable to achieve glycaemic control with oral antidiabetic medications or GLP-1RAs.[6–8] Premixed/self-mixed insulin comprises both a basal and bolus component, provides stable fasting and postprandial glycaemic control, and is an attractive alternative to classical basal–bolus therapy as fewer daily injections are required.[9] In most Asian countries, one of the most frequently prescribed insulin treatment regimens for both insulin initiation and intensification is twice-daily premixed/self-mixed insulin.[10] A 2017 retrospective database analysis of Chinese patients showed that premixed insulin was prescribed in 77.3% of those initiating insulin therapy[11]; however, the majority of Chinese patients receiving insulin treatment exhibit inadequate glycaemic control.[2]

Postprandial hyperglycaemia is more common in Asian than European populations; this is probably attributable to a combination of factors, including higher carbohydrate consumption, higher glycaemic response to carbohydrates, and poorer β-cell function, resulting in greater glucose intolerance in Asian populations.[12–16] Premixed insulin provides postprandial glycaemic control with the bolus component, in addition to the basal component, thereby meeting the needs of Asian populations.

Currently available premixed/self-mixed insulin products only offer intermediate-acting protaminated insulins as the basal component. This is because the previously available long-acting basal insulins (insulin glargine and insulin detemir) cannot be mixed with a rapid-acting insulin because the formulation of insulin glargine is incompatible and there is a tendency for insulin detemir to form hybrid insulin hexamers (resulting in unreliable activity profiles).[17,18] BIAsp 30 is a mixture of 30% soluble, non-protaminated (rapid-acting) and 70% protaminated (intermediate-acting) insulin aspart (IAsp), and requires resuspension prior to use.[19]

IDegAsp (Ryzodeg®) is the first coformulation of ultra-long-acting basal (70%, insulin degludec [degludec]) and rapid-acting bolus (30%, IAsp) insulins.[20] Unlike BIAsp 30, IDegAsp is a soluble coformulation and, therefore, does not need to be resuspended before use. Also, compared with BIAsp 30, the degludec component of IDegAsp produces a flat and stable glucose-lowering action profile that exceeds 24 hours, enabling a flexible injection schedule.[21,22] Together with IAsp, which provides postprandial control of glycaemia, this coformulation therapy is delivered in a single injection via a second-generation pen device (FlexTouch®; Novo Nordisk A/S, Bagsvaerd, Denmark).[23] IDegAsp is intended to be more convenient for patients than a regimen requiring resuspension before use (such as BIAsp 30), and is therefore expected to improve adherence to treatment while providing long-term, stable glycaemic control with fewer hypoglycaemic episodes than traditional premixed insulins, as has been observed in previous randomized clinical trials in the global development programme.[24–27]

This phase III, randomized trial (NCT02762578) was performed to assess the efficacy and safety of IDegAsp twice daily compared with BIAsp 30 twice daily, both ± metformin, as an intensification regimen for Chinese adults with T2D inadequately controlled on once-daily or twice-daily premixed/self-mixed or basal insulin ± metformin.

## 2 | MATERIALS AND METHODS

### 2.1 | Trial design

This 26-week, phase III, open-label, treat-to-target, 2:1 randomized trial was conducted at 40 sites in China, in adults with inadequately controlled T2D. A list of participating investigators is available (Table S1). A web-based randomization system was used to allocate participants to receive IDegAsp twice daily or BIAsp 30 twice daily. In accordance with local health authority regulations, the trial population was randomized 2:1 to ensure that at least 300 participants received IDegAsp twice-daily treatment, and to provide additional information on safety outcomes. The study was conducted according to the Declaration of Helsinki and its amendments, and Good Clinical Practice guidelines.[28] All participants provided written informed consent prior to any trial-related activities.

### 2.2 | Trial population

Men and women (age ≥ 18 years) with clinically diagnosed T2D for ≥6 months and receiving once-daily or twice-daily premixed/self-mixed or basal insulin ± metformin, were enrolled in the trial. All participants had to be on a treatment regimen unchanged for ≥8 weeks

prior to randomization, and had to have a central laboratory-assessed glycated haemoglobin (HbA1c) concentration of 53 to 86 mmol/mol (7.0–10.0%), inclusive, and a body mass index (BMI) of ≤40.0 kg/m$^2$. Patients were excluded from the trial if treated with other insulin regimens within 8 weeks prior to randomization; if treated with sulphonylureas, meglitinides, dipeptidyl peptidase-4 inhibitors, or α-glucosidase inhibitors within 8 weeks prior to screening; or if treated with thiazolidinediones or GLP-1RAs within 12 weeks prior to screening. Additional exclusion criteria can be found in the Supporting Information.

### 2.3 | Treatment and titration

Participants were switched to IDegAsp twice daily or BIAsp 30 twice daily from previous once-daily insulin treatment by dividing the total previous dose into two equal doses. Those receiving insulin twice daily before the trial were transferred to IDegAsp twice-daily or BIAsp 30 twice-daily treatment at the same dose. A treat-to-target principle was used to adjust insulin dose once weekly to achieve pre-breakfast and pre-main evening meal self-monitored blood glucose (SMBG) targets of 4.0 to 5.0 mmol/L (71–90 mg/dL). A titration algorithm (Table S2) was specified, in which the mean pre-breakfast and pre-main evening meal SMBG measurements from the preceding 3 days were reported during a once-weekly visit or telephone call to determine insulin dose for the following week. Pre-breakfast glucose values were used to determine titration of pre-main evening meal treatment dose, and pre-main evening meal values were used to determine pre-breakfast treatment dose. Trial insulin treatments were administered at breakfast and main evening meal. Both IDegAsp and BIAsp 30 were administered at a concentration of 100 U/mL using 3-mL prefilled injection pens (FlexTouch® and FlexPen®, respectively, both Novo Nordisk A/S). Participants treated with metformin before study enrolment continued metformin treatment at the same dose and frequency for the duration of the trial.

### 2.4 | Trial endpoints

The primary objective of the study was to compare and confirm the efficacy of IDegAsp twice daily versus BIAsp 30 twice daily, with the primary efficacy endpoint being change in HbA1c from baseline to end of trial (26 weeks). Confirmatory secondary endpoints were: change from baseline in fasting plasma glucose (FPG) after 26 weeks of treatment; number of nocturnal confirmed hypoglycaemic episodes; number of confirmed hypoglycaemic episodes; change from baseline in body weight after 26 weeks of treatment; and response without hypoglycaemic episodes (defined based on whether a participant had met the American Diabetes Association HbA1c target of <53 mmol/mol [<7.0%] after 26 weeks of treatment, without confirmed hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days after last randomized treatment, including only participants exposed for at least 12 weeks).

Supportive secondary efficacy endpoints were: percentage of participants achieving HbA1c <53 mmol/mol (<7.0%); mean SMBG profiles; and time to reach the titration target. Supportive secondary safety endpoints were: incidence of severe hypoglycaemic episodes; insulin dose after 26 weeks of treatment; and adverse events (AEs). The primary, confirmatory secondary, and supportive secondary efficacy endpoint analyses were based on all randomized participants (full analysis set). Supportive secondary safety endpoints were analysed using data from all participants exposed to at least one dose of treatment (safety analysis set).

### 2.5 | Definition of hypoglycaemia

A confirmed hypoglycaemic event was defined as either a severe episode (ie, requiring the assistance of another person to actively administer carbohydrate/glucagon, or to provide other resuscitative actions) or an episode confirmed by a plasma glucose level < 3.1 mmol/L (<56 mg/dL), with or without symptoms consistent with hypoglycaemia. Hypoglycaemic episodes that occurred between 12:01 and 5:59 AM (both inclusive) were recorded as nocturnal hypoglycaemic episodes.

### 2.6 | Statistical methods

A hierarchical testing process was employed in the analysis of this study. Endpoints were assessed sequentially, starting with non-inferiority testing of the primary endpoint (change in HbA1c from baseline to week 26), which was confirmed if the upper bound of the two-sided 95% confidence interval (CI) was below 0.4%. Testing for superiority of the confirmatory secondary endpoints was performed in the following order: change from baseline in FPG; nocturnal hypoglycaemic episodes; total confirmed hypoglycaemic episodes; change in body weight; and proportion of responders with no confirmed hypoglycaemic episodes. Superiority could be verified for each of the confirmatory secondary endpoints if the IDegAsp group had a significantly lower result compared with the BIAsp 30 group. If non-inferiority (for change in HbA1c) or superiority (for a confirmatory secondary endpoint) was not confirmed in an analysis, then superiority assessments lower in the hierarchy could not be performed, irrespective of any *P* value obtained. Endpoint results were analysed using an analysis of variance model with treatment, antidiabetic therapy at screening, and sex as fixed factors, and age and baseline response as covariates; estimated treatment differences (ETDs) were assessed using a one-sided *P* value test. The rate of hypoglycaemic episodes was analysed using a negative binomial model with a log-link function and the logarithm of the time period, in which a hypoglycaemic episode was considered treatment-emergent as offset. Missing values were imputed using last observed value.

## 3 | RESULTS

### 3.1 | Patient disposition and baseline characteristics

Of the 702 adults screened, 543 were randomized 2:1 to receive either IDegAsp twice daily (n = 361) or BIAsp 30 twice daily

(n = 182), and 541 were exposed to treatment (Figure 1). A total of 518 participants (95.4%) completed the study, with 15 (4.2%) in the IDegAsp group and 10 (5.5%) in the BIAsp 30 group withdrawing. No participant withdrew because of lack of efficacy, and only seven participants (six from the BIAsp 30 group) withdrew as a result of AEs. Three participants (two from the IDegAsp group; one from the BIAsp 30 group) were randomized in error; these events were recorded as protocol violations and data from these participants are included in the randomized participant group analyses.

Demographics and baseline characteristics were similar in the two treatment groups (Table 1). The majority of participants (57.3%) were receiving metformin at screening. Premixed/self-mixed insulins were used by 80.1% of participants and basal insulins were used by 19.5%.

## 3.2 | Primary and confirmatory endpoints

### 3.2.1 | Change in HbA1c

The observed mean HbA1c after 26 weeks of treatment was similar between treatment groups (IDegAsp: 52 mmol/mol [6.95%]; BIAsp 30: 53 mmol/mol [7.01%]; Figure 2A); non-inferiority for HbA1c was confirmed for IDegAsp twice daily versus BIAsp 30 twice daily with respect to change from baseline to week 26, with an ETD of −0.08% (95% CI −0.20; 0.05; $P < 0.0001$).

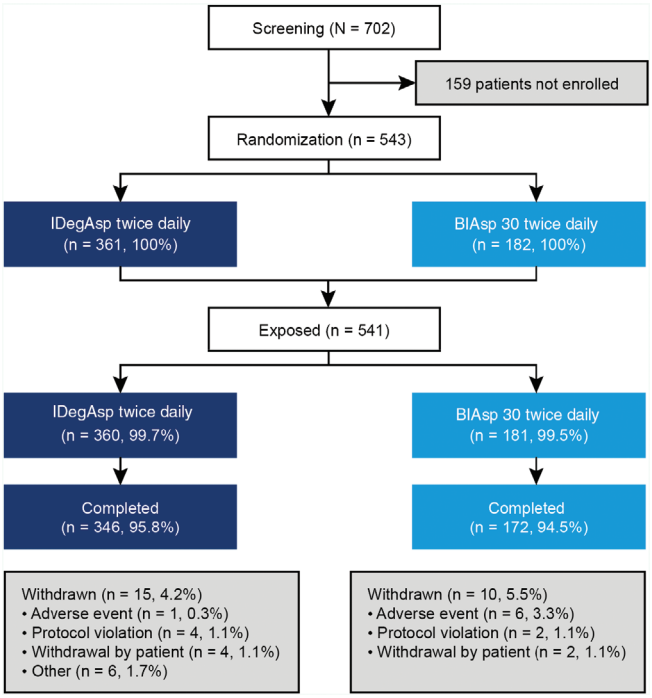


**FIGURE 1** Participant disposition. Three participants who were previously treated with bolus insulin were randomized in error: two participants in the IDegAsp group who had been treated with bolus insulin with metformin and one participant in the BIAsp 30 group who was categorized as receiving "premixed/self-mixed insulin" but had previously received basal plus bolus medication. BIAsp 30, biphasic insulin aspart 30; IDegAsp, insulin degludec/insulin aspart; n, number of participants; N, total number of participants

**TABLE 1** Baseline characteristics

| | IDegAsp twice daily (n = 361) | BIAsp 30 twice daily (n = 182) | Total (N = 543) |
|---|---|---|---|
| **Demographics** | | | |
| Age, years | 59.6 (9.0) | 58.8 (9.4) | 59.4 (9.2) |
| Men, n (%) | 198 (54.8) | 99 (54.4) | 297 (54.7) |
| Body weight, kg | 68.5 (11.6) | 69.4 (12.4) | 68.8 (11.9) |
| BMI, kg/m$^2$ | 25.5 (3.3) | 25.7 (3.4) | 25.5 (3.3) |
| Duration of diabetes, years | 12.7 (6.2) | 13.1 (6.9) | 12.8 (6.4) |
| HbA1c | | | |
| mmol/mol | 67 | 67 | 67 |
| % | 8.3 (0.8) | 8.3 (0.8) | 8.3 (0.8) |
| FPG, mmol/L | 9.1 (2.2) | 9.1 (2.5) | 9.1 (2.3) |
| **Antidiabetic treatment, n (%)** | | | |
| Basal insulin only | 16 (4.4) | 12 (6.6) | 28 (5.2) |
| Basal insulin + metformin[a] | 50 (13.9) | 28 (15.4) | 78 (14.4) |
| Premix/self-mix only | 140 (38.8) | 64 (35.2)[b] | 204 (37.6) |
| Premix/self-mix + metformin[a] | 153 (42.4) | 78 (42.9) | 231 (42.5) |
| Bolus + metformin[c] | 2 (0.6) | 0 (0.0) | 2 (0.4) |
| **Insulin dose, units** | | | |
| Pre-breakfast | 18.81 (8.34) | 19.23 (7.94) | 18.95 (8.20) |
| Pre-main evening meal | 17.03 (7.46) | 17.45 (7.58) | 17.17 (7.49) |

Abbreviations: BIAsp 30, biphasic insulin aspart 30; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; IDegAsp, insulin degludec/insulin aspart; n, number of participants; N, total number of participants.
Data are mean (SD) unless otherwise indicated, and used the full analysis set. [a]Metformin or metformin hydrochloride. [b]Includes one patient who had received basal plus bolus insulin but was randomized in error. [c]Randomized in error.

### 3.2.2 | Fasting plasma glucose

The observed mean FPG levels at week 26 were lower in the IDegAsp group compared with the BIAsp 30 group (6.07 vs. 7.48 mmol/L; Figure 2B); superiority in FPG, with respect to change from baseline after 26 weeks of treatment, was confirmed for IDegAsp twice daily versus BIAsp 30 twice daily, with an estimated treatment difference of −1.42 mmol/L (95% CI −1.74; −1.10; $P < 0.0001$).

### 3.2.3 | Hypoglycaemic episodes

The observed rates of nocturnal confirmed hypoglycaemic episodes per 100 participant-years of exposure (PYE) were 34.9 vs. 61.0 with IDegAsp twice daily and BIAsp 30 twice daily, respectively; the observed rates of total confirmed hypoglycaemic episodes were 237.2 vs. 412.2 per 100 PYE with IDegAsp twice daily and BIAsp 30 twice daily, respectively (Table 2). Similar rates of nocturnal

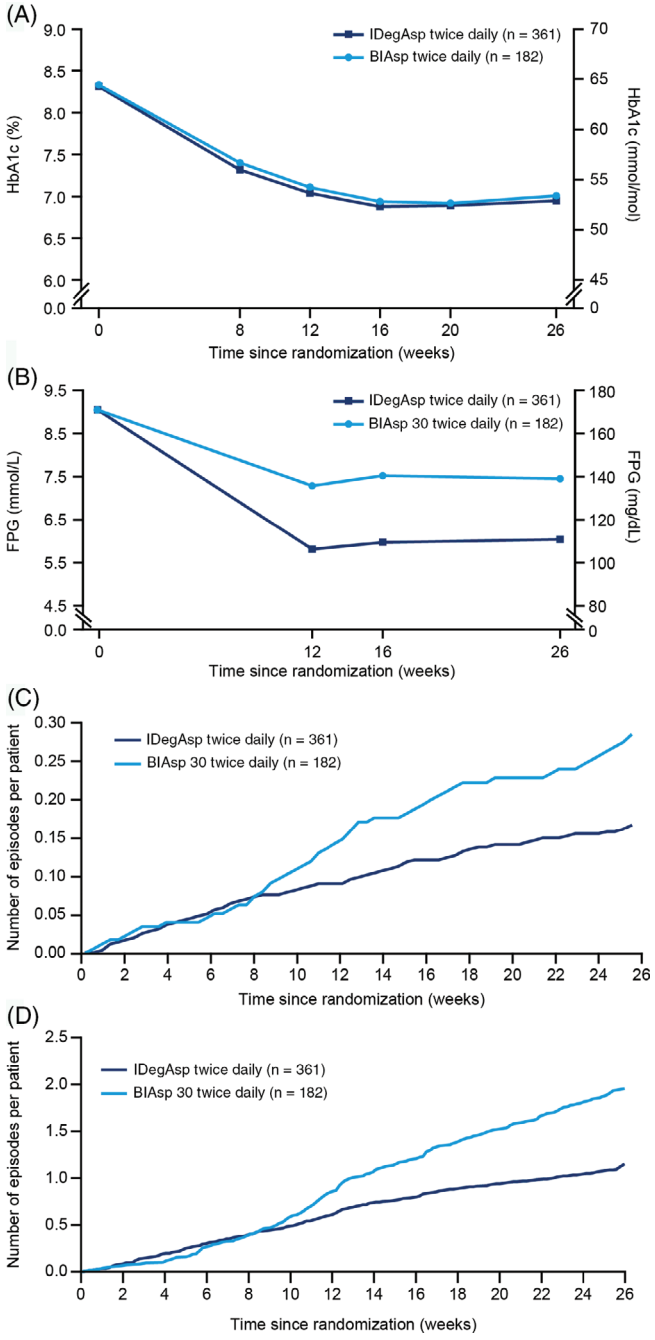


**FIGURE 2** Confirmed endpoints between baseline and week 26: **A,** glycated haemoglobin (HbA1c); **B,** fasting plasma glucose (FPG) levels; **C,** nocturnal confirmed hypoglycaemic episodes; and **D,** confirmed hypoglycaemic episodes. HbA1c (A) and FPG (B) data are shown for all randomized participants; hypoglycaemia data (C and D) are shown for participants who were exposed to treatment. Data at week 26 are last observed values. BIAsp 30, biphasic insulin aspart 30; IDegAsp, insulin degludec/insulin aspart; n, number of patients

confirmed and total confirmed hypoglycaemic episodes were observed between treatment groups for the first 8 weeks of the study, after which the groups diverged, with a higher number of episodes reported in the BIAsp 30 group compared with the IDegAsp group, up to week 26 (Figure 2C–D).The estimated rates of nocturnal confirmed and total confirmed hypoglycaemic episodes were lower with IDegAsp twice daily than with BIAsp 30 twice daily by 47% (ETD 0.53 [95% CI 0.33; 0.87]; $P = 0.0056$) and 43% (ETD 0.57 [95% CI 0.42; 0.77]; $P = 0.0001$), confirming superiority of IDegAsp twice daily for these endpoints.

### 3.2.4 | Body weight

An increase in body weight was seen in both treatment groups, with an estimated least squares (LS) mean (SE) change from baseline to week 26 of 2.82 (0.14) kg for IDegAsp twice daily and 2.21 (0.19) kg for BIAsp 30 twice daily; superiority of IDegAsp twice daily over BIAsp 30 twice daily was not shown (ETD 0.61 [95% CI 0.15; 1.08]; $P = 0.9954$) and the hierarchical statistical testing process was stopped at this stage.

### 3.2.5 | Percentage of responders without hypoglycaemic episodes

Because of the halting of hierarchical testing, superiority of IDegAsp twice daily compared with BIAsp 30 twice daily with regard to the percentage of participants reaching an HbA1c target of <53 mmol/mol (<7.0%) without confirmed hypoglycaemia could not be assessed. However, the observed proportion of participants achieving this target was 42.4% and 26.4% with IDegAsp twice daily and BIAsp 30 twice daily, respectively; participants in the IDegAsp group were more than twice as likely to reach this target than those in the BIAsp 30 group (odds ratio 2.22 [95% CI 1.47; 3.35]; $P < 0.0001$).

## 3.3 | Secondary efficacy and safety endpoints

### 3.3.1 | HbA1c target <53 mmol/mol

The percentage of participants who achieved an HbA1c target of <53 mmol/mol (<7.0%) was higher in the IDegAsp group (55.7%) than in the BIAsp 30 group (48.4%); however, the difference was not significant (ETD 1.42 [95% CI 0.97; 2.07]; $P = 0.0687$).

### 3.3.2 | Self-measured blood glucose

The estimated mean of the nine-point SMBG profile at week 26 was significantly lower for IDegAsp twice daily compared with BIAsp 30 twice daily (7.71 vs. 8.11 mmol/L; ETD −0.40 [95% CI −0.69; −0.11]; $P = 0.0070$). Specifically, significantly lower LS mean SMBG levels were observed with IDegAsp twice daily compared with BIAsp 30 twice daily at pre-breakfast (5.75 vs. 6.70 mmol/L; ETD −0.96 [95% CI −1.21; −0.70]; $P < 0.0001$), 90 minutes after breakfast (8.62 vs. 9.44 mmol/L; ETD −0.82 [95% CI −1.36; −0.28]; $P = 0.0029$), pre-main evening meal (6.96 vs. 7.78 mmol/L; ETD −0.82 [95% CI −1.26; −0.39]; $P = 0.0002$); at 4:00 AM (6.00 vs. 6.77 mmol/L; ETD −0.77 [95% CI −1.13; −0.41]; $P < 0.0001$), and pre-breakfast the following day (5.66 vs. 6.79 mmol/L; ETD −1.14 [95% CI −1.42; −0.86]; $P < 0.0001$ [Figure S1]). The only timepoint for which the LS mean SMBG level was significantly higher in the IDegAsp group compared

**TABLE 2** Summary of hypoglycaemic episodes

| | IDegAsp twice daily (n = 360) | | | BIAsp 30 twice daily (n = 181) | | | |
|---|---|---|---|---|---|---|---|
| | n (%) | E | R | n (%) | E | R | Estimated treatment ratio (95% CI)[a] |
| Confirmed hypoglycaemia | 169 (46.9) | 415 | 237.16 | 91 (50.3) | 358 | 412.16 | 0.57 (0.42; 0.77) $P$ = 0.0002 |
| Severe hypoglycaemia | 0 (0) | - | - | 6 (3.3) | 9 | 10.36 | n/a |
| Nocturnal confirmed hypoglycaemia | 45 (12.5) | 61 | 34.86 | 35 (19.3) | 53 | 61.02 | 0.53 (0.33; 0.87) $P$ = 0.0112 |
| Nocturnal severe hypoglycaemia | 0 (0) | - | - | 3 (1.7) | 4 | 4.61 | n/a |

Abbreviations: BIAsp 30, biphasic insulin aspart 30; CI, confidence interval; E, number of episodes; IDegAsp, insulin degludec/insulin aspart; n, number of participants; n/a, not applicable; R, rate (number of episodes divided by patient-years of exposure multiplied by 100).
Data used the safety analysis set.
[a]Statistics were performed using the full analysis set. Confirmed hypoglycaemia is defined as either severe episodes or episodes with plasma glucose <3.1 mmol/L (56 mg/dL) with or without symptoms. The nocturnal period was defined as the period between 12:01 and 5:59 AM (both inclusive).

with the BIAsp 30 group was before bedtime (8.60 vs. 7.97 mmol/L; ETD 0.63 [95% CI 0.09; 1.17]; $P$ = 0.0218). By trial end, estimated LS mean SMBG level for dose adjustment was significantly lower for the IDegAsp group versus the BIAsp 30 group, both pre-breakfast (5.75 vs. 6.82 mmol/L; ETD −1.06 [95% CI −1.28; −0.84]; $P$ < 0.0001) and pre-main evening meal (6.98 vs. 7.74 mmol/L; ETD −0.77 [95% CI −1.10; −0.43]; $P$ < 0.0001). The mean within-participant coefficient of variation for dose adjustment in the nine-point SMBG profile before breakfast and the main evening meal was similar in the two treatment groups (Table S3).

### 3.3.3 | Time to reach titration target

The time (weeks) to first achieve a titration target SMBG of 4.0 to 5.0 mmol/L for both pre-breakfast and pre-main evening meal was significantly shorter for participants in the IDegAsp group compared with the BIAsp 30 group (hazard ratio 2.65 [95% CI 1.64; 4.30]; $P$ < 0.0001). The median time to first achievement of the pre-breakfast target was 8 weeks for the IDegAsp group, while <50% of participants receiving BIAsp 30 twice daily achieved this target by week 26. The time taken for 25% of the IDegAsp group to achieve the pre-breakfast target was 3 weeks compared with 15 weeks for the BIAsp 30 group. The pre-main evening meal target was achieved by 25% of the IDegAsp group by week 11, whereas <25% of the BIAsp 30 group achieved this target by week 26.

### 3.3.4 | Severe hypoglycaemic episodes

No severe hypoglycaemic episodes were recorded in the IDegAsp group, whereas six participants (3.3%) in the BIAsp 30 group reported nine severe hypoglycaemic episodes corresponding to a rate of 10.36 episodes per 100 PYE (Table 2). Among participants who had received BIAsp 30 twice daily, three (1.7%) had a total of four episodes of nocturnal severe hypoglycaemia, with a rate of 4.61 episodes per 100 PYE (Table 2). Rates of nocturnal and total confirmed hypoglycaemic episodes are shown in the 'Primary and confirmatory endpoints' section.

### 3.3.5 | Insulin dose

At baseline, both treatment groups received similar mean insulin doses (Table 1). At week 26, daily insulin dose (U/kg, mean [SD]) was numerically lower by 20% in participants who received IDegAsp twice daily versus BIAsp 30 twice daily (0.78 [0.35] vs. 0.95 [0.35] U/kg; dose ratio 0.80). Higher mean (U/kg, mean [SD]) insulin doses were used pre-breakfast compared with pre-main evening meal in both treatment groups, both at baseline (IDegAsp twice-daily: 0.28 [0.12] vs. 0.25 [0.10] U/kg; BIAsp 30 twice daily: 0.28 [0.11] vs. 0.25 [0.10] U/kg, respectively), and at week 26 (IDegAsp twice daily: 0.48 [0.22] vs. 0.30 [0.18]; BIAsp 30 twice daily: 0.53 [0.19] vs. 0.42 [0.18], respectively).

### 3.3.6 | Adverse events

Overall AE rates (number of AEs per 100 PYE) were comparable between treatment groups (321.74 for IDegAsp twice daily vs. 348.82 for BIAsp 30 twice daily), demonstrating that both treatments were well tolerated (Table S4). There was a lower rate of serious AEs with IDegAsp twice daily compared with BIAsp 30 twice daily (10.86 vs. 21.87), and no fatal AEs occurred in either treatment group. The most frequently reported AEs (reported by ≥5% of participants) were upper respiratory tract infection (21.1% and 25.4% with IDegAsp twice daily and BIAsp 30 twice daily, respectively), viral upper respiratory tract infection (2.5% and 5.5%, respectively), and diabetic retinopathy (10.0% and 6.6%, respectively). Diabetic retinopathy events were mild or moderate in severity and were all reported at the pre-planned, end-of-trial visit, during which an eye examination was routinely performed. No new safety signals were identified during this trial.

## 4 | DISCUSSION

IDegAsp is the first soluble coformulation of an ultra-long-acting basal and rapid-acting bolus insulin (70:30). It is intended to increase treatment adherence and convenience, leading to improved long-term glycaemic control and a reduction in complications relating to chronic hyperglycaemia.[20] Compared with BIAsp 30 twice-daily, IDegAsp

twice daily demonstrated non-inferiority with respect to change in HbA1c from baseline to week 26 and superiority with respect to change in FPG from baseline to week 26 in the present phase III, randomized trial in Chinese adults with T2D.

This is consistent with results from two previous phase IIIa trials that compared IDegAsp twice daily with BIAsp 30 twice daily in insulin-experienced patients with T2D, namely BOOST: INTENSIFY PREMIX I (NCT01009580)[26] and BOOST: INTENSIFY ALL (NCT01059812).[27,29]

Despite pre-breakfast and pre-main evening meal SMBG levels being lower in the IDegAsp group compared with the BIAsp 30 group throughout the study period, there was a lower estimated rate of nocturnal confirmed and total confirmed hypoglycaemia with IDegAsp twice daily versus BIAsp 30 twice daily (47% and 43% fewer episodes per 100 PYE, respectively). Furthermore, no severe hypoglycaemic episodes (nocturnal or diurnal) were reported with IDegAsp twice daily. The lower incidence of hypoglycaemia with IDegAsp may be attributable to the pharmacodynamic profile of the degludec component of IDegAsp, which has a long duration of action of ≥24 hours, and four-times lower day-to-day variability (when compared with insulin glargine, another long-acting insulin) as a result of the formation of soluble, stable hexamers upon injection that gradually disassociate.[21,30,31] Participants in the IDegAsp group also required lower pre-breakfast and pre-main evening meal insulin doses than those in the BIAsp 30 group by the end of the trial, probably as a result of these differences in pharmacodynamic profiles and in line with results of previous global trials.[26,27] This, and the lower incidence of hypoglycaemia observed, may imply economic benefits to IDegAsp twice-daily treatment compared with BIAsp 30 twice-daily treatment.[32] Higher mean SMBG levels before bedtime in the IDegAsp group may be attributed to the lower mean pre-main evening meal insulin dose taken compared with the BIAsp 30 group, although SMBG levels remained within the target range in both groups. The time taken to first achieve a titration target SMBG of 4.0 to 5.0 mmol/L for both pre-breakfast and pre-main evening meal was significantly shorter for participants in the IDegAsp group compared with the BIAsp 30 group.

The baseline characteristics of patients in this trial were comparable to those of patients enrolled in the BOOST: INTENSIFY PREMIX I global clinical trial of IDegAsp twice daily versus BIAsp 30 twice daily, except for BMI.[26] The Chinese participants in the present study had a lower mean BMI, as would be expected, than participants in the international study; a lower BMI may increase susceptibility to severe hypoglycaemia, but this was not observed when comparing the percentage of participants who reported a severe hypoglycaemic event in these two studies with either insulin treatment (IDegAsp twice daily: 0.0% vs. 3.1%; BIAsp 30 twice daily: 3.3% vs. 7.2% for the present vs. the global study).[26] In the BOOST: INTENSIFY PREMIX I trial, lower rates of nocturnal confirmed and total confirmed hypoglycaemic episodes (73% and 32% fewer episodes per PYE, respectively) were observed with IDegAsp twice daily than with BIAsp 30 twice daily,[26] in line with the results of the present trial in a Chinese population.

In the present study, plasma glucose values were self-measured by patients at specific time intervals using finger-prick testing; a continuous glucose monitoring (CGM) device was not used; therefore, there is limited information on the 24-hour plasma glucose profiles. Although CGM devices are typically expensive to use and require frequent calibration, emerging technologies, such as flash CGM devices, are cheaper alternatives, and the use of these newer devices, if feasible, may benefit future trials that investigate the efficacy and safety of novel insulins.[33]

In conclusion, in the present study, we aimed to assess, for the first time, the efficacy and safety of IDegAsp twice daily versus BIAsp 30 twice daily in a large Chinese population with T2D. Similar efficacy in the two treatment groups with regard to HbA1c reduction was observed with IDegAsp twice daily versus BIAsp 30 twice daily, and superiority with reduced FPG and risk of hypoglycaemia was shown. These results support the findings of previous international studies, which together demonstrate that IDegAsp is beneficial for use in global populations.

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## CONFLICT OF INTEREST

A.M.N. is an employee and a stock/shareholder of Novo Nordisk A/S. W.L. and L.P. are employees of Novo Nordisk (China) Pharmaceuticals Co. Ltd. T.H. is on an advisory panel and is a speakers' bureau member for Novo Nordisk, Sanofi, AstraZeneca and Merck Serono, is on an advisory panel for Merck Sharp & Dohme, and is a speakers' bureau member for Eli Lilly and Bayer. W.Y., J.M., M.L., H.M., Y.P., C.W., X.X., T.Y. and Z.W. have no conflicts of interest to declare. No other potential conflicts of interest relevant to this article are reported.

## AUTHOR CONTRIBUTIONS

All named authors were involved in the study concept and design, acquisition, analysis and/or interpretation of data, and all authors contributed to the writing and review of the manuscript and approved the final version for submission. W.Y. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors also acknowledge the contributions of Edmond Gabriel Fita, Maoyi Xu, Jing Yang, Jing Zhu, Beibei Xu, and Lu Jing for review and input into this manuscript.

## DATA SHARING

Data will be shared with bona fide researchers submitting a research proposal requesting access to data, for use as approved by the Independent Review Board according to the Independent Review Board Charter (see novonordisk-trials.com). The data will be available permanently after research completion and approval of product and product use in both the European Union and the United States, with no end date. Individual participant data will be shared in datasets in a de-identified/−anonymized format. The study protocol and redacted Clinical Study Report will be available according to Novo Nordisk data sharing commitments. An access request proposal form and the access criteria can be found at novonordisk-trials.com. The data will be made available on a specialized SAS data platform.

## PRIOR PRESENTATION

These trial data have been previously presented as a poster at the American Diabetes Association 78th Scientific Sessions, June 22–26, 2018, Orlando, FL, USA and the 54th Annual Meeting of the European Association for the Study of Diabetes, October 1–5, 2018, Berlin, Germany.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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