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Comparison of insulin degludec with insulin detemir in type 1 diabetes: a 1-year treat-to-target trial

The long-term safety and tolerability of insulin degludec (IDeg) was compared with that of insulin detemir (IDet), as basal treatment in participants with type 1 diabetes mellitus (T1DM). In the present multinational, 26-week core + 26-week extension, controlled, open-label, parallel-group trial, adults with T1DM were randomized to IDeg or IDet as basal insulin treatment combined with meal-time bolus insulin aspart. IDeg was administered once daily, whilst IDet was administered once or twice daily depending on patients' glycaemic control. After 1 year, IDeg provided a 33% lower rate of nocturnal hypoglycaemia compared with IDet: estimated rate ratio (IDeg : IDet) 0.67 [95% confidence interval (CI) 0.51; 0.88]; $p < 0.05$. IDeg improved glycated haemoglobin after 1 year of treatment, similarly to IDet, but IDeg also provided a significantly greater reduction in fasting plasma glucose compared with IDet: estimated difference (IDeg − IDet) −1.11 (95% CI −1.83; −0.40) mmol/l; $p < 0.05$. The present study confirmed the long-term safety and tolerability profile of IDeg in patients with T1DM. IDeg provided a lower risk of nocturnal confirmed hypoglycaemia than IDet.
Keywords: basal-bolus, hypoglycaemia, insulin aspart, insulin degludec, insulin detemir, insulin therapy, type 1 diabetes mellitus

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Introduction

Insulin degludec (IDeg) is a basal insulin with a unique mode of protraction that provides a consistent, flat plasma glucose-lowering profile with low variability and an ultra-long duration of action in a once-daily injection [1–3]. In a 26-week randomized, open-label, treat-to-target, non-inferiority trial involving participants with type 1 diabetes mellitus (T1DM), the efficacy and safety of IDeg were compared with that of insulin detemir (IDet) as part of a basal-bolus treatment regimen. Non-inferiority was confirmed for IDeg versus IDet. IDeg effectively improved long-term glycaemic control in participants, with a lower risk of nocturnal confirmed hypoglycaemia than that associated with IDet [4]. The objective of the present extension study was to compare the long-term safety and tolerability of IDeg with that of IDet for 1 year of treatment.

Methods

The study design has been described previously [4]. The core trial was a 26-week randomized, controlled, open-label, parallel-group, non-inferiority trial in which 456 patients with T1DM were randomized (2 : 1) to IDeg (n = 303) or IDet (n = 153). Patients who completed the core trial and provided informed consent entered the 26-week extension trial, continuing on their previous treatment regimen. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines [5,6]. Basal insulin doses were administered once daily in the evening (from start of main evening meal to bedtime). In the IDet treatment arm, a second daily dose of basal insulin could be added if there was inadequate glycaemic control after 8 weeks of treatment. The criteria for adding an additional dose (all of which had to be fulfilled) were: lack of improvement in glycaemic control [for patients with baseline glycated haemoglobin (HbA1c) <8.0%, any deterioration in HbA1c; for patients with baseline HbA1c of 8.0–10.0% (both inclusive), improvement in HbA1c of <0.5 percentage point]; mean pre-dinner plasma glucose >6.0 mmol/l (108 mg/dl); and no diagnosis of treatable concurrent disease causing hyperglycaemia. The second IDet dose was administered in the morning (before breakfast). At the start of the core trial, insulin doses were initiated in a 1 : 1 ratio with the patient's existing insulin regimen. All measurements performed with capillary blood were automatically calibrated to plasma-equivalent glucose values [self-monitored plasma glucose (SMPG)], using the plasma glucose meter and documented by the trial participant. Basal insulin was titrated to target pre-breakfast SMPG of 3.9–4.9 mmol/l based on the mean of pre-breakfast SMPG values of the preceding three consecutive days. Insulin aspart (IAsp) was administered immediately before breakfast, lunch and dinner, and an additional dose was permitted to cover an additional meal/snack. To assess the immunogenicity of IDeg and to minimize interference with antibody measurements, a 1-week washout period was scheduled at the end of treatment for both the 26-week core trial and the extension trial, during which all participants in both arms were switched to NPH insulin + meal-time IAsp.

Primary safety endpoints for the extension trial included adverse events, hypoglycaemia, immunogenicity, insulin dose and body weight. Confirmed hypoglycaemia was defined

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as plasma glucose <3.1 mmol/l, regardless of symptoms or severe episodes (requiring third-party assistance). Nocturnal episodes were episodes with onset between 00:01 and 05:59 hours inclusive. Safety endpoints were evaluated using the safety analysis set (SAS). The SAS included all subjects exposed to treatment in the core trial. Statistical analysis of hypoglycaemic episodes and body weight was carried out on the full analysis set (all randomized subjects in the core trial). The number of hypoglycaemic events 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 is considered treatment-emergent as offset. The model included treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. Efficacy variables assessed in the core and extension trials included HbA1c, laboratory-measured fasting plasma glucose (FPG) and nine-point SMPG. Safety and efficacy endpoints were summarized descriptively. Treatment differences in key continuous endpoints were evaluated using analysis of variance, with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and corresponding baseline value as covariates. Post-baseline missing values were imputed using the last observation carried forward method. Statistical analysis results include estimated mean treatment differences (or ratios) with their two-sided 95% confidence intervals (CIs) and p values (*post hoc*) for two-sided testing.

Results

In the core trial there were 283 (94%) IDeg and 138 (90%) IDet completers, of whom 248 patients in the IDeg arm and 122 in the IDet arm entered the extension trial. In the IDeg and IDet treatment arms, 242 (98%) and 115 patients (94%) completed the extension study period (Figure S1). In both treatment arms, baseline characteristics were similar (Table 1). Insulin regimen and daily insulin dose at screening are shown in Tables S1 and S2, respectively.

Safety

Confirmed hypoglycaemia was reported by 94.7 and 92.8% of subjects treated with IDeg and IDet, respectively (See Figure 1 for definitions of hypoglycaemia). Rates of overall confirmed hypoglycaemia were similar in both treatment arms, with 3778 and 3926 episodes per 100 patient-years of exposure (PYE) for IDeg and IDet, respectively [estimated rate ratio IDeg : IDet 0.95 (95% CI 0.78; 1.17)], and no significant difference between treatments (Figure 1A). The rate of nocturnal confirmed hypoglycaemia was 33% lower in the IDeg-treated group (338 episodes per 100 PYE) compared with IDet (481 episodes per 100 PYE) [estimated rate ratio (ERR) 0.67 (95% CI 0.51; 0.88); $p < 0.05$ (Figure 1B)]. There was no significant difference in the rate of severe hypoglycaemic episodes between IDeg and IDet [ERR 0.86 (95% CI 0.46; 1.62)]. Over the entire study period 82.4 and 77.6% of IDeg- and IDet-treated subjects reported adverse events, respectively. The rate of severe adverse events was 23 and 35 events per 100 PYE in the IDeg and IDet treatment groups, respectively. Immunogenicity of IDeg, assayed by IDeg-specific antibodies (median = 0.0% bound/total radioactivity) and antibodies cross-reacting between IDeg and human insulin (median = 4.0% bound/total radioactivity), was low throughout treatment. Mean daily basal insulin doses at end of trial were 0.36 ± 0.19 U/kg for IDeg and 0.44 ± 0.27 U/kg for IDet (Figure 1C). At end of trial, 36.8% of patients in the IDet group were administered basal insulin twice daily. Mean daily bolus insulin doses at end of trial were 0.55 ± 0.41 U/kg for IDeg and 0.63 ± 0.41 U/kg for IDet (data not shown). Body weight increased from baseline in both treatment arms, but the increase was greater in the IDeg compared with the IDet treatment arm: estimated difference 1.07 kg (95% CI 0.47; 1.67); $p < 0.05$.

Table 1. Baseline characteristics: full analysis set.

	IDeg once daily	IDet
n	302	153
Gender: % male	49.7	56.2
Age*, years	41.1 ± 14.9	41.7 ± 14.4
Racial group, n (%)		
White	133 (44.0)	70 (45.8)
Black or African American	2 (0.7)	0 (0.0)
Asian Indian	40 (13.2)	20 (13.1)
Asian non-Indian	125 (41.4)	62 (40.5)
Other	2 (0.7)	1 (0.7)
Diabetes duration*, years	13.7 ± 10.6	14.4 ± 9.7
BMI*, kg/m^2	24.0 ± 3.5	23.7 ± 3.4
HbA_{1c}*, %	8.0 ± 1.0	8.0 ± 0.9
FPG* central laboratory, mmol/l	9.9 ± 4.0	9.5 ± 4.0

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; IDeg, insulin degludec; IDet, insulin detemir.
*Arithmetic mean ± standard deviation.

Efficacy

After 1 year, HbA1c decreased from 8.0 ± 1.0% at baseline to 7.5 ± 1.1% with IDeg and from 8.0 ± 0.9 to 7.5 ± 0.9% with IDet; estimated difference (IDeg − IDet) −0.01 (95% CI −0.17; 0.14) was not significant and the upper CI was below the 0.4% non-inferiority margin that was defined in the main trial (Figure 1D). FPG decreased over 1 year from a baseline value of 9.9 ± 4.0 to 7.7 ± 3.6 mmol/l in the IDeg treatment arm, and from 9.5 ± 4.0 to 8.7 ± 3.8 mmol/l in the IDet treatment arm. The decrease in the IDeg treatment arm was significantly greater: estimated difference −1.11 (95% CI −1.83; −0.40) mmol/l; $p < 0.05$ (Figure 1E). The mean SMPG values were lower with IDeg before the main evening meals [estimated difference −0.98 mmol/l (95% CI −1.66; −0.29)] and higher with IDeg during early morning [at 04:00 hours; estimated difference 0.92 mmol/l (95% CI 0.22; 1.63)] compared with IDet. For the remaining time points, there was no statistically significant difference between the treatment groups (Figure 1F).

Discussion

The principal findings of the present study are that, administered once daily as part of a basal-bolus regimen, IDeg is associated with a significantly lower risk of nocturnal hypoglycaemia

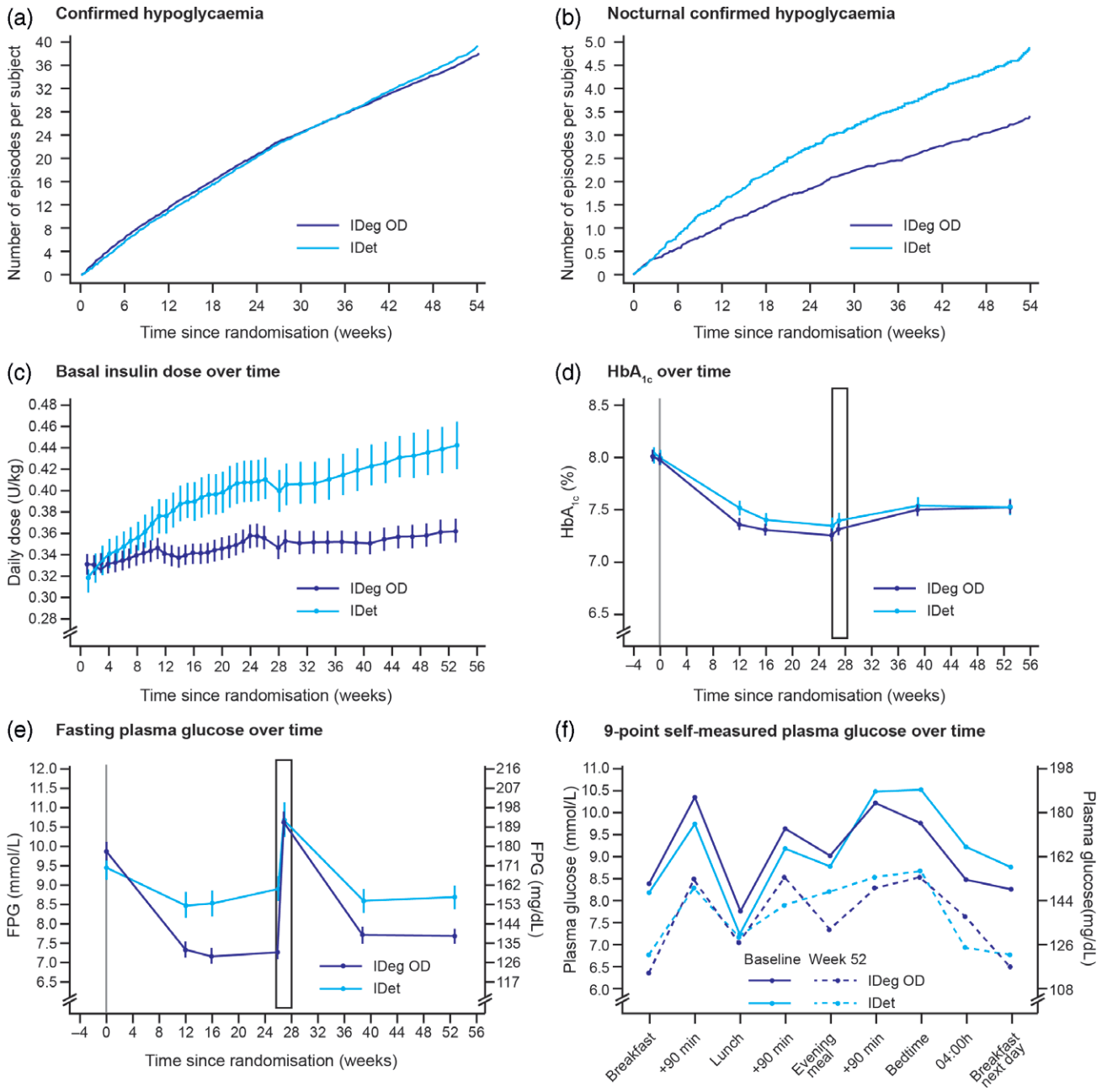

Figure 1. Safety and efficacy endpoints in the insulin degludec (IDeg) and insulin detemir (IDet) treatment arms. (A) Overall confirmed hypoglycaemic episodes. (B) Nocturnal confirmed hypoglycaemic episodes. (C) Basal insulin dose over time. (D) Glycated haemoglobin (HbA1c) versus time. (E) Fasting plasma glucose versus time. (F) Nine-point self-monitored plasma glucose (SMPG) at baseline and 1 year. The box in (D) and (E) on the horizontal axes between weeks 26 and 27 denotes the 1-week basal insulin washout period during which participants switched to NPH insulin and total insulin dose was reduced by 20%. Confirmed hypoglycaemic episodes included either episodes confirmed by SMPG corresponding to plasma glucose value <3.1 mmol/l or severe episodes requiring assistance. Episodes occurring between 00:01 and 05:59 hours (both inclusive) were classified as nocturnal. Glycaemic efficacy data are reported as the mean ± standard error of the mean. Missing post-baseline data were imputed using the last observation carried forward approach. Baseline was defined as the time of randomization in the core trial.

compared with IDet administered once or twice daily. Sustained HbA1c reduction is observed after 1 year of treatment with IDeg, similar to IDet. Over the same period, IDeg also provided a significantly greater reduction in FPG compared with IDet. The lower risk of nocturnal hypoglycaemia, despite reduced FPG, in the IDeg treatment arm may be explained by differences in the nine-point SMPG profiles, during the nocturnal period in particular when plasma glucose was higher in the IDeg than the IDet arm. The lower weight gain observed with IDet is consistent with previous observations [7, 8]. The present study confirms that the benefits of IDeg are maintained over the long term. IDeg provides an alternative treatment option

for patients with T1DM, which may help to improve glycaemic control and provides a lower risk of nocturnal hypoglycaemia.

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Conflict of Interest

M. D. has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, Astra Zeneca and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. She has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi-Aventis and Lilly. J. L. G. has attended scientific advisory panels for Boehringer Mannheim, Eli Lilly and Novo Nordisk, has received grants/research support from Boehringer Mannheim, Bristol-Myers Squibb, Eli Lilly, Janssen Cilag, Novo Nordisk and GlaxoSmithKline, and received speaker fees from Boehringer Mannheim, Bristol-Myers Squibb, Eli Lilly and Novo Nordisk. G. B. has received speaker fees from Novo Nordisk. H. S. has received speaker fees from Ono Pharmaceutical Co. Ltd, Novartis Pharma K.K. and Sanofi K.K. T. S. and Y. O. have no conflicts of interest to disclose. M. D. acts as guarantor for the contents of this article. D. T., on behalf of Novo Nordisk A/S, and T. N., on behalf of Novo Nordisk Pharma Ltd., were involved in critical analysis and interpretation of the data, drafting/critically revising the article and shared the final responsibility for the content of the manuscript and the decision to submit it for publication.

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Supporting Information

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

Figure S1. Subject disposition.
Table S1. Insulin type at screening.
Table S2. Pre-trial daily insulin dose.

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