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Similar glycaemic control with less nocturnal hypoglycaemia in a 38-week trial comparing the IDegAsp co-formulation with insulin glargine U100 and insulin aspart in basal insulin-treated subjects with type 2 diabetes mellitus

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ABSTRACT

Aims: To confirm non-inferiority of insulin degludec/insulin aspart (IDegAsp) once-daily (OD) versus insulin glargine (IGlar) U100 OD + insulin aspart (IAsp) OD for HbA_{1c} after 26 weeks, and compare efficacy and safety between groups at W26 + W38.

Methods: A 38-week, randomised, open-label, treat-to-target (HbA_{1c} < 7.0%) trial in adults with type 2 diabetes mellitus (on basal insulin ± oral antidiabetic drugs; HbA_{1c} 7.0–10.0%). Randomisation (1:1): IDegAsp or IGlar U100 + IAsp. Intensification to IDegAsp twice daily (BID) was permitted at W26 + W32, or with additional IAsp injections at W26 (maximum IAsp BID) or W32 (maximum IAsp three-times daily).

Results: For W0–W26, mean percentage-change (standard deviation) HbA_{1c} was: IDegAsp, −1.1 (0.9); IGlar U100 + IAsp, −1.1 (0.8); estimated treatment difference: 0.07% (95% confidence interval [CI]: −0.06; 0.21) confirmed non-inferiority. At W26 and W38, target HbA_{1c} achievement, and mean fasting and postprandial glucose were similar across groups. At W38, more subjects achieved target HbA_{1c} without hypoglycaemia with IDegAsp (22.5%) than with IGlar U100 + IAsp (21.1%), with significantly fewer nocturnal episodes (W0–W38, estimated rate ratio: 0.61 [95% CI: 0.40; 0.93]). Safety profiles were similar across treatment groups throughout.

Conclusions: IDegAsp OD/BID are effective treatment intensification options versus multiple injection basal–bolus therapies, achieving similar glycaemic control, with significantly less nocturnal hypoglycaemia.

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1. Introduction

Type 2 diabetes mellitus, a progressive disorder, is characterised by insulin resistance and impaired insulin secretion, resulting in chronic hyperglycaemia that worsens with disease progression [1]. Several landmark studies demonstrate the importance of maintaining tight glycaemic control, to reduce the risk of long-term diabetes-related complications (e.g. UKPDS [2]; DCCT/EDIC [3]).

Current clinical guidelines from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) follow a stepwise approach to treatment intensification, combining lifestyle changes with pharmacological interventions [4,5]. If patients do not achieve target HbA_{1c} with basal insulin, further treatment intensification is recommended. Treatment intensification can involve additional injections of bolus insulin for more tailored dosing, addition of a glucagon-like peptide-1 receptor agonist (GLP-1 RA), or use of combined basal and bolus products (which may require fewer injections, and thus be more convenient for the patient).

Insulin degludec/insulin aspart (IDegAsp) is a soluble coformulation of 70% insulin degludec (IDeg; providing basal coverage) and 30% insulin aspart (IAsp; providing postprandial coverage), approved for the treatment of diabetes mellitus in adults in many countries [6,7]. To date, no head-to-head trials compare the effect of IDegAsp once-daily (OD) therapy with a multiple injection basal–bolus regimen (involving separate and potentially escalating numbers of bolus insulin injections, together with a basal insulin).

The primary objective of this randomised, treat-to-target, parallel-group, open-label trial was to confirm the effect of IDegAsp OD versus insulin glargine (IGlar) U100 OD + IAsp OD on glycaemic control (HbA_{1c}) after 26 weeks of treatment. Additional objectives included: comparison of other efficacy and safety parameters after 26 weeks (IDegAsp OD versus IGlar U100 OD + IAsp OD), and the comparison of other efficacy and safety parameters after 38 weeks (IDegAsp OD or twice-daily [BID] versus IGlar U100 OD + IAsp OD, BID, or three-times-daily [TID]).

2. Subjects

2.1. Subject disposition and patient flow

From a total of 734 subjects who were screened, 532 fulfilled eligibility criteria and were randomised (IDegAsp, n = 267; IGlar U100 + IAsp, n = 265) (Table S1).

2.2. Inclusion and exclusion criteria

Key inclusion criteria: male or female, aged ≥18 years; diagnosed with type 2 diabetes mellitus; treated for ≥90 days prior to screening with any basal insulin either alone or with a stable dose of oral antidiabetic drugs (OADs) (individual, or any combination of: biguanides, sulphonylureas, glinides, dipeptidyl peptidase-4 [DPP-4] inhibitors, alpha-glucosidase inhibitors, or sodium/glucose cotransporter-2 [SGLT2] inhibitors); HbA_{1c} 7.0–10.0% (53–86 mmol/mol, both inclusive), and body mass index ≤45 kg/m^2.

Key exclusion criteria: treatment with any diabetes/obesity medication not stated in the inclusion criteria; acute decompensation of glycaemic control requiring immediate intensification of treatment to prevent severe metabolic dysregulation within 90 days prior to screening; myocardial infarction, stroke or hospitalisation for unstable angina or transient ischaemic attack within 180 days prior to screening; New York Heart Association Class IV; planned coronary, carotid or peripheral artery revascularisation; and anticipated initiation or change in concomitant medications (for >14 consecutive days) known to affect weight/glucose metabolism.

3. Materials and methods

3.1. Trial design

A 38-week, randomised, open-label, multinational, treat-to-target trial (www.clinicaltrials.gov identifier: NCT02906917) in adults with type 2 diabetes mellitus, treated with basal insulin ± OADs and in need of treatment intensification. The trial was conducted in seven countries, that each contributed the following number of randomised, exposed patients: Algeria: n = 46, Czech Republic: n = 60, India: n = 51, Russia: n = 110, Serbia: n = 46, Turkey: n = 65 and the United States: n = 150. An overview of the trial design is provided in Fig. S1.

3.2. Randomisation, stratification and treatment intensification

All patients were randomised (1:1) from their previous basal insulin regimen to either: IDegAsp (Weeks 0–26: OD only; Weeks 27–38: OD/BID), or IGlar U100 + IAsp (Weeks 0–26: IGlar U100 OD + IAsp OD only; Weeks 27–38: IGlar U100 OD + IAsp OD/BID/TID). Patients were stratified equally into the two treatment groups, based on pre-trial basal insulin regimens (OD versus BID/TID). Patients could be intensified (at physician discretion, based on the needs of the individual patient) following intensification visits at Weeks 26 and 32, if HbA_{1c} was not on target in the previous week (target, <7%).

Titration data (e.g., self-measured blood glucose [SMBG]; prescribed insulin dose; actual insulin units and date and time given) were to be entered into the eCRF within 24 h of a site visit or home contact on weekdays for review by Novo Nordisk to reduce the time a subject may receive suboptimal treatment.

3.3. Switching from previous treatment after randomisation

Patients on a prior OD regimen were shifted unit-to-unit, whereas patients on a BID regimen received either IDegAsp (unit-to-unit, previous dose), or IGlar U100 + IAsp (with a 20% reduction of the total daily basal [IGlar U100] dose, and IAsp initiated at 4 U with the largest meal). Sulphonylureas and glinides were discontinued at randomisation; other OADs

continued unchanged. Diet and exercise counselling was provided throughout the study for all subjects (as per standard of care at all investigational sites).

3.4. Details of treatment regimens

IDegAsp OD/BID was administered with the largest meal(s) each day. Investigators were trained during investigator meetings (through inspection of example meal plates) regarding how to best train patients to identify their 'largest meal' (nominally the meal containing the greatest amount of bread, rice, potatoes, pasta or sugar) and encouraged to discuss the identification process with patients during scheduled visits/-phone contacts. After 26 weeks, if IDegAsp was intensified to be administered BID, one meal for dosing was to be evening dinner; the other was either lunch or breakfast (depending on which was identified as largest). Intensification from IDegAsp OD to BID was performed by splitting the total daily dose of IDegAsp OD into two doses (doses could be uneven, depending on the size of each meal). IGlar U100 was administered OD in accordance with the local label throughout the trial. IAsp OD/BID/TID was administered with the largest meal(s), identified in the same manner as with IDegAsp. Rescue therapy was permitted by the trial protocol, if patients exceeded pre-specified blood glucose thresholds.

3.5. Trial products

The following products were used throughout: IDegAsp 100 units (U)/mL (Ryzodeg®, Novo Nordisk A/S), delivered via a 3 mL prefilled FlexTouch® pen (Novo Nordisk A/S); insulin glargine 100 U/mL (Lantus®, Sanofi S.A.), delivered via a 3 mL pre-filled SoloStar® pen (Sanofi S.A.); insulin aspart 100 U/mL (NovoRapid®/NovoLog®, Novo Nordisk A/S), delivered via a 3 mL prefilled FlexPen® pen (Novo Nordisk A/S).

3.6. Dose titration

Patients self-titrated to the following SMBG targets: IDegAsp and IGlar U100, 4–5 mmol/L; IAsp, 4–6 mmol/L. The algorithms used to determine dose adjustments (including details of the meals used for titration) are displayed in Table S2A (IDegAsp and IGlar U100) and Table S2B (IAsp).

3.7. Statistical operations

3.7.1. Data sets

The full analysis set (FAS) was used for the evaluation of efficacy endpoints. The FAS contained all randomised subjects. Statistical evaluation of the FAS followed the intention to treat (ITT) principle, and subjects contributed "as randomised".

Safety outcomes were evaluated using the safety analysis set (SAS). The SAS contained all subjects who received one or more dose(s) of trial drug. Subjects in the SAS contributed to the evaluation "as treated".

Sensitivity analyses were conducted using the FAS and two additional data sets: the per protocol analysis set (PP), which included individuals from the FAS who did not violate any inclusion criteria or fulfil any exclusion criteria, had an HbA_{1c} measurement at screening or randomisation, one or more HbA_{1c} measurement(s) after 12 weeks of exposure and a minimum of 12 weeks of exposure on-treatment; and the completer analysis set (CAS), which included all randomised subjects who remained in the trial and on-treatment at Week 26.

3.7.2. Statistical analyses

The primary estimand ("estimand", the estimated treatment effect on a given parameter) followed the ITT principle, and used the FAS to assess effectiveness in all randomised subjects (whether adherent to treatment or not), to determine the non-inferiority of IDegAsp OD versus IGlar U100 OD + IAsp OD in terms of HbA_{1c} reduction at Week 26, with a pre-specified non-inferiority margin of 0.4%. Subjects who discontinued treatment prior to Week 26 were included in the analysis and missing data were imputed using multiple imputation (MI), with a separate imputation for each treatment group, based upon on- and off-treatment data. In the IDegAsp group, all imputed values and off-treatment values at Week 26 were penalised by 0.4%. Data were analysed using analysis of covariance (ANCOVA), with treatment, region, sex, previous insulin treatment regimen, and previous OAD treatment as categorical fixed effects, and baseline response and age as covariates. Results were pooled using Rubin's rule.

The secondary estimand, in order to assess treatment effects on all randomised subjects, applied a mixed model for repeated measurements (MMRM) to the FAS. The MMRM assumed subjects remained on-treatment throughout. Furthermore, several sensitivity analyses were performed and are displayed with a brief description of each analysis in Fig. S2. The sensitivity analyses included analyses of the PP and CAS analysis sets (accounting for missing data using MI or the MMRM), and an uncorrected estimate of the difference between the two treatments (the "sensitivity: MI, no non-inferiority-penalty, FAS" analysis) performed as per the primary analysis, but without a 0.4% penalty for subjects in the IDegAsp arm.

The statistical analyses of total insulin dose, body weight, fasting plasma glucose (FPG), SMBG and postprandial glucose increments were performed as per the primary analysis, without applying a 0.4% penalty to the IDegAsp arm.

Responder analyses (to determine achievement of HbA_{1c} targets) were based on the FAS, with missing data imputed using MI, with no penalty applied to the IDegAsp treatment group. Subjects with $HbA_{1c} < 7\%$ were considered "responders"; those with $HbA_{1c} \geq 7\%$ or with <16 weeks of treatment, "non-responders". Responder analyses were based on a logistic regression model which included treatment, sex, previous insulin treatment regimen, previous OAD treatment, and region as fixed factors, and age and baseline HbA_{1c} as covariates.

Comparisons of hypoglycaemia between treatment groups were made using negative binomial regression, and included treatment, previous insulin treatment regimen, previous OAD treatment, sex, and region as factors and age as a covariate.

3.8. Hypoglycaemia classification

The evaluation of hypoglycaemia included severe (ADA 2013 definition: an episode requiring assistance of another person

to actively administer carbohydrate, glucagon, or take other corrective actions; plasma glucose concentrations may not be available, however, neurological recovery following return of plasma glucose to normal to be considered sufficient evidence of a severe episode [8]), or symptomatic blood glucose-confirmed (<3.1 mmol/L) episodes. Nocturnal episodes occurred 00.01–05.59 (both inclusive).

4. Results

4.1. Subject disposition

The following number of subjects contributed to each data set, respectively: the FAS: IDegAsp, n = 267; U100 + IAsp, n = 265; the SAS: IDegAsp, n = 265; U100 + IAsp, n = 263; the PP: IDegAsp, n = 250; U100 + IAsp, n = 248; and the CAS: n = 243 from both treatment groups.

A total of 243 (91.0%) subjects in the IDegAsp group remained on-treatment at Week 26, and 235 (88.0%) completed the trial on-treatment at Week 38. In the IGlar U100 + IAsp group a total of 243 (91.7%) remained on-treatment at Week 26, and 236 (89.1%) completed the trial on-treatment at Week 38. No patient required rescue therapy. More information on the reasons for treatment discontinuation and withdrawals is provided in Table S1.

4.2. Baseline demographics and patient characteristics

The baseline demographics of randomised subjects (Table 1) were balanced between the treatment groups. The mean baseline HbA_{1c} values were: IDegAsp, 8.2% (66 mmol/mol) and IGlar U100 + IAsp, 8.1% (65 mmol/mol). Prior to randomisation, the majority (>80%) of both treatment groups were on an OD rather than a BID basal regimen and none were on a TID basal regimen (Table S3). Most patients were being prescribed OADs (percentage in receipt of OADs at screening: IDegAsp, 96.3%; IGlar U100 + IAsp, 92.5%), and the percentages in receipt of one, two, or more than two OADs were well balanced between groups (Table S3).

Table S4 provides information on the OAD regimens at screening. The majority of patients were in receipt of biguanides (>80% of each group). Sulphonylureas were also commonly prescribed (>40% of each group), as were DPP-4 inhibitors (~20% of each group). Few patients were in receipt of SGLT2 inhibitors or alpha-glucosidase inhibitors (4–11% of each group), and <4% of patients in each group were taking combination OADs (i.e. >1 OAD combined in a single oral medication). A total of four patients, randomised in error, were in receipt of OADs not permitted by the protocol (in each group, one subject was on a GLP-1 RA and one was on a thiazolidinedione).

4.3. Description of treatment regimens throughout the trial

Fig. S3 provides an overview of the percentage of patients in each treatment group assigned to OD/BID/TID regimens throughout Weeks 1–26, 27–31 and 32–38. Details of the number of patients in each group who met the eligibility criteria for treatment intensification and who were/were not subsequently intensified at each assessment visit are in Table S5. The majority (>90%) of patients in both groups who achieved target HbA_{1c} of <7% were not intensified at either Week 26 or 32. For eligible patients not meeting the HbA_{1c} target at Week 26, a high percentage of both groups had treatment intensified (approximately 97% of each treatment group). At Week 32, approximately two-thirds of patients in both treatment groups not reaching target in the previous week and eligible for further intensification were intensified.

An overview of the dosing meals for each treatment group at key time points (i.e. before and after treatment intensification was permitted) is provided in Table S6. Prior to intensification, the majority of patients in each treatment group received OD dosing at dinner (~49–55%), followed by lunch (~30–38%), and then breakfast (~13–15%). After intensification was permitted, similar percentages of the IDegAsp group received BID doses at breakfast + dinner (~27–29%) and lunch + dinner (~25–28%), whereas the IGlar U100 + IAsp group tended not to receive IAsp doses at breakfast (most received IAsp doses at either lunch, dinner, lunch + dinner, or with all meals [Table S6]).

4.4. Number of daily injections

At Week 26, the number of daily injections (as per protocol) was: IDegAsp, one; IGlar U100 + IAsp, two. At Week 38, the mean (standard deviation [SD]) number of daily injections for

Table 1 – Baseline demographic data.

	IDegAsp, N = 267	IGlar U100 + IAsp, N = 265
Age (years)	58.2 ± 8.9	59.2 ± 9.1
Female (%)	53.2	48.3
Weight (kg)	88.6 ± 18.5	88.5 ± 17.5
BMI (kg/m^2)	31.7 ± 5.5	31.7 ± 5.1
Diabetes duration (years)	12.9 ± 6.9	13.0 ± 6.5
HbA_{1c} (%) [mmol/mol]	8.2 ± 0.8 [66 ± 8]	8.1 ± 0.7 [65 ± 8]
FPG (mmol/L) [mg/dL]	9.0 ± 2.7 [162 ± 48]	8.8 ± 2.7 [158 ± 48]

Data are mean ± standard deviation, or percentages.
BMI, body mass index; FPG, fasting plasma glucose; IDegAsp, insulin degludec/insulin aspart fixed-ratio combination once- or twice-daily; IGlar U100 + IAsp, insulin glargine 100 units/mL once-daily + insulin aspart once-, twice- or three-times daily.

both groups had increased, to 1.62 ± 0.49 for the IDegAsp, and to 2.85 ± 0.87 for the IGlar U100 + IAsp groups, respectively.

4.5. *Efficacy results*

Both treatment groups had similar HbA_{1c} values throughout (Fig. 1). Across Weeks 0–26, similar changes in mean (SD) HbA_{1c} were observed in both groups: IDegAsp OD: −1.1% (0.9); IGlar U100 OD + IAsp OD: −1.1% (0.8). The primary estimand confirmed the non-inferiority of IDegAsp for change in HbA_{1c}: estimated treatment difference (ETD) 0.07% (95% confidence interval [CI]: −0.06; 0.21). The secondary estimand (ETD 0.01% [95% CI: −0.12; 0.14]) and several sensitivity analyses confirmed the robustness of the results in terms of glycaemic control for 0–26 weeks (Fig. S2).

During Weeks 26–38, further treatment intensification was permitted, and the HbA_{1c} values of both groups continued to decrease (Fig. 1). At Week 38, there was no significant difference between the treatment groups in the primary and secondary estimands for HbA_{1c} (Fig. S2).

Improvements in glycaemic control in both groups were reflected by decreases in FPG, with similar profiles observed throughout Weeks 0–38 in both groups. At Week 26, the mean (SD) reduction of FPG was similar in both groups: IDegAsp OD: −2.3 (2.9) mmol/L; IGlar U100 OD + IAsp OD: −2.3 (3.3) mmol/L. At Week 38, IDegAsp was associated with a numerically greater mean (SD) reduction in FPG (−2.7 [3.0]), versus −2.3 [3.1] mmol/L with IGlar U100 + IAsp); however, the ETD was not statistically significant (Table 2).

In Week 1, the mean pre-breakfast SMBG level (used for titration) was higher with IDegAsp OD (8.8 mmol/L) than with IGlar U100 OD + IAsp OD (8.3 mmol/L). At Week 26, the pre-breakfast SMBG values were statistically higher with IDegAsp (ETD, 0.28 [95% CI: 0.05; 0.51]). By Week 38, however, the pre-breakfast SMBG values were no longer statistically different (ETD, −0.00 [95% CI: −0.22; 0.22]). For both treatment groups, the shapes of the mean 24-h 9-point SMBG profiles (from pre-breakfast, through to breakfast the following day) were comparable, with a shift towards lower values as the trial progressed (Fig. S4). Mean postprandial SMBG increments were reduced in both groups after 26 and 38 weeks, with no statistical difference between groups found at either time point (Table 2).

4.6. *Insulin dose*

The mean total insulin doses were similar at baseline (IDegAsp, 35.2 U; IGlar U100 + IAsp, 34.6 U). Following treatment initiation, the total insulin doses diverged, with a significantly lower dose associated with IDegAsp OD versus IGlar U100 OD + IAsp OD at Week 26 (70.9 U versus 79.4 U, respectively [a 10.7% lower dose]; odds ratio (OR) 0.88 U [95% CI: 0.81; 0.95]). By the end of the trial, the dose associated with IDegAsp was significantly lower (6.6%) than that associated with IGlar U100 + IAsp (83.4 U versus 89.3 U, respectively; OR 0.91 U [95% CI: 0.83; 0.99]).

Differences in total insulin dose may be attributed to the basal, rather than the bolus effect. At Week 38, the mean total basal doses were: IDegAsp: 58.4 U; IGlar U100 + IAsp: 65.3 U, and mean total bolus doses were: IDegAsp: 25 U; IGlar U100 + IAsp: 24 U.

4.7. *Safety results*

4.7.1. *Hypoglycaemia*

No clustering of overall, or nocturnal, confirmed symptomatic hypoglycaemic episodes were observed in the first few weeks following randomisation: Fig. 2A and B.

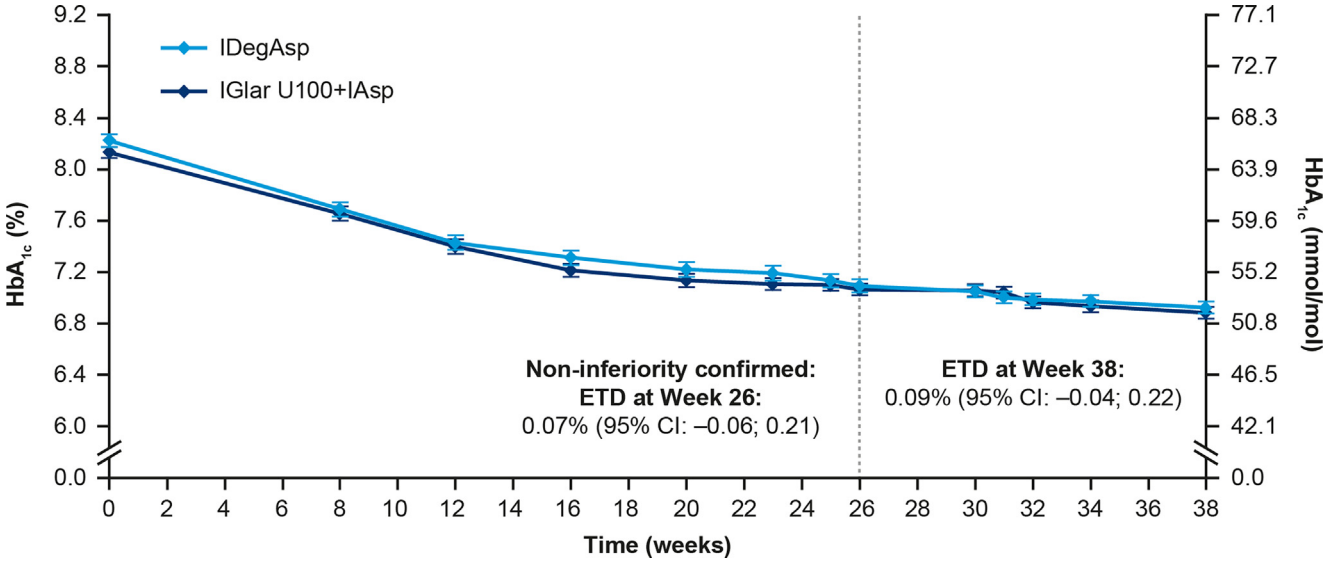

Fig. 1 – Change in HbA_{1c} over the treatment period. Dashed line shows start of treatment intensification (permitted Weeks 26–38). Error bars show standard error of the mean. Primary effectiveness estimand (full analysis set; missing data imputed using multiple imputation; pre-specified non-inferiority margin at Week 26: 0.4%). CI, confidence interval; ETD, estimated treatment difference; IDegAsp, insulin degludec/insulin aspart fixed-ratio combination once- or twice-daily; IGlar U100+IAsp, insulin glargine 100 units/mL once-daily + insulin aspart once-, twice- or three-times daily.

Table 2 – Key endpoints.

	Treatment initiation (Weeks 0–26)			Baseline–end of treatment (Weeks 0–38)		
	IDegAsp (N = 267)	IGlar U100 + IAsp (N = 265)	ETD, OR or RR[†] (95% CI)	IDegAsp (N = 267)	IGlar U100 + IAsp (N = 265)	ETD, OR or RR[†] (95% CI)
Change from baseline HbA_{1c} (%), mean (SD)	−1.1 (0.9)	−1.1 (0.8)	ETD 0.07 (−0.06; 0.21)	−1.3 (0.8)	−1.2 (0.8)	ETD 0.09 (−0.04; 0.22)
Change from baseline HbA_{1c} (mmol/L), mean (SD)	−12 (9)	−12 (9)	ETD 0.82 (−0.64; 2.28)	−14 (9)	−14 (9)	ETD 0.95 (−0.48; 2.38)
Percentage of HbA_{1c} responders (<7%)	44.9	45.3	OR 1.07 (0.74; 1.54)	52.1	52.8	OR 0.95 (0.66; 1.38)
Overall hypoglycaemia,[‡] mean rate (events/100 PYE)	258.5	296.1	RR 0.90 (0.67; 1.22)	287.1	343.3	RR 0.86 (0.65; 1.14)
Nocturnal hypoglycaemia,[‡] mean rate (events/100 PYE)	47.9	92.9	RR 0.55 (0.34; 0.90)	60.4	101.4	RR 0.61 (0.40; 0.93)
Total daily insulin dose (units), mean (SD)	70.9 (41.5)	79.4 (37.7)	OR 0.88 (0.81; 0.95)	83.4 (51.3)	89.3 (43.1)	OR 0.91 (0.83; 0.99)
Change from baseline FPG (mmol/L), mean (SD)	−2.3 (2.9)	−2.3 (3.3)	ETD 0.04 (−0.34; 0.42)	−2.7 (3.0)	−2.3 (3.1)	ETD −0.24 (−0.60; 0.13)
Change from baseline SMBG postprandial increment (mmol/L), mean (SD)	−0.6 (2.6)	−0.5 (2.3)	ETD 0.10 (−0.23; 0.43)	−1.0 (2.2)	−1.1 (2.5)	ETD 0.30 (−0.01; 0.62)
Total number of injections/day, mean (SD)	1 (0.00)	2 (0.00)	Not tested	1.62 (0.49)	2.85 (0.87)	Not tested

Data are observed values except ETD, OR and RR (estimated values). [†]ETD = IDegAsp – IGlar U100 + IAsp; RR = IDegAsp/IGlar U100 + IAsp. [‡]Hypoglycaemia included severe (American Diabetes Association 2013 definition: an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions) or blood glucose-confirmed (<3.1 mmol/L) symptomatic episodes. Nocturnal episodes occurred 0.01–05.59 (both inclusive). CI, confidence interval; ETD, estimated treatment difference; FPG, fasting plasma glucose; IDegAsp, insulin degludec/insulin aspart fixed-ratio combination once- or twice-daily; IGlar U100 + IAsp, insulin glargine 100 units/mL once-daily + insulin aspart once-, twice- or three-times daily; OR, odds ratio; PYE, patient–years of exposure; RR, estimated rate ratio; SD, standard deviation; SMBG, self-measured blood glucose.

During treatment initiation (Week 0–26) there were numerically fewer overall confirmed symptomatic episodes per subject associated with IDegAsp OD compared with IGlar U100 OD + IAsp OD; however, the difference was not statistically significant (Fig. 2A). In the same period, there were significantly fewer nocturnal confirmed symptomatic episodes per subject associated with IDegAsp (estimated rate ratio [RR] 0.55 [95% CI: 0.34; 0.90]; a 45% rate-reduction versus IGlar U100 + IAsp [Fig. 2B]).

Similarly, when the entire treatment period (Weeks 0–38) was considered, there were numerically fewer overall confirmed symptomatic hypoglycaemic episodes per subject associated with IDegAsp compared with IGlar U100 + IAsp, but the difference between treatment groups was not statistically significant (Fig. 2A). In the same period there were significantly fewer nocturnal confirmed symptomatic episodes per subject associated with IDegAsp compared with IGlar U100 + IAsp (RR 0.61 [95% CI: 0.40; 0.93]; a 39% rate-reduction versus IGlar U100 + IAsp [Fig. 2B]).

Rates of severe hypoglycaemic episodes were low throughout, with seven episodes reported in the IDegAsp group and nine in the IGlar U100 + IAsp group. Additional information on hypoglycaemia throughout the trial is provided in Table S7.

At Weeks 26 and 38, the percentage of patients with HbA_{1c} on-target (<7.0%) who did not experience a confirmed symptomatic hypoglycaemic episode was 27.3% and 22.5%, respectively, for IDegAsp compared with 23.0% and 21.1%, respectively, for IGlar U100 + IAsp. Prior to the treatment intensification period at Week 26, when nocturnal episodes were considered, the percentage of patients achieving target HbA_{1c} without nocturnal hypoglycaemia was 40.8% for IDegAsp and 34.0% for IGlar U100 + IAsp (OR: 1.49 [95% CI: 1.03; 2.17]). At Week 38, the significant difference between the groups was no longer observed with the percentage of patients achieving target HbA_{1c} without nocturnal hypoglycaemia being similar in both treatment groups: IDegAsp: 38.6%; IGlar U100 + IAsp: 35.5% (OR: 1.18 [95% CI: 0.81; 1.71]).

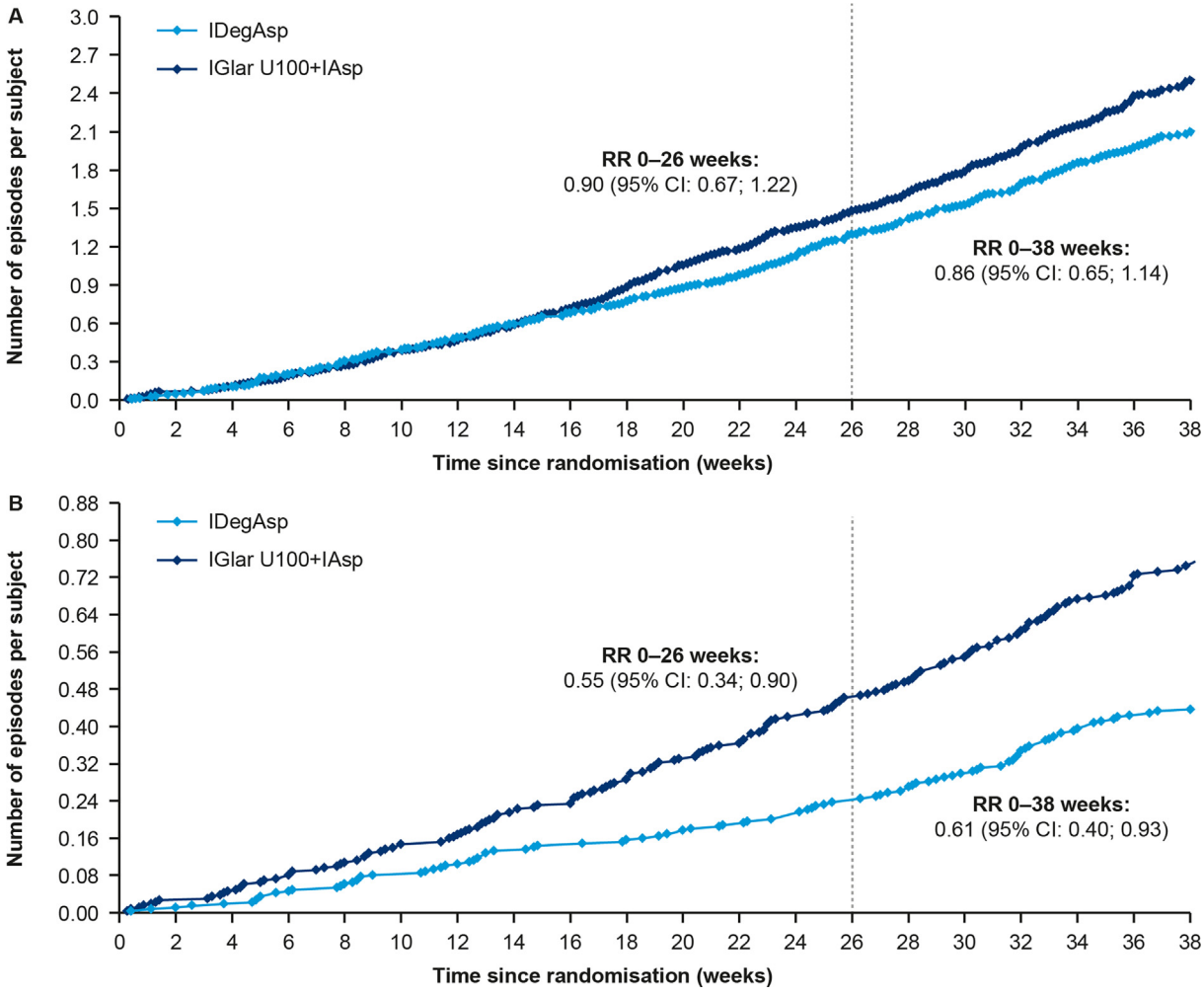

Fig. 2 – Rates of symptomatic blood glucose-confirmed hypoglycaemia. Panel A. all episodes; Panel B. nocturnal episodes (00.01–05.59, both inclusive). Graphs: safety analysis set, comparisons (full analysis set) were made using negative binomial regression. Dashed line shows start of treatment intensification (permitted Weeks 26–38). CI, confidence interval; IDegAsp, insulin degludec/insulin aspart fixed-ratio combination once- or twice-daily; IGlar U100+IAsp, insulin glargine 100 units/mL once-daily + insulin aspart once-, twice- or three-times daily; RR, estimated rate ratio (IDegAsp/IGlar U100 + IAsp).

The lower rates of confirmed symptomatic nocturnal hypoglycaemia associated with IDegAsp (events per 100 patient–years of exposure at Week 38: IDegAsp: 60.42 events; IGlar U100 + IAsp: 101.38 events [Table S7]) translated into the following numbers needed to treat for 1 year with IDegAsp versus treatment with IGlar U100 + IAsp, in order to avoid one symptomatic nocturnal hypoglycaemic episode: 2.40 patients at Week 26; 2.52 patients at Week 38.

4.7.2. *Adverse events*

There were similar rates of treatment-emergent adverse events reported in both treatment groups. The majority were neither serious, nor judged to be related to trial products (Table 3). There were two deaths reported in the IGlar U100 + IAsp group, both were considered unrelated to the trial products (one subject had *pancreatic carcinoma metastatic* with subsequent hepatic metastases, intra-abdominal lymph node metastasis and cancer of the tail of the pancreas; the other, *myocardial ischaemia* as a result of ischaemic heart disease [however, possibility of a severe hypoglycaemic episode could not be excluded as an alternative cause of death by the investigator]).

4.7.3. *Body weight*

Similar mean baseline body weights were observed in both treatment groups (IDegAsp: 88.6 kg; IGlar U100 + IAsp: 88.5 kg, Table 1), and the increases in body weight observed after 38 weeks were similar for both treatment groups: IDegAsp: +2.5 kg; IGlar U100 + IAsp: +2.4 kg. No statistical differences in body weight were found at Week 26 (ETD 0.43 [95% CI: −0.13; 0.99]), or Week 38 (ETD 0.16 [95% CI: −0.47; 0.79]).

5. Discussion

This trial confirmed a similar glycaemic effect for IDegAsp OD versus IGlar U100 OD + IAsp OD over 26 weeks of treatment, with fewer injections, significantly less nocturnal hypoglycaemia and a lower insulin dose associated with IDegAsp. These findings were consistent over the 38-week treatment period, where IDegAsp OD/BID provided equivalent glycaemic control, with statistically significantly less nocturnal hypoglycaemia, fewer injections, and a lower insulin dose compared with IGlar U100 OD + IAsp OD/BID/TID.

This trial is important, as it offers clinical guidance on how, when and why to use IDegAsp in patients with type 2 diabetes mellitus not achieving target HbA_{1c} with basal insulin. The IDegAsp treatment modality was compared with an established multiple injection basal–bolus regimen (considered to be more complex, due to requirements for more injections and use of two titration algorithms). IDegAsp was titrated according to a "precise sliding scale" algorithm, using pre-breakfast SMBG goals. The IDegAsp algorithm was similar to the basal treatment algorithm, maintaining familiarity and simplicity for the patient, through a unit-to-unit transfer.

The results of this trial also offer specific guidance on the further intensification of IDegAsp OD, splitting the dose when necessary, and demonstrating that IDegAsp is as effective for intensification of treatment as a multiple injection basal–bolus regimen, with a more desirable nocturnal hypoglycaemia profile. Furthermore, these data may be relevant to general practitioners treating patients with type 2 diabetes mellitus in need of intensification. IDegAsp represents a simple, adaptable treatment option requiring a single injection, which may better suit patient lifestyle compared with more complex alternatives, with a lower daily injection frequency (compared with basal–bolus regimens) likely to be perceived by patients as less burdensome [9].

Nocturnal hypoglycaemia is a widely recognised and feared complication of diabetes mellitus, representing a barrier to treatment intensification for some patients, with a detrimental impact on quality of life and/or serious clinical consequences [10–12]. It is therefore of importance that nocturnal hypoglycaemia was significantly reduced with IDegAsp, compared with IGlar U100 + IAsp. Furthermore, it was reassuring no safety concerns were associated with the switch from pre-trial regimens, with no clustering of hypoglycaemic episodes noted in the weeks immediately post-randomisation in either group. It is likely that nocturnal hypoglycaemic events are attributable to the pharmacokinetic/pharmacodynamic (PK/PD) properties of the basal insulin component (IGlar U100) [13]. It has been previously demonstrated that insulin degludec provides a very flat glucose-lowering PK/PD profile with low variability [14], and that this translates into a risk reduction for nocturnal hypoglycaemia versus IGlar [15].

Table 3 – Treatment-emergent adverse events (Week 0–38).

	IDegAsp, N = 265				IGlar U100 + IAsp, N = 263			
	N	(%)	E	R	N	(%)	E	R
Adverse event	175	(66.0)	614	328.30	168	(63.9)	525	281.61
Serious	18	(6.8)	24	12.83	20	(7.6)	26	13.95
Fatal*	0	–	–	–	2	(0.8)	2	1.07
Not recovered	68	(25.7)	129	68.97	71	(27.0)	124	66.51
Severe	9	(3.4)	14	7.49	11	(4.2)	18	9.66
Probably/possibly related to trial product	31	(11.7)	84	44.91	22	(8.4)	46	24.67

Safety analysis set. *Fatal events: myocardial ischaemia and pancreatic carcinoma metastatic. E, number of events; IDegAsp, insulin degludec/insulin aspart fixed-ratio combination once- or twice-daily; IGlar U100 + IAsp, insulin glargine 100 units/mL once-daily + insulin aspart once-, twice- or three-times daily; N, number of subjects with ≥1 event; R, rate per 100 patient–years of exposure; %, percentage of subjects with ≥1 event.

The current trial had several strengths. The trial design was close to routine clinical practice, with the treat-to-target aspect allowing optimisation of glycaemic control for patients on an individual basis, and selecting IGlar U100 as a comparator enabled comparison with one of the most widely used basal insulins [12]. In addition, high completion rates were recorded for both treatment groups. Limitations included the open-label design as a potential source of bias (however, it should be noted that blinding in such a trial would not be feasible due to the number of injections differing between the treatment groups).

In summary, the trial confirms IDegAsp OD is as effective as the IGlar U100 + IAsp multiple injection basal–bolus regimen in terms of glycaemic control, but with significantly less nocturnal hypoglycaemia. Furthermore, stepwise intensification from IDegAsp OD to BID seems feasible with respect to both glycaemic control and safety.

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Declarations of interest

AP-T has been a researcher and advisor for AstraZeneca, Dexcom, Lilly, Novo Nordisk and Sanofi, and an advisor for Merck. DR has received personal fees and non-financial support from Hikma, Novo Nordisk and Sanofi. BAB, EGF and AMN are employees of Novo Nordisk. KA, YG, AH and TD have no conflicts of interest to declare.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2018.10.024.

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