Insulin Degludec in Type 1 Diabetes

A randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine

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OBJECTIVE—Insulin degludec (IDeg) is a basal insulin that forms soluble multihexamers after subcutaneous injection, resulting in an ultra-long action profile. We assessed the efficacy and safety of IDeg formulations administered once daily in combination with mealtime insulin aspart in people with type 1 diabetes.

RESEARCH DESIGN AND METHODS—In this 16-week, randomized, open-label trial, participants (mean: 45.8 years old, A1C 8.4%, fasting plasma glucose [FPG] 9.9 mmol/L, BMI 26.9 kg/m^2) received subcutaneous injections of IDeg(A) (600 μmol/L; *n* = 59), IDeg(B) (900 μmol/L; *n* = 60), or insulin glargine (IGlar; *n* = 59), all given once daily in the evening. Insulin aspart was administered at mealtimes.

RESULTS—At 16 weeks, mean A1C was comparable for IDeg(A) (7.8 ± 0.8%), IDeg(B) (8.0 ± 1.0%), and IGlar (7.6 ± 0.8%), as was FPG (8.3 ± 4.0, 8.3 ± 2.8, and 8.9 ± 3.5 mmol/L, respectively). Estimated mean rates of confirmed hypoglycemia were 28% lower for IDeg(A) compared with IGlar (rate ratio [RR]: 0.72 [95% CI 0.52–1.00]) and 10% lower for IDeg(B) compared with IGlar (RR: 0.90 [0.65–1.24]); rates of nocturnal hypoglycemia were 58% lower for IDeg(A) (RR: 0.42 [0.25–0.69]) and 29% lower for IDeg(B) (RR: 0.71 [0.44–1.16]). Mean total daily insulin dose was similar to baseline. The frequency and pattern of adverse events was similar between insulin treatments.

CONCLUSIONS—In this clinical exploratory phase 2 trial in people with type 1 diabetes, IDeg is safe and well tolerated and provides comparable glycemic control to IGlar at similar doses, with reduced rates of hypoglycemia.

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Improved glucose control delays and prevents the development of macrovascular and microvascular complications in type 1 diabetes (1,2). Unfortunately, a large proportion of people with type 1 diabetes is still unable to reach or maintain recommended A1C levels (3). Tighter glycemic control is typically accompanied by increased risk of hypoglycemia, and a compromise has to be made in each individual between optimal glycemic control and the person's tolerated frequency of hypoglycemia (4).

Despite the advantages offered by current basal insulin analogs (5,6), hypoglycemia remains a treatment limitation (7,8), causing decreased conscious level, inconvenience, embarrassment, and anxiety and can, as a result, lead to increased food intake and decreased insulin dosage. These important and occasionally life-threatening consequences all have a significant impact on quality of life (9–11).

Insulin degludec (IDeg) is a new-generation ultra-long-acting basal insulin. The ultra-long effect of IDeg is primarily a result of the slow release of IDeg monomers from soluble multihexamers that form after subcutaneous injection, resulting in a long half-life and a smooth and stable pharmacokinetic profile at steady state (12). These attributes are expected to provide improved glycemic control and to lower the risk of hypoglycemia, relative to currently available basal insulin analogs.

The present clinical exploratory trial compared the efficacy, safety, and tolerability of two different IDeg formulations (IDeg(A) and IDeg(B)) with insulin glargine (IGlar), all in combination with insulin aspart (IAsp) as mealtime insulin, in people with type 1 diabetes.

RESEARCH DESIGN AND METHODS

This clinical exploratory, 16-week, randomized, controlled, open-label, three-arm, parallel-group study compared two formulations of IDeg to IGlar. IDeg(A) was of the same molar concentration as IGlar (600 μmol/L, 1 unit = 6 nmol); IDeg(B) was a higher strength formulation (900 μmol/L; 1 unit = 9 nmol).

Participants

Study participants were enrolled at 28 centers across five countries: Australia, Germany, Norway, Sweden, and the U.S. Eligible participants were men and women 18–75 years of age diagnosed with type 1 diabetes ≥12 months before study, treated continually with insulin using any regimen, and having an A1C of 7.0–11.0%. People with clinically significant concomitant illnesses, impaired renal and hepatic function, and a history of recurrent major hypoglycemia or of hypoglycemia unawareness were excluded from participation. Pregnant or breast-feeding women were also excluded.

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Written informed consent was obtained from all participants before enrollment. The study was carried out in accordance with the Declaration of Helsinki (13) and Good Clinical Practice (14) and was approved by ethics committees and health authorities according to local regulations.

Randomization and interventions

Eligible participants were randomized 1:1:1 via a remote interactive voice/web response system to be treated with either IGlar (100 units/mL; Lantus, sanofi-aventis, Paris, France), IDeg(A) (600 μmol/L; 1 unit = 6 nmol; Novo Nordisk, Bagsvaerd, Denmark), or IDeg(B) (900 μmol/L; 1 unit = 9 nmol; Novo Nordisk), all in combination with IAsp at mealtimes (NovoRapid/NovoLog; 100 units/mL; Novo Nordisk A/S, Bagsvaerd, Denmark). Basal insulin was administered subcutaneously, preferably in the thigh, once daily in the evening, in the period between 1 h before the last main meal and bedtime, but approximately at the same time each day. IAsp was administered subcutaneously just before each main meal, preferably in the abdominal wall. IAsp, IDeg(A), and IDeg(B) were administered using a 3-mL FlexPen (Novo Nordisk A/S). IGlar was administered either using a 3-mL Optiset pen (sanofi-aventis) or, in the U.S., from 10-mL vials using a BD Microfine needle (31 G × 8 mm) and 1 cc syringe (both BD, Franklin Lakes, NJ). The 16-week study period included 12 visits to the clinic and seven scheduled telephone consultations.

Participants receiving once-daily basal insulin treatment before the study switched to trial insulin using a one-to-one unit dose switch. Participants receiving twice-daily basal insulin treatment before the study were to commence trial insulin at a dose corresponding to 80% of their pretrial daily basal insulin dose.

Based on self-measured fasting plasma glucose (FPG) levels taken before breakfast (lowest FPG value from 3 consecutive days), basal insulin doses were individually adjusted once a week (during a clinic visit or a telephone contact) throughout the study, aiming at an FPG target of 4.0–6.0 mmol/L (72–108 mg/dL). Doses for IDeg and IGlar were increased by 2 units if FPG was 6.1–10.0 mmol/L (109–180 mg/dL), by 4 units if FPG was 10.1–15.0 mmol/L (181–270 mg/dL), or by 6 units if FPG was >15.0 mmol/L (270 mg/dL). Doses of IDeg or IGlar were decreased by 2 units if FPG was 3.1–3.9 mmol/L (56–71 mg/dL) or by 5% if dose >45 units, by 4 units if FPG was <3.1 mmol/L (56 mg/dL) or by 10% if dose >45 units.

The same dosing algorithm was used for all three treatments. The higher concentration of IDeg(B) (1 unit = 9 nmol) translated into higher initial doses (by 50%) and larger dosing adjustments (by 50%) compared with the two other formulations.

Mealtime insulin (IAsp) was continued at the same dose as the pretrial mealtime insulin. When the basal insulin dose had been optimized (FPG 4.0–6.0 mmol/L [72–108 mg/dL]), mealtime IAsp doses could be titrated on a weekly basis with clinic or telephone contact advice. Titration was based on the lowest self-measured postprandial plasma glucose (PPG) level from three consecutive days to attain a 2-h postprandial target of 4.0–8.0 mmol/L (72–144 mg/dL). The dose of IAsp was increased by 2 units if PPG was 8.1–10.0 mmol/L (145–180 mg/dL) and by 4 units if postprandial PPG was >10.0 mmol/L (180 mg/dL). The IAsp dose was decreased by 2 units if PPG was <4.0 mmol/L (72 mg/dL).

Assessments

The primary assessment was A1C after 16 weeks of treatment. Secondary efficacy assessments included changes in basal and mealtime insulin doses, laboratory-measured FPG, and nine-point self-measured plasma glucose (SMPG) profiles (measured before and 2 h after each meal). Blood samples for FPG were taken at clinic visits.

Tolerability and safety variables included hypoglycemic episodes, adverse events (AEs) including injection site reactions, serum insulin antibodies (IDeg-specific, IAsp-specific, and those cross-reacting between IDeg and IAsp), body weight, vital signs, physical examination, fundoscopy, electrocardiogram (ECG), and standard biochemical and hematology measures.

Hypoglycemia was classified as severe (if assistance from another person was required) or confirmed (if confirmed by a PG measurement of <3.1 mmol/L [56 mg/dL] irrespective of any symptoms or if classified as severe). Confirmed hypoglycemic episodes were considered nocturnal if the time of onset was between 2300 and 0559 h, both inclusive.

A central laboratory (Quintiles Central Laboratories, East Lothian, U.K.) performed laboratory analyses. A1C was assayed using a validated high-performance liquid chromatography (HPLC) method certified by the National Glycohemoglobin Standardization Program (NGSP). FPG was measured using the Gluco-quant system (Roche, Mannheim, Germany). Insulin antibodies were analyzed by Celerion (Fehraltorf, Switzerland), using a subtraction radioimmunoassay method (15) that was validated according to standard procedures (16). Participants were provided with glucose meters (Precision Xceed/Xceed Optium/Xido Xceed; Abbott Diabetes Care, Alameda, CA) to determine SMPG and recorded values in their diaries.

Statistical methods

The statistical evaluation of A1C, FPG, and hypoglycemic episodes was based on all randomized participants following the intention-to-treat principle. Missing values for A1C and FPG were imputed using last observation carried forward (LOCF). Treatment differences in A1C and FPG values after 16 weeks of treatment were estimated by ANOVA, adjusted by country, sex, age, and A1C (or FPG) at randomization. The rate of hypoglycemic episodes during the exposure to trial insulin was estimated by a negative binomial regression model, in which the number of episodes per patient year of exposure (events per patient year) was adjusted by country, sex, age, and A1C at randomization (17).

The aim of this phase 2 trial was not to determine superiority or noninferiority of IDeg but rather to estimate a treatment difference (in A1C) with a sufficient precision. Fifty completed subjects per group were estimated to provide a 95% CI for the treatment difference with a total width of 0.8% (absolute). No confirmatory hypotheses were prespecified, no formal statistical testing was undertaken, and therefore no *P* values were reported. Based on the chosen precision for A1C and an expected dropout ratio of 17%, 60 participants were to be randomized to each treatment arm.

Values are presented as means ± SD for descriptive statistics, as estimated treatment differences (95% CI) for inferential statistics from the ANOVA, and as estimated rate ratios (RR) (95% CI) from the negative binomial model.

RESULTS

Participant characteristics

Of 200 people screened, 178 were considered eligible for the clinical trial and

were randomized and exposed to trial insulin products. Apart from a small difference in the baseline dose of basal insulin between IDeg and IGlar, there were no major differences in baseline characteristics between the groups (Table 1). Minor differences in sex, age, baseline A1C, and FPG were adjusted for in the statistical model. A similar proportion of participants completed the study in all treatment groups, and the reasons for withdrawal did not differ markedly between groups. At study entry, most participants were using a basal + mealtime insulin regimen, with either once- or twice-daily injections of basal insulin (Table 1).

Glycemic control

After 16 weeks, mean A1C had decreased by 0.57 ± 0.76 %-point from baseline in the IDeg(A) group, by 0.54 ± 0.78 %-point in the IDeg(B) group, and by 0.62 ± 0.68 %-point in the IGlar group (Fig. 1), to similar mean end-of-trial levels (7.8 ± 0.8, 8.0 ± 1.0, and 7.6 ± 0.8%, respectively). Estimated mean treatment differences were 0.10 %-point [−0.14 to 0.34] (IDeg(A) − IGlar) and 0.18 %-point [−0.06 to 0.42] (IDeg(B) − IGlar).

Laboratory-measured FPG decreased from baseline in all groups: by 1.60 ± 4.66 mmol/L for IDeg(A), by 2.06 ± 5.17 mmol/L for IDeg(B), and by 0.54 ± 4.36 mmol/L for IGlar. After 16 weeks, FPG was 8.3 ± 4.0 mmol/L, 8.3 ± 2.8 mmol/L, and 8.9 ± 3.5 mmol/L for IDeg(A), IDeg(B), and IGlar, respectively. Estimated mean treatment differences were −0.56 mmol/L [−1.84 to 0.73] (IDeg(A) − IGlar) and −0.76 mmol/L [−2.04 to 0.52] (IDeg(B) − IGlar).

At study end, the plasma glucose levels in the nine-point SMPG profiles were slightly reduced in all treatment groups; the overall shape of the SMPG profiles was similar between treatments (Supplementary Data; Fig. 1).

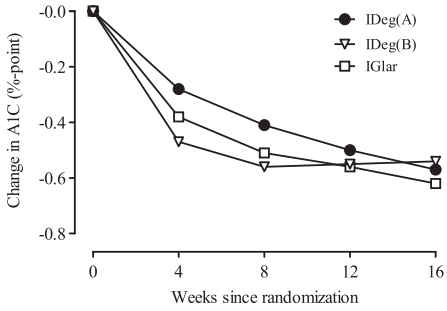

Figure 1—*Mean change from baseline in A1C. Data are mean (last observation carried forward) for each time point.*

Hypoglycemic episodes

Estimated mean rates of confirmed hypoglycemia were numerically lower for IDeg(A) and IDeg(B) than IGlar (47.9, 59.5, and 66.2 events/patient year, respectively) corresponding to rate reductions of 28% for IDeg(A) (RR: 0.72 [0.52–1.00]) and 10% for IDeg(B) (RR: 0.90 [0.65–1.24]), relative to IGlar.

Similarly, estimated mean rates of confirmed nocturnal hypoglycemia were numerically lower for IDeg(A) and IDeg(B) compared with IGlar (5.1, 8.8, and 12.3 events/patient year, respectively), corresponding to rate reductions of 58% for IDeg(A) (RR: 0.42 [0.25–0.69]) and 29% for IDeg(B) (RR: 0.71 [0.44–1.16]), relative to IGlar.

Of the confirmed hypoglycemic episodes, the number of symptomatic (asymptomatic) episodes was 800 (97), 835 (177), and 873 (231) for IDeg(A), IDeg(B), and IGlar, respectively. Low absolute numbers of severe hypoglycemic episodes were reported for IDeg(A), IDeg(B), and IGlar (seven, eight, and six episodes, respectively).

In the immediate period after randomization, there was no apparent excess of hypoglycemic episodes with either insulin. After the first few weeks of treatment, an apparent difference in hypoglycemia frequency was observed, with a lower number of confirmed hypoglycemic episodes (overall and nocturnal) in the IDeg(A)- and IDeg(B)-treated groups compared with IGlar (Fig. 2).

Insulin doses

The average total daily insulin dose did not change substantially from pretrial to end of trial for the IDeg(A) group (from 60 ± 22 to 60 ± 25 units) or the IGlar group (from 52 ± 21 to 51 ± 22 units),

Table 1—*Clinical characteristics of randomized population*

	IDeg(A)	IDeg(B)	IGlar
Randomized, *n*	59	60	59
Exposed, *n* (%)	59 (100)	60 (100)	59 (100)
Withdrawn, *n* (%)	7 (12)	5 (8)	7 (12)
Adverse event*	2 (3)	0 (0)	1 (2)
Noncompliance	2 (3)	1 (2)	1 (2)
Ineffective therapy	1 (2)	2 (3)	0 (0)
Other	2 (3)	2 (3)	5 (9)
Completed trial, *n* (%)	52 (88)	55 (92)	52 (88)
Sex, *n* (%)			
Men	37 (63)	37 (62)	32 (54)
Women	22 (37)	23 (38)	27 (46)
Race, *n* (%)			
White	58 (98)	59 (98)	57 (97)
Black or African	1 (2)	0 (0)	0 (0)
Asian	0 (0)	1 (2)	1 (2)
Other	0 (0)	0 (0)	1 (2)
Age (years)	44.5 ± 12.7	45.6 ± 12.5	47.2 ± 13.5
Weight (kg)	80.9 ± 11.8	80.5 ± 14.5	77.7 ± 14.2
BMI (kg/m^2)	27.2 ± 3.4	27.1 ± 3.6	26.3 ± 3.9
Diabetes duration (years)	22.7 ± 14.6	20.8 ± 10.6	19.1 ± 10.8
Baseline A1C (%)	8.4 ± 0.9	8.5 ± 1.0	8.3 ± 0.8
Baseline FPG (mmol/L)	9.9 ± 3.3	10.3 ± 4.8	9.5 ± 3.8
Pretrial insulin regimen, *n* (%)			
Basal (once daily + mealtime)	30 (51)	30 (50)	33 (56)
Basal (twice daily + mealtime)	25 (42)	26 (43)	25 (42)
Premix insulin	1 (2)	1 (2)	1 (2)
Pump (CSII)	2 (3)	3 (5)	0 (0)
Mealtime only	1 (2)	0 (0)	0 (0)
Basal insulin dose at baseline (units)	29 ± 12	28 ± 13	23 ± 11
Mealtime insulin dose at baseline (units)	31 ± 15	30 ± 14	29 ± 14
Total insulin dose at baseline (units)	60 ± 22	59 ± 23	52 ± 21

*Adverse event withdrawals: diabetic ketoacidosis (IGlar), nausea (IDeg(A)), abdominal distension (IDeg(A)). CSII: continuous subcutaneous insulin infusion.

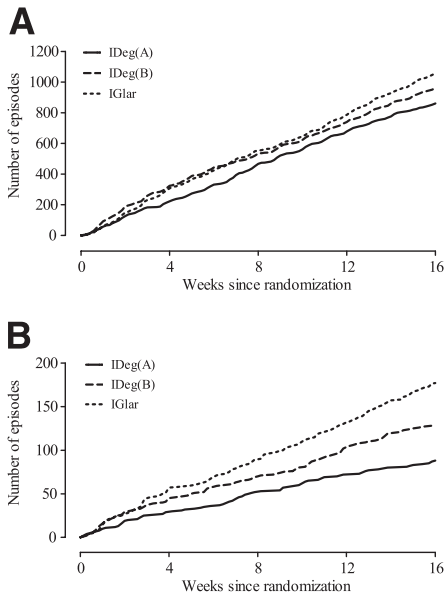

Figure 2—*Cumulative number of hypoglycemic episodes.* A: *confirmed episodes (PG <3.1 mmol/L or requiring assistance).* B: *Nocturnal episodes (all confirmed episodes between 2300 and 0559 h, inclusive).*

with an approximately equal split between basal and bolus insulin for both groups throughout the study. Small increases in mean daily basal insulin dose were observed from pretrial to end of trial for IDeg(A) (from 29 ± 12 to 30 ± 13 units) and IGlar (from 23 ± 11 to 26 ± 13 units). After 16 weeks, the mean daily bolus insulin dose was 30 ± 15 units in the IDeg(A) group and 26 ± 11 units in the IGlar group. For the IDeg (B) group, decreases from pretrial to end of trial in mean daily basal insulin dose (from 28 ± 13 to 23 ± 13 units) and mean daily bolus dose (from 30 ± 14 to 26 ± 14 units) were observed, resulting in the mean total daily insulin dose decreasing from 59 ± 23 (pretrial) to 49 ± 23 units (end of trial).

Adverse events and other safety measures

The overall rates of AEs for IDeg(A), IDeg(B), and IGlar were 8.7, 6.5, and 9.1 events/patient year. There were no specific patterns or clustering of the AEs; most were mild or moderate in severity and judged by the investigator as having an unlikely relation to the trial insulin products. No injection-site reactions were reported.

Four serious AEs were reported: diabetic ketoacidosis (IGlar), abdominal distension (IDeg(A)), hypoglycemic unconsciousness (IDeg(A)), and hypoglycemia (IDeg(B)).

Body weight change after 16 weeks was +0.1 ± 2.7 kg for IDeg(A), +1.0 ± 2.5 kg for IDeg(B), and +0.7 ± 1.6 kg for IGlar. After 16 weeks, there were no obvious differences between treatment groups in clinical laboratory tests, ECG, fundoscopy, vital signs, or physical examination.

For all participants, the level of IDeg-specific antibodies was close to, or below, the limit of detection at screening and remained at the same level after 16 weeks of treatment with IDeg. Similarly, IAsp-specific antibodies remained at a low, stable level throughout the study. No obvious trend was observed in the development of cross-reacting antibodies (Supplementary Data; Table 1), since the values were constant in the majority of participants. There was no apparent association between the levels of cross-reacting antibodies and A1C, body weight, insulin dose, or hypoglycemic episodes (data not shown).

CONCLUSIONS—No safety or tolerability issues unique to IDeg were seen in this exploratory clinical trial in people with type 1 diabetes. Similar A1C levels were achieved with comparable mean total daily doses of insulin.

The difference in end-of-trial basal insulin doses between IDeg(A) and IGlar reflected the fact that a higher basal insulin dose was used in the IDeg(A) group already at study entry. The observed decrease in mean dose in the IDeg(B) group suggested that the chosen starting dose for this higher strength basal insulin formulation (900 μmol/L) was too high.

It was evident that the rates of confirmed hypoglycemia (overall and nocturnal) were lower for IDeg compared with IGlar throughout the trial, indicating a better tolerability profile that was most apparent for IDeg(A). The trend for a lower rate of overall hypoglycemia for IDeg(A) versus IGlar (RR: 0.72 [0.52–1.00]) creates the opportunity for confirming this finding via similar treatment algorithms in larger, longer-term clinical trials. It remains to be proven whether it will be possible for patients treated with IDeg to achieve lower mean glycemic values at equivalent rates of hypoglycemia to other basal insulin preparations.

Recently, it has been reported that IDeg has a significantly (4 times) lower within-subject variability of action compared with IGlar (18). It is proposed that the unique mechanism of protraction of IDeg, based on soluble multihexamer formation in the subcutaneous depot, provides a buffering effect against changes in absorption rate, which thereby contributes to a stable and more consistent activity. This lower within-subject variability could provide a mechanistic explanation for the lower rate of hypoglycemic episodes observed with IDeg.

This was a short-term, exploratory study with a relatively small number of exposed participants, not specifically powered for superiority or noninferiority. Nonetheless, the results of the study strongly support the continued clinical development of 600 μmol/L formulation of IDeg (clinical development of the IDeg(B) formulation has been discontinued).

The limitations of this phase 2 study are the small number of people studied and the short duration of study, in the setting of a chronic condition with disparate insulin effects in different individuals. Small numbers of participants and short duration also limit the amount of safety and tolerability data collected, issues that will be better addressed in the phase 3 development program. Moreover, inclusion of patients with a history of recurrent hypoglycemia and using a higher plasma glucose value for defining confirmed hypoglycemia would likely have led to higher reported rates of hypoglycemia for all treatment groups. The open-label design (necessitated by different insulin delivery systems) could also have influenced efforts to attain blood glucose control by participants and investigators, and perhaps even the reporting of hypoglycemia and adverse events. However, insulin doses revealed no evidence of trial-induced bias, and hypoglycemia rates were consistently different throughout the study (Fig. 2).

In summary, this clinical trial showed that IDeg, used in combination with mealtime IAsp, is a well-tolerated and efficacious treatment when used in people with type 1 diabetes, providing comparable glycemic control to insulin glargine at comparable doses, but with lower rates of hypoglycemia.

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