

# Efficacy and safety of insulin degludec given as part of basal–bolus treatment with mealtime insulin aspart in type 1 diabetes: a 26-week randomized, open-label, treat-to-target non-inferiority trial

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**Aims:** The efficacy and safety of insulin degludec (IDeg) was compared with insulin detemir (IDet), both administered once daily (OD) as basal treatment in participants with type 1 diabetes mellitus (T1DM). The primary outcome was non-inferiority of IDeg to IDet in glycated haemoglobin (HbA1c) reduction after 26 weeks.

**Methods:** This multinational, 26-week, controlled, open-label, parallel-group trial randomized adults with T1DM to IDeg or IDet as OD basal insulin treatment combined with mealtime bolus insulin aspart (IAsp). Participants with T1DM treated with any basal–bolus insulin regimen for  $\geq 12$  months prior to the trial, a mean HbA1c  $\leq 10.0\%$  (85.8 mmol/mol) and body mass index (BMI)  $\leq 35.0$  kg/m<sup>2</sup> at screening participated in the trial (IDeg: N = 302; IDet: N = 153).

**Results:** After 26 weeks, HbA1c decreased 0.73% (8.0 mmol/mol) (IDeg) and 0.65% (7.1 mmol/mol) (IDet) [estimated treatment difference (ETD) IDeg–IDet:  $-0.09\%$  ( $-0.23; 0.05$ )<sub>95% CI</sub> ( $-10.0$  mmol/mol [ $-2.6; 0.6$ ]<sub>95% CI</sub>); confirming non-inferiority]. Mean fasting plasma glucose improved in both groups, and was lower with IDeg than IDet [ETD IDeg–IDet:  $-1.66$  mmol/l ( $-2.37; -0.95$ )<sub>95% CI</sub>,  $p < 0.0001$ ]. The rate of confirmed hypoglycaemia was similar with IDeg and IDet [45.83 vs. 45.69 episodes per patient-year of exposure (PYE); estimated rate ratio (RR) IDeg/IDet: 0.98 (0.80; 1.20)<sub>95% CI</sub>,  $p = 0.86$ ]. The rate of nocturnal confirmed hypoglycaemia was lower with IDeg than IDet [4.14 vs. 5.93 episodes per PYE; RR IDeg/IDet: 0.66 (0.49; 0.88)<sub>95% CI</sub>,  $p = 0.0049$ ]. Adverse event profiles were similar between groups.

**Conclusion:** IDeg administered OD in basal–bolus therapy effectively improved long-term glycaemic control in participants with T1DM with a lower risk of nocturnal confirmed hypoglycaemia than IDet.

**Keywords:** glycaemic control, hypoglycaemia, insulin aspart, insulin degludec, insulin detemir, insulin therapy, type 1 diabetes mellitus

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## Introduction

Basal–bolus insulin therapy in people with type 1 diabetes mellitus (T1DM) aims to mimic the endogenous insulin secretion profile in healthy individuals and has been shown to improve glycaemic control and reduce the risk of long-term complications [1,2]. Despite these advantages, the focus on decreasing glycated haemoglobin (HbA1c) in people with T1DM also presents the risk of increased rates of hypoglycaemia [2], leading to impaired hypoglycaemia awareness [3]

affecting many aspects of patient well-being that can reduce treatment adherence and lead to suboptimal glycaemic control [4–7]. Nocturnal hypoglycaemia can impair quality of sleep, increase fatigue and cause morning headaches [5]. Moreover, people with T1DM have impaired plasma epinephrine responses to hypoglycaemia, with an increased risk of severe hypoglycaemia, especially during sleep [8,9]. Basal insulin analogues have been developed to provide a long duration of action to cover insulin requirements over an extended period of time while providing a lower risk of hypoglycaemia. Insulin detemir (IDet) and insulin glargine (IGlar) are basal insulin analogues that have shown a longer duration of action and a decreased risk of hypoglycaemia, particularly nocturnal, compared to neutral protamine Hagedorn (NPH) insulin [10–12]. IDet and IGlar have similar time–action profiles [13] and produce similar levels of glycaemic control [14], but IDet

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is associated with less variability in plasma glucose (PG) than both IGLar and NPH insulin [15]. Insulin degludec (IDeg) is a novel basal insulin with an ultra-long, flat and stable action profile. Upon subcutaneous injection, IDeg forms soluble multihexamers that slowly and steadily dissociate and release insulin monomers into the circulation. This results in a stable and consistent glucose-lowering effect of >42 h at steady state [16–20] and lower rates of hypoglycaemia than IGLar [21–23]. In this BEGIN Basal–bolus Type 1 trial being part of the phase 3a programme for IDeg, we compared the efficacy and safety of IDeg with IDet, both administered once daily (OD) in a basal–bolus regimen with rapid-acting insulin aspart (IAsp) as mealtime insulin in participants with T1DM.

## Materials and Methods

### Trial Design and Participants

This 26-week randomized, controlled, open-label, parallel-group, non-inferiority trial was conducted between 22 February 2010 and 8 December 2010 and included participants from clinical sites in Brazil, Finland, India, Italy, Japan, Macedonia and the UK. Adults ( $\geq 18$  years or  $\geq 20$  years for Japan) diagnosed with T1DM for  $\geq 12$  months, currently treated with any basal–bolus insulin regimen for  $\geq 12$  months prior to screening and with HbA1c  $\leq 10.0\%$  (85.8 mmol/mol) and body mass index (BMI)  $\leq 35.0$  kg/m<sup>2</sup> at time of screening were eligible for participation. Exclusion criteria included clinically significant concomitant diseases, including impaired renal and hepatic function; a history of recurrent major hypoglycaemia or hypoglycaemic unawareness; and cardiovascular disease within the previous 6 months prior to the trial. The trial was conducted in accordance with the Declaration of Helsinki [24] and Good Clinical Practice Guidelines [25]. Signed informed consent was obtained from each participant before any trial-related activities.

### Randomization and Interventions

Eligible participants were randomized 2 : 1 to either OD IDeg (Tresiba<sup>®</sup>, 100 U/ml) or OD IDet (Levemir<sup>®</sup>, 100 U/ml) as basal insulin, both in combination with mealtime IAsp (NovoRapid<sup>®</sup> 100 U/ml) (all Novo Nordisk, Bagsværd, Denmark). Insulin products were injected subcutaneously using a 3-ml FlexPen<sup>®</sup> (Novo Nordisk). For randomization, an interactive voice/web response system with centralized block randomization was used. While participants and investigators in this open-label trial were unblinded to trial treatment, due to the different appearance of the IDeg and IDet FlexPen<sup>®</sup>, all personnel working with assessment, handling and evaluation of trial data were blinded from trial drug allocation until the data were locked for statistical analysis.

Participants were transferred from their pre-trial insulin treatment to their randomized trial treatment on a 1 : 1 unit basis. If basal insulin was taken in a OD regimen prior to the trial, the same number of units OD was prescribed. If basal insulin was taken more than OD prior to the trial, the total daily basal dose was calculated and transferred 1 : 1 as the OD starting dose for both IDeg and IDet. The starting dose

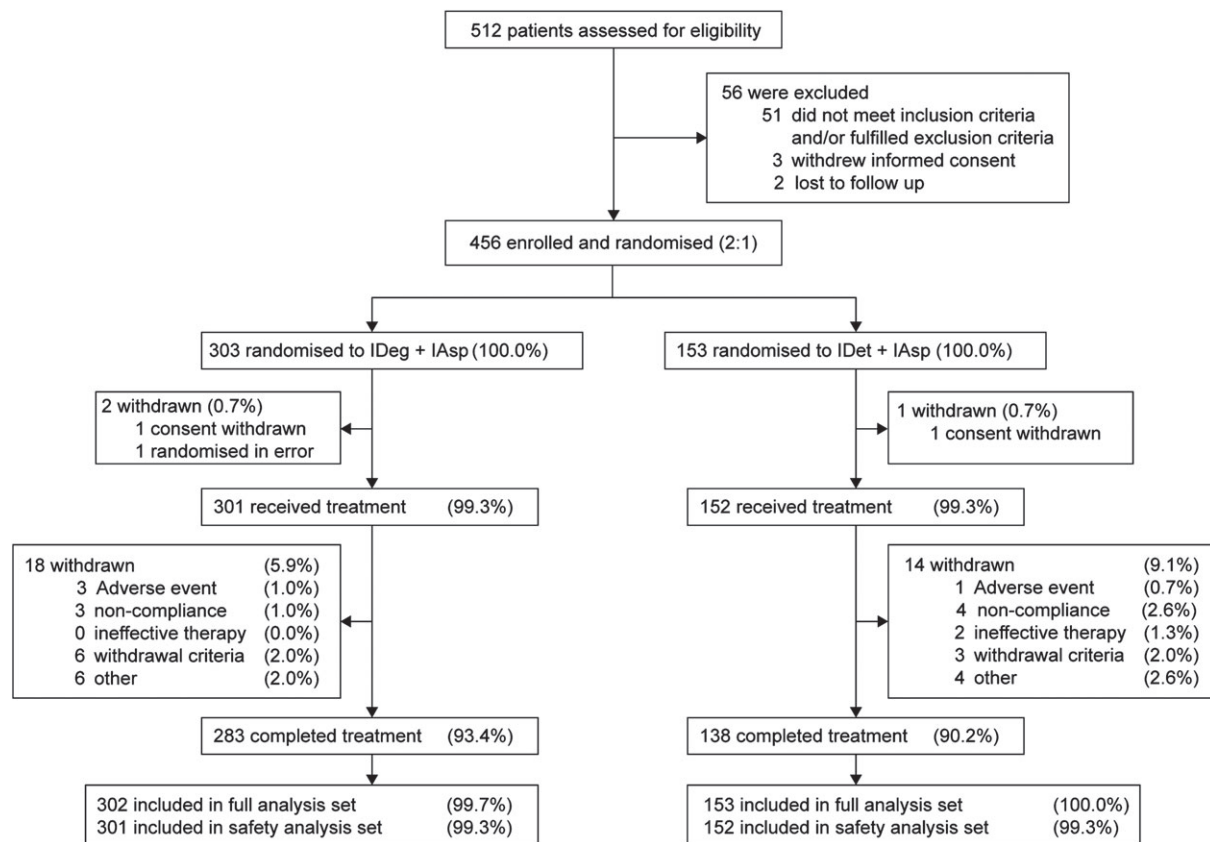
of IDeg and IDet could be adjusted at the discretion of the investigator to reduce the risk of hypoglycaemia. On the basis of pre-breakfast self-measured blood glucose measurements (mean value from 3 consecutive days), IDeg and IDet were titrated individually once a week to a PG of 3.9–4.9 mmol/l using a titration algorithm (Table S1, Supporting Information). Basal insulin was administered between the start of the evening meal and bedtime. In the IDet group, a second dose of IDet could be added if there was inadequate glycaemic control after  $\geq 8$  weeks of treatment. Inadequate glycaemic control was defined as <0.5% point improvement in HbA1c [participants with baseline HbA1c  $\geq 8.0\%$  (63.9 mmol/mol)] or any deterioration of HbA1c [participants with baseline HbA1c < 8.0% (63.9 mmol/mol)] in conjunction with a mean pre-dinner PG > 6.0 mmol/l and no diagnosis of a treatable concurrent disease causing hyperglycaemia. Participants were to continue on an equivalent dose of IAsp to their pre-trial mealtime insulin dose. IAsp was administered immediately prior to breakfast, lunch and dinner, and an additional dose was permitted to cover an additional meal/snack. The dose of IAsp was adjusted weekly based on the mean of three self-measured pre-prandial PG values (Table S1). Optimization of basal insulin dose was to be prioritized over changes to the mealtime insulin dose during the first 8 weeks. At the end of the trial (26 weeks), participants were switched from IDeg and IDet to twice daily (BID) NPH insulin in combination with IAsp for 1 week, to minimize interference with antibody measurements.

### Assessments

The primary assessment was change in HbA1c after 26 weeks of treatment. Secondary efficacy assessments included laboratory measured fasting plasma glucose (FPG), 9-point self-measured plasma glucose (SMPG) profiles and doses of basal and mealtime insulin. Safety variables included number of hypoglycaemic episodes, adverse events (AEs), body weight, standard clinical and laboratory assessments (including insulin antibodies), electrocardiogram (ECG), fundoscopy/fundus photography and injection-site reactions. Confirmed hypoglycaemia was defined as PG < 3.1 mmol/l, regardless of symptoms or severe episodes (requiring assistance from another person). Nocturnal episodes were confirmed episodes with onset between 00:01 and 05:59 hours and confirmed episodes with onset between 06:00 and 00:00 hours were classified as diurnal. Laboratory analyses (except antibody analyses) were performed by Quintiles Laboratories (West Lothian, UK and Mumbai, India), Medca Japan (Tenjin, Japan) and Diagnósticos da America (São Paulo, Brazil). Antibodies were analysed at Celerion Switzerland AG (Fehraltorf, Switzerland), via a subtraction radioimmunoassay method [26,27]. An independent external event adjudication committee (EAC) performed adjudication, standardization and assessment of cardiovascular events in accordance with pre-defined classifications.

### Statistical Methods

The primary objective was to confirm non-inferiority of IDeg to IDet as assessed by mean change from baseline in HbA1c after 26 weeks of treatment. The primary endpoint was



**Figure 1.** Trial flow diagram. Of the randomized participants, three participants were withdrawn prior to exposure to trial products; two (one from each group) withdrew their informed consent, and one randomized to insulin degludec (IDeg) was withdrawn because the participant was randomized in error in spite of a screening failure. Of the six participants who were withdrawn due to withdrawal criteria in IDeg, three met withdrawal criterion #3 ('Major protocol deviation having influence on efficacy or safety data as judged by the investigator'), one met withdrawal criterion #1 ('Pregnancy or intention of becoming pregnant'), one met withdrawal criterion #2 ('Hypoglycaemia posing a safety problem as judged by the investigator') and one met withdrawal criterion #4 ['Initiation or significant change of any systemic treatment which in the investigator's opinion could have interfered with glucose metabolism (inhaled corticosteroids were allowed)']. Of the three participants in the insulin detemir (IDet) group who were withdrawn due to withdrawal criteria, two were withdrawn due to withdrawal criterion #2 (see above) and one due to withdrawal criterion #4 (see above). %, proportion of randomized participants; IAsp, insulin aspart.

analysed using an ANOVA with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA1c as covariates. Non-inferiority was confirmed if the upper limit of the 95% confidence interval (CI) was  $\leq 0.4\%$  points in HbA1c. Assuming a standard deviation (s.d.) of 1.1% for the primary endpoint, the trial had 90% power with 360 participants randomized 2:1. A hierarchical (fixed-sequence) testing procedure was used to control the type I error rate for selected endpoints in the following order: change in HbA1c, number of nocturnal and overall confirmed hypoglycaemic episodes, change in laboratory measured FPG and within-participant variability in pre-breakfast SMPG (data for the latter not presented) (Figure S1). The number of overall confirmed, diurnal confirmed (*post hoc* analysis), nocturnal confirmed and severe hypoglycaemic episodes was analysed using a negative binomial regression model which included treatment, antidiabetes therapy at screening, sex and region as fixed factors and age as covariate. Change from baseline in mean FPG after 26 weeks of treatment was analysed using an ANOVA similar to that used for the primary endpoint.

Variability in the 9-point SMPG profile (defined as the integrated absolute distance from mean profile value divided by measurement time) was log transformed and analysed using an ANOVA similar to that used for the primary endpoint. Statistical analysis was performed on the full analysis set (FAS) for efficacy endpoints including hypoglycaemia and safety endpoints were summarized using the safety analysis set (SAS). Missing values were imputed using last observation carried forward [28]. Non-rounded HbA1c (%) values was converted to HbA1c (mmol/mol) using the following formula:  $\text{HbA1c (mmol/mol)} = [\text{HbA1c (\%)} \times 10.93] - 23.5$ . The trial was registered with clinicaltrials.gov. number NCT01074268.

## Results

Of 512 participants screened, 456 were randomized (2:1) to IDeg (303) or IDet (153). Three (3) randomized participants were withdrawn before exposure to trial treatment (IDeg: 2, IDet: 1) (Figure 1). One (1) of these participants randomized to IDeg was withdrawn because the participant was randomized

**Table 1.** Baseline characteristics.

	IDeg + IAsp	IDet + IAsp	Overall population
Number of participants (FAS)	302	153	455
Female (%)	50.3	43.8	48.1
Race (% White/Black/Asian*/Other)	44.0/0.7/54.6/0.7	45.8/0.0/53.6/0.7	44.6/0.4/54.3/0.7
Country of residence (%)			
Brazil	4.6	5.2	4.8
Finland	9.9	9.8	9.9
India	13.2	13.1	13.2
Italy	10.3	7.8	9.5
Japan	41.1	40.5	40.9
Republic of Macedonia	6.0	7.8	6.6
UK	14.9	15.7	15.2
Age, years	41.1 (14.9)	41.7 (14.4)	41.3 (14.7)
Body weight, kg	66.5 (14.9)	66.7 (13.4)	66.6 (14.4)
Body mass index, kg/m <sup>2</sup>	24.0 (3.5)	23.7 (3.4)	23.9 (3.5)
Duration of diabetes, years	13.7 (10.6)	14.4 (9.7)	13.9 (10.3)
HbA1c, %	8.0 (1.0)	8.0 (0.9)	8.0 (0.9)
HbA1c, mmol/mol	63.7 (10.7)	63.9 (9.6)	63.8 (10.3)
Fasting plasma glucose, mmol/l	9.9 (4.0)	9.5 (4.0)	9.8 (4.0)
Fasting plasma glucose, mg/dl	178.2 (71.9)	170.8 (72.4)	175.7 (72.1)
Serum creatinine, µmol/l	74 (16)	76 (15)	75 (15)
Serum albumin, g/l	44 (3)	43 (3)	44 (3)
Diabetes treatment at screening			
Basal insulin OD	197 (65.2)	116 (75.8)	313 (68.8)
Basal insulin BID or more	105 (34.8)	37 (24.2)	142 (31.2)
Basal insulin type at screening			
Insulin glargine	140 (46.4)	81 (52.9)	221 (48.6)
Insulin detemir	112 (37.1)	53 (34.6)	165 (36.3)
NPH insulin	50 (16.6)	19 (12.4)	69 (15.2)
Bolus insulin type at screening			
Insulin aspart	169 (56.0)	87 (56.9)	256 (56.3)
Insulin lispro	72 (23.8)	34 (22.2)	106 (23.3)
Human insulin	48 (15.9)	25 (16.3)	73 (16.0)
Other†	13 (4.3)	7 (4.7)	20 (4.4)

Data are number (%) or mean (s.d.). BID, twice daily; FAS, full analysis set; HbA1c, glycated haemoglobin; IAsp, insulin aspart; IDeg, insulin degludec; IDet, insulin detemir; NPH, neutral protamine Hagedorn; OD, once daily.

\*Indian or Japanese.

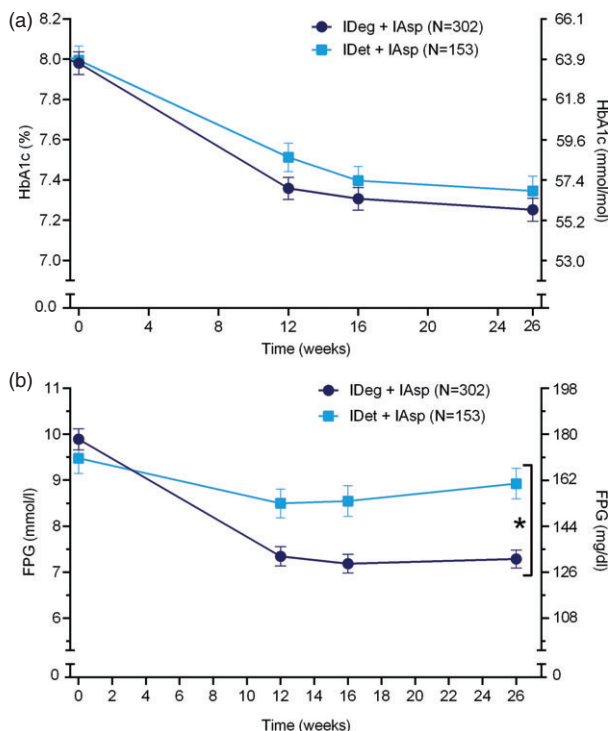
†Insulin glulisine, human insulin + insulin aspart, human insulin + insulin lispro.

in error in spite of being a screening failure. Therefore, 456 participants were randomized and 455 participants were included in the FAS. A similar proportion of participants completed the trial in the IDeg (93.4%) and IDet (90.2%) groups. Participant withdrawal was evenly spread throughout the trial with no specific clustering of withdrawal reasons in either treatment group. Trial participants had a mean (s.d.) baseline HbA1c of 8.0% (0.9) [63.8 mmol/mol (10.3)] and a mean (s.d.) diabetes duration of 13.9 years (10.3). At screening, all participants were in treatment with basal insulin (mainly IDet or IGlarg) and mealtime insulin (mainly IAsp or insulin lispro) (Table 1). In addition, 34.8% of the participants randomized to IDeg had come from a greater than or equal to BID dose of basal insulin compared to 24.2% of participants treated with IDet.

The observed mean reduction in HbA1c from baseline to end of trial was 0.73% (8.0 mmol/mol) and 0.65% (7.1 mmol/mol) with IDeg and IDet, respectively. As anticipated by the treat-to-target approach, HbA1c was reduced to similar levels

with IDeg and IDet, with an observed mean [standard error (s.e.)] HbA1c of 7.3% (0.06) [55.8 mmol/mol (0.6)] for IDeg and 7.3% (0.07) [56.8 mmol/mol (0.8)] for IDet at the end of the treatment (Figure 2a). The mean estimated treatment difference (ETD) between IDeg and IDet was  $-0.09\%$  ( $-0.23; 0.05$ )<sub>95%CI</sub> [ $-10.0$  mmol/mol ( $-2.6; 0.6$ )<sub>95%CI</sub>];  $p = 0.21$ , and since the upper limit of the CI (0.05) was  $<0.4$ , we demonstrated that IDeg was non-inferior to IDet in lowering HbA1c. The results of the primary analysis were supported by a per-protocol analysis and additional sensitivity analyses (Table S2).

No statistically significant difference was found between IDeg and IDet with respect to the proportion of participants achieving an HbA1c of  $<7.0\%$  (53.0 mmol/mol) (specified by the American Diabetes Association [29]) [41.1 vs. 37.3%; estimated odds ratio (EOR) (IDeg/IDet): 1.27 (0.77; 2.09)<sub>95%CI</sub>,  $p = 0.34$ ] or  $\leq 6.5\%$  (47.5 mmol/mol) (specified by the International Diabetes Federation/American Association of Clinical Endocrinologists [30]) [24.2 vs. 21.6%; EOR (IDeg/IDet): 1.15 (0.68; 1.96)<sub>95%CI</sub>,  $p = 0.61$ ]. Likewise, no

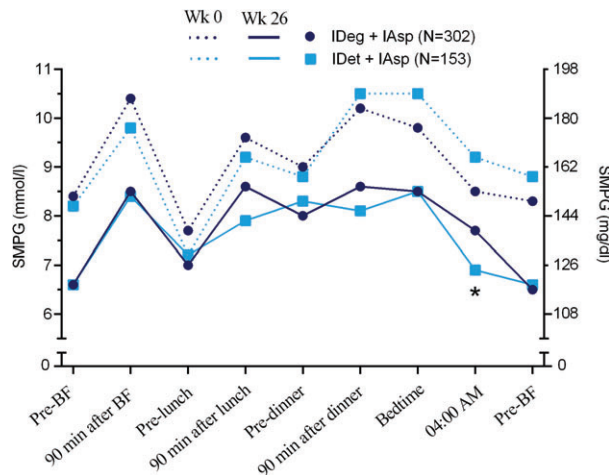


**Figure 2.** (a) Mean HbA1c over time. Treatment difference at week 26 was not significant. (b) Mean fasting plasma glucose (FPG) over time. Treatment difference at week 26 ( $p < 0.0001$ ). Error bars show standard error of the mean. IDeg, insulin degludec; IDet, insulin detemir; IAsp, insulin aspart; N, full analysis set.

statistically significant difference was found between IDeg and IDet in terms of the proportion of participants who attained an HbA1c of  $<7.0\%$  ( $53.0$  mmol/mol) without severe hypoglycaemia [ $39.7$  vs.  $36.6\%$ , EOR (IDeg/IDet):  $1.26$  ( $0.76; 2.09$ )<sub>95%CI</sub>,  $p = 0.38$ ].

At the end of treatment, observed FPG decreased  $2.60$  mmol/l (s.e.  $0.28$ ) with IDeg and  $0.62$  mmol/l (s.e.  $0.37$ ) with IDet to mean (s.e.) levels of  $7.29$  mmol/l ( $0.20$ ) and  $8.93$  mmol/l ( $0.33$ ), respectively (Figure 2b). The reduction of FPG was statistically significantly greater with IDeg than IDet [ETD IDeg–IDet:  $-1.66$  mmol/l ( $-2.37; -0.95$ )<sub>95%CI</sub>,  $p < 0.0001$ ]. The proportion of participants who achieved before breakfast SMPG concentration of between  $3.9$  and  $4.9$  mmol/l at the end of treatment was similar with IDeg ( $23.8\%$ ) and IDet ( $24.2\%$ ). At baseline, the 9-point SMPG profiles were similar between treatment groups, as was the decrease in PG after 26 weeks where the 9-point SMPG profiles were similar except at 04:00 hours where PG concentration was lower with IDet than IDeg [ETD IDeg–IDet:  $0.89$  mmol/l ( $0.19; 1.58$ )<sub>95%CI</sub>,  $p = 0.013$ ] (Figure 3). The variability of the 9-point SMPG profile was similar at  $1.5$  mmol/l with both IDeg and IDet after 26 weeks of treatment [estimated mean treatment ratio (IDeg/IDet):  $0.95$  ( $0.85; 1.07$ )<sub>95%CI</sub>,  $p = 0.43$ ].

The mean total (basal and bolus) daily insulin doses at baseline were similar with IDeg ( $0.75$  U/kg) and IDet ( $0.78$  U/kg). At the end of treatment, the mean total daily insulin dose was  $0.89$  and  $1.03$  U/kg with IDeg and IDet,



**Figure 3.** Mean 9-point self-measured plasma glucose (SMPG) profiles at baseline (dashed lines) and week 26 (full lines). AM, ante meridian (before mid-day); BF, breakfast; IDeg, insulin degludec; IDet, insulin detemir; IAsp, insulin aspart; N, full analysis set, Wk, week. \*Treatment difference at week 26,  $p = 0.013$ .

**Table 2.** Mean (s.e.m.) basal (IDeg or IDet), bolus (IAsp) and total (basal + bolus) insulin doses at baseline and end of treatment (26 weeks).

	IDeg + IAsp (N = 301)	IDet + IAsp (N = 152)
Basal dose, U/kg (s.e.m.)		
Baseline	0.33 (0.01)	0.32 (0.01)
End of treatment	0.36 (0.01)	0.41 (0.02)
Bolus dose, U/kg (s.e.m.)		
Baseline	0.42 (0.01)	0.46 (0.02)
End of treatment	0.54 (0.02)	0.63 (0.03)
Total dose, U/kg (s.e.m.)		
Baseline	0.75 (0.02)	0.78 (0.03)
End of treatment	0.89 (0.03)	1.03 (0.04)

N, safety analysis set; IAsp, insulin aspart; IDeg, insulin degludec; IDet, insulin detemir; s.e.m., standard error of the mean; U, units.

respectively (Table 2). At baseline, the mean daily basal insulin dose was similar with IDeg ( $0.33$  U/kg) and IDet ( $0.32$  U/kg) and at the end of treatment, the mean daily basal insulin dose was  $0.36$  and  $0.41$  U/kg with IDeg and IDet, respectively (Table 2). At the end of the trial,  $32.9\%$  of participants in the IDet group administered IDet BID, as allowed per protocol. At the end of treatment, the IDeg/IDet ratio of the mean daily basal insulin dose (U/kg) was  $0.87$ . Similarly, the IDeg/IDet ratio of the mean total insulin (basal and bolus) dose (U/kg) was  $0.87$ . The ratio of the mean daily bolus insulin dose (U/kg) between the IDeg and IDet treatment groups at the end of treatment was  $0.86$ . The split of basal and bolus insulin was similar at baseline and at the end of treatment for both the IDeg and IDet groups (Table 3).

The rate of severe hypoglycaemia was similar between IDeg and IDet [ $0.31$  vs.  $0.39$  episodes per patient-year of exposure (PYE), respectively; estimated rate ratio (RR) IDeg/IDet:  $0.92$  ( $0.46; 1.81$ )<sub>95%CI</sub>,  $p = 0.80$ ]. The rate of

**Table 3.** Basal–bolus split of total daily insulin dose (units/kg) at baseline and end of treatment (26 weeks).

	IDeg + IAsp Basal/Bolus	IDet + IAsp Basal/Bolus
Baseline	44%/56%	41%/59%
End of treatment	40%/60%	40%/60%

Data derived from mean doses computed from last observation carried forward imputed data in safety analysis set. Basal, percentage basal insulin; bolus, percentage bolus insulin; IAsp, insulin aspart; IDeg, insulin degludec; IDet, insulin detemir.

confirmed hypoglycaemia was similar between IDeg and IDet [45.83 vs. 45.69 episodes per PYE; RR IDeg/IDet: 0.98 (0.80; 1.20)<sub>95%CI</sub>,  $p = 0.86$ ]. (Table 4; Figure 4a). IDeg was associated with a significant, 34% lower rate of nocturnal confirmed hypoglycaemia than IDet [4.14 vs. 5.93 episodes per PYE; RR IDeg/IDet: 0.66 (0.49; 0.88)<sub>95%CI</sub>,  $p = 0.0049$ ] (Table 4; Figure 4b). Few episodes of nocturnal severe hypoglycaemia were reported during the trial with the rate low for both IDeg (0.09 per PYE) and IDet (0.08 per PYE). The rate of diurnal hypoglycaemia (*post hoc* analysis) was similar with IDeg and IDet [41.42 vs. 39.46 episodes per PYE, respectively; RR IDeg/IDet: 1.03 (0.84; 1.27)<sub>95%CI</sub>,  $p = 0.77$ ].

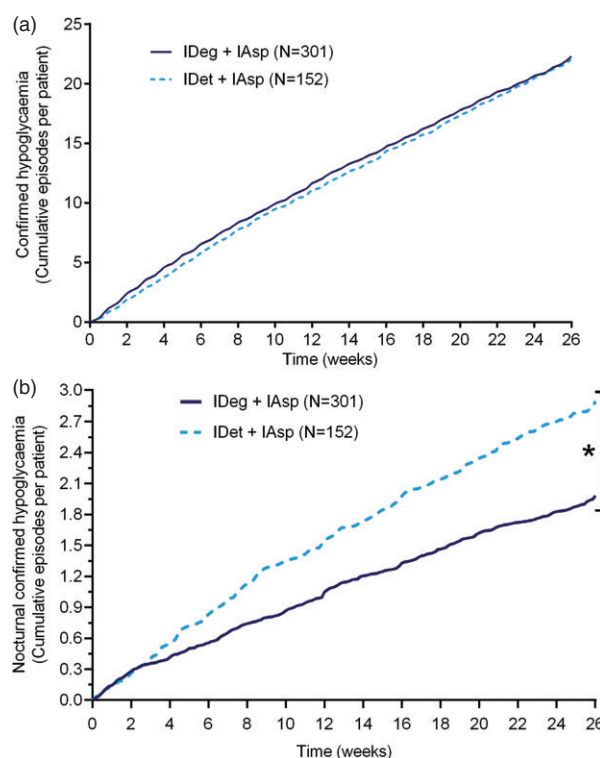
Mean (s.e.) body weight increased from baseline to end of treatment with both IDeg [1.5 kg (0.2)] and IDet [0.4 kg (0.2)] [ETD IDeg–IDet: 1.08 kg (0.58; 1.57)<sub>95%CI</sub>,  $p < 0.0001$ ].

The percentage of participants with AEs was similar with IDeg (73%) and IDet (74%) as was the rate of AEs (5.45 vs. 4.84 events per PYE, respectively) (Table S3). The most frequently reported AEs in both treatment groups were nasopharyngitis, headache and hypoglycaemia (Table S3). The majority (>90%) of AEs were mild or moderate and few of the AEs in either treatment group were severe (Table S3). The rate of both severe AEs and AEs possibly or probably related to investigational product was similar with IDeg and IDet (Table S3). No AEs with fatal outcome were reported and no cardiovascular events that qualified for adjudication by the EAC were reported. The rate of serious adverse events (SAEs) was similar with IDeg and IDet (0.23 vs. 0.18 SAEs per PYE, respectively) and the most frequently reported SAE was hypoglycaemia in both treatment groups. The percentage of participants reporting injection-site

**Table 4.** Hypoglycaemic episodes occurring on or after the first day of exposure to treatment and no later than 7 days after the last day of treatment with insulin degludec (IDeg) or insulin detemir (IDet).

Randomization 2 : 1 (IDeg + IAsp : IDet + IAsp)	IDeg + IAsp (N = 301)			IDet + IAsp (N = 152)			Estimated rate ratio of IDeg + IAsp : IDet + IAsp (95% CI) p value	
	n (%)	E	Rate per PYE	n (%)	E	Rate per PYE		
Severe hypoglycaemia	32 (10.6)	45	0.31	16 (10.5)	28	0.39	0.92 (0.46; 1.81)	0.80
Overall confirmed hypoglycaemia	280 (93.0)	6673	45.83	139 (91.4)	3295	45.69	0.98 (0.80; 1.20)	0.86
Diurnal confirmed hypoglycaemia	277 (92.0)	6031	41.42	135 (88.8)	2846	39.46	1.03 (0.84; 1.27)	0.77
Nocturnal confirmed hypoglycaemia	176 (58.5)	603	4.14	89 (58.6)	428	5.93	0.66 (0.49; 0.88)	<0.0001

Nocturnal episodes were confirmed episodes with onset between 00:01 and 05:59 hours. Diurnal episodes were confirmed episodes with onset between 06:00 and 00:00 hours. Estimated rate ratio was calculated on the full analysis set. CI, confidence interval; E, number of events; IAsp, insulin aspart; N, safety analysis set; n, number of patients with events; %, percentage of all randomized participants in treatment group; rate, episodes per patient-year of exposure (PYE).

**Figure 4.** (a) Cumulative number of confirmed and (b) nocturnal confirmed hypoglycaemic episodes. Nocturnal episodes were confirmed episodes with onset between 00:01 and 05:59 hours. IDeg, insulin degludec; IDet, insulin detemir; IAsp, insulin aspart; N, safety analysis set. \*Treatment difference at week 26,  $p = 0.0049$ .

reactions was similar with IDeg (4.0%) and IDet (2.0%); none were classified as serious.

Mean levels of IDeg-, IDet- and IAsp-specific antibodies were low at baseline, and remained low throughout the treatment period (data not shown). With both IDeg and IDet, mean levels of antibodies cross-reacting to human insulin were low at baseline, decreasing slightly with IDeg and increasing slightly with IDet during the treatment period (data not shown).

For lipid parameters, no clinically relevant changes from baseline to the end of the trial were found (data not shown).

Serum creatinine tended to decrease slightly during the trial, but the mean and median values were within the reference range at baseline and at end of treatment for both groups (data not shown).

No clinically relevant differences from baseline to end of treatment or between treatment groups were observed in vital signs, ECG, fundoscopy/fundus photography, physical examination or standard laboratory values (data not shown).

## Discussion

In this trial in participants with T1DM, reduction in HbA1c from baseline with IDeg and IDet was similar and non-inferiority of IDeg to IDet was established. The level of overall glycaemic control (HbA1c) obtained with IDeg and IDet in this trial was comparable to that achieved in previous treat-to-target trials with IDet at a similar treatment regimen [10,14].

It was notable that the reduction of laboratory measured FPG in the present trial was greater with IDeg than IDet. This is in line with previous, similar trials reporting a lower mean FPG with IDeg versus IGLar in participants with T1DM [31]. The greater reduction in FPG with IDeg did not translate into a lower HbA1c level compared to IDet and the areas under the curve of the 9-point SMPG profiles were similar with IDeg and IDet. When interpreting this, it should be considered that HbA1c is influenced by various factors including FPG, post-prandial PG and hypoglycaemia. Moreover, variability in insulin action could influence the frequency and duration of low blood glucose values which in turn (despite not meeting the definition of hypoglycaemia of  $<3.1$  mmol/l) impacts the HbA1c result. It could be speculated that the higher FPG concentration seen in the morning with IDet to a certain extent may have been counterbalanced by longer periods at lower glucose levels during the night, as reflected by the statistically higher rate of nocturnal hypoglycaemia. Furthermore, the lower PG concentration at 04:00 hours with IDet than IDeg seen on the 9-point SMPG profile could support this argument.

At the end of the trial, 32.9% of participants received IDet BID, as allowed per protocol, which is similar to what has been reported for IGLar in people with T1DM [32]. The mean daily basal insulin dose, the total daily bolus insulin doses and the total insulin dose were numerically lower in the IDeg group than in the IDet group. This indicates that a lower dose of IDeg was required to achieve similar levels of overall group glycaemic control in the present population. In the light of similar observations of a lower bolus dose in a basal-bolus trial comparing IDeg with IGLar [22], one could consider the need and opportunity to optimize individual patient treatment regarding the use of bolus insulin, which could lower the risk of bolus-induced hypoglycaemia.

Severe hypoglycaemia rates were low and comparable between groups. The rate of confirmed hypoglycaemia was similar with IDeg and IDet throughout this trial whereas the rate of nocturnal confirmed hypoglycaemia was significantly lower with IDeg. This mirrors the results from a comparison of IDeg and IGLar in participants with T1DM [22]. However, the transfer from pre-trial dose to baseline dose was performed differently than in the current trial. For participants receiving

basal insulin BID prior to the trial, the dose was transferred 1 : 1 for IDeg but reduced 20–30% for IGLar according to approved labelling. This resulted in a lower starting dose for IGLar than IDeg, which during the first 4 weeks seemed to have an impact on hypoglycaemia, resulting in a non-significant 7% higher rate of overall confirmed hypoglycaemia with IDeg than IGLar at the end of the trial. The small imbalance in starting doses in that trial was not observed in the current trial where pre-trial basal insulin doses were switched on a 1 : 1 basis for both IDeg and IDet.

The lower rate of nocturnal hypoglycaemia associated with IDeg compared to IDet and IGLar could be explained by the more consistent pharmacokinetic and pharmacodynamic profile of IDeg, namely the longer duration of action as well as lower day-to-day and hour-to-hour pharmacodynamic variability [16,33]. From a clinician's perspective, the differences seen in the rate of nocturnal hypoglycaemia in this trial means that to avoid one nocturnal confirmed hypoglycaemic episode one would need to treat 1 patient for 7 months with IDeg or if 100 patients are treated for 1 year with IDeg there would be 179 fewer confirmed nocturnal hypoglycaemic episodes than with IDet as the comparator.

In general, AE and SAE profiles were similar between treatment groups. Body weight increased slightly in both treatment groups as expected from intensive basal-bolus insulin therapy but the increase was numerically lower with IDet than IDeg. The lower weight gain observed with IDet in this trial is consistent with previous observations [34,35].

As with any insulin therapy, injection-site reactions occurred. However, the percentage of participants experiencing injection-site reactions was  $<5\%$  in both treatment groups, with no serious episodes. For both groups, insulin-specific antibodies were low at baseline and remained low throughout the trial.

A general limitation of this trial, as in any open-label trial, is the risk of an underlying reporting bias. In general, it can be anticipated that investigators, as well as participants, are likely to be more alert when administering new insulin products such as IDeg. This could influence insulin titration and dose optimization as investigators may tend to be more cautious when initiating and adjusting doses of IDeg.

In conclusion, IDeg administered OD as part of basal-bolus therapy effectively improves long-term glycaemic control in participants with T1DM and is associated with a significantly lower risk of nocturnal confirmed hypoglycaemia in conjunction with a significantly larger reduction in mean FPG than basal-bolus therapy with IDet. IDeg was well tolerated and switching from other insulin regimens to IDeg and IAsp as basal-bolus therapy was safe. However, treatment should always be adjusted according to individual patient needs.

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## Conflict of Interest

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

## Supporting Information

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

**Figure S1.** Hierarchical testing scheme.

**Table S1.** Titration algorithm for basal and bolus insulin.

**Table S2.** Sensitivity analyses of the primary endpoint (change from baseline in HbA1c concentration after 26 weeks of treatment).

**Table S3.** Summary of adverse events.

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