

## ORIGINAL ARTICLE

# Lower rates of hypoglycemia during maintenance treatment with insulin degludec/insulin aspart versus biphasic insulin aspart 30: a combined analysis of two Phase 3a studies in type 2 diabetes\*

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[Corrections added on 12 May 2016, after first online publication: All occurrences of BOOST<sup>®</sup> and HbA<sub>1c</sub> have been corrected throughout the article; “NS, not significant; SEM, standard error of the mean” added to Figure 1 legend; “; SEM, standard error of the mean” added to Figure 2 legend; “Values represent EOR” is deleted in Figure 4 legend and References for 13–23 are re-numbered. All corrections are denoted by ^ symbol.]

## Abstract

**Background:** Insulin degludec/insulin aspart (IDegAsp) is a soluble coformulation of the basal analog insulin degludec and the rapid-acting prandial insulin aspart in a single injection. The present combined analysis of two Phase 3a trials compared the incidence of hypoglycemia in participants treated twice daily with IDegAsp or biphasic insulin aspart 30 (BIAsp 30).

**Methods:** Hypoglycemia data were analyzed from two similarly designed randomized controlled open-label treat-to-target Phase 3a clinical trials of adults with type 2 diabetes (T2D). Participants were treated twice daily with IDegAsp or BIAsp 30, with breakfast and their main evening meal.

**Results:** Over 26 weeks, the rates of overall confirmed, nocturnal confirmed and severe hypoglycemic events were 19%, 57%, and 39% lower, respectively, with IDegAsp ( $n = 504$ ) than BIAsp 30 ( $n = 364$ ); estimated rate ratios were 0.81 (95% confidence interval [CI] 0.67, 0.98;  $P = 0.0341$ ), 0.43 (95% CI 0.31, 0.59;  $P = 0.0001$ ), and 0.61 (95% CI 0.26, 1.45;  $P = \text{NS}$ ). The between-treatment differences were more pronounced during the maintenance period ( $\geq 16$  weeks); compared with BIAsp 30, rates of overall confirmed, nocturnal confirmed and severe hypoglycemic events with IDegAsp were 0.69 (95% CI 0.55, 0.87;  $-31\%$ ;  $P = 0.0015$ ); 0.38 (95% CI 0.25, 0.58;  $-62\%$ ;  $P < 0.0001$ ), and 0.16 (95% CI 0.04, 0.59;  $-84\%$ ;  $P = 0.0061$ ), respectively.

**Conclusions:** Compared with BIAsp 30 twice daily, IDegAsp twice daily provided similar improvements in glycaemic control with a lower risk of hypoglycemia, particularly nocturnal hypoglycemia, in subjects with T2D previously treated with insulin.

**Keywords:** b.i.d. treatment, biphasic insulin aspart 30, hypoglycemia, insulin degludec/insulin aspart, type 2 diabetes.

**Significant findings of the study:** Compared with BIAsp 30 administered twice daily, IDegAsp twice daily was associated with greater reductions in fasting plasma glucose, lower total daily insulin dose, and significantly less weight gain, as well as reductions in overall confirmed, nocturnal, and severe hypoglycemia, particularly during the maintenance period ( $\geq 16$  weeks to end of trial).

**What this study adds:** For people requiring insulin intensification, the availability of the coformulation IDegAsp offers a more flexible therapeutic option for improved glycaemic control with a lower risk of hypoglycemia.

## Introduction

Insulin is an effective treatment for improving glycemic control in people with type 2 diabetes (T2D). As the disease progresses, many people require further intensification of their treatment<sup>1</sup> by either the sequential addition of bolus insulin to basal regimens, the transition to injections of premixed insulin,<sup>2</sup> or the addition of a glucagon-like peptide-1 receptor agonist.<sup>2</sup> Adding bolus insulin as a separate injection offers more precise control of meal-time blood glucose than premixed insulin, but people may find this regimen complex to administer and titrate.<sup>3</sup> In addition, concerns over weight gain and practical issues, such as the fear of injections and the increased risk of hypoglycemia as a result of insulin intensification, are considerable treatment barriers.<sup>4</sup>

A prospective preplanned meta-analysis of data from seven Phase 3 clinical trials (five in people with T2D and two in people with type 1 diabetes [T1D])<sup>5</sup> demonstrated that the basal insulin with an ultra-long duration of action (i.e. insulin degludec [IDeg]), significantly reduced the risk of overall and nocturnal confirmed hypoglycemia compared with insulin glargine (IGlar). Insulin-naïve participants experienced significantly lower rates of overall (rate ratio [RR] 0.83; 95% confidence interval [CI] 0.70, 0.98) and nocturnal confirmed (RR 0.64; 95% CI 0.48, 0.86) hypoglycemia episodes with IDeg compared with IGlar. Reductions were most pronounced during the maintenance period ( $\geq 16$  weeks), after stable glycemic control and insulin dose had been attained.<sup>5</sup>

Insulin degludec/insulin aspart (IDegAsp; Ryzodeg; Novo Nordisk A/S, Søborg, Denmark) is a soluble coformulation of IDeg, providing an ultra-long duration of action, and IAsp, a rapid-acting insulin, in a single injection<sup>6</sup> that can be administered once or twice daily with the main meal(s).<sup>7</sup>

At steady state, pharmacodynamic data showed that IDegAsp provides distinct basal and prandial glucose-lowering effects, with a peak action due to IAsp and a flat, stable basal effect due to IDeg, which was sustained for  $\geq 24$  h.<sup>8</sup> In contrast, biphasic insulin aspart (BIAsp) has a shorter duration of action, lasting up to 22 h after once-daily dosing.<sup>8</sup> With simulated twice-daily use of IDegAsp, exposure to the IDeg component was estimated to be similar over the first and second 12-h periods,<sup>9</sup> and the pattern of the prandial peaks was maintained and clearly separated from the flat basal glucose-lowering effects in participants with T1D, indicating that no stacking should be observed with IDegAsp when dosed twice daily.<sup>10</sup>

The clinical trial program for IDegAsp included two Phase 3a open-label trials of twice-daily dosing versus BIAsp 30 in people with T2D previously treated with

insulin: BOOST<sup>®</sup>: INTENSIFY PREMIX I (global patient population) and BOOST<sup>®</sup>: INTENSIFY ALL (Asian patient population).<sup>11,12</sup> The trials followed similar designs and used the same dose-titration algorithms to attain glycemic targets, an atypical advantage in performing a combined analysis of two studies.

Previously, a prespecified meta-analysis of hypoglycemia rates demonstrated that improvements in HbA<sub>1c</sub> can be achieved with fewer hypoglycemic episodes, particularly nocturnal episodes, with IDeg versus IGlar across a broad spectrum of people with diabetes.<sup>5</sup> To extend the findings of that meta-analysis, a combined analysis of the two Phase 3a IDegAsp clinical trials in people with T2D was performed in the present analysis using similar methodology in order to demonstrate the superiority of IDegAsp over BIAsp 30 in terms of fewer hypoglycemic episodes in people with T2D. Herein we report the findings of a combined analysis of these two trials.

## Methods

### Trial design and participants

The present combined analysis comprised pooled participant data from two Phase 3a clinical trials of IDegAsp twice daily versus BIAsp 30 twice daily in insulin users with advanced T2D. Both were randomized (1 : 1 in the BOOST<sup>®</sup>: INTENSIFY PREMIX I trial and 2 : 1 in the BOOST<sup>®</sup>: INTENSIFY ALL trial) controlled open-label multicenter trials with a treat-to-target design of 26 weeks duration (Table 1).<sup>11,12</sup> Key recruitment criteria included no history of recurrent severe hypoglycemia ( $\leq 1$  severe hypoglycemic event in the previous 12 months) and baseline HbA<sub>1c</sub> 53–86 mmol/mol (7.0%–10.0%). All participants were previously treated for  $\geq 3$  months with either premixed insulin (once or twice daily)  $\pm$  oral antidiabetic drugs (OADs; metformin, dipeptidyl peptidase-4 inhibitors and pioglitazone) in the BOOST<sup>®</sup>: INTENSIFY PREMIX I trial or with basal, premixed or self-mixed insulin  $\pm$  metformin in the BOOST<sup>®</sup>: INTENSIFY ALL trial. In both trials, insulin was given with breakfast and the main evening meal, and the dose was titrated using the same algorithm to attain prebreakfast/pre-evening meal self-monitored plasma glucose targets of 4.0–5.0 mmol/L. The protocol, its amendments, consent forms, and subject information sheet were reviewed and approved by health authorities according to local regulations and by the local independent ethics committees prior to trial initiation. In both studies, all HbA<sub>1c</sub> measurements were performed with the same methodology at Quintiles central laboratories (Quintiles Transnational, Durham, NC, USA). Blood samples for HbA<sub>1c</sub> assessment were analyzed using a Bio-Rad (Hercules, CA, USA) HPLC

**Table 1** Summary of trial designs and inclusion criteria

Trial (no. in the FAS)	BOOST <sup>®</sup> : INTENSIFY PREMIX I (Global patient population; n = 446)	BOOST <sup>®</sup> : INTENSIFY ALL (Asian patient population; n = 422)
Participating countries	Australia, Denmark, Finland, India, Malaysia, Poland, Sweden, Taiwan, Thailand, Turkey	Hong Kong, Japan, Malaysia, South Korea, Taiwan
Previous treatment(s)	Premixed insulin (once or twice daily) ± OADs for ≥3 months	Basal, premixed or self-mixed insulin ± metformin for ≥3 months
Trial treatment	IDegAsp twice daily ± metformin ± DPP-4i ± pio vs BAsp30 ± metformin ± DPP-4i ± pio	IDegAsp twice daily ± metformin vs BAsp30 ± metformin
Trial design	Open randomized treat-to-target	Open randomized treat-to-target
Duration of trial (weeks)	26	26
Randomization ratio (IDegAsp vs BAsp30)	1 : 1	2 : 1

BAsp 30, biphasic insulin aspart 30; DPP-4i; dipeptidyl peptidase-4 inhibitor; FAS, full analysis set; IDegAsp, insulin degludec/insulin aspart; pio, pioglitazone; OADs, oral antidiabetic drugs.

method, which was NGSP certified. The HbA<sub>1c</sub><sup>^</sup> samples were collected at Visits 1, 2, 14, 18, and 28. Blood samples to assess fasting plasma glucose (FPG) were analyzed using a Roche Pharmaceuticals (Basel, Switzerland) enzymatic method at the clinics. The FPG samples were collected at Visits 2, 14, 18, and 28. Subjects had to attend these visits while fasting.

These studies have been registered with ClinicalTrials.gov (Global: ID NCT01009580; Asia: ID NCT01059812).

### Assessments and statistical analysis

The primary endpoint in the present analysis was the incidence of overall confirmed hypoglycemia (plasma glucose <3.1 mmol/L [56 mg/dL]; see Table 2) over the full trial duration, including the maintenance period (≥16 weeks of treatment). During the maintenance period, hypoglycemic episodes were analyzed using a negative binomial regression model, with treatment, trial, sex, region, antidiabetic medicine at screening (basal, premix), and age as explanatory variables. Severe hypoglycemia, nocturnal confirmed hypoglycemia (0001–0559 hours) and non-severe hypoglycemia were

evaluated separately as subsets of overall confirmed hypoglycemia (Table 2). In addition, overall symptomatic confirmed and nocturnal confirmed hypoglycemia were evaluated over the full trial period (Table 2). Non-severe daytime and non-severe nocturnal hypoglycemia were evaluated as subsets of overall hypoglycemia (minus severe hypoglycemia) and hypoglycemia rates were compared between treatments during the full trial period, the titration period, and the maintenance period (see Table S1, available as Supplementary Material to this paper). A linear regression model (analysis of covariance [ANCOVA]) was used to analyze HbA<sub>1c</sub><sup>^</sup>, FPG, insulin dose (log transformed) and body weight, with treatment, trial, sex, region, antidiabetic medicine at screening (basal, premix), age and appropriate baseline measurements as explanatory variables. Treatment-emergent hypoglycemic episodes were counted for each subject in each of the trials and analyzed using a negative binomial regression model with a log-link function adjusted for treatment, trial, sex, geographic region, antidiabetic medicine at screening (basal, premix), and age and exposure period as an offset. The negative binomial model was chosen because it allows for the

**Table 2** Classification of hypoglycemic episodes

Category of hypoglycemic episode	Definition used in IDegAsp Phase 3a studies
Non-severe hypoglycemia	Episodes of hypoglycemia (symptomatic or asymptomatic) with confirmation of plasma glucose <3.1 mmol/L (56 mg/dL) or corresponding to full blood glucose <2.8 mmol/L (50 mg/dL) that are handled by the subject himself/herself
Confirmed hypoglycemia	Episodes of hypoglycemia (symptomatic or asymptomatic) with a documented plasma glucose level of <3.1 mmol/L (56 mg/dL), including episode(s) of severe hypoglycemia (below)
Severe hypoglycemia	Episodes during which the subject required assistance in administering carbohydrates, glucagon or other required resuscitative treatment
Nocturnal confirmed hypoglycemia	Episodes of confirmed hypoglycemia that occurred between 0001 and 0559 hours (inclusive)
Symptomatic confirmed hypoglycemia	An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration (≤56 mg/dL; ≤3.1 mmol/L)

heterogeneity between subjects that may arise because of within-subject correlation.

All randomized subjects in the two trials were included on the intent-to-treat principle. Rates of hypoglycemia were expressed as the cumulative number of episodes per patient-year of exposure; treatment differences were reported as estimated rate ratios (ERRs) of IDegAsp/BIAsp 30 with 95% CIs. Endpoints for HbA<sub>1c</sub><sup>^</sup>, FPG, insulin dose (log transformed), body weight, and health-related quality of life (HRQoL) were analyzed using a linear regression ANCOVA model, with treatment, trial, sex, region, antidiabetic medicine at screening (basal, premix), age and appropriate baseline measurements as explanatory variables (except for HRQoL). Norm-based scoring has been applied in this trial for the HRQoL data (SF-36).<sup>13^</sup>

## Results

### Characteristics of baseline populations

The combined analysis included 868 participants, 504 treated with IDegAsp twice daily and 364 treated with BIAsp 30 twice daily. Baseline characteristics for participants in each of the Phase 3a trials are given in Table 3. There were some differences in ethnicity between the trial populations by design that reflect the trial locations: because one trial was performed in 10 countries across three continents and the trial population was classified as 'global', whereas the other trial was performed in South-East Asian countries.

### Glycemic control

Analyses of the secondary efficacy endpoints (HbA<sub>1c</sub><sup>^</sup> and FPG) are shown in Figures 1, 2. The estimated mean treatment difference (IDegAsp–BIAsp 30) in HbA<sub>1c</sub><sup>^</sup> at

the end of the trial period was 0.00% (95% CI –0.11, 0.10; *P* = NS), indicating no difference between IDegAsp and BIAsp 30 in a treat-to-target setting. In the individual trials, the end-of-trial HbA<sub>1c</sub><sup>^</sup> data for the global and Asian population trials were –0.03 (95% CI –0.18, 0.13; *P* < 0.001) and 0.05 (95% CI –0.10, 0.20; *P* < 0.001), respectively. However, a significantly greater reduction in FPG was observed with IDegAsp compared with BIAsp 30. The estimated mean treatment difference was –1.12 mmol/L (95% CI –1.38, –0.85 [20.18 mg/dL; 95% CI –24.87, 15.31]; *P* < 0.0001). The end-of-trial FPG values for the global and the Asian population trials were –1.14 (95% CI –1.53, –0.76; *P* < 0.001) and –1.06 mmol/L (95% CI –1.43, –0.70; *P* < 0.001), respectively.

### Hypoglycemia

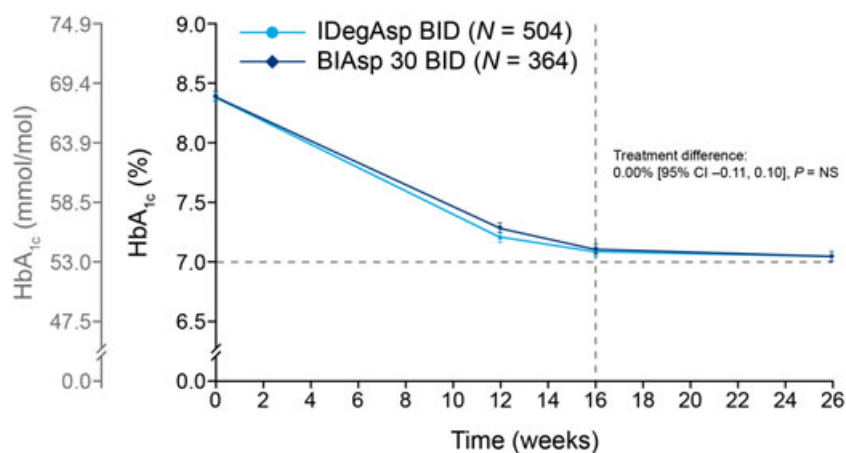
Over the full trial period, there was a 19% lower rate of overall confirmed hypoglycemia with IDegAsp compared with BIAsp 30 (ERR 0.81; 95% CI 0.67, 0.98; *P* = 0.03; Fig. 3a; Table 4). The rates of daytime non-severe hypoglycemic events reported with IDegAsp were 11% lower than those reported with BIAsp 30 (Table S1). There was also a 57% reduction in the rate of nocturnal confirmed hypoglycemia with IDegAsp (ERR 0.43; 95% CI 0.31, 0.59; *P* < 0.0001; Fig. 3b) and a 39% lower rate of severe hypoglycemia (ERR 0.61; 95% CI 0.26, 1.45; *P* = 0.27) compared with BIAsp 30.

The between-treatment reductions in hypoglycemia rates were more pronounced during the maintenance phase of treatment (from Week 16 until the end of the trial; Table 4). Compared with BIAsp 30, IDegAsp was associated with a 31% lower risk of overall confirmed hypoglycemia (ERR 0.69; 95% CI 0.55, 0.87; *P* = 0.0015), a 62% lower risk of nocturnal confirmed hypoglycemia

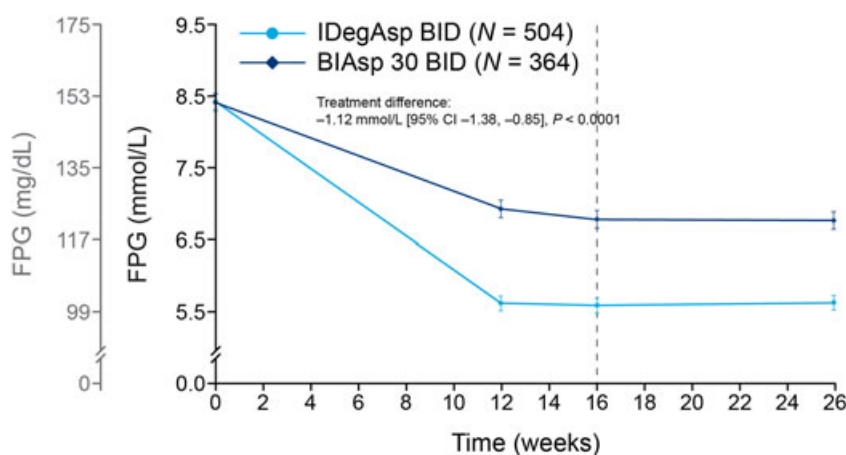
**Table 3** Baseline characteristics of the type 2 diabetes populations in the Phase 3a studies included in the combined analysis

Characteristic	BOOST <sup>®</sup> : INTENSIFY PREMIX I (Global patient population)		BOOST <sup>®</sup> : INTENSIFY ALL (Asian patient population)	
	IDegAsp b.i.d.	BIAsp 30 b.i.d.	IDegAsp b.i.d.	BIAsp 30 b.i.d.
Full analysis set (n)	224	222	280	142
Men (%)	57.6	53.6	53.9	55.6
Race: White/Black/Asian/Other (%)	54.0/0.4/45.1/0.4	50.9/0.0/49.1/0.9	0.0/0.0/99.7/0.4	0.0/0.0/100.0/0.0
Age (years)	58.8 ± 9.9	58.8 ± 9.8	59.1 ± 10.2	61.2 ± 9.5
Weight (kg)	81.5 ± 18.1	78.9 ± 17.6	66.1 ± 11.2	66.0 ± 11.2
Body mass index (kg/m <sup>2</sup> )	29.6 ± 4.6	29.0 ± 4.9	25.4 ± 3.4	25.4 ± 3.7
Duration of diabetes (years)	12.8 ± 6.8	13.1 ± 7.4	16.3 ± 7.9	16.3 ± 8.2
HbA <sub>1c</sub> (%)	8.3 ± 0.8	8.4 ± 0.9	8.4 ± 0.8	8.4 ± 0.9
Mean HbA <sub>1c</sub> (mmol/mol)	67	68	68	68
FPG (mmol/L)	8.9 ± 2.9	8.6 ± 2.6	7.9 ± 2.5	7.9 ± 2.5

Unless stated otherwise, data are the mean ± SD. BIAsp 30, biphasic insulin aspart 30; FPG, fasting plasma glucose; IDegAsp, insulin degludec/insulin aspart.



**Figure 1** Reduction in HbA<sub>1c</sub> over time during twice-daily (b.i.d.) treatment with insulin degludec/insulin aspart (IDegAsp) and biphasic insulin aspart 30 (BIAsp 30). Data are the mean  $\pm$  SEM based on full analysis set and last observation carried forward-imputed data. The vertical line at 16 weeks indicates the beginning of the maintenance period. CI, confidence interval; NS, not significant; SEM, standard error of the mean.



**Figure 2** Reduction in fasting plasma glucose (FPG) over time during twice-daily (b.i.d.) treatment with insulin degludec/insulin aspart (IDegAsp) and biphasic insulin aspart 30 (BIAsp 30). Data are the mean  $\pm$  SEM based on full analysis set and last observation carried forward-imputed data. The vertical line at 16 weeks indicates the beginning of the maintenance period. CI, confidence interval; SEM, standard error of the mean.

(ERR 0.38; 95% CI 0.25, 0.58;  $P < 0.0001$ ), and an 84% lower risk of severe hypoglycemia (ERR 0.16; 95% CI 0.04, 0.59;  $P = 0.0061$ ).

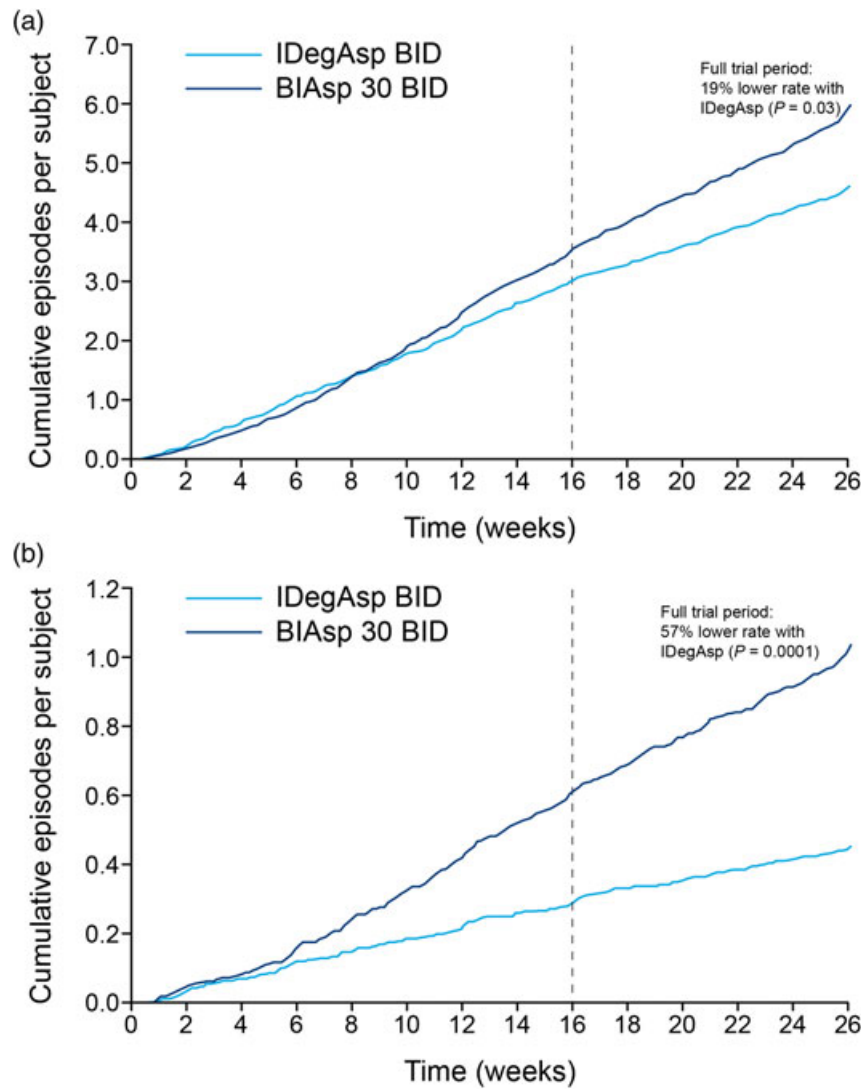
The rates of overall symptomatic confirmed hypoglycemia reported over the full trial period were 28% lower with IDegAsp (ERR 0.72; 95% CI 0.58, 0.89;  $P = 0.0025$ ) than BIAsp 30, whereas in the maintenance period they were 36% lower with IDegAsp (ERR 0.64; 95% CI 0.49, 0.83;  $P = 0.0009$ ) than BIAsp 30 (Table 4). In addition, the rates of nocturnal symptomatic confirmed hypoglycemia reported over the full trial period were 63% lower with IDegAsp (ERR 0.37; 95% CI 0.26, 0.52;  $P < 0.0001$ ) than BIAsp 30, whereas in the maintenance period they were 64% lower with IDegAsp (ERR 0.36; 95% CI 0.22, 0.57;  $P < 0.0001$ ) than BIAsp 30 (Table 4).

### Insulin dose

Mean total daily insulin dose at the end of the trial period was 16% lower for IDegAsp than BIAsp 30 (0.9 vs 1.1 U/kg; estimated mean dose ratio 0.84 [95% CI 0.80, 0.89];  $P < 0.0001$ ). Post hoc analyses revealed that the RRs for end-of-trial insulin dose (IDegAsp/BIAsp 30) were 0.89 ( $P = 0.002$ ) and 0.79 ( $P < 0.0001$ ) for the individual BOOST<sup>®</sup>: INTENSIFY PREMIX I and BOOST<sup>®</sup>: INTENSIFY ALL trials, respectively.

### Weight gain

The pooled analysis identified a significant difference between IDegAsp and BIAsp 30 in weight gain (estimated mean treatment difference [IDegAsp–BIAsp 30]  $-0.50$  kg; 95% CI  $-0.88, -0.11$ ;  $P < 0.05$ ). In the individual



**Figure 3** Cumulative rate of (a) nocturnal confirmed hypoglycemia and (b) nocturnal confirmed hypoglycemia in the full 26-week period of the Phase 3a clinical trials of insulin degludec/insulin aspart (IDegAsp) twice daily (b.i.d.) compared with biphasic insulin aspart 30 (BIAsp 30) twice daily. Data show mean values based on the safety analysis set. Estimated risk reduction and *P*-values are from a negative binomial model. The vertical line at 16 weeks indicates the beginning of the maintenance period.

**Table 4** Combined analysis of hypoglycemia risk in subjects with type 2 diabetes in Phase 3a clinical trials of insulin degludec/insulin aspart

	ERR (95% CI) IDegAsp/BIAsp 30	
	Full trial period (26 weeks)	Maintenance period (≥16 weeks to end of trial)
Confirmed hypoglycemia	0.81 (0.67, 0.98; <i>P</i> = 0.03)	0.69 (0.55, 0.87; <i>P</i> = 0.0015)
Nocturnal confirmed hypoglycemia	0.43 (0.31, 0.59; <i>P</i> < 0.0001)	0.38 (0.25, 0.58; <i>P</i> < 0.0001)
Severe hypoglycemia	0.61 (0.26, 1.45; <i>P</i> = NS)	0.16 (0.04, 0.59; <i>P</i> = 0.0061) <sup>A</sup>
Symptomatic confirmed hypoglycemia	0.72 (0.58, 0.89; <i>P</i> = 0.0025)	0.64 (0.49, 0.83; <i>P</i> = 0.0009)
Nocturnal symptomatic confirmed hypoglycemia	0.37 (0.26, 0.52; <i>P</i> < 0.0001)	0.36 (0.22, 0.57; <i>P</i> < 0.0001)

<sup>A</sup>Based on three events in the insulin degludec/insulin aspart (IDegAsp) arm and 14 events in the biphasic insulin aspart 30 (BIAsp 30) arm. ERR, estimated rate ratio; CI, confidence interval.

trials, there was a significant difference reported for the global population trial (treatment difference [IDegAsp–BIAsp 30] –0.62 kg; 95% CI –1.15, –0.10; *P* < 0.05), but no significant difference was reported in the Asian

population (treatment difference [IDegAsp–BIAsp 30] – 0.38 kg; 95% CI –0.96, 0.21).

### Health-related quality of life outcome

Based on data from the SF-36 questionnaire, IDegAsp was associated with an improvement in the domain Role-Emotional (between-treatment difference 1.43; 95% CI 0.06, 2.8). No significant between-treatment differences were observed in any other domains.

### Composite efficacy endpoints

Although there was no significant between-treatment difference in the proportion of participants achieving  $HbA_{1c} < 7.0\%$ , the estimated odds ratio (EOR) was 1.68 (95% CI 1.13, 2.49;  $P = 0.0103$ ; Fig. 4). The EOR for participants who achieved an FPG target  $< 5$  mmol/L was 2.81 (95% CI 2.05, 3.86;  $P < 0.0001$ ) and the EOR for those who achieved an FPG target  $< 5$  mmol/L without nocturnal confirmed hypoglycemia was 2.74 (95% CI 1.92, 3.92; Fig. 4).

### Adverse events

Both IDegAsp twice daily and BIAsp 30 twice daily were tolerated well. The overall incidence and rate of adverse events (AEs) was similar in the two trials. The most frequent AEs in both treatment groups (in both trials) were nasopharyngitis and upper respiratory tract infection. The incidence of major adverse cardiovascular events was low in both trials: three (1.3%) and two (0.9%) events in the IDegAsp and BIAsp 30 arms of the BOOST<sup>®</sup>: INTENSIFY PREMIX I trial, respectively, and one (0.4%) and five (3.5%) events in the IDegAsp

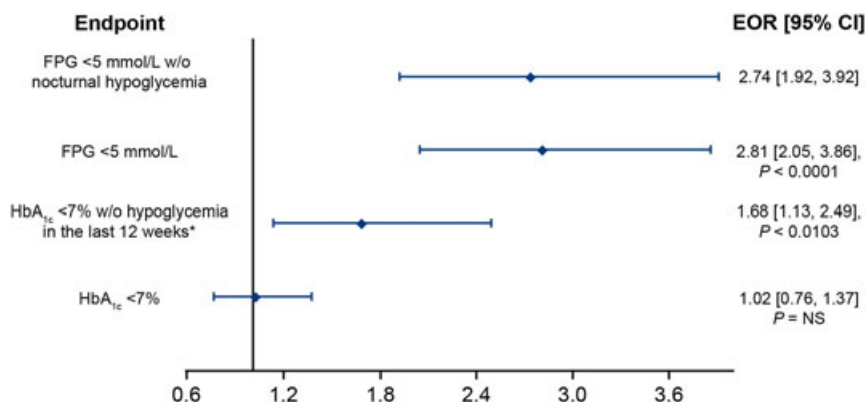
and BIAsp 30 arms of the BOOST<sup>®</sup>: INTENSIFY ALL trial, respectively.

### Discussion

The present combined analysis of two randomized controlled open-label treat-to-target Phase 3a clinical trials of adults with T2D demonstrates that treatment with IDegAsp twice daily provides effective overall glycemic control that is comparable to BIAsp 30, with superior reduction in FPG consistent with the individual trials.<sup>11,12</sup> The rates of overall confirmed, nocturnal confirmed, and severe hypoglycemic events were lower with IDegAsp, particularly during the maintenance period ( $\geq 16$  weeks to end of trial).

These results resemble those from a meta-analysis of the IDeg clinical development program comparing IDeg once daily to IGlaxar once daily,<sup>5</sup> which demonstrated that IDeg achieved similar glycemic control to IGlaxar with significantly lower rates of overall confirmed, nocturnal confirmed, and severe hypoglycemia that were more pronounced during the maintenance period in subjects with T2D. The lower rates of hypoglycemia, particularly nocturnal hypoglycemia, may be linked to the ultra-long and stable pharmacokinetic profile and lower day-to-day variability in glucose-lowering action of IDeg.<sup>14</sup>

When coformulated in IDegAsp, the basal glucose-lowering effect of IDeg is preserved and, at steady state, IDegAsp displays a distinct peak (due to IAsp) and a separate, flat, basal action (due to IDeg) that are retained following each dose.<sup>9</sup> In contrast, the pharmacodynamic profile of BIAsp 30 exhibits an initial peak, with a shoulder effect observed due to the overlapping effects of the two forms of IAsp (30% soluble IAsp and 70% protaminated IAsp), followed by a gradual decline,



**Figure 4** Estimated odds ratio (EOR). Participants achieving  $HbA_{1c} < 7.0\%$  and  $< 7.0\%$  without hypoglycemia in the last 12 weeks of treatment and fasting plasma glucose (FPG) targets of  $< 5.0$  mmol/L and  $< 5.0$  mmol/L without (w/o) nocturnal hypoglycemia. Error bars represent 95% confidence intervals (CI). \*This includes subjects exposed for at least 12 weeks, who met their  $HbA_{1c}$  target without confirmed hypoglycemia during the last 12 weeks of treatment or within 7 days from the last treatment.

returning to baseline values 18–22 h after injection.<sup>9</sup> When compared side-by-side, the pharmacodynamic profiles of the two insulins may explain the superior reductions in FPG observed with IDegAsp reported here. These properties of IDegAsp may also be associated with the higher proportion of people achieving HbA<sub>1c</sub> <7.0% without confirmed hypoglycemia in the past 12 weeks, as well as the chances of achieving an FPG target <5 mmol/L without confirmed nocturnal hypoglycemia.

Subjects receiving IDegAsp had lower rates of confirmed and nocturnal confirmed hypoglycemia, reductions that were more pronounced during the maintenance period (≥16 weeks to end of trial), and a lower rate of severe hypoglycemia during the maintenance period. The rates of symptomatic confirmed and nocturnal symptomatic confirmed hypoglycemia across the full trial period were also lower with IDegAsp than BIAsp 30 and were sustained during the maintenance period (Table 4). More detailed data on hypoglycemia rates can be found in Tables S1, S2.

The clinical implications of a lower incidence of hypoglycemia during the trial can be exemplified using a ‘numbers-needed-to-treat’ analysis. Based on the ERR for the maintenance period and the observed rates of hypoglycemia, this means that for every 10 people treated for 1 year with IDegAsp instead of BIAsp 30, there would be 47 fewer overall hypoglycemic events, 19 fewer nocturnal hypoglycemic events, and three fewer severe hypoglycemic events.

The lower rate of hypoglycemia with IDegAsp is clinically important because concerns over potential hypoglycemic events are a well-established barrier to people with diabetes and physicians intensifying insulin therapy.<sup>3,15</sup> Hypoglycemic events affect HRQoL and cognitive function<sup>16</sup> and are linked to cardiac effects, including arrhythmias, myocardial ischemia, and cardiac failure.<sup>16,17</sup> Severe hypoglycemic events create a major economic burden due to emergency treatment and healthcare costs,<sup>18,19</sup> but non-severe hypoglycemic events occur more frequently than severe events and account for the majority of total events, incurring substantial economic costs for employers and people with diabetes.<sup>20</sup>

In the present post hoc analysis, end-of-trial daily insulin dose was lower with IDegAsp, a finding that was consistent with the individual trials, in which RRs for end-of-trial insulin dose were lower with IDegAsp than BIAsp.<sup>11,12</sup>

The lower dose requirement of IDegAsp may impact cost-effectiveness, particularly in the Asian population, in which premixed insulin is used more commonly.<sup>21</sup> Some endocrinologists prefer not to use fixed-dose insulin preparations because of a perception that separating the basal and bolus components allows insulin dosages

to be better tailored to the person’s individual needs.<sup>22</sup> This is true, but the clear separation of basal and bolus components in IDegAsp, together with the flexibility in the timing of administration,<sup>7,23</sup> provides more possibilities for individualizing treatment than traditional premixed preparations.

No unexpected safety issues associated with IDegAsp were revealed in the present combined analysis, and there were no apparent differences between IDegAsp and BIAsp 30 with regard to the incidence and type of AEs.

A few of the limitations of this combined analysis include that both studies were open label because of differences in appearance between formulations. In addition, despite the similarity of design of the two trials, there were important differences between the two populations: participants from the Asian population trial had lower body weight, but a longer duration of diabetes<sup>12</sup> compared with the global population trial, which may have affected insulin dose requirements and the risk of hypoglycemia. Subjects in the BOOST<sup>®</sup>: INTENSIFY PREMIX I trial<sup>11</sup> may also have had higher OAD usage because of differences in the inclusion criteria. In addition, there were differences in the pretrial insulin treatments allowed within the inclusion criteria; however, these differences were balanced across the treatment arms, so their impact on the combined analysis was minimal.

In conclusion, the findings of the present combined analysis show that IDegAsp twice daily provides comparable HbA<sub>1c</sub> reductions and significantly lower rates of hypoglycemia than BIAsp 30 twice daily. This head-to-head comparison of twice-daily dosing provides an important comparison of IDegAsp with BIAsp 30, the most commonly used premixed insulin. For individuals requiring insulin intensification, the availability of IDegAsp with its ultra-long duration of action and rapid-acting prandial component offers an important new therapeutic option to improve glycemic control with a markedly lower risk of hypoglycemia.

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## Disclosure

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Nordisk A/S. He was involved in the design of the trial and data analysis. GF is on the advisory panel for and has received speaker fees from Novo Nordisk, Janssen, Boehringer Ingelheim, and MSD. He has also received research support from Novo Nordisk.

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## Supporting information

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

**Table S1.** Combined analysis of hypoglycemia rate ratios.

**Table S2.** Combined analysis of symptomatic hypoglycemia risk.