Low-Volume Insulin Degludec 200 Units/mL Once Daily Improves Glycemic Control Similarly to Insulin Glargine With a Low Risk of Hypoglycemia in Insulin-Naïve Patients With Type 2 Diabetes

A 26-week, randomized, controlled, multinational, treat-to-target trial: The BEGIN LOW VOLUME trial

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OBJECTIVE—The 200 units/mL formulation of insulin degludec (IDeg 200 units/mL) contains equal units of insulin in half the volume compared with the 100 units/mL formulation. We compared the efficacy and safety of IDeg 200 units/mL once daily with 100 units/mL insulin glargine (IGlar) in insulin-naïve subjects with type 2 diabetes (T2DM) inadequately controlled with oral antidiabetic drugs.

RESEARCH DESIGN AND METHODS—In this 26-week, open-label, treat-to-target trial, subjects (n = 457; mean HbA_{1c} 8.3% [67 mmol/mol], BMI 32.4 kg/m^2, and fasting plasma glucose [FPG] 9.6 mmol/L [173.2 mg/dL]) were randomized to IDeg 200 units/mL or IGlar, both given once daily in combination with metformin with or without a dipeptidyl peptidase-4 inhibitor. Basal insulin was initiated at 10 units/day and titrated weekly to an FPG target of <5 mmol/L (<90 mg/dL) according to mean prebreakfast self-measured blood glucose values from the preceding 3 days.

RESULTS—By 26 weeks, IDeg reduced HbA_{1c} by 1.30% and was not inferior to IGlar. Mean observed FPG reductions were significantly greater with IDeg than IGlar (−3.7 vs. −3.4 mmol/L [–67 vs. –61 mg/dL]; estimated treatment difference: −0.42 [95% CI −0.78 to −0.06], P = 0.02). Despite this difference, rates of overall confirmed hypoglycemia were not higher with IDeg than with IGlar (1.22 and 1.42 episodes/patient-year, respectively), as were rates of nocturnal confirmed hypoglycemia (0.18 and 0.28 episodes/patient-year, respectively). Mean daily basal insulin dose was significantly lower by 11% with IDeg 200 units/mL compared with IGlar. IDeg was well-tolerated, and the rate of treatment-emergent adverse events was similar across groups.

CONCLUSIONS—In this treat-to-target trial in insulin-naïve patients with T2DM, IDeg 200 units/mL improved glycemic control similarly to IGlar with a low risk of hypoglycemia.

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Basal insulins are an important treatment option for persons with type 2 diabetes (T2DM), with progressively higher doses of insulin required over the duration of the disease. Moreover, approximately 90% of those with T2DM in the U.S. are overweight (1), and obese patients often are less sensitive to exogenous insulin and therefore require higher doses to maintain good glycemic control. Globally, approximately 30% of patients with T2DM who use basal insulin require >60 units daily (2). The use of a highly concentrated formulation of regular insulin, U-500 regular insulin (Humulin R U-500; Eli Lilly and Company, Indianapolis, IN), was originally developed to address high insulin requirements. The frequency of use of U-500 regular insulin increased dramatically by >70% in the U.S. between 2007 and 2008 (3), corresponding to the escalating number of people with T2DM and obesity.

Currently marketed insulin pen devices only allow the administration of a maximum of 80 units per injection, and administration of larger volumes of insulin has typically required the use of a vial and syringe or the addition of a second injection. Very large doses of insulin delivered as a single injection with a syringe may be painful and cause discomfort at the site of injection, and it can be physically challenging to deliver such a large volume smoothly (4). Together, these limitations highlight the need for an insulin formulation with a higher concentration that allows administration of higher doses of insulin in a single injection.

Insulin degludec (IDeg) is an ultra–long-acting basal insulin that is in clinical development. On subcutaneous injection, IDeg forms soluble multihexamers that slowly dissociate into monomers to produce a flat and consistent insulin action profile, with a duration of action >42 h (5,6). To meet the need for higher insulin doses in patients who use prefilled pen devices, a more concentrated 200 units/mL formulation of IDeg was developed at the same time as the 100 units/mL preparation. IDeg 200 units/mL is bioequivalent to IDeg 100 units/mL and demonstrates

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a similar glucose-lowering effect (7). Clinical trials comparing IDeg 100 units/mL with insulin glargine (IGlar) at 100 units/mL have demonstrated that IDeg 100 units/mL provides glycemic efficacy similar to that of IGlar, with lower rates of hypoglycemia (8–10).

IDeg 200 units/mL contains the same number of units of insulin in half the volume compared with IDeg 100 units/mL and, when administered in the new FlexTouch pen device, can deliver as much as 160 units of insulin in a single injection. There is no dose correction or calculation necessary, because the FlexTouch pen internally corrects for the 200 units/mL concentration. Thus only the injected volume of a given dose of insulin differs between the 200 units/mL pen device and other devices. This eliminates any potential dose confusion when changing between currently available 100 units/mL basal insulin products and the possibility of mistakenly interchanging IDeg 100 units/mL and 200 units/mL insulin pens (on their approval by the U.S. Food and Drug Administration).

The purpose of this study was to compare efficacy and safety between IDeg 200 units/mL and IGlar, both administered once daily in combination with metformin with or without a dipeptidyl peptidase-4 (DPP-4) inhibitor, in insulin-naïve patients with T2DM requiring an intensification of treatment.

RESEARCH DESIGN AND METHODS

Trial design

This phase 3a, 26-week, randomized, controlled, open-label, multinational, treat-to-target, noninferiority trial compared efficacy and safety between IDeg 200 units/mL and IGlar, both administered once daily in combination with metformin with or without a DPP-4 inhibitor in insulin-naïve participants with T2DM previously treated with oral antidiabetic drugs, who qualified for intensification of treatment. The trial was open-label because of the lack of availability of appropriate placebo-containing injection devices. The trial was conducted between 1 March and 26 November 2010 at 106 sites in 8 countries (Canada, France, Ireland, the Russian Federation, South Africa, Ukraine, the U.K., and the U.S.).

The study was completed in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines; institutional review boards reviewed and approved the protocol for each study site; and all patients provided written, informed consent before participation in the trial (11,12). The trial is registered at ClinicalTrials.gov as NCT01068665.

Participants

Candidates who were insulin-naïve adults with T2DM for ≥6 months, HbA_{1c} 7–10% (53–86 mmol/mol, inclusive), BMI ≤45 kg/m^2, and previous treatment with metformin with or without additional oral antidiabetic drugs for ≥3 months were eligible to participate in the study. Key exclusion criteria included thiazolidinedione, exenatide, or liraglutide use within 3 months of participation in the trial, cardiovascular disease (e.g., stroke, myocardial infarction, unstable angina pectoris) within 6 months of the trial, uncontrolled hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg), impaired liver function (alanine aminotransferase ≥2.5 times the upper limit of normal), impaired renal function (serum creatinine ≥125 μmol/L or ≥1.4 mg/dL for males and ≥110 μmol/L or ≥1.3 mg/dL for females), recurrent severe hypoglycemia (more than one episode requiring assistance in the previous 12 months) or hypoglycemic unawareness, hospitalization for diabetic ketoacidosis within 6 months of the trial, and proliferative retinopathy or maculopathy.

Treatments

By means of an interactive voice/web response system, eligible participants were randomized 1:1 to either once-daily IDeg 200 units/mL (3-mL FlexTouch; Novo Nordisk, Bagsværd, Denmark) or once-daily IGlar (Lantus 100 units/mL, 3-mL SoloStar; Sanofi U.S. LLC, St. Louis, MO) and continued metformin with or without DPP-4 inhibitor treatment. Trial participants were instructed to continue the same total daily dose of metformin and DPP-4 inhibitor treatment as before the start of the trial. In countries where DPP-4 inhibitor treatment did not have the indication of combination with insulin treatment, participants discontinued DPP-4 inhibitor treatment at randomization.

IDeg 200 units/mL was administered once-daily with the main evening meal and, consistent with its product labeling, IGlar was administered once daily at the same time each day. Insulin treatments were injected subcutaneously in the thigh, upper arm, or abdomen. The starting dose for each insulin was 10 units and, during the treatment period, the dose was systematically titrated using a treat-to-target approach striving for a prebreakfast self-measured blood glucose (SMBG) level of <5 mmol/L (<90 mg/dL). Both IDeg 200 units/mL and IGlar were titrated once weekly (Supplementary Table 1) according to the average of three preceding prebreakfast SMBG levels and other available data (e.g., symptoms of hypoglycemia or hyperglycemia, previous responses to dose adjustments, and any additional nonmandatory blood glucose measurements). The treatment period was 26 weeks, and doses were individually titrated in an effort to achieve a specific target of <5 mmol/L (<90 mg/dL) with both treatments. After the 26-week treatment period, participants switched their basal insulin treatment to the intermediate-acting NPH insulin for 1 week to wash out the investigational exogenous insulins and minimize interference with insulin antibody measurements.

The safety committee from the sponsor performed ongoing blinded safety surveillance. Titration of insulin doses was monitored by the outside company Quintiles (Singapore, U.S., and Switzerland) and reviewed by the sponsor's titration committee. Cardiovascular events were adjudicated and assessed by an independent external event adjudication committee.

Primary and secondary end points

The primary end point for this study was change in HbA_{1c} from baseline after 26 weeks of treatment. Secondary confirmatory end points tested were number of treatment-emergent confirmed hypoglycemic episodes, change from baseline in central laboratory–measured fasting plasma glucose (FPG), within-subject variability as measured by coefficient of variation, and frequency of participants achieving HbA_{1c} <7% (<53 mmol/mol) without confirmed hypoglycemic episodes. The supportive secondary end points included 9-point SMBG profiles, frequency of participants achieving HbA_{1c} <7% (<53 mmol/mol), and Health-Related Quality of Life (Short Form 36) questionnaire scores. The safety assessments included adverse events (AEs), hypoglycemic episodes, insulin dose, body weight, physical examination, vital signs, fundoscopy, electrocardiogram, and laboratory tests (including antibodies). Confirmed hypoglycemic episodes

were defined as episodes of SMBG of <3.1 mmol/L (<56 mg/dL) or severe episodes requiring assistance (13). Hypoglycemic episodes occurring between 0001 and 0559 h (inclusive) were classified as nocturnal.

Laboratory analyses were performed by Quintiles Central Laboratories in Scotland, South Africa, and the U.S. Insulin antibodies were analyzed at Celerion Switzerland AG (Fehraltorf, Switzerland).

Statistical analysis

Analyses of all efficacy end points were based on the full analysis set, which included all randomized participants. The safety analysis set included all participants who received at least one dose of the investigational product or the comparator. Missing values were imputed with the last observation carried forward method.

The primary objective of this trial was to confirm the noninferiority of IDeg 200 units/mL once daily to IGlar once daily as assessed by change in HbA_{1c} from baseline after 26 weeks of treatment. Type I error was controlled by adopting a hierarchical (fixed-sequence) testing procedure for selected end points, including change in HbA_{1c}, number of confirmed hypoglycemic episodes, change in FPG, within-subject variability in prebreakfast blood glucose, and responders without hypoglycemic episodes. Noninferiority was confirmed if the upper limit of the 95% CI for the treatment difference was ≤0.4%. Sample size was determined on the basis of the primary objective with a *t* statistic under the assumption of a one-sided *t* test of size 2.5%, a zero mean treatment difference, and a 1.3% SD for HbA_{1c}.

Treatment difference in change from baseline in HbA_{1c} after 26 weeks was analyzed with an ANOVA model with treatment, antidiabetic therapy at screening, sex, and region (Europe, North America, or South Africa) as fixed factors and age and baseline HbA_{1c} as covariates. Treatment differences in FPG, Health-Related Quality of Life (Short Form 36) score, body weight, and insulin dose (log transformed) at the end of trial were analyzed by means of ANOVA with treatment, antidiabetic therapy at screening, sex, and region as fixed factors and age and relevant baseline values as covariates. A mixed-effects model was fitted to the 9-point SMBG profile data, which included treatment, time, interaction between treatment and time, antidiabetic therapy at screening, sex, and region as fixed factors; age as covariate; and subject as a random factor. Logarithm-transformed SMBG prebreakfast values were analyzed as repeated measures in a linear mixed model with treatment, antidiabetic therapy at screening, sex, and region as fixed factors; age as covariate; and subject as random factor. The model assumed independent within- and between-subject errors, with variances depending on treatment. The within-subject coefficient of variation was derived from the estimated within-subject variability (σ^2) as square root ($\exp(\sigma^2) - 1$). Responder (HbA_{1c}) analysis was based on a logistic regression model using treatment, antidiabetic therapy at screening, sex, and region as fixed factors and age and baseline HbA_{1c} as covariates. The number of treatment-emergent confirmed hypoglycemic episodes was analyzed according to a negative binomial regression model including treatment, antidiabetic therapy at screening, sex, and region as fixed factors and age as covariate. A similar model was used for post hoc analysis of treatment-emergent confirmed hypoglycemic episodes in participants requiring ≥60 and ≥80 units of insulin by the end of the trial; however, nocturnal confirmed hypoglycemic episodes for participants requiring ≥80 units by the end of trial were analyzed by mean of a Poisson model with only treatment as a fixed factor.

RESULTS

Participant characteristics

A total of 697 candidates were screened for this study: 237 were excluded by screening, and the remaining 460 participants were randomly assigned (1:1) to the IDeg 200 units/mL and IGlar treatment groups. Of these 460 participants, 3 were randomized in error and were withdrawn from the trial without any trial treatments. One randomized subject in the IGlar group withdrew consent before the trial drug was given. Accordingly, 457 (IDeg 200 units/mL *n* = 228 and IGlar *n* = 229) and 456 (IDeg 200 units/mL *n* = 228 and IGlar *n* = 228) participants were exposed to treatment and comprised the intent-to-treat and safety populations (Supplementary Fig. 1). Treatment groups had similar baseline characteristics and demographic data (Table 1).

Efficacy

Glycemic control, in terms of change in HbA_{1c} from baseline, improved with both IDeg 200 units/mL and IGlar after 26 weeks of treatment. Mean HbA_{1c} decreased by 1.3 ± 1.01% (14.3 ± 11.0 mmol/mol, mean ± SD) for both treatment groups, with an estimated treatment difference (ETD [IDeg – IGlar]) of 0.04 (95% CI −0.11 to 0.19) (Fig. 1*A*). Thus IDeg 200 units/mL was noninferior to IGlar in reducing HbA_{1c}. Similar proportions of participants achieved the HbA_{1c} target of <7% (<53 mmol/mol) at the end of trial with IDeg 200 units/mL (52%) and IGlar (56%), with no statistically significant difference between the treatment groups (treatment odds ratio IDeg 200 units/mL /IGlar 0.85 [95% CI 0.56–1.30]). A similar proportion of participants (45%) achieved this target at the end of the trial without treatment-emergent hypoglycemia during the last 12 weeks of treatment.

IDeg 200 units/mL resulted in a statistically significantly greater FPG reduction than IGlar after 26 weeks of treatment (Fig. 1*B*). Central laboratory–measured FPG decreased by 3.7 mmol/L (66.7 mg/dL) to 5.9 mmol/L (105.7 mg/dL) with IDeg 200 units/mL and by 3.4 mmol/L (60.9 mg/dL) to 6.3 mmol/L (113.1 mg/dL) with IGlar (ETD −0.42 [95% CI −0.78 to −0.06]). Overall, the 9-point SMBG profiles were similar between IDeg 200 units/mL and IGlar and decreased in both treatment groups after 26 weeks (Fig. 1*C*). The estimated treatment ratio for within-subject variation in prebreakfast SMBG was 0.92 (95% CI 0.84–1.01). The proportions of participants meeting the prebreakfast SMBG target of <5 mmol/L (<90 mg/dL) by week 26 were 35% for IDeg 200 units/mL and 33% for IGlar. Median times to achievement of the prebreakfast SMBG target for the first time were 12 weeks with IDeg 200 units/mL and 14 weeks with IGlar (estimated hazard ratio 1.15 [95% CI 0.93–1.41], *P* = NS).

Dosing

At the end of the trial, after 26 weeks of treatment, mean daily insulin dose was significantly lower by 11% with IDeg 200 units/mL than with IGlar (0.53 and 0.60 units/kg, respectively); estimated mean ratio IDeg 200 units/mL /IGlar was 0.89 (95% CI 0.82–0.98, $P < 0.05$). For both treatment groups, the largest increase in insulin dose was observed during the first few weeks of the trial, but dose continued to increase gradually throughout the trial (Supplementary Fig. 2). At the end of the trial, the percentages of participants who required >80 units of insulin were 21.2% and 20.9%, and the percentages requiring

Table 1—*Demographic data and baseline characteristics*

Characteristic	IDeg 200 units/mL OD	IGlar OD
Participants in the full analysis set, *n*	228	229
Participants in the safety analysis set, *n*	228	228*
Female	109 (47.8%)	105 (45.9%)
Race		
White	180 (78.9%)	178 (77.7%)
Black	31 (13.6%)	32 (14.0%)
Asian (Indian or non-Indian)	8 (3.5%)	9 (3.9%)
Other	24 (10.5%)	25 (10.8%)
Ethnicity (Hispanic or Latin American)	20 (8.8%)	16 (7.0%)
Age, years	57.8 (9.0)	57.3 (9.4)
Body weight, kg	92.2 (18.5)	92.7 (18.4)
BMI, kg/m^2	32.2 (5.4)	32.7 (5.3)
Duration of diabetes, years	8.4 (6.7)	8.0 (5.6)
HbA_{1c}, %	8.3 (1.0)	8.2 (0.9)
HbA_{1c}, mmol/mol	67.1 (10.7)	66.6 (9.4)
FPG, mmol/L	9.6 (2.9)	9.7 (2.6)
FPG, mg/dL	172.4 (51.7)	174.1 (46.8)
Systolic blood pressure, mmHg	131.2 (13.9)	131.0 (13.6)
Diastolic blood pressure, mmHg	78.1 (8.3)	79.2 (8.4)
HDL cholesterol, mg/dL	43.3 (11.6)	42.9 (11.2)
LDL cholesterol, mg/dL	92.8 (38.3)	94.4 (39.8)
Total cholesterol, mg/dL	170.5 (43.7)	172.9 (52.6)
Triglycerides, mg/dL	184.07 (215.93)	184.96 (221.24)
OADs at screening		
Metformin	228 (100.0%)	229 (100.0%)
SU	149 (65.3%)	151 (65.9%)
DPP-4 inhibitor†	39 (17.1%)	34 (14.8%)
Glinide	0 (0.0%)	4 (1.7%)
α-Glucosidase inhibitor	4 (1.8%)	1 (0.4%)
Antidiabetic treatment at screening		
1 OAD	62 (27.2%)	70 (30.6%)
2 OADs	141 (61.8%)	133 (58.1%)
>2 OADs	25 (11.0%)	26 (11.4%)

Data are presented as *n* (%) or mean (SD). OAD, oral antidiabetic drug; OD, once daily; SU, sulfonylurea. *One randomized participant withdrew consent and was never administered any drug product. †In countries where DPP-4 inhibitor treatment did not have an indication of combination with insulin treatment, 17 participants in each treatment arm discontinued their DPP-4 inhibitor treatment at randomization.

>160 units of insulin daily were 0.9% and 0.9% in the IDeg 200 units/mL and IGlar groups, respectively. The titration algorithm was closely adhered to, as indicated by the close to 0 units mean and median differences between the titration algorithm dose and the prescribed dose (Supplementary Fig. 3).

Safety

No subjects in either of the treatment groups reported episodes of severe hypoglycemia. The percentages of subjects who experienced one or more confirmed hypoglycemic episodes during the treatment period were 28.5% with IDeg and 30.7% with IGlar (Table 2). The event rates of confirmed hypoglycemia with IDeg 200 units/mL and IGlar were 1.22 and 1.42 episodes/patient-year, respectively (estimated rate ratio [ERR] for IDeg 200 units/mL /IGlar 0.86 [95% CI 0.58–1.28], $P = 0.46$) (Supplementary Fig. 4*A*). A total of 6.1% and 8.8% of participants in the IDeg 200 units/mL and IGlar treatment groups, respectively, experienced nocturnal confirmed hypoglycemic episodes with rates of 0.18 and 0.28 episodes/patient-year, respectively (ERR IDeg 200 units/mL /IGlar 0.64 [0.30–1.37], $P = 0.25$) (Table 2 and Supplementary Fig. 4*B*).

For participants requiring ≥60 units by the end of the trial, rates of confirmed hypoglycemic episodes were 0.74 and 0.80 episodes/patient-year for IDeg 200 units/mL and IGlar, respectively (ERR IDeg 200 units/mL /IGlar 0.84 [95% CI 0.43–1.65]), and were 0.39 and 0.70 episodes/patient-year for those requiring ≥80 units of IDeg 200 units/mL and IGlar, respectively (ERR IDeg 200 units/mL /IGlar 0.82 [0.24–2.80]). The rates of nocturnal confirmed hypoglycemic episodes in participants treated with ≥60 units and ≥80 units were 0.08 episodes/patient-year for IDeg 200 units/mL and 0.16 episodes/patient-year for IGlar, ERR IDeg 200 units/mL /IGlar 0.56 [0.13–2.37] and were 0.04 and 0.11 episodes/patient-year for IDeg 200 units/mL and IGlar, respectively (ERR IDeg 200 units/mL / IGlar 0.36 [0.04–3.41]).

Mean observed body weight gain from baseline to the end of trial was similar between IDeg 200 units/mL (1.9 kg) and IGlar (1.5 kg) groups (ETD 0.44 [95% CI –0.20 to 1.08], P = NS). There were no clinically relevant differences in vital signs, electrocardiogram, fundoscopy, physical examination, and laboratory values between the IDeg 200 units/mL and IGlar treatment groups. After 26 weeks of treatment, cross-reacting insulin antibodies remained low in both treatment groups (IDeg 200 units/mL 0.4% vs. IGlar 2.2% bound/total antibodies).

The most frequently reported AEs in both treatment groups were headache, diarrhea, and nasopharyngitis (Supplementary Table 2). Approximately 65% of participants treated with IDeg 200 units/mL and 68% of those treated with IGlar reported an AE, and most were mild or moderate in severity and unlikely to be related to the trial drug or trial device, as determined by the investigator. The rate of AEs possibly or probably related to trial product was numerically lower with IDeg 200 units/mL than with IGlar (0.38 and 0.52 events/patient-year, respectively). The percentages of participants with injection-site reactions were the same in the IDeg 200 units/mL and IGlar groups (6.1%). Most participants in both treatment groups recovered from the AEs. A total of nine participants (IDeg 200 units/mL $n = 5$ and IGlar $n = 4$) withdrew from the trial because of an AE (Supplementary Table 3).

Serious AEs were reported by 6.6% and 4.4% of participants in the IDeg 200 units/mL and IGlar treatment groups, respectively (Supplementary Table 4). The most frequently reported serious AE in the IDeg 200 units/mL group was in the class of general disorders and administration-site conditions (2.2%), whereas serious AEs were distributed evenly across a

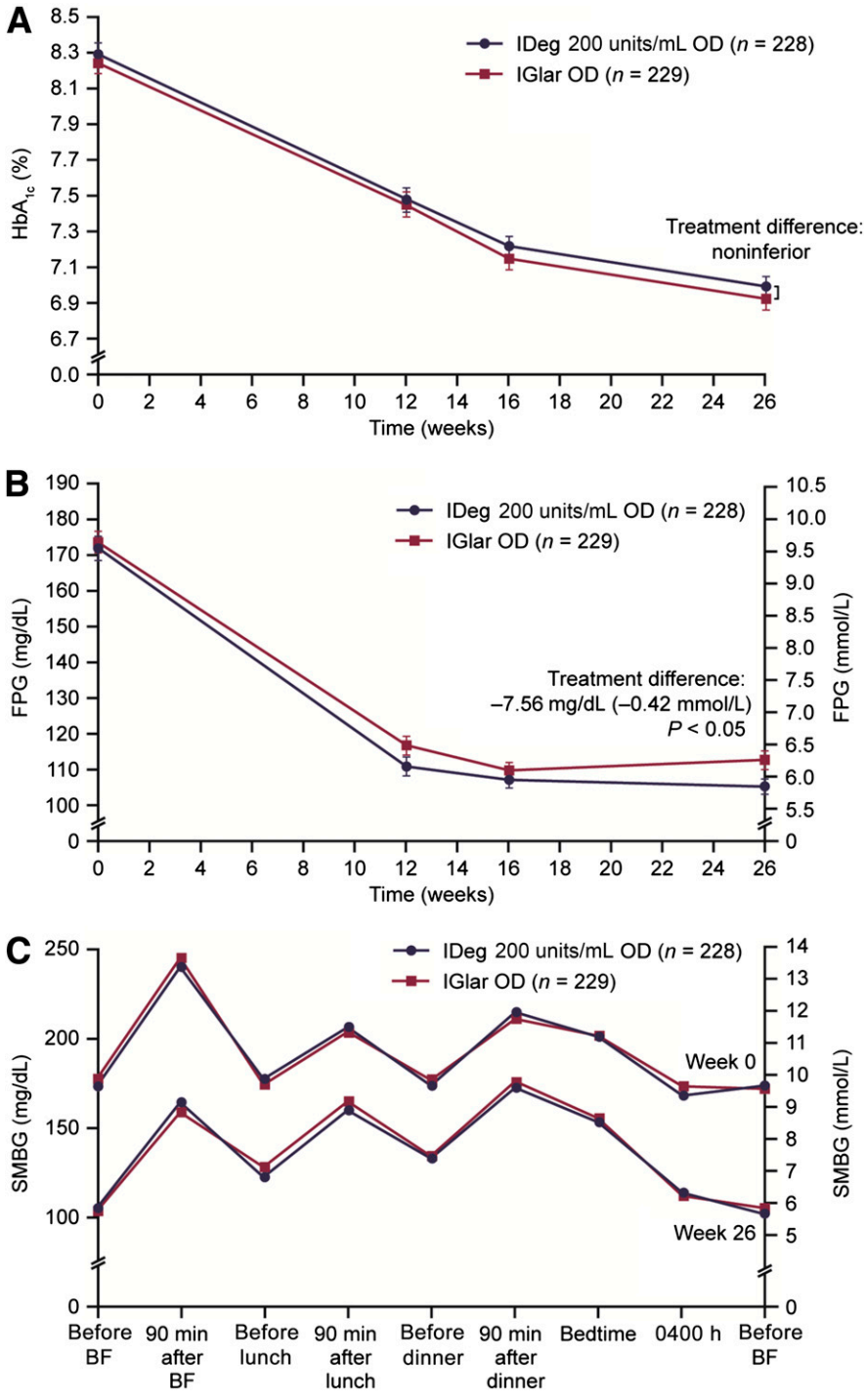

Figure 1—*Mean HbA_{1c} (A), FPG (B), and 9-point SMBG profile (C) over time. BF, breakfast; OD, once daily.*

variety of classes in the IGlar group. No serious AEs were considered to be related to the trial product, as determined by the trial investigator. Two fatal events were reported in this trial, both in the IGlar group. Both participants had medical histories of cardiovascular disease and died during the trial (of cardiac arrest and acute coronary syndrome).

Quality-of-life assessments

The mean observed physical component Health-Related Quality of Life (Short Form 36) scores improved by 1.3 with IDeg 200 units/mL and by 1.2 with IGlar, and the mean observed mental component scores improved by 1.7 with IDeg 200 units/mL and by 0.3 with IGlar. After 26 weeks, two of eight domains in the Health-Related Quality of Life (Short Form 36) questionnaire significantly favored IDeg 200 units/mL, including less bodily pain (ETD 1.6 [95% CI 0.1–3.2], $P = 0.04$) and improved vitality (ETD 1.5 [0.1–3.0], $P = 0.04$) (Fig. 2).

CONCLUSIONS—Results from this 26-week, treat-to-target study demonstrate that IDeg 200 units/mL improves glycemic control, as measured by HbA_{1c}, and is noninferior to IGlar in insulin-naïve patients with T2DM requiring intensification of treatment beyond oral therapy. Moreover, findings from this and other IDeg phase 3 trials demonstrate that systematic weekly insulin dose adjustments are a safe method for patients to achieve glycemic targets. Because of the use of the low-volume preparation, participants in the IDeg 200 units/mL treatment group received their required insulin dose with smaller injection volumes, and participants in the IDeg 200 units/mL group who required >80 units of basal insulin per day (approximately 20%, the same in both groups) were able to administer the full dose in a single injection, rather than the two injections needed by participants in the IGlar group.

The similar HbA_{1c} levels achieved in this study, reflective of the treat-to-target study design, allow a comparison of potential differences in the safety profile of these two basal insulins. Treatment with both insulins demonstrated a total absence of severe hypoglycemic episodes and a particularly low number of confirmed and nocturnal confirmed hypoglycemic episodes when used in a structured, treat-to-target titration designed to reach a fasting glucose target <5 mmol/L (<90 mg/dL). Hypoglycemia is a significant barrier to good glycemic control in T1DM; however, it is infrequently emphasized in the T2DM population, possibly because of the lower relative risk of occurrence in this population (14). The impact that hypoglycemia can have on a patient's health is twofold, including the neurologic and cardiovascular impairments it can cause as well as compromising the ability to achieve good glycemic control, thereby placing patients at risk for future complications (15). Moreover, costs to the patient, including loss of work productivity, direct and indirect medical expenses, and extended periods of hospitalization, can be costly for both the patient and the health care system (15). Given these hypoglycemia-related consequences, any reduction of hypoglycemia

Table 2—*Hypoglycemic episodes*

	IDeg 200 units/mL OD (*N* = 228)			IGlar OD (*N* = 228)				
	Participants	Episodes	Rate*	Participants	Episodes	Rate*	ERR†	*P* value
Severe	0 (0)	0	0	0 (0)	0	0	—	—
Overall confirmed	65 (28.5)	129	1.22	70 (30.7)	152	1.42	0.86 (0.58–1.28)	NS
Nocturnal confirmed	14 (6.1)	19	0.18	20 (8.8)	30	0.28	0.64 (0.30–1.37)	NS

Numbers of participants with each type of hypoglycemic episode are given as *n* (%). OD, once daily. *Rate refers to the rate of hypoglycemia in hypoglycemic episodes per participant-year of exposure. †Calculated as ratio between rates with IDeg 200 units/mL and with IGlar, with 95% CI.

would arguably have beneficial implications for the overall quality of life for patients and the economic and resource burden on the health care system.

Despite the recognized advantages of prefilled insulin pen devices (including superior dosing accuracy, improved patient adherence, and greater ease of use compared with the vial and syringe), the use of pen devices in the U.S. remains low (approximately 15%), perhaps in part limited by the need to inject larger doses than currently possible with prefilled devices (16). IDeg 200 units/mL was developed to address the high insulin requirements of the growing population of patients with T2DM who require higher insulin doses than permitted in a single injection with currently available pens. Furthermore, this formulation offers the added benefit relative to other available insulins of administering a larger dose in a smaller volume. This is likely to be particularly beneficial for insulin-resistant patients who require large insulin doses that cannot be administered by a single injection because of the limited maximum volume delivery (60–80 units) of currently available pen devices.

Many patients with T2DM who require insulin do not adequately titrate their insulin dose, which may be due in part to a fear or risk of hypoglycemia and can lead to suboptimal glycemic control (17). Quality-of-life concerns may also result in patients omitting or skipping insulin injections (18). Likewise, administration of large injection volumes that result in a large subcutaneous depot may be painful, which also could contribute to poor patient adherence (3,19). IDeg 200 units/mL may help to overcome some of these barriers in patients with T2DM, particularly those who require a high insulin dose, by offering a well-tolerated, effective insulin in a convenient pen device that permits insulin dosage to be delivered in a smaller volume than with other currently available pen devices. Additionally, the unique features of the FlexTouch Pen for IDeg 200 units/mL ensure that the dose dialed and shown in the dose counter of the pen is the delivered dose.

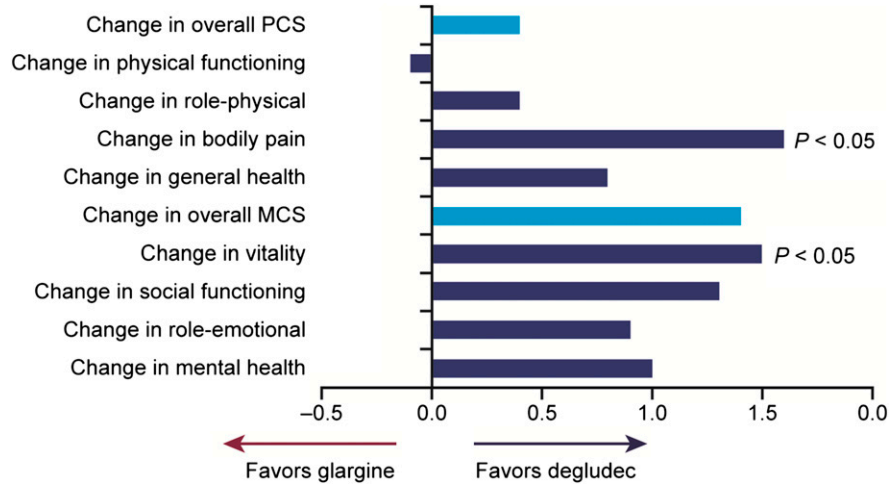

Figure 2—*Between-treatment differences in Health-Related Quality of Life Short Form 36 scores by domain. Each trial participant's general health state was assessed with a validated questionnaire. PCS, physical component score; MCS, mental component score.*

The limitations of the trial should be considered when interpreting the results. First, this study was not conducted in a double-blind fashion. Open-label trial designs pose an underlying risk for greater caution with adjustment of doses for the new drug (in this case IDeg 200 units/mL) and can impose bias in patient-reported outcomes. Second, the duration of the study (26 weeks) may be regarded as a limitation of the trial, especially in comparison with other 52-week insulin trials. From this and other trials of longer duration, however, it is evident that HbA_{1c} levels stabilize by 26 weeks, thus allowing a relevant estimate of treatment effect. The results from this trial comparing IDeg 200 units/mL with IGlar are consistent with results from the previously published 52-week phase 3 (BEGIN) trials comparing IDeg 200 units/mL with IGlar (8–10). The shorter duration of 26 weeks may, however, have led to an underestimation of the potential benefits of IDeg 200 units/mL, because as T2DM progresses more patients are likely to require larger doses of insulin. Third, although IDeg 200 units/mL resulted in a statistically significantly greater FPG reduction than did IGlar after 26 weeks of treatment as measured in the central laboratory, this was not seen in the SMBG data. This difference probably reflects a higher degree of accuracy from the central laboratory compared with the individual self-reported fingerstick test results seen in the SMBG data. Moreover, the weekly titrations were based on the mean of the preceding 3 days' SMBG values, recorded by a handheld home monitoring meter and measured prebreakfast (and thus often early in the morning), whereas the target FPG was based on a single central laboratory value taken at the clinic. Overall, about a third of the patients achieved the fasting glucose target, although the algorithm appeared to be adhered to as evaluated by the concordance between the prescribed dose and the dose

recommended by the algorithm. Finally, the timing of the daily dose of basal insulin was not recorded unless there was a hypoglycemic event associated with treatment administration, so the potential effects of differences in daily dose timing of IDeg 200 units/mL and IGlar on hypoglycemia cannot be evaluated.

Treatment with IDeg 200 units/mL resulted in similar HbA_{1c} reductions as IGlar, with significantly better FPG reductions and a low rate of hypoglycemia. The 200 units/mL formulation of IDeg offers the potential dual benefit of administering insulin doses in a lower volume and administering as much as 160 units in a single injection with the FlexTouch Pen. IDeg 200 units/mL addresses an unmet need for patients with T2DM, particularly those who require high doses of basal insulin, and has the potential to improve treatment compliance and health outcomes.

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S.C.L.G., A.B., R.J., and R.M.B. contributed to data collection, analysis, and interpretation. H.M. contributed to the design and treatment considerations for the trial and was involved in the analysis and interpretation of the data. S.R. contributed to analysis and interpretation of the data. All authors contributed to discussion and reviewed, edited, and approved the final manuscript before submission. S.C.L.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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