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ORIGINAL RESEARCH

# Initiating or Switching to Insulin Degludec/Insulin Aspart in Adults with Type 2 Diabetes: A Real-World, Prospective, Non-interventional Study Across Six Countries

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## ABSTRACT

***Introduction***: Insulin degludec/insulin aspart (IDegAsp) is a fixed-ratio co-formulation of insulin degludec (a basal insulin) and insulin aspart (a prandial insulin). The aim of this study was to investigate clinical outcomes in people with type 2 diabetes (T2D) after initiating IDegAsp treatment in a real-world setting.

***Methods***: This 26-week, open-label, non-interventional study was conducted in Australia, India, Malaysia, Philippines, Saudi Arabia, and South Africa. Data were obtained from 1102 adults with T2D initiating or switching to IDegAsp from antidiabetic treatments (including oral antidiabetic drugs, basal insulin, basal–bolus insulin, premix insulin, and glucagon-like peptide 1 receptor agonist) per local clinical practice.

***Results***: Compared with baseline, there was

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significant improvement in HbA1c at end of study (EOS, first visit within weeks 26–36; estimated change − 1.4% [95% CI − 1.51; − 1.29]; $P < 0.0001$ [primary outcome]). From baseline to EOS, there were significant reductions in fasting plasma glucose (− 2.7 mmol/L [95% CI − 2.98; − 2.46]; $P < 0.0001$), body weight (− 1.0 kg [95% CI − 1.51; − 0.52]; $P < 0.0001$), and basal insulin dose in insulin-experienced participants (− 2.3 units [95% CI − 3.51; − 1.01]; $P < 0.001$). The incidence rates of non-severe (overall and nocturnal) and severe hypoglycaemia decreased significantly ($P < 0.001$) between the period before baseline and before EOS.

***Conclusion***: In adults with T2D, initiating or switching to IDegAsp from previous antidiabetic treatment was associated with improved glycaemic control, lower basal insulin dose (in insulin-experienced participants), and lower rates of hypoglycaemia.

***Trial Registration***: Clinical trial registration NCT04042441.

**Keywords:** Glycaemic control; Insulin degludec/insulin aspart; Real-world; Type 2 diabetes

**Key Summary Points**

**Why carry out this study?**

Insulin degludec/insulin aspart (IDegAsp) is a fixed-ratio co-formulation of insulin degludec (a long-acting basal insulin) and insulin aspart (a rapid-acting prandial insulin).

The BOOST randomised clinical trial (RCT) programme demonstrated that IDegAsp can provide effective glycaemic control with a low risk of hypoglycaemia in people with type 2 diabetes (T2D), along with flexible dose timing and a low daily injection burden.

The aim of this real-world study was to investigate clinical outcomes in people with T2D who initiated or switched to IDegAsp in local clinical practice across six countries.

**What was learned from the study?**

In a real-world population of people with T2D, initiating IDegAsp, or switching to it from previous antidiabetic treatment, was associated with improved glycaemic control, lower basal insulin dose (in insulin-experienced participants), and lower rates of hypoglycaemia.

The results of this real-world study add to the body of evidence from RCTs evaluating the impact of initiating or switching to IDegAsp in people with T2D.

## INTRODUCTION

Type 2 diabetes (T2D) is characterised by both insulin resistance and inadequate insulin secretion. Pharmacological management of T2D typically begins with the introduction of oral antidiabetes drugs (OADs), but the majority of people with T2D will eventually require exogenous insulin therapy [1]. Insulin therapy is often initiated as a long-acting basal insulin alone or as a premix insulin [1]. Basal–bolus insulin therapy is considered the gold standard for people with T2D failing to achieve glycaemic targets with basal or premix insulin alone or in combination with OADs [1]. However, clinical inertia—the failure to establish appropriate targets and escalate treatment to achieve treatment goals—is prevalent in clinical practice, and is particularly problematic with the initiation and intensification of insulin in T2D [2, 3]. The reasons for clinical inertia are multifactorial for both people with T2D and physicians, and include fear of hypoglycaemia and the burden of multiple daily injections [4]. To overcome these barriers, there is a need for insulin regimens that can match dynamic physiological insulin needs with fewer daily injections and greater flexibility compared with basal–bolus regimens.

Insulin degludec/insulin aspart (IDegAsp; Ryzodeg®, Novo Nordisk A/S, Søborg, Denmark) is a co-formulation in a fixed ratio of 70%

insulin degludec, a basal insulin, and 30% insulin aspart (IAsp), a prandial insulin [5]. IDegAsp is administered immediately before a main meal; its unique pharmacodynamic profile provides a stable basal insulin action over a 24-h period owing to the flat, ultra-long effect of IDeg, with the short-acting IAsp component providing prandial control for that meal and limiting postprandial hyperglycaemia [5]. The efficacy and safety of IDegAsp in people with T2D who were either insulin-naïve or previously treated with insulin have been extensively investigated in the BOOST clinical trial programme [6–10]. These treat-to-target randomised controlled trials (RCTs) demonstrated that once- or twice-daily IDegAsp provides effective glycaemic control with a relatively low risk of hypoglycaemia and a simpler titration regimen than premix or basal–bolus regimens. In addition, owing to the long duration of action and low day-to-day variation in glucose-lowering effect of the basal component, IDegAsp has been shown to allow for flexibility in the timing of insulin administration without deterioration in glycaemic control, as long as it is dosed with the main meal(s) [11, 12].

Although RCTs are the gold standard for comparing the safety and efficacy of different therapies, they are limited by their study design and patient inclusion criteria. Real-world evidence (RWE) studies are required to complement data generated from RCTs. At present, only a small number of RWE studies have been conducted into treatment with IDegAsp. A small retrospective study in India reported a decrease in HbA1c and fasting plasma glucose (FPG) after 12 months of IDegAsp treatment in a mixed population of insulin-naïve and insulin-experienced people with T2D [13]. Additionally, a recent prospective study in Japanese adults with T2D previously treated with basal insulin with or without prandial insulin showed switching to IDegAsp to be associated with maintenance of glycaemic control, a reduced daily total and basal insulin dose requirement, and a similar incidence of non-severe hypoglycaemia in comparison with baseline [14]. There remains, however, a need for multicentre RWE studies examining treatment with IDegAsp, to provide evidence of the generalisability of the results from the BOOST clinical trial programme to wider populations in actual clinical settings.

The aim of this study was to investigate glycaemic control and other clinical outcomes in a real-world clinical setting in people with T2D who initiated IDegAsp, or switched to it from previous antidiabetic treatment, according to local clinical practice across six different countries.

## METHODS

### Study Design and Population

The study design has been published previously [15]. Briefly, this was a 26-week, multicentre, prospective, open-label, non-interventional study investigating clinical outcomes in people with T2D after initiating or switching to IDegAsp as per the local label at the discretion of their treating physician (ClinicalTrials.gov, NCT04042441). The study consisted of a baseline visit (informed consent and treatment initiation), observation visits in accordance with local clinical practice, and an end-of-study visit (EOS, the first visit within the window from weeks 26 to 36). The decision to initiate or switch to treatment with IDegAsp was taken prior to baseline and was independent of the decision to include the participant in the study. The physician determined the starting dose and frequency of IDegAsp administration, as well as any adjustments thereafter. Dose adjustment or discontinuation of other glucose-lowering medication during the study was permitted. No additional diagnostic or monitoring procedures beyond local standard clinical practice were performed.

Data were collected from 65 sites across six countries between August 2019 and December 2020. Enrolment was not competitive, and the sites were selected on the basis of their ability to enrol a sufficient number of participants. Investigators were compensated for each patient enrolled in accordance with the Good Pharmaco-epidemiological Practices (GPP) guidelines. Sites were compensated for time spent documenting informed consent, data entry in the electronic Case Report Form, and

other study-specific activities such as system training that were not part of their routine clinical care. All hourly rate payments were in line with fair market value for the respective country.

The study was conducted in accordance with the Declaration of Helsinki (2013) [16]. The protocol and participant consent forms were approved by research ethics boards/institutional review boards for all sites (Table S1 in the electronic supplementary material). Informed written consent was obtained from all participants before any study-related activities.

Participants were selected for this study by physicians on the basis of the inclusion and exclusion criteria. Adults (at least 18 years of age) with a diagnosis of T2D were eligible for inclusion if they had been treated with any antidiabetic medications other than IDegAsp for at least 26 weeks and had an HbA1c value recorded no more than 12 weeks prior to signing informed consent and initiating treatment (baseline visit). Exclusion criteria included prior participation in the study, previous IDegAsp treatment, hypersensitivity to the active substance or to any of the excipients specified in the IDegAsp local label, and mental incapacity, unwillingness to participate or language barriers that would lead to inadequate understanding or cooperation.

## Study Objectives and Endpoints

The main objective of this study was to evaluate glycaemic control and other clinical outcomes after initiating or switching to IDegAsp. Secondary objectives were to describe the clinical use of IDegAsp in a real-world setting, including reasons for initiating or discontinuing treatment.

The primary endpoint was change in HbA1c from baseline to EOS. Secondary endpoints included the proportion of participants achieving HbA1c $< 7.0\%$ at EOS, the proportion of participants achieving HbA1c levels below a pre-defined individualised treatment target at EOS (categories of target ranges were $< 6.5\%$, $6.5\%$ to $< 7.0\%$, $7.0\%$ to $< 7.5\%$, $7.5\%$ to $< 8.0\%$, and $\geq 8.0\%$), and change from baseline to EOS in FPG, total, basal, and prandial insulin dose, and body weight. Additional endpoints included patient-reported non-severe hypoglycaemic episodes (overall and nocturnal) occurring within 4 weeks prior to IDegAsp initiation and within 4 weeks prior to EOS, and severe hypoglycaemic episodes occurring within 26 weeks prior to IDegAsp initiation and during the 26-week study duration. Non-severe hypoglycaemia was defined as an episode with symptoms and/or self-measured blood glucose value $\leq 3.9$ mmol/L that the patient was able to self-treat, and a nocturnal event was defined depending on whether the patient perceived the event to have occurred at night. Severe hypoglycaemia was defined as an episode of hypoglycaemia requiring the assistance of another person to actively administer carbohydrate or glucagon, or take other corrective action to relieve neurocognitive symptoms. Data on the reasons for initiating IDegAsp treatment at baseline, reasons for discontinuing IDegAsp treatment, and the proportion of participants discontinuing treatment during the study period were also collected. Exploratory endpoints included healthcare resource utilisation (HRU) associated with management of diabetes and its complications observed within 12 weeks prior to IDegAsp initiation and within 12 weeks prior to EOS or discontinuation, and HRU associated with severe hypoglycaemia observed within 26 weeks prior to IDegAsp initiation, and during the 26 weeks prior to EOS.

## Statistical Methods

The sample size calculation was based on the primary endpoint and aimed to have sufficient power for primary endpoint analysis, both overall and in each of the six participating countries. Assuming a mean change in HbA1c of 0.5% (standard deviation [SD], 1.8%) and a missing HbA1c value at EOS in 25% of participants, we planned to enrol 1112 people, with a minimum of 139 in each country, to detect the HbA1c difference at 90% power.

The full analysis set (FAS) included all eligible participants who signed the informed consent and initiated treatment with IDegAsp.

Primary analysis of the primary endpoint was conducted using crude and adjusted mixed models for repeated measurements (MMRM). The analysis was based on all participants in the FAS with at least one post-baseline HbA1c measurement using the 'in-study' observation period. This observation period represented the time period during which participants were considered to be in the study, regardless of IDegAsp treatment discontinuation. The crude model included baseline HbA1c and time of HbA1c as covariates. The adjusted model included baseline HbA1c, time of HbA1c, age, sex, body mass index (BMI), study site, and previous antidiabetic treatment as covariates. Secondary analyses of the primary endpoint were conducted on the basis of the 'on-treatment' observation period. This observation period represented the time period during which participants were receiving IDegAsp, and thus values measured after treatment discontinuation were disregarded.

Primary and secondary analyses were repeated for change from baseline to EOS in FPG, insulin dose, and body weight, with the baseline value of the relevant endpoint included as covariate. The incidence rates of non-severe (overall and nocturnal) and severe hypoglycaemia were analysed using negative binomial regression models with the log-transformed follow-up time as offset.

Here, we present the results of the primary analyses using the adjusted MMRM for the in-study observation period, except for HRU which was analysed using the on-treatment observation period only. Endpoints analysed using the on-treatment observation period are listed in Table S2 in the electronic supplementary material.

# RESULTS

## Study Population Demographics and Clinical Characteristics

Of the 1462 people with T2D assessed for eligibility, 1102 were initiated or switched to IDegAsp and included in the FAS (Fig. S1 in the electronic supplementary material). Of these, 92.1% of participants completed the study. The demographic and clinical characteristics of participants at baseline are presented in Table 1. Among the 1102 participants in the FAS, mean (SD) age at baseline was 58.6 (12.23) years, mean HbA1c was 9.8 (1.99)%, and mean duration of diabetes was 13.3 (8.33) years. Of the 1057 participants with prior antihyperglycaemic treatment data, 35.1% were receiving OADs only, 21.9% premix insulin, 21.8% basal insulin, 13.0% basal–bolus insulin, and 8.2% glucagon-like peptide 1 receptor agonist (GLP-1 RA) ± insulin. Baseline characteristics by country subgroup are shown in Table S3 in the electronic supplementary material.

At treatment initiation, 52.2% of participants ($n = 575$) received IDegAsp once daily (OD) and 47.6% of participants ($n = 525$) received IDegAsp twice daily (BID). Dosing frequency was described as 'other' in two participants. The mean (SD) starting daily dose of IDegAsp was 35.9 (25.43) U in the overall study population and 24.3 (15.79) U in prior OAD-only users. The majority of participants (62.7%) had an individual target HbA1c of 7.0% to $< 7.5\%$. Physicians' reasons for initiating IDegAsp are summarised in Table 2 (note that physicians could report more than one reason for initiation). The most frequently reported reason was to improve the patient's glycaemic control (93.1%). Physicians also reported lowering the risk of hypoglycaemia (26.4%) and specific characteristics of IDegAsp itself, including flexibility in the dosing regimen (26.0%), fewer injections than basal and bolus therapy (25.1%), and avoidance of the need for reconstitution as reasons for treatment initiation (8.9%). Reasons for discontinuing IDegAsp treatment are listed in Table S4 in the electronic supplementary material.

## Glycaemic Control

In participants contributing to the analysis of the primary endpoint, observed mean (SD) HbA1c at baseline was 9.7 (1.95)% and the estimated mean (SD) at EOS was 8.3 (0.05)%. HbA1c was statistically significantly lower at EOS compared with baseline (estimated

**Table 1** Demographic and clinical characteristics at baseline

| | Overall *N* = 1102 |
|---|---|
| Age, mean (SD) | 58.6 (12.23) |
| Male, *n* (%) | 591 (53.6) |
| Duration of diabetes (years), mean (SD) | 13.3 (8.33) |
| Body weight (kg)[a], mean (SD) | 79.5 (19.56) |
| BMI (kg/m$^2$), mean (SD) | 29.2 (5.86) |
| HbA1c (%)[a], mean (SD) | 9.8 (1.99) |
| FPG (mmol/L)[a], mean (SD) | 11.0 (4.22) |
| Antidiabetic treatment, *n* (%) | |
| OADs only | 371 (35.1) |
| Premix insulin ± bolus insulin (± OADs) | 232 (21.9) |
| Basal insulin only (± OADs) | 230 (21.8) |
| Basal–bolus insulin (± OADs) | 137 (13.0) |
| GLP-RA ± insulin (± OADs) | 87 (8.2) |
| Dose of previous prandial insulin (U), mean (SD) | 25.8 (22.84) |
| Diabetes complications, *n* (%) | |
| Diabetic neuropathy | 216 (24.7) |
| Diabetic nephropathy | 178 (20.3) |
| Cardiovascular disease | 150 (17.1) |
| Diabetic retinopathy | 102 (11.6) |
| Peripheral vascular disease | 15 (1.7) |
| Individual target HbA1c, *n* (%) | |
| < 6.5% | 28 (2.5) |
| 6.5% to < 7.0% | 195 (17.7) |
| 7.0% to < 7.5% | 691 (62.7) |
| 7.5% to < 8.0% | 112 (10.2) |
| ≥ 8.5% | 76 (6.9) |

OADs included sulfonylureas, meglitinides, biguanides, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, sodium-glucose co-transporter 2 inhibitors, and α-glucosidase inhibitors

*BMI* body mass index, *FPG* fasting plasma glucose, *GLP-1 RA* glucagon-like peptide 1 receptor agonist, *OAD* oral antidiabetic drug, *N* number of participants in the full analysis set, *n* number of participants, *SD* standard deviation, *U* unit

[a]Baseline assessments from ≤ 12 weeks prior to signing informed consent and initiating IDegAsp treatment

**Table 2** Physicians' reasons for initiating or switching to IDegAsp

| | Overall *N* = 1102 |
|---|---|
| To improve the patient's glycaemic control | 1026 (93.1) |
| To lower the risk of hypoglycaemia | 291 (26.4) |
| Flexibility in the dosing regimen | 286 (26.0) |
| Fewer injections than basal and bolus therapy | 277 (25.1) |
| No reconstitution needed | 98 (8.9) |
| Change in coverage status favouring IDegAsp | 82 (7.4) |
| Other | 54 (4.9) |

Physicians could select more than one reason for each patient. A change in coverage status favouring IDegAsp refers to a change in healthcare insurance or reimbursement requirements that led to better access to the drug

*IDegAsp* insulin degludec/insulin aspart, *N* number of participants in the full analysis set

difference − 1.4% [95% CI − 1.51; − 1.29]; $P < 0.0001$) (Fig. 1). Results of the primary analysis using the crude MMRM and secondary analysis based on the on-treatment observation period were consistent with the main result (Table S2 in the electronic supplementary material).

A statistically significant reduction in HbA1c was observed in all prior treatment subgroups (Fig. 1). The reduction was numerically greatest in the OAD-only subgroup (estimated difference − 2.0% [95% CI − 2.17; − 1.85]; $P < 0.0001$) and smallest in the basal–bolus (estimated difference − 0.9% [95% CI − 1.20; − 0.52]; $P < 0.0001$) and premix insulin (estimated difference − 0.9% [95% CI − 1.17; − 0.64]; $P < 0.0001$) subgroups. Significant reductions in HbA1c from baseline to EOS were also observed across the six individual countries, with the largest reduction in the Saudi Arabian cohort (estimated difference − 2.0% [95% CI − 2.31; − 1.78]; $P < 0.0001$) and the smallest in the Australian

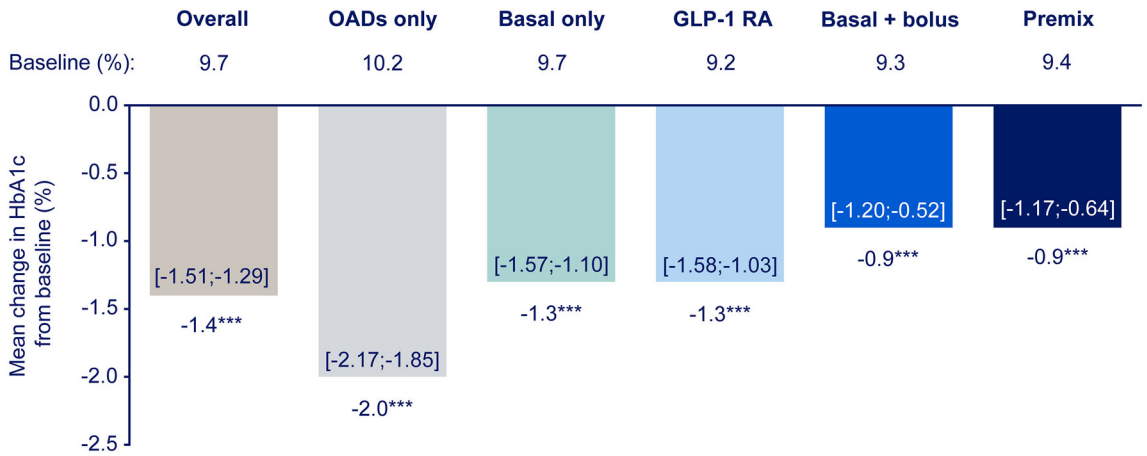


**Fig. 1** Change in HbA1c from baseline to EOS. ***$P < 0.0001$. Data are mean [95% CI]. Baseline data are for participants contributing to the analysis. The full adjusted model included baseline value, time, time-squared for HbA1c measure, age, sex, BMI, previous antidiabetic regimen, and study site. To handle (quadratic) deviation from linearity, a random coefficient model with time and time squared as fixed coefficients, and patient and patient time as random coefficients was used. An unstructured covariance matrix was used to describe the variability for repeated measurements. *BMI* body mass index, *basal only* basal insulin only (± OADs); *basal–bolus* basal–bolus insulin (± OADs), *CI* confidence interval, *EOS* end of study, *GLP-1 RA* glucagon-like peptide 1 receptor agonist ± insulin (± OADs), *OAD* oral antidiabetic drug, *premix* premix insulin ± bolus insulin (± OADs)

cohort (estimated difference − 0.8% [95% CI − 1.05; − 0.56]; $P < 0.0001$) (Fig. S2 in the electronic supplementary material). Similarly, there was a significant reduction in FPG from baseline to EOS in the overall study population (estimated difference − 2.7 mmol/L [95% CI − 2.98; − 2.46]; $P < 0.0001$).

At EOS, 14.9% of participants had an HbA1c level < 7.0% compared with 4.3% of participants at baseline, while 14.9% of participants achieved an HbA1c level below their pre-defined individual target by EOS compared with 2.5% of participants at baseline.

## Insulin Dose

In insulin-experienced participants (prior basal insulin only, basal–bolus insulin, and premix insulin users), the observed mean total daily insulin dose at baseline was 49.1 (SD 33.88) U and the estimated total daily insulin dose at EOS was 48.1 (standard error [SE] 1.08) U. There was a significant increase in daily prandial insulin dose from baseline to EOS. Observed mean daily prandial insulin dose was 15.6 (SD 22.39) U at baseline, increasing to an estimated 17.0 (SE 0.61) U at EOS (estimated difference 1.8 U [95% CI 0.62; 3.02], $P = 0.0031$). There was also a significant reduction in basal daily insulin dose from baseline to EOS. Observed mean daily basal insulin dose was 33.5 (SD 20.96) U at baseline, decreasing to an estimated 31.3 (SE 0.64) U at EOS (estimated difference − 2.3 U [95% CI − 3.51; − 1.01], $P = 0.0004$).

In the prior treatment subgroups, there were significant reductions in total daily insulin dose in prior premix insulin and prior basal–bolus users. Mean (SD) total daily insulin decreased from 56.8 U at baseline to 52.6 U at EOS in the premix insulin subgroup (estimated difference − 5.9 U [95% CI − 8.94; − 2.90]; $P = 0.0002$) and from 68.3 U at baseline to 54.2 U at EOS in the basal–bolus subgroup (estimated difference − 13.8 U [95% CI − 18.24; − 9.27]; $P < 0.0001$).

## Hypoglycaemia

The observed incidence rates of overall and nocturnal non-severe hypoglycaemia and severe hypoglycaemia in the period prior to

**Table 3** Hypoglycaemic episodes occurring prior to initiation of IDegAsp (baseline) and prior to EOS or discontinuation

| | *n* | *n* with event | Events | Rate | Estimated rate ratio [95% CI] |
|---|---|---|---|---|---|
| Non-severe | | | | | |
| Within 4 weeks of initiation | 1038 | 128 | 364 | 4.57 | 0.46 [0.30; 0.71] |
| Within 4 weeks prior to EOS or discontinuation | 1001 | 44 | 162 | 2.11 | $P = 0.0004$ |
| Nocturnal non-severe | | | | | |
| Within 4 weeks of initiation | 1038 | 59 | 142 | 1.78 | 0.23 [0.12; 0.43] |
| Within 4 weeks prior to EOS or discontinuation | 1001 | 14 | 31 | 0.40 | $P < 0.0001$ |
| Severe | | | | | |
| Within 26 weeks of initiation | 1058 | 23 | 51 | 0.10 | 0.06 [0.02; 0.24] |
| Within 26 weeks prior to EOS | 1005 | 3 | 3 | 0.01 | $P < 0.0001$ |

Data based on the full analysis set. Negative binomial regression models specifying a log-transformed follow-up time offset term were used to examine the incidence rate of hypoglycaemic events occurring prior to initiation of IDegAsp and prior to end of study or at discontinuation

*CI* confidence interval, *EOS* end of study, *IDegAsp* insulin degludec/insulin aspart, *n* number of participants contributing to the analysis, *rate* events per patient-year

initiating IDegAsp and the period before EOS or discontinuation are shown in Table 3. In the overall study population, there was a significant reduction in the rate of non-severe hypoglycaemia (estimated rate ratio [RR] 0.46 [95% CI 0.30; 0.71]; $P = 0.0004$), non-severe nocturnal hypoglycaemia (RR 0.23 [95% CI 0.12; 0.44; $P < 0.0001$), and severe hypoglycaemia (RR 0.06 [95% CI 0.02; 0.24]; $P < 0.0001$) after initiating or switching to IDegAsp. Secondary analyses of hypoglycaemia rates were consistent with the primary analyses (Table S2 in the electronic supplementary material).

## Body Weight

There was a significant reduction in body weight in the overall study population at EOS compared with baseline (estimated difference − 1.0 kg [95% CI − 1.51; − 0.52]; $P < 0.0001$) (Fig. 2), and this was consistent with the secondary analysis (Table S2 in the electronic supplementary material). In the prior treatment subgroups, body weight reduction was statistically significant in prior OAD-only users (estimated difference − 1.4 kg [95% CI − 2.32; − 0.49]; $P = 0.0028$), basal insulin users (estimated difference − 1.1 kg [95% CI − 2.09; − 0.07]; $P = 0.0362$), and basal–bolus insulin users (estimated difference − 1.5 kg [95% CI − 2.70; − 0.23]; $P = 0.0212$). There was a small increase in body weight in participants previously treated with GLP-1 RA ± insulin (estimated difference 0.3 kg [95% CI − 1.10; 1.77]), and this was not statistically significant.

## Healthcare Resource Utilisation

For HRU associated with diabetes and its complications, initiating or switching to IDegAsp resulted in a significant decrease in the incidence of self-reported outpatient visits (RR 0.44 [95% CI 0.35; 0.54]; $P < 0.0001$), emergency room visits (RR 0.22 [95% CI 0.11; 0.44]; $P < 0.0001$), work days missed (RR 0.06 [95% CI 0.03; 0.14]; $P < 0.0001$), and in-patient hospitalisations (RR 0.24 [95% CI 0.14; 0.41]; $P < 0.0001$) between the 12-week period prior to baseline and the 12-week period before EOS or discontinuation (Table S5 in the electronic supplementary material). For HRU associated with severe hypoglycaemia, initiating or

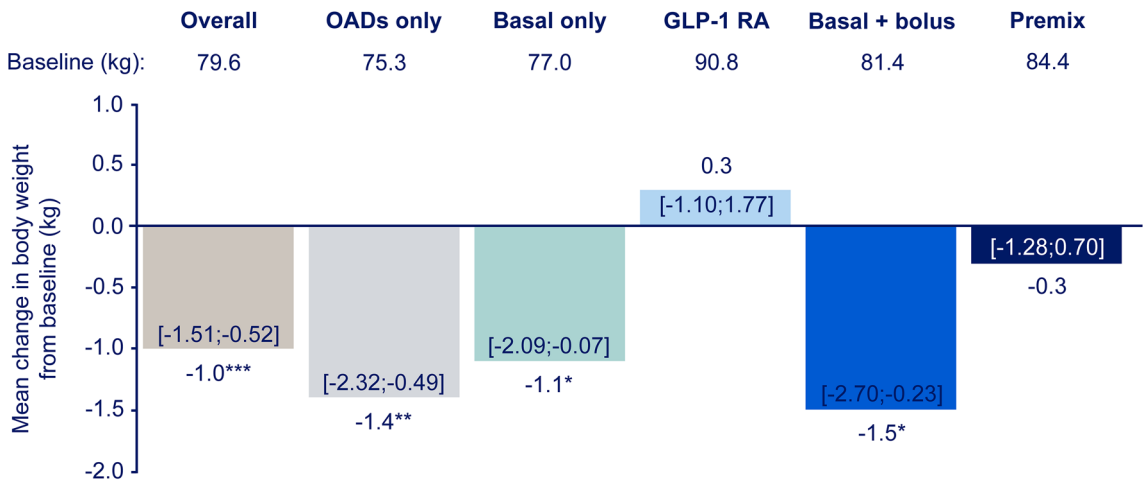


**Fig. 2** Change in body weight from baseline to EOS. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.0001$. Data are mean [95% CI]. Baseline data are for participants contributing to the analysis. The full adjusted model included baseline value, time, time-squared of body weight measure, age, sex, BMI, previous antidiabetic treatment regimen, and study site. To handle (quadratic) deviation from linearity, a random coefficient model with time and time squared as fixed coefficients, and patient and patient time as random coefficients was used. An unstructured covariance matrix was used to describe the variability for repeated measurements. *BMI* body mass index, *basal only* basal insulin only (± OADs), *basal–bolus* basal–bolus insulin (± OADs), *CI* confidence interval, *EOS* end of study, *GLP-1 RA* glucagon-like peptide 1 receptor agonist ± insulin (± OADs), *OAD* oral antidiabetic drug, *premix* premix insulin ± bolus insulin (± OADs)

switching to IDegAsp resulted in a significant decrease in the incidence of self-reported emergency room visits (RR 0.19 [95% CI 0.05; 0.70]; $P = 0.0124$), in-patient visits (RR 0.21 [95% CI 0.05; 0.83]; $P = 0.0262$), and work days missed (RR 0.10 [95% CI 0.01; 0.76]; $P = 0.0261$) between the 26-week period prior to baseline and the 26-week period before EOS (Table S5 in the electronic supplementary material).

### Adverse Events

In total, 172 adverse events (AEs) were reported in 99 participants (Table S6 in the electronic supplementary material). Of these, 57 serious AEs were reported in 39 participants. Most serious AEs were classed as 'unlikely related' to IDegAsp treatment. Two serious AEs were classed as 'probably related' to IDegAsp treatment, and these were reported by one patient who experienced a severe hypoglycaemic event resulting in a fall and fracture of the femur. By system organ class, the most common AEs were metabolism and nutrition disorders (2.7%). Seven deaths were reported during the study.

## DISCUSSION

In this real-world, prospective, non-interventional study, people with T2D were initiated or switched to IDegAsp from previous antidiabetic treatment as part of routine clinical practice. In the overall study population, representing six countries, use of IDegAsp for 26–36 weeks was associated with a significant reduction in HbA1c, FPG, and body weight, and significantly reduced rates of severe, non-severe, and non-severe nocturnal hypoglycaemia overall compared with baseline. In insulin-experienced participants, there was a reduced daily basal insulin dose requirement. The results of this study provide data on the impact of initiating or switching to IDegAsp in a real-life clinical setting and add to the body of evidence from RCTs evaluating IDegAsp in comparison with existing insulin regimens in people with T2D.

A statistically significant improvement in HbA1c was seen in each of the six countries, with the Saudi Arabian cohort showing the largest reduction and the Australian cohort the smallest reduction from baseline to EOS. Change in HbA1c was also broadly similar across prior treatment subgroups, with a numerically greater improvement in prior OAD-only users. The high baseline HbA1c in the OAD-only subgroup suggests a degree of clinical inertia, and hence insulin hesitancy, in this patient population. The reasons for initiating or switching to IDegAsp are likely to be different for prior OAD users compared with prior insulin users (e.g. need for improved glycaemic control versus fewer injections/greater flexibility/avoidance of hypoglycaemia), and this may impact upon the HbA1c level achieved in the different subgroups.

The percentage of participants with an HbA1c $< 7.0\%$ was numerically higher at EOS compared with baseline, but the number of participants reaching this target was relatively low. Hence, this study shows that, while IDegAsp improves outcomes in a real-world setting, the level of improvement is less than is typically seen in similar-length RCTs, where more regular follow-ups and more aggressive titration algorithms are enforced. This suggests that it may be pertinent to investigate the use of stricter titration algorithms for potential incorporation into routine care. As mean baseline HbA1c was relatively high, longer treatment periods may be required for people to obtain target HbA1c levels, particularly if clinicians have concerns regarding development of diabetic retinopathy associated with rapid decrease in HbA1c. It is also important to note that, in routine clinical practice, HbA1c targets may be higher than 7.0%. In this study, 79.8% of participants had an individual treatment target at baseline of $\geq 7.0\%$, and this may have affected achievement of the $< 7.0\%$ target.

The significant reduction in FPG following the initiation of IDegAsp reflects the reduction observed in HbA1c. Importantly, the improvements in glycaemic control were achieved with no negative impact on hypoglycaemia. As the basal component of IDegAsp has a very low pharmacokinetic/pharmacodynamic (PK/PD) variability versus other basal insulins, clinicians should be less concerned about the complexities of dose titration when prescribing IDegAsp. There is also a much clearer PK/PD separation of the basal and prandial components in IDegAsp versus premix insulins. This means that the prandial effect is better able to match the physiological need following a large meal, with less risk of late postprandial hypoglycaemia. The fear of hypoglycaemia is a significant barrier to insulin initiation and intensification among people with T2D and physicians, and lowering the risk of hypoglycaemia was the second most common reason selected by the physicians for initiating or switching to IDegAsp.

Over the study period, treatment with IDegAsp was associated with a significant decrease in daily basal insulin dose in insulin-experienced participants. In participants receiving premix or basal–bolus insulin prior to the study, the switch to IDegAsp was associated with significant reductions in daily total insulin dose. A reduced insulin dose can have positive implications in clinical practice, such as fewer AEs and lower healthcare costs.

There was a reduction in body weight in the overall study population ($-$ 1.0 kg) and in the prior OAD-only, basal insulin, and basal–bolus subgroups. Potential reasons for this finding may differ depending on prior treatment. People in the OAD-only subgroup may have been switched from high doses of sulfonylureas (especially in Saudi Arabia and India, where there is a strong preference for this treatment approach), which are associated with weight gain [17–20]. The lower total daily insulin dose in prior basal–bolus insulin users ($-$ 13.8 U) may also have contributed to the weight loss observed in this subgroup. As insulin is an anabolic hormone, a decrease in dose may positively affect protein catabolism and lipolysis and, to some degree, decrease lipogenesis, resulting in weight loss [21]. Additionally, the reduction in hypoglycaemia after switching to IDegAsp from other insulin regimens may have resulted in less so-called 'defensive snacking' (driven by fears of hypoglycaemia), thus reducing overall food intake [22]. Lastly, baseline HbA1c and BMI values indicate that this was an

overweight population (near obese) in need of treatment intensification. A renewed focus on diet or exercise modifications following the switch to IDegAsp treatment may have also impacted upon body weight.

Exploratory analysis suggests that, following the initiation or switch to IDegAsp, there was a reduction in the number of outpatient visits, emergency room visits, work days missed, and in-patient hospitalisations associated with diabetes and its complications, and a reduction in the number of emergency room visits, in-patient hospitalisations, and work days missed associated with severe hypoglycaemia. The reduction in HRU associated with IDegAsp treatment is encouraging and reflects the improvements observed in the clinical parameters. However, it should be noted that, as an exploratory endpoint, the study may not be adequately powered for these analyses, and the HRU results should be accepted with caution.

Consistent with our findings, improvements in glycaemic control, a reduced risk of hypoglycaemia, and lower basal insulin dose requirement in prior insulin users were also reported in the BOOST clinical trial programme [6–11]. A recent meta-analysis of five phase 3, 26-week, treat-to-target trials comparing IDegAsp BID with premix insulin or basal–bolus insulin demonstrated similar HbA1c results, significantly lower FPG level, lower insulin dose, and lower rates of overall and nocturnal hypoglycaemia with IDegAsp versus the comparators across a spectrum of patient baseline characteristics [23].

There can be discrepancies between the results of RCTs and real-life clinical practice driven in part by non-adherence to complex regimens [24]. However, the positive alignment found between this study and the BOOST clinical trials may reflect the advantages of IDegAsp over other insulin regimens in people with T2D. Compared with premix regimens such as biphasic insulin aspart 30/70, IDegAsp does not require resuspension before each injection, and allows flexibility in the time of administration, as long as it is dosed with the main meal(s) of the day [12]. This allows people to be more flexible with the timing of their main meal, rather than eating at the same time every day. IDegAsp may also be preferable to basal–bolus regimens in terms of simplicity, reduced resource usage (as fewer needles and blood glucose monitoring tests are required), and in cases where fear of injections is a barrier to the transition to insulin.

This study provides important insights into the clinical outcomes associated with initiating or switching to IDegAsp in a real-world setting. The large cohort size, multicentre design, and broad inclusion and exclusion criteria make the results generalisable to a wide population of people with T2D. Data collected from study sites located across a diverse group of six countries also provide insights across different clinical practices and healthcare systems. However, there are some key limitations that should be considered when interpreting the results of this study. Participants were empirically selected with the expectation that they would benefit from a change of regimen to IDegAsp. As a result of the prospective nature of the study, it is possible that the physician's therapeutic choice may have been involuntarily influenced by their site's participation in the study. The non-interventional design means there was no control over baseline parameter ranges, insulin titration methods, and insulin titration frequency. As a single-arm study with no comparator group, the contribution of a placebo effect cannot be ruled out, and any other additional factors, such as changes in concomitant OAD therapy, that resulted in clinical changes could not be investigated. Between-country differences may also have affected the results; differences in local clinical practice, dosing and titration practices, and insurance coverage exist, and these may have affected the treatment participants received. Subgroup analyses performed by previous treatment regimens or by country used lower sample sizes and this may have resulted in reduced statistical precision in these analyses. Finally, the movement restrictions and social distancing imposed during the COVID-19 pandemic period, which coincided with this study, may have impacted upon healthcare access and standard of care.

## CONCLUSIONS

In this real-world, prospective, non-interventional study in people with T2D, initiating or switching to IDegAsp was associated with improved glycaemic control, lower basal insulin dose in insulin-experienced participants, and significantly lower rates of non-severe (overall and nocturnal) and severe hypoglycaemia in comparison with baseline.

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***Data Availability.*** The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.



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