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ORIGINAL ARTICLE

Insulin degludec versus insulin glargine, both once daily as add-on to existing orally administered antidiabetic drugs in insulin-naive Japanese patients with uncontrolled type 2 diabetes: subgroup analysis of a pan-Asian, treat-to-target phase 3 trial

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Abstract Insulin degludec (IDeg) is a novel basal insulin analogue with an ultralong duration of action that provides flat and stable reductions in blood glucose. The BEGIN ONCE ASIA trial was a phase 3 pan-Asian study examining the efficacy and safety of IDeg once daily (OD) versus insulin glargine (IGlar) OD in insulin-naive patients with type 2 diabetes (T2D). In this multinational, 26-week, open-label, treat-to-target trial, participants were randomised (2:1) to IDeg OD or IGlar OD, administered with one or more antidiabetic drugs (OAD) per os. Here we report the results from a post hoc analysis of Japanese patients enrolled in the trial [$n = 133$; 63.2 % male; mean age 61.0 years; mean body mass index 24.1 kg/m^2; mean glycosylated haemoglobin (HbA_{1c}) 8.5 %]. After 26 weeks, mean HbA_{1c} levels were similar between the two groups [estimated mean treatment difference 0.11 %; 95 % confidence interval (CI) −0.09, 0.31]. Confirmed hypoglycaemia was reported in 53.4 and 61.4 % of patients in the IDeg OD and IGlar OD groups [rate ratio (IDeg/IGlar) 0.87; 95 % CI 0.51, 1.48]. Confirmed nocturnal hypoglycaemia was reported in 17.0 and 22.7 % of patients in the IDeg OD and IGlar OD groups, respectively [rate ratio (IDeg/IGlar) 0.50; 95 % CI 0.19, 1.32]. Adverse event rates were similar between treatment groups. Initiating insulin treatment with IDeg OD in Japanese patients with T2D, inadequately maintained on OADs and requiring treatment intensification, provided effective glycaemic control with low rates of confirmed and nocturnal confirmed hypoglycaemia.

Keywords Insulin degludec · Insulin-naive · Japan · Type 2 diabetes · Phase 3 · Once-daily

Introduction

Type 2 diabetes (T2D) is a progressive disorder characterised by both insulin resistance of peripheral tissues and deficiencies in insulin secretion due to deterioration of beta-cell function [1]. The relative impact of insulin resistance and reduced insulin secretion differs according to the ethnicity of the patient population [2, 3]. Impaired insulin secretion makes an early contribution to disease progression in Japanese patients [4]. Other characteristics also differ between Asian and Caucasian patients with T2D. In particular, Asian patients are generally younger, have a lower body mass index (BMI) and have narrower waist circumference measurements at onset than Caucasian patients [5].

Initial treatment usually involves antidiabetic drugs (OADs) per os and takes into account underlying ethnic differences. Traditionally, in most Asian countries, sulphonylureas (SUs) are the most widely used OADs; in those countries where insulin resistance is more common, metformin is the preferred initial therapy. With disease progression, additional treatments are required, often including injectable therapies such as insulin or glucagon-like peptide-1 (GLP-1) receptor agonists [6].

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Insulin degludec (IDeg) is a novel, basal insulin analogue with an ultralong duration of action and a flat pharmacodynamic profile that leads to stable reduction in blood glucose at steady state [7], resulting in four times less variability in glucose-lowering effect than insulin glargine (IGlar) [8]. Recent studies have confirmed that IDeg can provide similar glycaemic control to IGlar but with a lower risk of hypoglycaemia, including nocturnal confirmed hypoglycaemia, in insulin-naive patients with T2D inadequately controlled on OADs [9, 10].

The results from a phase 3 pan-Asian trial of patients with T2D previously uncontrolled on OADs have already been described [11]. This short report describes the efficacy and safety of IDeg versus IGlar administered once daily (OD) in a subpopulation of Japanese patients from the same study.

Materials and methods

Study design/procedures

Design, methodology and study procedures of the phase 3 pan-Asian trial (BEGIN ONCE ASIA) have been reported in full previously [11]. Briefly, the study was a 26-week, open-label, randomised, confirmatory, multicentre, multinational trial, with a treat-to-target design in line with current US Food and Drug Administration (FDA) recommendations for the evaluation of novel insulin preparations [12]. Eligible patients were randomised 2:1 using an interactive voice/Web system to receive either IDeg (100 U/mL, 3 mL FlexPen®; Novo Nordisk, Bagsværd, Denmark) dosed OD in the evening (start of main evening meal to bedtime), or IGlar (Lantus®; 100 U/mL, 3 mL SoloSTAR®; Sanofi, Paris, France) given according to approved local product labelling (in Japan: OD before breakfast or before bedtime). IDeg OD and IGlar OD were each administered subcutaneously with a recommended starting dose of 10 U. Both trial insulins were dose-titrated according to plasma glucose values converted from self-monitoring of blood glucose (SMBG) before breakfast, using the mean pre-breakfast blood glucose value from the three preceding consecutive days' measurements. Insulin doses were titrated individually once a week throughout the trial to a target SMBG of 70 to <90 mg/dL (3.9 to <5.0 mmol/L). Study participants were allowed to continue with their existing OADs without any change in dose or regimen, with the exception of dipeptidyl peptidase-4 (DPP-4) inhibitors, which were discontinued.

Study population: Japanese subpopulation

All male and female Japanese patients aged ≥20 years, with a clinical diagnosis of T2D for ≥6 months, were included in this subpopulation analysis of the pan-Asian phase 3 trial. Eligibility and exclusion criteria were reported previously for the full trial population [11].

Assessments

The primary efficacy endpoint was change from baseline in glycosylated haemoglobin (HbA_{1c}) after 26 weeks of treatment. Secondary efficacy endpoints included the proportion of indivudials achieving an HbA_{1c} target level of <7.0 % [1], the proportion reaching this target without confirmed hypoglycaemia, change from baseline in fasting plasma glucose (FPG) after 26 weeks and mean 9-point SMBG profile after 26 weeks. Safety assessments included adverse events (AEs), confirmed hypoglycaemic episodes (overall and nocturnal events), vital signs, insulin dose and body weight. Confirmed hypoglycaemic episodes were those classified as severe according to American Diabetes Association guidelines [13] or confirmed by a plasma glucose measurement of <56 mg/dL (<3.1 mmol/L). Hypoglycaemia was considered nocturnal if the time of onset was between 00.01 and 05.59 h. Additional safety assessments included physical examination, funduscopy/fundus photography, electrocardiogram, standard biochemical and haematology values and assessment of the development of insulin antibodies with respect to any cross-reaction between IDeg or IGlar and human insulin.

Statistical analyses

Analyses of the Japanese subpopulation were performed post hoc. In general, statistical approaches used were the same as for the preplanned analyses of the full trial population. The primary efficacy endpoint (change from baseline in HbA_{1c} after 26 weeks of treatment) was analysed using an analysis of variance (ANOVA) method, with treatment, antidiabetic therapy at screening and sex as fixed factors and age and baseline HbA_{1c} as covariates. Missing values (including intermittent missing values) were imputed using the last observation carried forward (LOCF) method. Secondary responder endpoints were analysed separately with a logistic regression model using the same fixed factors and covariates as the ANOVA model. Other secondary efficacy endpoints (e.g. change from baseline in FPG, body weight and mean 9-point SMBG profiles) were also analysed separately using the ANOVA method in a similar manner to the primary endpoint but with the associated baseline value as a covariate. The number of hypoglycaemic episodes was analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent as the offset.

The model included treatment, antidiabetic therapy at screening and sex as fixed factors, and age as a covariate. Insulin dose was summarised descriptively according to regimen as dose in units and units/kilogrammes. Other safety endpoints were analysed using descriptive statistics.

Results

Patient characteristics

Of 145 Japanese patients screened, 133 were randomised 2:1 to receive either IDeg OD ($n = 89$) or IGlar OD ($n = 44$) (Fig. 1). A total of 84 patients in the IDeg OD group and 44 in the IGlar OD group completed 26 weeks of study treatment. Baseline characteristics were generally comparable between groups (Table 1), except that the IDeg OD group had a greater proportion of male patients and a lower mean body weight compared with the IGlar OD group.

Glycaemic control

Mean HbA_{1c} levels at 26 weeks were similar between treatment groups (Fig. 2). The estimated change from baseline was −1.52 percentage points in the IDeg OD group and −1.63 percentage points in the IGlar OD group. The estimated mean treatment difference (ETD; IDeg OD–IGlar OD) was 0.11 percentage points; 95 % CI −0.09, 0.31.

The proportion of patients who attained the HbA_{1c} target of <7.0 % at week 26 was numerically lower with IDeg OD compared with IGlar OD, but did not reach statistical significance [42.7 and 56.8 %, respectively; estimated odds ratio (OR) 0.60; 95 % CI 0.27, 1.33]. No statistically significant difference was observed between the percentage of patients who achieved the HbA_{1c} target of <7.0 % without confirmed hypoglycaemia with IDeg OD and IGlar OD [30.6 and 34.1 %, respectively; OR 0.98; 95 % CI 0.41, 2.31]. Mean decreases from baseline in FPG after 26 weeks were similar for both treatment arms (Fig. 3). The ETD (IDeg OD–IGlar OD) was −5.30 mg/dL; 95 % CI −14.28, 3.68 (−0.29 mmol/L; 95 % CI −0.79, 0.20).

9-point SMBG

The 9-point SMBG profiles for IDeg OD and IGlar OD were similar at baseline and at Week 26, except for the lower plasma glucose level of IDeg OD compared with IGlar OD before breakfast on two consecutive days (Fig. 4). The ETD (IDeg OD–IGlar OD) was −11.40 mg/dL; 95 % CI −21.55, −1.24 (−0.63 mmol/L; 95 % CI −1.20, −0.07). At Week 26, the means of 9-point SMBG profiles for IDeg OD and IGlar OD were 150.0 mg/dL (8.3 mmol/L) and 152.8 mg/dL (8.5 mmol/L), respectively. The estimated mean treatment difference (ETD)

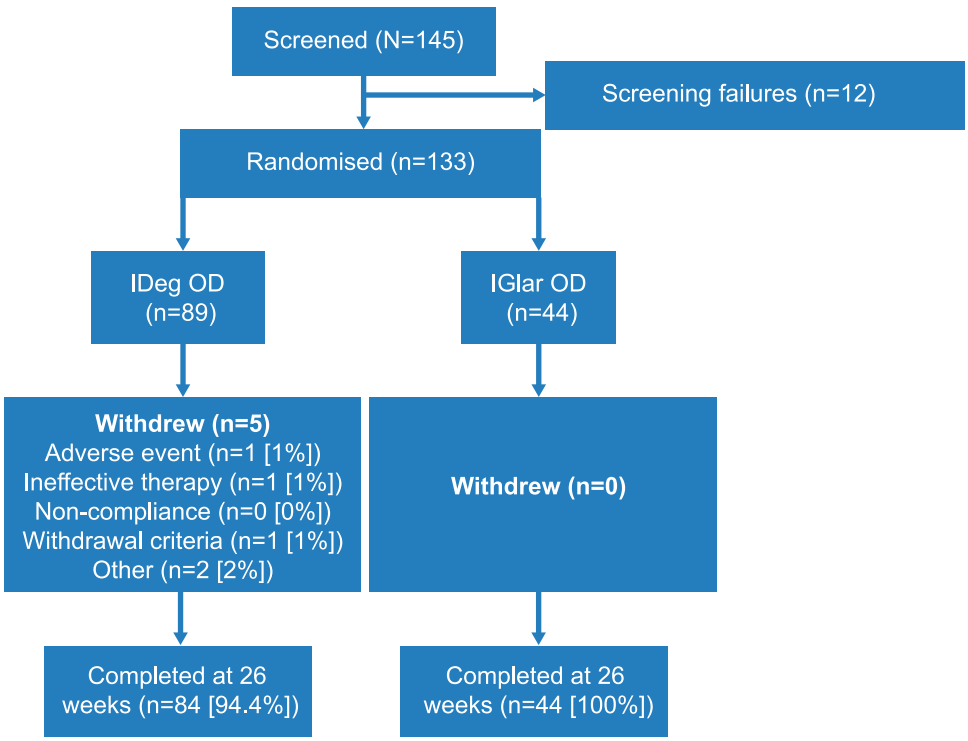

Fig. 1 Trial flow diagram (Japanese subpopulation). *IDeg* insulin degludec, *IGlar* insulin glargine, *OD* once daily

Table 1 Characteristics of the randomised Japanese subpopulation

Characteristic	IDeg OD ($n = 89$)	IGlar OD ($n = 44$)
Male gender (%)	67	55
Age (years)	61.1 (10.2)	60.6 (10.8)
Weight (kg)	62.8 (11.2)	66.5 (12.1)
BMI (kg/m^2)	23.5 (3.2)	25.4 (3.2)
Duration of diabetes (years)	12.8 (6.7)	11.9 (7.3)
HbA_{1c} (%)	8.6 (0.7)	8.4 (0.7)
FPG (mg/dL)/FPG (mmol/L)	164.1 (37.9)/9.1 (2.1)	169.7 (31.3)/9.4 (1.7)
Antidiabetic therapy at screening (%)		
1 OAD	24.7	22.7
2 OADs	51.7	52.3
≥3 OADs	23.6	25.0

Data are mean (SD) unless otherwise stated

IDeg insulin degludec, *IGlar* insulin glargine, *BMI* body mass index, *FPG* fasting plasma glucose level, *HbA_{1c}* glycosylated haemoglobin, *OD* once daily, *OAD* antidiabetic drugs orally

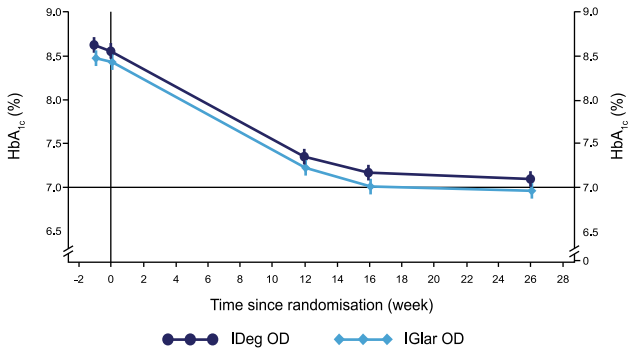

Fig. 2 Mean HbA_{1c} levels over 26 weeks of treatment with once-daily insulin degludec or insulin glargine in the Japanese subpopulation. FAS, LOCF imputed data. *Error bars* indicate ± standard error of the mean. *FAS* full analysis set, *HbA_{1c}* glycosylated haemoglobin, *IDeg* insulin degludec, *IGlar* insulin glargine, *LOCF* last observation carried forward, *OD* once daily

(IDeg OD–IGlar OD) was −0.26 mg/dL; 95 % CI −11.28, 10.76 (−0.01 mmol/L; 95 % CI −0.63, 0.60).

Body weight

Similarly, increases in body weight were seen from baseline to week 26 in both treatment groups, with a smaller numerical increase observed for IDeg OD (estimated change from baseline: IDeg OD, 1.65 kg; IGlar OD, 1.75 kg; ETD −0.10; 95 % CI −0.91, 0.72).

Insulin dose

At 26 weeks, the mean dose with IDeg OD (17 U) was lower than with IGlar OD (23 U) [dose ratio (IDeg/IGlar) 0.75]. This equated to 0.26 and 0.34 U/kg for IDeg OD and IGlar OD, respectively (dose ratio 0.77).

Hypoglycaemic events

Over 26 weeks, confirmed hypoglycaemia was reported in 53.4 and 61.4 % of patients in the IDeg OD and IGlar OD groups, respectively. The rates of overall confirmed hypoglycaemia with IDeg OD and IGlar OD were 355 and 447 events per 100 patient-years of exposure (PYE), respectively [treatment ratio (IDeg/IGlar) 0.87; 95 % CI 0.51, 1.48] (Fig. 5).

Over the same time period, confirmed nocturnal hypoglycaemia was reported in 17.0 and 22.7 % of patients in the IDeg OD and IGlar OD groups, respectively, and the rates of confirmed nocturnal hypoglycaemia were 59 and 128 events per 100 PYE, respectively [treatment ratio (IDeg/IGlar) 0.50; 95 % CI 0.19, 1.32]. No severe hypoglycaemic events were reported in either treatment group over the duration of the study.

Adverse events

Treatment-emergent AEs occurred in 71.6 and 65.9 % of patients in the IDeg OD and IGlar OD groups, respectively. The most frequent AEs reported in ≥5 % of patients in the two groups were nasopharyngitis (54 vs 78 events per 100 PYE, respectively), diabetic retinopathy (16 vs 18 events per 100 PYE, respectively) and back pain (5 vs 14 events per 100 PYE, respectively). Serious AEs were reported in four patients (4.5 %) in the IDeg OD arm. One patient in the IDeg OD treatment arm died due to drowning during the trial. The last recorded FPG levels did not suggest that drowning was the result of hypoglycaemia; however, it was recognised that the event was possibly related to the study medication. Injection-site reactions were reported by two patients (2.3 %) in the IDeg OD group and three (6.8 %) in the IGlar OD group. There were no clinically relevant

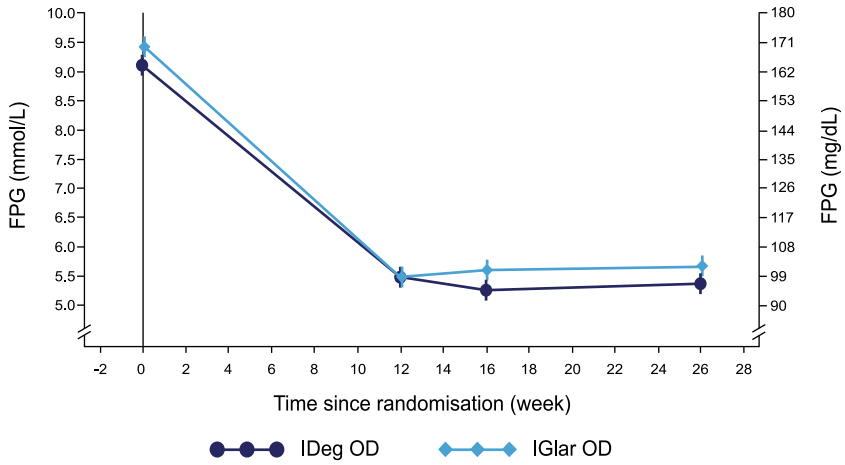

Fig. 3 Mean FPG levels over 26 weeks of treatment with once-daily insulin degludec or insulin glargine in the Japanese subpopulation. FAS, LOCF imputed data. *Error bars* indicate ± standard error of mean. *FAS* full analysis set, *FPG* fasting plasma glucose, *IDeg* insulin degludec, *IGlar* insulin glargine, *LOCF* last observation carried forward, *OD* once daily

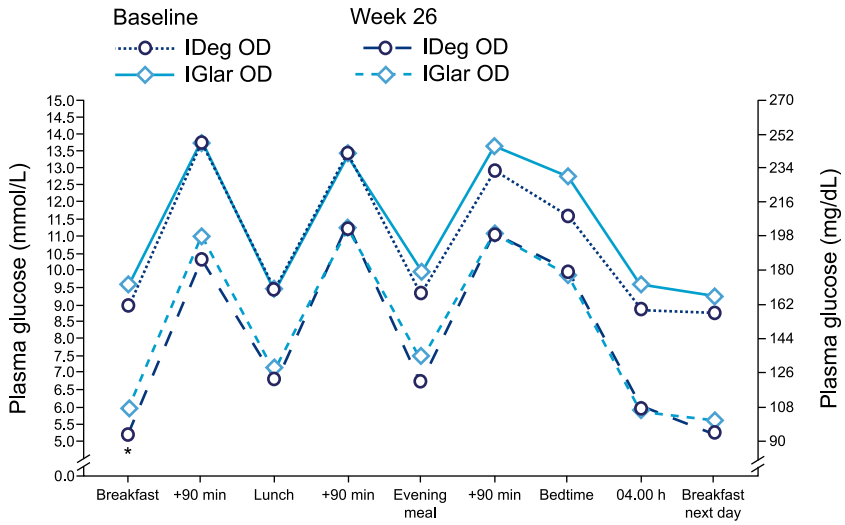

Fig. 4 Nine-point self-measured plasma glucose profiles at baseline and after 26 weeks of treatment with once daily insulin degludec or insulin glargine in the Japanese subpopulation. *Asterisk* denotes statistically significant difference between treatments at week 26. FAS, LOCF imputed data. *FAS* full analysis set, *IDeg* insulin degludec, *IGlar* insulin glargine, *LOCF* last observation carried forward, *OD* once daily

differences between IDeg OD and IGlar OD in other clinical or laboratory safety parameters.

Discussion

This study was a subpopulation analysis of Japanese patients from a phase 3 pan-Asian trial to confirm the efficacy and safety of IDeg OD in patients whose T2D was inadequately controlled with OADs and who required more intensive treatment. Efficacy and safety of IDeg OD in the Japanese subpopulation was consistent with results in the total population [11]. Of note is that the full population analysis required 426 randomised patients to be powered to 90 % to meet the primary endpoint. The Japanese post hoc analysis, however, randomised only 133 patients. Therefore, even large changes in hypoglycaemia rates over the 26-week study period did not reach statistical significance.

Baseline characteristics were similar between the Japanese subpopulation and the total patient population, with two exceptions. Firstly, gender distribution was equal between treatment arms in the total patient population, whereas there was a higher proportion of male patients in the IDeg OD arm of the Japanese subpopulation compared with IGlar OD. Secondly, baseline FPG levels were slightly higher in both treatment arms in the Japanese subpopulation compared with the total patient population.

IDeg OD and IGlar OD reduced HbA_{1c} levels to a similar extent over 26 weeks, consistent with results from the total patient population [11]. The number of patients who achieved the HbA_{1c} target of <7.0 % without confirmed hypoglycaemia was comparable with IDeg OD and IGlar OD. Mean reductions from baseline in FPG were also similar between treatment arms for both the total patient population and the Japanese subpopulation.

The rate and incidence of overall confirmed hypoglycaemia was lower with IDeg OD compared with IGlar OD in the Japanese subpopulation but did not reach statistical significance; again, this was consistent with the total

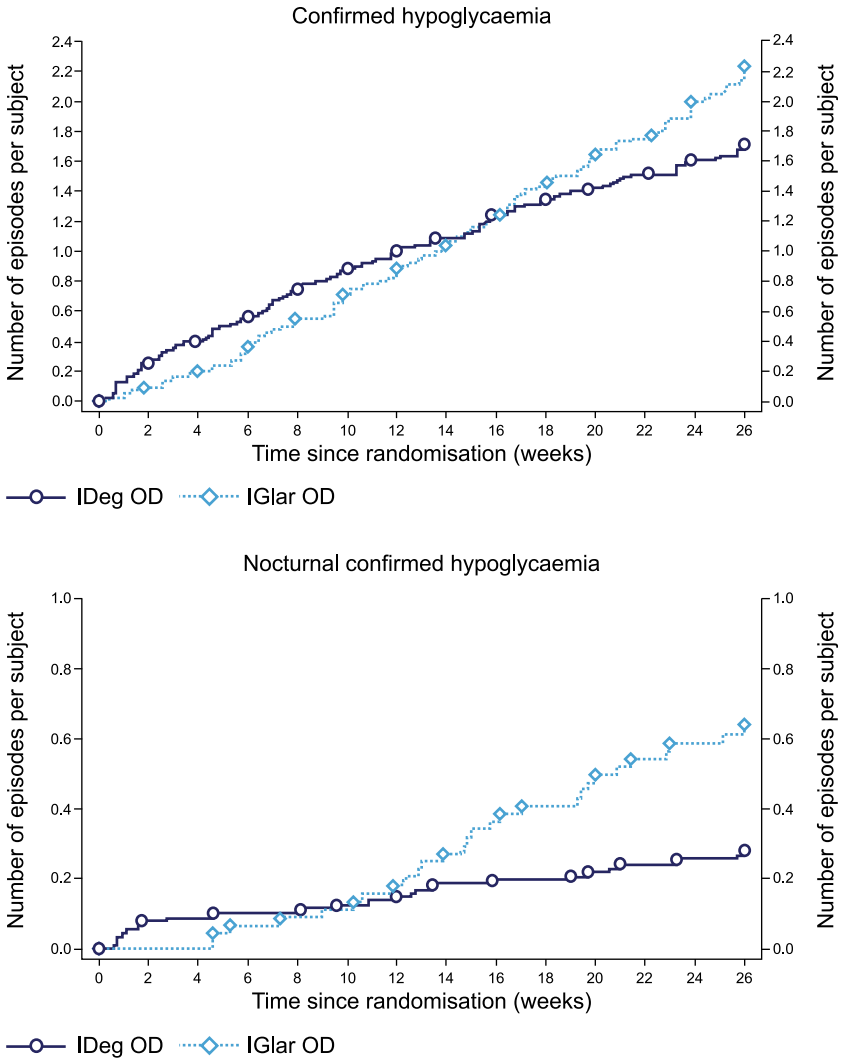

Fig. 5 Confirmed and nocturnal confirmed hypoglycaemic episodes over 26 weeks of treatment with once-daily insulin degludec or insulin glargine in the Japanese subpopulation. Nocturnal: 00:01–05:59 h (inclusive). *IDeg* insulin degludec, *IGlar* insuline glargine, *OD* once daily

population [11]. Although there was a trend towards a higher rate of hypoglycaemia with IDeg in the first weeks following treatment initiation, this was reversed by the end of the study. The small difference in rate of hypoglycaemia in the first 16 weeks may reflect the need for insulin-naive individuals to adjust to their new treatment regimen or could possibly be attributed to heightened awareness/report bias towards the investigational drug. Similar results were also observed in the BEGIN Once Long randomised, phase 3, treat-to-target, multinational trial with insulin-naive T2D patients [9, 10] in which IDeg OD was compared with IGlar OD (both given with metformin). In the BEGIN Once Long trial, the rate for confirmed hypoglycaemia was lower with IDeg compared with IGlar, which was not statistically significant. This lack of significance may likely be attributed to the low power of the study. In comparison, the difference in the rate of confirmed nocturnal hypoglycaemia reached statistical significance in the BEGIN Once Long trial, such that fewer episodes of confirmed nocturnal hypoglycaemia were observed with IDeg OD compared with IGlar OD [9, 10].

The AE profile seen among patients in each treatment arm was similar between the Japanese subpopulation and the total population.

In conclusion, the results of the subanalysis reported here are similar to those observed for the full trial population, indicating that results can be extrapolated to this subgroup. Data presented here suggest that initiating insulin treatment with IDeg OD in Japanese patients with T2D, inadequately maintained on OADs and requiring treatment intensification provided effective glycaemic control with few overall confirmed and nocturnal confirmed hypoglycaemic episodes compared with IGlar OD. Therefore, treatment with IDeg OD may be a suitable treatment option for insulin-naive Japanese patients with inadequately controlled T2D.

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Compliance with ethical standards

Conflict of interest T. Osonoi received honoraria for provision of consultation or manuscripts from Novo Nordisk, Astellas, Takeda Pharmaceutical, Sanwa Kagaku Kenkyusho, Mitsubishi Tanabe Pharma and Kowa Pharmaceuticals. He also received clinical research grants from Novo Nordisk, Sanwa Kagaku Kenkyusho, Mitsubishi Tanabe Pharma, Fujiflim Pharma, Eli Lilly Japan, Abbvie, Kowa Pharmaceuticals, Taisho Pharmaceuticals, GSK and Sumitomo Dainippon Pharma. Y. Onishi received honoraria from AstraZeneca. T. Nishida is an employee of Novo Nordisk. J. Hyllested-Winge is an employee of and shareholder in Novo Nordisk. Y. Iwamoto has received honoraria for participation on advisory panels from Novo Nordisk.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1964 and later revision. Informed consent or substitute for it was obtained from all patients for study inclusion.

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