# Research: Treatment

# Twice-daily insulin degludec/insulin aspart provides superior fasting plasma glucose control and a reduced rate of hypoglycaemia compared with biphasic insulin aspart 30 in insulin-naïve adults with Type 2 diabetes

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## Abstract

**Aim**  To evaluate the efficacy and safety of twice-daily insulin degludec/insulin aspart vs. twice-daily biphasic insulin aspart 30 in people with Type 2 diabetes mellitus who were naïve to insulin.

**Methods**  In this 26-week, multinational, open-label, controlled, two-arm, parallel-group, treat-to-target trial, participants [mean ($\pm$ SD) age 58.9 ($\pm 8.9$) years, duration of diabetes 9.5 ($\pm 5.9$) years, $HbA_{1c}$ 68 ($\pm 8.7$) mmol/mol or 8.4 ($\pm 0.8$)% and BMI 31.2 ($\pm 4.2$) kg/m$^2$] were randomized (1:1) to insulin degludec/insulin aspart ($n = 197$) or biphasic insulin aspart 30 ($n = 197$), administered with breakfast and the main evening meal, titrated to a self-monitored plasma glucose target > 3.9 and ≤ 5.0 mmol/l.

**Results**  The mean $HbA_{1c}$ was reduced to 49 mmol/mol (6.6%) with insulin degludec/insulin aspart and 48 mmol/mol (6.5%) with biphasic insulin aspart 30. Insulin degludec/insulin aspart achieved the prespecified non-inferiority margin (estimated treatment difference 0.02%; 95% CI −0.12, 0.17). Insulin degludec/insulin aspart was superior in lowering fasting plasma glucose (estimated treatment difference −1.00 mmol/l; 95% CI −1.4, −0.6; $P < 0.001$) and reducing overall and nocturnal confirmed hypoglycaemia at a similar overall insulin dose compared with biphasic insulin aspart 30. Similar proportions of participants in each arm experienced severe hypoglycaemia. Adverse events were equally distributed.

**Conclusions**  Consistent with previous findings, insulin degludec/insulin aspart twice daily effectively improved long-term glycaemic control, with superior reductions in FPG, and significantly less overall and nocturnal confirmed hypoglycaemia compared with biphasic insulin aspart 30 in people with Type 2 diabetes who were insulin-naïve.

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## Introduction

There is a need for effective early glycaemic control in order to achieve sustained, long-term reductions in Type 2 diabetes mellitus-related complications, the benefits of which appear to extend beyond the duration of the specific intervention (the so-called 'legacy effect') [1].

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Currently, the use of a prandial and basal insulin is recommended either by the sequential addition of a pre-meal rapid-acting insulin analogue to ongoing basal insulin or by switching to a premixed insulin. The initiation of the insulin treatment by means of both basal and bolus insulin is recommended in patients with very high $HbA_{1c}$ levels (≥ 75 mmol/mol or ≥ 9%) [2]. The fear of injections and the complexity of basal and bolus regimens requiring multiple daily injections may be a barrier to the initiation of insulin and long-term adherence to therapy in some people [3–5]. Insulin degludec/insulin aspart (IDegAsp) is a soluble co-formulation of a basal insulin with an ultra-long duration

> **What's new?**
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> - Insulin degludec/insulin aspart (IDegAsp) is the first soluble co-formulation that combines two insulin analogues. It provides effective basal and prandial glycaemic coverage.
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> - This trial aimed to compare twice-daily IDegAsp and twice-daily biphasic insulin aspart 30 (BIAsp 30) in people with Type 2 diabetes mellitus who were naïve to insulin.
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> - IDegAsp achieved the prespecified non-inferiority margin for HbA$_{1c}$ and was superior to BIAsp 30 in lowering fasting plasma glucose and overall and nocturnal confirmed hypoglycaemia at a similar insulin dose compared with BIAsp 30.
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> - The results of this study indicate that IDegAsp provides an effective means of initiating insulin treatment with a marked reduction in hypoglycaemia in people with Type 2 diabetes.

of action and a short-acting insulin analogue, containing 70% insulin degludec (IDeg) and 30% insulin aspart (IAsp) in a single injection [6,7]. In solution, the individual components of IDegAsp have been shown to exist as separate di-hexamers (IDeg) and hexamers (IAsp) [8,9]. On injection, the IDeg di-hexamers assemble to form long and stable multi-hexamers, resulting in a soluble depot in the subcutaneous tissue from which IDeg monomers slowly dissociate to meet basal insulin needs. At the same time, IAsp hexamers immediately dissociate into monomers that are rapidly absorbed into the circulation, providing meal-time coverage [7,8].

The glucose-lowering effect of IDegAsp has been shown in pharmacodynamic studies, and is characterized by a distinct prandial action (IAsp) and a separate sustained stable basal action (IDeg), lasting beyond 24 h under both steady-state and single-dose conditions [7,9,10]. Pharmacodynamic modelling of once-daily dosing data suggests that IDegAsp twice-daily dosing could provide prandial coverage over two separate meal-times, along with a flat and stable 24-h basal coverage [7]. Conversely, after a single dose of biphasic insulin aspart 30 (BIAsp 30), the glucose infusion rate returns to 0 after 18–22 h from the time of the injection. The interaction between the two forms of IAsp in BIAsp 30 results in a 'shoulder' effect, with prolonged activity and a less distinct prandial component [11], whereas the glucose infusion rate slowly declines because of the protracted action of the protamine form of IAsp [12].

Treatment with IDegAsp twice daily results in superior reductions in fasting plasma glucose (FPG) levels and significantly reduced rates of overall and nocturnal hypoglycaemia vs. BIAsp 30 twice daily in participants with Type 2 diabetes, with inadequately controlled glycaemia on pre- or self-mixed insulin with or without oral antidiabetic drugs, when treated to comparable glucose targets [13,14]. IDegAsp offers a potential initiation therapy for people with Type 2 diabetes who are naïve to insulin and who require prandial insulin and would benefit from a combined prandial and basal insulin therapy, available as a stable solution without the need for resuspension. In addition, the ultra-long duration of action of the basal component of IDegAsp offers the potential for flexible dosing times. Either once- or twice-daily dosing is possible, with IDegAsp taken before the meal (s) having the largest glycaemic impact [15].

Although IDegAsp has been previously shown to provide effective glycaemic control with reduced rates of hypoglycaemia in patients on previous insulin therapy, the present study aimed to evaluate the safety and efficacy of a pre-breakfast and pre-main evening meal twice-daily dosing schedule using IDegAsp or BIAsp 30 in people with Type 2 diabetes who were naïve to insulin and who were inadequately controlled on oral antidiabetic drugs.

## Materials and methods

### Study design

In total, 47 sites across 10 countries (Algeria, Bulgaria, Croatia, Czech Republic, Germany, Poland, Romania, Slovakia, Turkey and Ukraine), encompassing various dietary patterns, participated in this randomized, open-label, controlled, two-arm, parallel-group trial. The trial used a treat-to-target design, in line with current US Food and Drug Administration recommendations for the evaluation of novel insulin preparations [16]. Randomization was by interactive voice/web response service, stratified according to the antidiabetic medication at screening. The trial was registered with www.clinicaltrials.gov (NCT01513590) and was carried out according to the Declaration of Helsinki [17] and its amendments, and the International Conference on Harmonisation Good Clinical Practice Guidelines [18]. Participants provided written informed consent before any trial-related activities.

### Study population

Adults (≥ 18 years of age) with Type 2 diabetes for ≥ 24 weeks were enrolled if they were insulin-naïve, had HbA$_{1c}$ levels of 53–86 mmol/mol (7.0–10.0%) inclusive, and a BMI ≤ 40.0 kg/m$^2$. Participants were included if their glycaemia was uncontrolled on their current therapy of metformin (≥ 1000 mg daily) ± one additional oral antidiabetic drug (sulphonylurea, glinide, dipeptidyl peptidase-4 inhibitor or α-glycosidase inhibitor) for at least 12 weeks before randomization.

Key exclusion criteria included: treatment with antidiabetic regimens other than the above within the 12 weeks preceding randomization (visit 2) and treatment with thia-

zolidinediones or glucagon-like peptide-1 receptor agonists within 12 weeks preceding screening (visit 1); cardiovascular disease [heart failure (New York Heart Association class III or IV), unstable angina pectoris or a myocardial infarction, unstable angina pectoris, coronary arterial bypass graft or angioplasty] within 6 months preceding the trial; and uncontrolled severe hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg).

### Study procedures

Before randomization, eligible participants discontinued their current oral antidiabetic drugs, except metformin, which was continued at pre-trial dose. Participants were randomized (1:1) to twice-daily injections of IDegAsp [70% IDeg/30% IAsp (Ryzodeg®; Novo Nordisk A/S, Bagsværd, Denmark) 100 U/mL] or BIAsp 30 (NovoMix® 30; Novo Nordisk A/S) 100 U/ml, administered by subcutaneous injection with breakfast and the main evening meal for 26 weeks, in combination with metformin. Participants initiated treatments at a dose of 6 U twice daily with breakfast and dinner. During the treatment period, IDegAsp or BIAsp 30 were titrated based on the mean pre-breakfast plasma glucose value and the mean pre-main evening meal plasma glucose value from the preceding 3 days using a titration algorithm (Table S1). Titration of pre-main evening meal insulin dose was based on the participants' mean pre-breakfast glucose values and titration of pre-breakfast insulin dose was based on the mean pre-main evening meal glucose values. Participants were instructed to perform a nine-point profile [self-monitored plasma glucose (SMPG)] before visits 2, 14, 18 and 28 (weeks 0, 12, 16 and 26). The prandial plasma glucose increment for each meal was derived from the nine-point SMPG profile as the difference between plasma glucose values available 90 min after the meal and before the meal. The meters used for self-monitoring measured glucose from capillary blood but these values were automatically calibrated to equivalent plasma glucose values. Titration of pre-main evening meal insulin doses was based on the individual subject's mean pre-breakfast glucose values. Pre-breakfast insulin doses were based on the subject's mean pre-main evening meal glucose (see Table S1 for dose adjustment of pre-breakfast or pre-main evening meal dose of IDegAsp or BIAsp 30). At each visit, the investigator emphasized the necessity for the subject to adhere to trial procedure in order to encourage subject compliance.

### Study endpoints

The primary efficacy endpoint was non-inferiority of IDegAsp to BIAsp 30 in terms of change from baseline in $HbA_{1c}$ after 26 weeks of treatment. Testing for non-inferiority was aligned with the study's treat-to-target design, as mandated by the 2008 US Food and Drug Administration

guidance [16]. Secondary efficacy endpoints included change from baseline in FPG and nine-point SMPG profiles.

Safety variables included: overall and nocturnal (00.01–05.59 h) confirmed hypoglycaemia (events requiring external assistance or a plasma glucose measurement of < 3.1 mmol/l), severe hypoglycaemia (an episode requiring external assistance), adverse events, vital signs, electrocardiogram, fundoscopy, physical examination and laboratory values.

### Statistical methods

The primary objective of this trial was to demonstrate non-inferiority of IDegAsp to BIAsp 30 in terms of change from baseline $HbA_{1c}$ (prespecified non-inferiority limit of 0.4%). In the event that non-inferiority was established, superiority of IDegAsp over BIAsp 30 was assessed using a fixed-sequence testing procedure for a number of confirmatory endpoints, including, but not limited to, those indicated above. The primary endpoint was analysed using an ANOVA method, with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline $HbA_{1c}$ as covariates.

Sample size was determined using a t-statistic under the assumption of a one-sided test of size 2.5% and a zero mean treatment difference (i.e. D = 0%). Based on experience from previous phase III trials in participants with Type 2 diabetes treated with insulin, an estimate for the standard deviation (SD) of 1.3% for $HbA_{1c}$ was used in the sample size calculation. The sample size calculation was carried out using SAS 9.1.3. The minimum sample size required to meet the primary objective with at least 80% power was 334 with an assumed SD of 1.3%. As such, the sample size of 394 participants randomized was sufficient.

Change from baseline in FPG, body weight and SMPG were analysed using an ANOVA method similar to that used with the primary endpoint. Rates of confirmed hypoglycaemic episodes (overall and nocturnal) were analysed using a negative binomial regression model. Adverse events were examined using descriptive statistics.

## Results

### Baseline characteristics

Of the 525 participants screened in the study between January and November 2012, 394 (51.5% male, mean (±SD) age 58.9 (±8.9) years, duration of diabetes 9.5 (±5.9) years, $HbA_{1c}$ 68 (8.7) mmol/mol or 8.4 (±0.8)%, BMI 31.2 (±4.2) kg/m²] were randomized to receive either IDegAsp or BIAsp 30 (Fig. 1). A total of 187 (95%) participants in the IDegAsp treatment arm and 184 (93%) participants in the BIAsp 30 treatment arm completed the study. Baseline characteristics were broadly similar in the two treatment groups, including $HbA_{1c}$, duration of diabetes and BMI (Table 1).
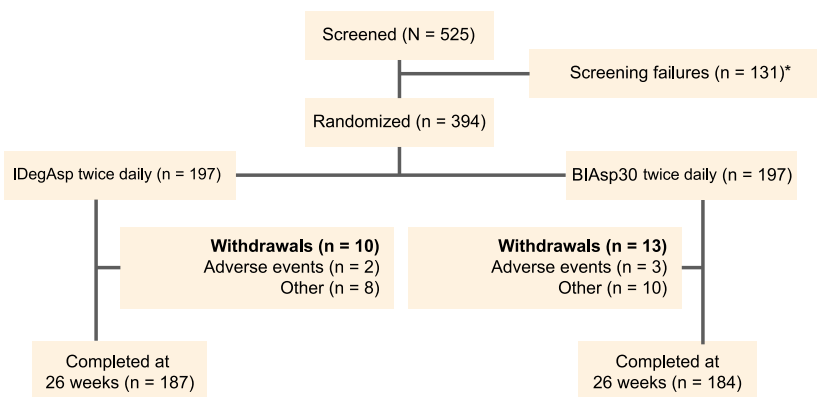
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                        Screened (N = 525)

                                    ──────────────  Screening failures (n = 131)*

                        Randomized (n = 394)

        ┌───────────────────────────┴───────────────────────────┐
IDegAsp twice daily (n = 197)                        BIAsp30 twice daily (n = 197)
        │                                                        │
        │       Withdrawals (n = 10)       Withdrawals (n = 13)  │
        │       Adverse events (n = 2)     Adverse events (n = 3)│
        │       Other (n = 8)              Other (n = 10)        │
        │                                                        │
   Completed at                                         Completed at
  26 weeks (n = 187)                                   26 weeks (n = 184)
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**FIGURE 1** Patient disposition. *Of the screening failures, 110 participants failed to comply with at least one of the specified inclusion or/and exclusion criteria; the majority of these were related to violation of the inclusion criterion concerning $HbA_{1c}$ 53–86 mmol/mol (7.0–10.0%; both inclusive) before entry. The participants were randomized based on measurements performed at the screening visit (visit 1) and baseline values were recorded approximately 1 week later at the randomization visit (visit 2). Some participants had $HbA_{1c}$ values that were above or below the inclusion criteria (53–86 mmol/mol) as the $HbA_{1c}$ of some participants had increased or decreased from visit 1 to visit 2. Of the remaining 21 participants who were screening failures for other reasons, 12 participants withdrew their consent, six participants faced issues with the shipping of their blood samples, one patient had a contaminated sample and was unable to come in for a retest in time, one patient's laboratory results were not obtained within the screening period window and one patient was screened by mistake. BIAsp 30, biphasic insulin aspart 30; IDegAsp, insulin degludec/insulin aspart.

## Glycaemic control

Reductions in $HbA_{1c}$ were observed with twice-daily IDegAsp and twice-daily BIAsp 30 over the course of

**Table 1** Baseline characteristics of randomized population

| Characteristic | IDegAsp twice daily | BIAsp 30 twice daily |
|---|---|---|
| Full analysis set, $n$ | 197 | 197 |
| Female/male, % | 48.2/51.8 | 48.7/51.3 |
| Race: white/black/ Asian/other, % | 99.5/0.5/0.0/0.0 | 100.0/0.0/0.0/0.0 |
| Ethnicity: Hispanic or Latin American, % | 2.5 | 3.6 |
| Age, years | 59.0 (±9.5) | 58.8 (±8.4) |
| Weight, kg | 88.0 (±15.0) | 88.5 (±14.9) |
| BMI, kg/m² | 31.2 (±4.3) | 31.1 (±4.2) |
| Duration of diabetes, years | 9.6 (±6.1) | 9.4 (±5.7) |
| $HbA_{1c}$* | | |
|   mmol/mol | 69 (±8.7) | 67 (±7.7) |
|   % | 8.5 (±0.8) | 8.3 (±0.7) |
| FPG | | |
|   mmol/l | 10.5 (±2.4) | 10.0 (±2.3) |
|   mg/dl | 189.0 (±43.2) | 180.0 (±41.4) |
| SMPG*†, mmol/l | | |
|   All meals | 2.6 (±1.7) | 2.7 (±1.8) |
|   Breakfast | 3.6 (±2.6) | 3.5 (±2.7) |
|   Lunch | 2.1 (±2.9) | 2.4 (±3.1) |
|   Main evening meal | 2.1 (±2.9) | 2.2 (±2.9) |

BIAsp 30, biphasic insulin aspart 30; FPG, fasting plasma glucose; IDegAsp, insulin degludec/insulin aspart; SMPG, self-monitored plasma glucose.
Values are mean (± SD) unless otherwise stated.
*Calculated, not measured.
†Prandial SMPG increments.
All meals at week 0, measured before each meal and 90 min after each meal.

26 weeks. By trial end, according to the treat-to-target design of the study, $HbA_{1c}$ was reduced to a similar degree in both treatment arms: to 49 mmol/mol (6.6%) and 48 mmol/mol (6.5%) with IDegAsp twice daily and BIAsp 30 twice daily, respectively (Fig. 2). The estimated mean change in $HbA_{1c}$ was −1.71% with IDegAsp and −1.73% with BIAsp 30. An estimated treatment difference of 0.02% (95% CI −0.12, 0.17) confirmed the primary endpoint of non-inferiority of IDegAsp twice daily to BIAsp 30 in lowering $HbA_{1c}$, as expected in a treat-to-target design.

## Fasting plasma glucose

After 26 weeks of treatment, the observed mean FPG decreased to 6.0 mmol/l (108.1 mg/dl) with IDegAsp and 7.0 mmol/l (126.1 mg/dl) with BIAsp 30 (Fig. 3). IDegAsp was superior to BIAsp 30 in terms of reduction in FPG, with an estimated mean change of −4.3 mmol/l (−78.4 mg/dl) and −3.3 mmol/l (−60.2 mg/dl), respectively. The estimated treatment difference was −1.0 mmol/l (95% CI −1.4, −0.6; $P < 0.001$; −18.0 mg/dl; 95% CI 25.6, −10.6).

## Nine-point self-monitored plasma glucose

Both IDegAsp and BIAsp 30 led to improvements from baseline in mean nine-point SMPG profiles (Fig. S1). Mean SMPG values were lower for IDegAsp than for BIAsp 30 before breakfast (estimated treatment difference −0.4 mmol/l; 95% CI −0.7, −0.1; $P < 0.05$), 90 min after breakfast (estimated treatment difference −0.6 mmol/l; 95% CI −1.0, −0.1; $P < 0.05$) and before breakfast the following day (estimated treatment difference −0.5 mmol/l; 95% CI −0.8, −0.2; $P < 0.05$). There were no significant differences
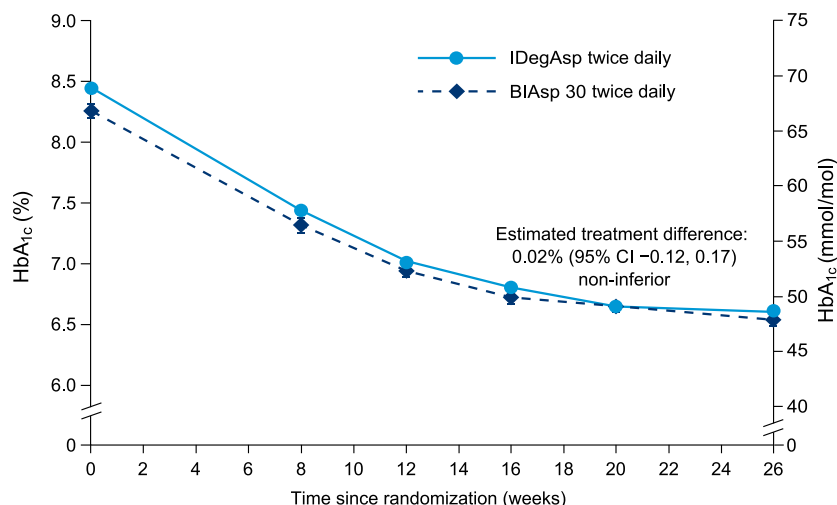
**FIGURE 2** Mean HbA$_{1c}$ over time. Mean ± SEM; full analysis set. Last observation carried forward. Comparisons: estimates adjusted for multiple covariates. BIAsp 30, biphasic insulin aspart 30; IDegAsp, insulin degludec/insulin aspart.

between treatment arms in mean nine-point SMPG profile (defined as the area under the profile divided by measurement time), fluctuation in SMPG or in prandial increments.

### Insulin dose

The mean total daily insulin dose after 26 weeks was similar for the IDegAsp arm (74 U and 0.80 U/kg) and the BIAsp 30 arm (74 U and 0.82 U/kg). In addition, the mean morning dose at the end of the trial was also similar for the IDegAsp and the BIAsp 30 treatment arms (0.44 vs 0.42 U/kg, respectively), as was the mean evening dose (0.35 vs 0.40 U/kg, respectively). Insulin dose over time was well matched from baseline to week 26 in the two treatment arms.

### Body weight

The estimated mean change in body weight was not significantly different between the treatment arms (3.53 kg with IDegAsp and 2.74 kg with BIAsp 30); the estimated treatment difference was 0.79 kg (95% CI −0.03, 1.61).

### Hypoglycaemic events

Overall confirmed hypoglycaemia was reported in 61% (120/196) of participants treated with IDegAsp and in 69% (134/195) of participants treated with BIAsp 30, with a rate of 5.80 episodes/patient-years of exposure (PYE) and 13.01 episodes/PYE, respectively. Superiority for IDegAsp was
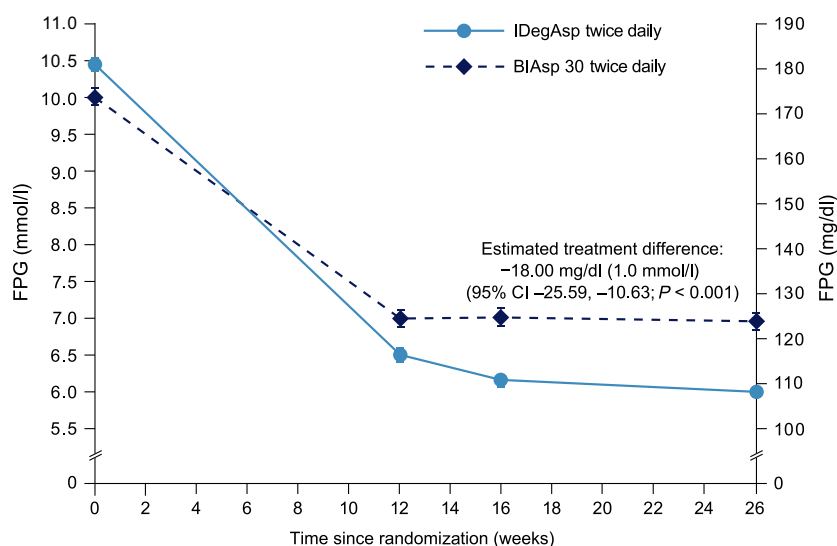


**FIGURE 3** Mean fasting plasma glucose (FPG) over time. Mean ± SEM; full analysis set. Last observation carried forward. Comparisons: estimates adjusted for multiple covariates. BIAsp 30, biphasic insulin aspart 30; IDegAsp, insulin degludec/insulin aspart.

demonstrated, with a 54% reduction in overall confirmed hypoglycaemia (estimated rate ratio 0.46; 95% CI 0.35, 0.61; *P* < 0.001; Fig. 4a). Nocturnal confirmed hypoglycaemia was reported in 19% of participants (37/196) treated with IDegAsp and in 40% of participants (77/195) treated with BIAsp 30. The rate of nocturnal confirmed hypoglycaemia was 0.63 episodes/PYE with IDegAsp and 2.77 episodes/PYE with BIAsp 30. Superiority of IDegAsp was also demonstrated for nocturnal hypoglycaemia, with a 75% reduction (estimated rate ratio 0.25; 95% CI 0.16, 0.38; *P* < 0.001), reflecting a 75% lower rate compared with BIAsp 30 (Fig. 4b). Severe hypoglycaemia was reported in 2.0% of participants (4/196) treated with IDegAsp and in 1.5% of participants (3/195) treated with BIAsp 30. The

rates of severe hypoglycaemia were similar between IDegAsp and BIAsp 30, with 0.05 episodes/PYE vs. 0.03 episodes/PYE.

### Adverse events

Similar proportions of participants reported adverse events in the IDegAsp and BIAsp 30 treatment arms (40.3 and 36.4%, respectively). The majority of events were mild or moderate in severity. Rates of serious adverse events were low in the IDegAsp and BIAsp 30 groups (21 and 13 events per 100 PYE, respectively; Table S2). Three deaths were reported: two in the IDegAsp arm, one from pulmonary oedema and the other from metastatic pancreatic carcinoma, and one in
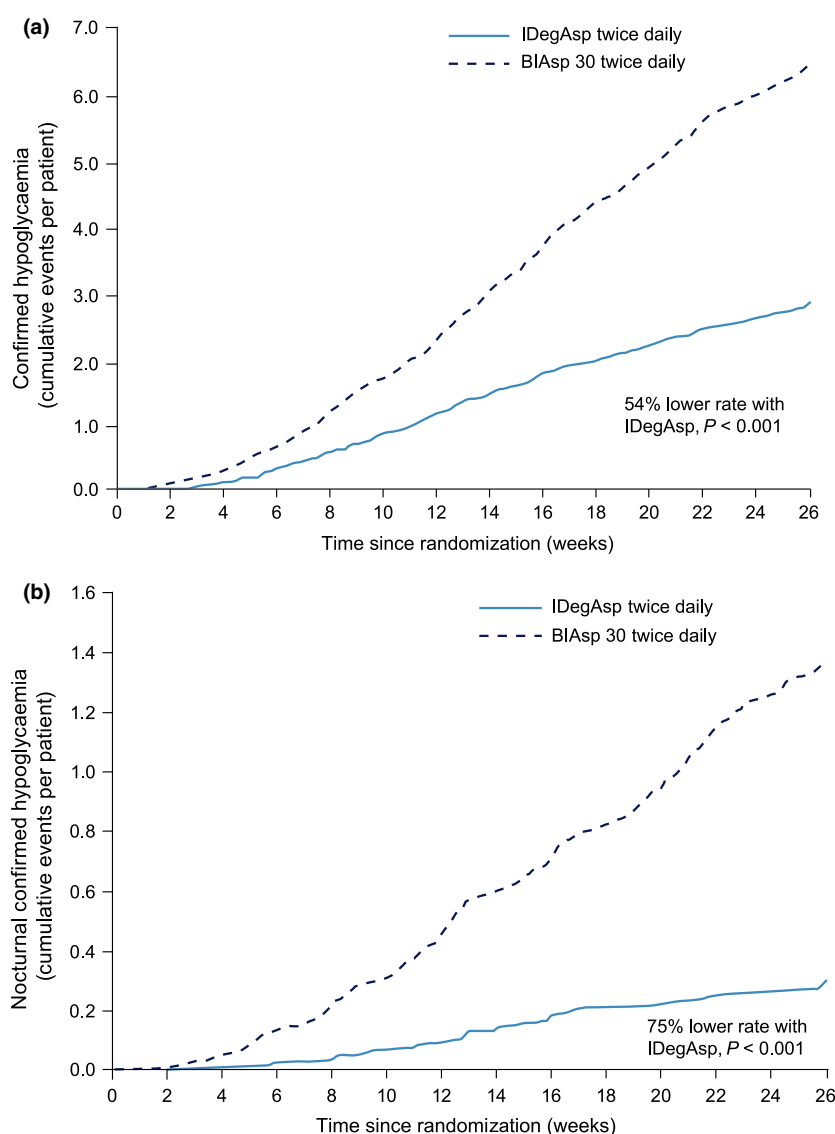


**FIGURE 4** (a) Overall confirmed hypoglycaemia (cumulative events per patient). Safety analysis set. Comparisons: estimates adjusted for multiple covariates based on full analysis set. (b) Nocturnal confirmed hypoglycaemia (cumulative events per patient). Safety analysis set. Comparisons: estimates adjusted for multiple covariates based on full analysis set. BIAsp 30, biphasic insulin aspart 30; IDegAsp, insulin degludec/insulin aspart.

the BIAsp 30 arm, from myocardial ischaemia and coronary artery insufficiency. All deaths were considered unlikely to be related to the investigational product. Few participants withdrew from the trial as a result of adverse events in either the IDegAsp (1.0%) or BIAsp 30 (1.5%) treatment arms. No clinically relevant differences were observed in vital signs, electrocardiogram, fundoscopy, physical examination or laboratory values.

## Discussion

In this randomized, controlled, 26-week, treat-to-target trial, IDegAsp effectively improved long-term glycaemic control, as demonstrated by a reduction in HbA$_{1c}$, and was non-inferior to BIAsp 30. The results also show that IDegAsp twice daily is superior in terms of improving FPG control and reducing overall and nocturnal confirmed hypoglycaemia vs. BIAsp 30 twice daily in insulin-naïve adults with Type 2 diabetes. In addition, this study showed that the mean SMPG values were significantly lower for IDegAsp than BIAsp 30 before breakfast, 90 min after breakfast and before breakfast the following day, probably reflecting the extended basal component of IDegAsp, which remains stable over 24 h [7,10], compared with the basal component of BIAsp 30, which is 70% IAsp protamine suspension and may contribute to greater variability and a shorter duration of action [7]. People in the BIAsp 30 group also had higher FPG levels than those in the IDegAsp group in this treat-to-target trial, suggesting that differences in clinical profile between the treatments may be attributable to the properties of the basal insulin components of IDegAsp (IDeg) and BIAsp 30 (protaminated IAsp). Insulin doses were similar over time, suggesting that a similar rate of titration was required for glycaemic control.

The efficacy results from this study (improvement in HbA$_{1c}$, superior control of FPG compared with BIAsp 30 and improved morning SMPG values) are consistent with two similar trials involving participants who had previously been treated with insulin [13,14], suggesting that IDegAsp has the potential to be used both as an insulin initiation and intensification treatment, particularly as this comparison is made to the current standard of care for people requiring a less complex injection regimen to cover basal and prandial needs (BIAsp 30). In the above studies [13,14], IDegAsp twice daily was shown to be effective in providing glycaemic control in participants with Type 2 diabetes previously on insulin. The present study has shown that the efficacy of IDegAsp twice daily is equally effective in improving long-term glycaemic control with significantly less overall and nocturnal confirmed hypoglycaemia vs. BIAsp 30 in people with Type 2 diabetes who are naïve to insulin.

We found that IDegAsp was superior to BIAsp 30 in lowering the risk of overall and nocturnal confirmed hypoglycaemia. A 54% reduction was achieved in overall confirmed hypoglycaemia and a 75% reduction in nocturnal confirmed hypoglycaemia, which is also consistent with previous findings from a phase II study in people with Type 2 diabetes who were naïve to insulin [19] and with a composite analysis of the aforementioned phase III studies [13,14,20]. There were relatively low rates of nocturnal confirmed hypoglycaemia in both treatment arms; however, the rates were significantly (75%) lower in the IDegAsp arm. These results echo those from 2-year data in insulin-naïve participants obtained during a previous IDeg trial, in which the rate of nocturnal hypoglycaemia was significantly lower for IDeg compared with insulin glargine [21]. Taken together, these reductions in hypoglycaemia can be explained by the longer duration of action and reduced intra- and inter-variability of IDeg compared with previous generations of insulins, as observed in pharmacokinetic/pharmacodynamic trials [7,10].

The clinical implications of a lower incidence of hypoglycaemia over the full trial period can be exemplified by using number-needed-to-treat data. Based on the observed rates of hypoglycaemia, if 10 people were treated for 1 year with IDegAsp instead of BIAsp 30, there would be 72 fewer overall confirmed hypoglycaemic episodes, and 21 fewer nocturnal confirmed hypoglycaemic events; however, it should be noted that a possible limitation is that these rates may not take into account episodes of asymptomatic hypoglycaemia that can sometimes occur with long disease duration and with nocturnal episodes, where hypoglycaemia may occur during sleep [22]. Current mismatch between glycaemic control achieved using insulin therapy in randomized trials and in the 'real-world' clinical setting is probably derived in part through non-adherence to complex regimens [5]. IDegAsp has an advantage over premixed regimens such as BIAsp 30 in terms of simplicity as it does not require resuspension before each injection and allows flexibility in the time of the administration, as long as it is dosed with the main meal(s) of the day [15,23]. However, given the lower number of daily injections required, IDegAsp may also be preferable to basal and bolus regimens in terms of simplicity, and in cases where fear of injections is a barrier to the transition to insulin [3–5].

The strengths of the present study include its large size and multinational, multicentre design; however, there are also limitations to the trial design. There was a lack of racial diversity within the study population, which was overwhelmingly white (99.5%), although similar results have been achieved in a study of Asian participants who had previously been treated with insulin [14]. In addition, because of differences in the formulation (IDegAsp is a clear solution, whereas BIAsp 30 is cloudy) and in the preparation of the two therapies (BIAsp 30 requires resuspension, IDegAsp does not), an open-label design was necessary, and therefore the possibility of bias cannot be excluded.

In conclusion, the results of the present study, as well as those previously conducted in people with Type 2 diabetes already on insulin therapy, show effective glycaemic control

with a low risk of hypoglycaemia with twice-daily IDegAsp. This combination treatment provides an effective means of initiating insulin treatment in people with Type 2 diabetes, particularly those who would benefit from the simplicity provided by a single pre-filled pen-based therapy without the need for resuspension.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Titration algorithm for adjusting dose of insulin.
**Table S2.** Adverse events.
**Figure S1.** Mean nine-point self-monitored plasma glucose profiles.

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