Insulin degludec/insulin aspart versus biphasic insulin aspart 30 twice daily in insulin-experienced Japanese subjects with uncontrolled type 2 diabetes: Subgroup analysis of a Pan-Asian, treat-to-target Phase 3 Trial

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Abstract

Background: The present study was a subgroup analysis of a Pan-Asian Phase 3 open-label randomized treat-to-target trial evaluating insulin degludec/insulin aspart (IDegAsp) and biphasic insulin aspart 30 (BIAsp 30) in Japanese subjects with type 2 diabetes inadequately controlled on insulin.

Methods: Eligible subjects (n = 178) were randomized (2: 1) to twice-daily (b.i.d.) IDegAsp or BIAsp 30 with or without metformin for 26 weeks, titrated to a blood glucose target of between 3.9 and < 5.0 mmol/L. Changes in HbA1c, the proportion of responders reaching the HbA1c target, and changes in fasting plasma glucose, nine-point self-monitored plasma glucose profiles, and body weight were assessed.

Results: At 26 weeks, the decrease in HbA1c was similar in both groups. Fasting plasma glucose was lower with IDegAsp than BIAsp 30 (estimated treatment difference -1.50 mmol/L; 95 % confidence interval [-1.98, -1.01]). Overall confirmed hypoglycemia rates were similar; the nocturnal confirmed hypoglycemia rate was lower with IDegAsp than BIAsp 30 (estimated rate ratio 0.44; 95 % CI 0.20, 0.99). No severe hypoglycemic episodes were reported.

Conclusions: The results indicate that IDegAsp b.i.d. improves glycemic control and, compared with BIAsp 30, lowers the rate of nocturnal confirmed hypoglycemia.

Keywords: glycemic control, insulin degludec/insulin aspart, nocturnal hypoglycemia.

Introduction

In Asian populations, type 2 diabetes (T2D) develops at a younger age and at a lower body mass index (BMI) than is typical in Caucasian patients. In conjunction with basal insulin, additional prandial control of blood glucose through mealtime insulin is often considered.

To date, coformulation of prandial and basal insulin analogs has not been feasible because of incompatibility between the two types of insulin. However, the unique properties of insulin degludec (IDeg), a basal insulin with an ultralong pharmacodynamic profile and less variability in glucose-lowering effect than insulin glargine, allows stable coformulation with rapid-acting insulin
aspart (IASp): insulin degludec/insulin aspart (IDeg/Asp 70%/30% v/v). The IDegAsp coformulation retains the distinct properties of both components, providing complete 24-h basal insulin coverage with prandial control for mealtimes in a single injection.

In a recent Phase 3 Pan-Asian clinical trial in insulin-experienced subjects with uncontrolled T2D, IDegAsp administered twice daily (b.i.d.) improved glycemic control and provided greater reduction in fasting plasma glucose (FPG) levels with a similar rate of overall confirmed hypoglycemia and a numerically lower rate of nocturnal hypoglycemia compared with biphasic insulin aspart 30/70 (BIAsp 30).9 In this paper, we present a subgroup analysis of efficacy and safety data of IDegAsp and BIAsp 30 in Japanese subjects from the Pan-Asian trial.

Methods
Study design and procedures
Ethical considerations, design, methodology, and study procedures of the 26-week Phase 3, randomized, open-label, treat-to-target Pan-Asian trial (BOOST: Intensify All) have been reported previously.9 Following written consent, eligible subjects were randomized 2:1 to receive b.i.d. injections of either IDegAsp (70% IDeg and 30% IAsp; Novo Nordisk, Copenhagen, Denmark; 100 U/mL) or BIAsp 30 (NovoMix 30; Novo Nordisk; 100 U/mL), with or without metformin. Trial insulins were dose titrated according to a pre-breakfast and pre-main evening meal self-monitored plasma glucose (SMPG) target of between 3.9 and <5.0 mmol/L. The blood glucose meters used plasma-calibrated test strips. Therefore, all measurements performed with capillary blood were automatically calibrated to plasma-equivalent glucose values, which were shown on the display and recorded.

Study population
All Japanese subjects from the parent trial, which analyzed data of patients from Hong Kong, Japan, Malaysia, South Korea, and Taiwan, were included in the present analysis.9

Assessments
The primary endpoint was change from baseline HbA1c after 26 weeks’ treatment. Secondary endpoints included the proportion of responders to HbA1c targets <7.0%, as recommended by the American Diabetes Association (ADA),10 the proportion reaching this target without confirmed hypoglycemia during the last 12 weeks of treatment, change from baseline in fasting plasma glucose (FPG), nine-point SMPG profiles, and body weight.

Safety variables included adverse events, insulin doses, hypoglycemic episodes, clinical assessments, and laboratory tests, including insulin antibodies (IDeg-specific, IAsp-specific and antibodies cross-reacting with human insulin), as reported previously.9 Confirmed hypoglycemic episodes were those classified as “severe” according to the ADA10 or confirmed by plasma glucose measurements <3.1 mmol/L. Hypoglycemia was classified as “nocturnal” if onset was between 0001 and 0559 hours.

Statistical analyses
The same statistical approaches were used for the present post hoc analysis as for the full trial population (see the Statistical Analyses section in the Supporting Information and Kaneko et al.9).

Results
Patient characteristics
Of the 208 subjects screened, 178 were randomized to receive either IDegAsp (n = 118) or BIAsp 30 (n = 60; Fig. 1); 109 patients in the IDegAsp group and 55 in the BIAsp 30 group completed 26 weeks’ treatment. The rates of discontinuation were comparable between the treatment groups, with treatment discontinuation in 8.3% and 7.6% of participants receiving BIAsp 30 and IDegAsp, respectively. The main reasons for discontinuation for both treatments were

Figure 1 Trial flow diagram (Japanese patient subgroup). BIAsp 30, biphasic insulin aspart 30/70; IDegAsp, insulin degludec/insulin aspart.
adverse events, which were unlikely related to the trial treatments as assessed by the trial investigator. Baseline characteristics were comparable between groups (see Table S1, available as Supplementary Material to this paper).

Glycemic control
By Week 26, mean HbA1c had decreased in both groups (Fig. 2a) by a similar level: −1.40 percentage points with IDegAsp and −1.29 percentage points with BIAsp 30. The estimated mean treatment difference (ETD) IDegAsp–BIAsp 30 was −0.13 percentage points (95% confidence interval [CI] −0.31, 0.04). In addition, HbA1c < 7.0% was achieved by Week 26 by 52.5% and 48.3% of subjects in the IDegAsp and BIAsp 30 groups, respectively (odds ratio [OR] IDegAsp/BIAsp 30 1.20; 95% CI 0.59, 2.46). In the last 12 weeks, 21.2% and 14.0% of subjects achieved HbA1c < 7.0% without confirmed hypoglycemia in the IDegAsp and BIAsp 30 groups, respectively (OR 1.63; 95% CI 0.66, 4.06).

Fasting plasma glucose
Fasting plasma glucose was improved to a greater extent by IDegAsp than BIAsp 30 (ETD −1.50 mmol/L; 95% CI −1.98, −1.01; Fig. 2b).

Nine-point SMPG
Nine-point SMPG profiles were similar between the IDegAsp and BIAsp 30 groups at baseline (Fig. 3). Overall, nine-point SMPG profiles were lower after 26 weeks with IDegAsp than BIAsp 30 (ETD BIAsp 30–BIAsp 30–0.62 mmol/L; 95% CI −1.08, −0.17), with significant differences at five time points (Fig. 3).

Body weight
Body weight increase from baseline to Week 26 was similar in both groups (1.44 and 1.57 kg in the IDegAsp and BIAsp 30 groups, respectively; ETD BIAsp 30–BIAsp 30–0.14 kg, 95% CI −1.01, 0.74).

Insulin dose
Mean (±SD) daily insulin dose at Week 1 in the IDegAsp and BIAsp 30 groups was 0.42 ± 0.24 and 0.36 ± 0.19 U/kg, respectively. After 26 weeks’ treatment, the mean daily insulin dose in the IDegAsp and BIAsp 30 groups was 0.58 ± 0.33 and 0.65 ± 0.32 U/kg, respectively (mean ratio IDegAsp/BIAsp 30: 0.89). The morning/evening dose split after 26 weeks was 55%/45% for IDegAsp and 51%/49% for BIAsp 30.

Hypoglycemic episodes
Confirmed hypoglycemia was reported by 74.6% and 68.3% of subjects in the IDegAsp and BIAsp 30 groups, respectively, with a corresponding 9.1 and 9.5 episodes/patient-years of exposure (PYE). The rate of nocturnal confirmed hypoglycemia was significantly lower with IDegAsp than BIAsp 30 (0.77 vs 1.62 episodes/PYE; estimated rate ratio BIAsp 30/BIAsp 30: 0.44; 95% CI 0.20, 0.99). No severe hypoglycemic episodes were reported.

Adverse events
The incidence of adverse events was similar with IDegAsp (75.4%) and BIAsp 30 (81.7%). Most adverse events were mild to moderate (Table S2). One subject in the IDegAsp group died of interstitial lung disease, which was considered unlikely to be related to the study treatment. Only one subject reported an injection-site reaction (in the IDegAsp group). There were no clinically relevant changes in clinical or laboratory safety parameters (data not shown). The mean level of insulin antibodies cross-reacting...
with human insulin increased slightly from baseline with BIAsp 30, but remained similar with IDegAsp. IDeg- and IAsp-specific antibody levels remained low throughout the treatment period (data not shown).

Discussion
The present post hoc analysis of Japanese subjects enrolled in a Phase 3 Pan-Asian trial in patients with T2D supports the efficacy and safety of IDegAsp and BIAsp 30 administered b.i.d. in patients inadequately controlled with basal, premix or self-mixed insulin, with or without metformin. Baseline characteristics were similar between the Japanese subgroup and the full trial population, although there was a higher male: female ratio in the Japanese subgroup compared with the overall study population (IDegAsp 62% / 38% vs 54% / 46%; BIAsp 30 68% / 32% vs 56% / 44%, respectively). In the present analysis, IDegAsp improved overall glycemic control over time, which is reflected in comparable HbA1c levels with those seen after BIAsp 30 treatment, as expected in a trial with a treat-to-target design and in line with observations in the full trial population. The reduction in HbA1c with IDegAsp relative to BIAsp 30 was numerically greater than in the overall trial population (ETD Japanese subjects: −0.13 percentage points; overall trial population: 0.05 percentage points). The present subgroup analysis also demonstrated that IDegAsp improved FPG control to a greater extent than BIAsp 30, as would be expected from the flat pharmacodynamic profile of IDeg at steady state, providing stable 24-h control of FPG. Despite a lower FPG level, IDegAsp treatment was associated with a statistically significant lower rate of nocturnal confirmed hypoglycemia compared with BIAsp 30, which is likely attributable to the long-acting effect and the more stable pharmacodynamics of IDeg, compared with the more fluctuating glucose-lowering effect of the basal component in BIAsp 30, which may increase the risk of nocturnal hypoglycemia. Similar findings were reported in the full population of the Pan-Asian trial and another recent Phase 3 clinical trial of insulin-experienced patients with T2D inadequately controlled on pre- or self-mixed insulin regimens.

In the subgroup analysis, rates of overall confirmed hypoglycemia were similar in both groups and no episodes of severe hypoglycemia were reported. Low rates of hypoglycemia have also been reported in a meta-analysis comparing IDegAsp with BIAsp 30 in adults with T2D who achieved an HbA1c target of <7%. The frequency, type, and severity of non-hypoglycemic adverse events in Japanese subjects with T2D is consistent with that reported in other IDegAsp clinical trials.

For Japanese patients with inadequately controlled T2D, IDegAsp b.i.d. offers 24-h basal insulin coverage combined with prandial control and a significantly lower rate of nocturnal confirmed hypoglycemia than BIAsp 30 b.i.d. The results of the present subgroup analysis indicate that IDegAsp may be a convenient and efficacious treatment for Japanese patients with T2D requiring mealtime insulin intensification.

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Supporting information
Additional Supporting Information may be found in the online version of this article:
Table S1 Baseline characteristics of the randomized Japanese patient subgroup.
Table S2 Adverse events reported in the Japanese patient subgroup.