Insulin Degludec Versus Insulin Glargine in Insulin-Naive Patients With Type 2 Diabetes

A 1-year, randomized, treat-to-target trial (BEGIN Once Long)

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OBJECTIVE—To compare ultra-long-acting insulin degludec with glargine for efficacy and safety in insulin-naive patients with type 2 diabetes inadequately controlled with oral antidiabetic drugs (OADs).

RESEARCH DESIGN AND METHODS—In this 1-year, parallel-group, randomized, open-label, treat-to-target trial, adults with type 2 diabetes with A1C of 7−10% taking OADs were randomized 3:1 to receive once daily degludec or glargine, both with metformin. Insulin was titrated to achieve prebreakfast plasma glucose (PG) of 3.9−4.9 mmol/L. The primary end point was confirmation of noninferiority of degludec to glargine in A1C reduction after 52 weeks in an intent-to-treat analysis.

RESULTS—In all, 1,030 participants (mean age 59 years; baseline A1C 8.2%) were randomized (degludec 773, glargine 257). Reduction in A1C with degludec was similar (noninferior) to that with glargine (1.06 vs. 1.19%), with an estimated treatment difference of degludec to glargine of 0.09% (95% CI −0.04 to 0.22). Overall rates of confirmed hypoglycemia (PG <3.1 mmol/L or severe episodes requiring assistance) were similar, with degludec and glargine at 1.52 versus 1.85 episodes/patient-year of exposure (PYE). There were few episodes of nocturnal confirmed hypoglycemia in the overall population, and these occurred at a lower rate with degludec versus glargine (0.25 vs. 0.39 episodes/PYE; $P = 0.038$). Similar percentages of patients in both groups achieved A1C levels <7% without hypoglycemia. End-of-trial mean daily insulin doses were 0.59 and 0.60 units/kg for degludec and glargine, respectively. Adverse event rates were similar.

CONCLUSIONS—Insulins degludec and glargine administered once daily in combination with OADs provided similar long-term glycemic control in insulin-naive patients with type 2 diabetes, with lower rates of nocturnal hypoglycemia with degludec.

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The increasing prevalence of type 2 diabetes and its associated complications pose a significant global health care and economic burden (1). The landmark U.K. Prospective Diabetes Study demonstrated the benefits of improved glucose control and highlighted the progressive nature of type 2 diabetes as a result of β-cell failure. Approximately 50% of patients with type 2 diabetes may require insulin therapy in addition to oral antidiabetic drugs (OADs) within 6 years of diabetes diagnosis (2,3). Clinical guidelines by the American Diabetes Association and European Association for the Study of Diabetes currently recommend initiating basal insulin in patients with type 2 diabetes either directly after metformin or after maximizing a combination of OADs with or without glucagonlike peptide-1 receptor agonists and then titrating insulin to meet a glycosylated hemoglobin (A1C) target of 7% without significant hypoglycemia (4,5).

Several barriers to introducing insulin have been identified that may result in delayed achievement of glycemic control and progression of diabetes complications (6,7). These barriers include patients' fear of injections and misconceptions about insulin therapy, clinicians' fear of perceived complexity of insulin regimens, and both parties' fear that introducing insulin will negatively affect patient lifestyle and weight gain (8). Additionally, the risk, consequences, and fear of hypoglycemia remain a significant limiting factor in intensifying insulin therapy and optimizing glycemic control (9).

Long-acting insulin analogs have been developed to produce a more physiological basal insulin action than seen with such human insulin preparations as neutral protamine Hagedorn (NPH) insulin, and they are associated with lower hypoglycemia rates (particularly nocturnal) while achieving similar glycemic control (10–12). These analogs have lowered the barrier for insulin introduction in patients with type 2 diabetes and are recommended when OADs alone cannot maintain glucose control (10,12,13). There is still a need, however, for the development of basal insulins with improved pharmacokinetics and pharmacodynamics, with the goal of achieving glycemic targets in more patients with even less hypoglycemic risk (14). Insulin degludec is a novel, ultra-long-acting basal insulin. On subcutaneous injection, degludec forms a depot of soluble multihexamers that

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dissociates slowly and consistently, resulting in a flat, stable profile and a duration of action longer than 42 h (15,16). A previous phase 2 clinical trial comparing once daily degludec with glargine in insulin-naive patients with type 2 diabetes (17) and two phase 3 studies comparing once daily degludec with glargine in basal-bolus therapy in patients with type 1 (18) and type 2 diabetes (19) demonstrated that degludec provides similar glycemic control with less hypoglycemia than glargine.

BEGIN Once Long is the largest phase 3 study in the clinical development program of insulin degludec and was designed as a 52-week, treat-to-target trial to compare the efficacy and safety of insulin degludec with those of insulin glargine, both administered in a basal regimen in combination with metformin, in insulin-naive participants with type 2 diabetes inadequately controlled with OADs.

RESEARCH DESIGN AND METHODS

—This 52-week, randomized, controlled, parallel-group, open-label, multinational, treat-to-target, noninferiority trial compared the efficacy and safety of once daily insulin degludec with those of once daily insulin glargine, both administered subcutaneously in combination with metformin, in insulin-naive participants requiring intensification of their therapy for type 2 diabetes inadequately controlled with OADs. Dipeptidyl peptidase-4 (DPP-4) inhibitors could be continued as adjunct therapy, but fewer than 2% of patients (distributed similarly between treatment groups) continued use of a DPP-4 inhibitor throughout the trial.

The trial took place between 1 September 2009 and 17 January 2011 and was conducted in accordance with the Declaration of Helsinki (20) and the Good Clinical Practice guidelines (21) and approved by institutional review boards and independent ethics committees before initiation. Signed informed consent was obtained from participants before trial entry. The trial was conducted at 166 sites in 12 countries: Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Norway, Serbia and Montenegro, Spain, and the U.S.

Participants included adults ≥18 years of age diagnosed with type 2 diabetes for ≥6 months, with A1C 7–10% (inclusive) and BMI ≤40 kg/m^2, treated with unchanged doses and dosing frequency of OADs (metformin monotherapy or metformin in any combination with insulin secretagogues [sulfonylurea or glinide, DPP-4 inhibitor] or α-glucosidase-inhibitor) for ≥3 months before screening. Participants were excluded if they received thiazolidinediones, exenatide or liraglutide within 3 months of screening or if they had clinically significant cardiovascular, hepatic, renal or oncologic disease; recurrent severe hypoglycemia; hypoglycemia unawareness; or proliferative retinopathy.

Eligible participants were randomized 3:1 to receive once daily degludec (100 U/mL, 3 mL PDS290; Novo Nordisk, Bagsværd, Denmark) or glargine (Lantus, 100 U/mL, 3 mL SoloStar; sanofi-aventis, Paris, France) by means of a centralized, computer–generated, interactive voice and web response system that generated randomization blocks. Randomization (3:1) ensured adequate exposure to degludec in accordance with regulatory guidelines (22). Investigators and participants were not blinded to treatment. Treatment group assignment was blinded for individuals involved as titration surveillance monitors, internal safety committee members, external committee members responsible for cardiovascular event adjudication, and personnel involved in defining analysis sets until data were locked for statistical analysis. An independent ad hoc group was to be established to maintain blinding if the internal safety committee members requested unmasking; however, this did not occur during the trial.

At randomization (week 0), eligible participants discontinued all OADs, with the exception of metformin and a DPP-4 inhibitor (the latter was continued if country-specific approved labeling allowed combining a DPP-4 inhibitor with insulin), maintaining their pretrial dose and dosing frequency, and were randomized to treatment with degludec or glargine in parallel groups. Insulin degludec was administered once daily, with the main evening meal, and glargine was administered once daily at the same time every day, as chosen by patient and investigator, in accordance with approved labeling. The starting dose for both insulins was 10 units. In the subsequent 52 treatment weeks, each participant's insulin dose was titrated on the basis of the average of prebreakfast self-measured blood glucose (SMBG) values of 3 consecutive days preceding a visit, ensuring titration toward a predefined prebreakfast plasma glucose (PG) target of 3.9–4.9 mmol/L. Participants measured blood glucose with a glucose meter (Abbott Diabetes Care, Abbott Park, IL), with test strips calibrated to plasma values to obtain PG readings. The frequent visit schedule for first 26 weeks and treat-to-target approach were chosen to ensure optimal titration.

The primary end point was change in A1C from baseline after 52 weeks. Other efficacy assessments included change from baseline in central laboratory–measured fasting PG (FPG), SMBG, A1C <7% responders, and functional health status (assessed by the 36-item short-form health survey version 2.0 [SF-36]).

Safety assessments included adverse events (AEs), hypoglycemic episodes, insulin dose, body weight, injection site reactions, abnormal findings related to physical examination, vital signs, fundoscopy, electrocardiogram (ECG), and laboratory tests (including insulin antibodies). Confirmed hypoglycemic episodes included either episodes confirmed by SMBG corresponding to PG value <3.1 mmol/L or severe episodes requiring assistance (no SMBG confirmation) (4). Hypoglycemic episodes occurring from 0001 to 0559 h (inclusive) were classified as nocturnal. Treatment-emergent events were described as 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 or insulin glargine.

After 52 weeks, participants switched to NPH insulin and continued with OADs for a 1-week washout period for accurate assessment of anti-insulin antibody levels by a subtraction radioimmunoassay method (23,24). Laboratory analyses were performed by Quintiles Laboratories Europe (West Lothian, U.K.) and Quintiles Laboratories Limited (Marietta, GA). ECG central reading was performed at Quintiles ECG Services (Mumbai, India). Insulin antibodies were analyzed at Celerion Switzerland AG (Fehraltorf, Switzerland).

The trial's primary objective was to confirm noninferiority of insulin degludec to glargine, as assessed by change in A1C from baseline after 52 weeks, with a noninferiority limit of 0.4% for the treatment difference (22). For secondary confirmatory end points, type I error rate (false-positive results) was controlled by means of a hierarchical (fixed-sequence) testing procedure (Supplementary Fig. 1). *P* values provided for hypothesis testing outside this procedure were not controlled for multiplicity. Sample size was determined on basis of the primary objective with a *t* statistic under the

Table 1—*Patient disposition, demographics, and baseline characteristics*

	IDeg od	IGlar od
Participants randomized (full analysis set)	773	257
Participants withdrawn before receiving treatment*	7 (0.9)	0 (0.0)
Participants exposed to treatment (safety analysis set)	766 (99.1)	257 (100)
Participants withdrawn after receiving treatment	159 (20.6)	60 (23.3)
AEs†	20 (2.6)	5 (1.9)
Noncompliance	46 (6.0)	18 (7.0)
Ineffective therapy‡	7 (0.9)	2 (0.8)
Withdrawal criteria	9 (1.2)	5 (1.9)
Other§	77 (10)	30 (11.7)
Participants completing treatment	607 (78.5)	197 (76.7)
Participants in per-protocol analysis set	665 (86.0)	221 (86.0)
Female	302 (39.1)	90 (35.0)
Race		
White	680 (88.0)	231 (89.9)
Black	57 (7.4)	16 (6.2)
Asian	18 (2.3)	3 (1.2)
Other	18 (2.3)	7 (2.7)
Ethnicity: Hispanic or Latin American	129 (16.7)	48 (18.7)
Age (years)	59.3 ± 9.7	58.7 ± 9.9
Body weight (kg)	89.4 ± 17.7	91.8 ± 15.8
BMI (kg/m^2)	30.9 ± 4.8	31.6 ± 4.4
Duration of diabetes (years)	9.4 ± 6.3	8.6 ± 5.7
A1C (%)	8.2 ± 0.8	8.2 ± 0.8
A1C (mmol/mol)¤	66.1 ± 8.7	66.1 ± 8.7
FPG (mmol/L)	9.6 ± 2.6	9.7 ± 2.6
Systolic blood pressure (mmHg)	133.8 ± 15.2	133.8 ± 15.1
Diastolic blood pressure (mmHg)	79.7 ± 8.7	79.8 ± 8.5
HDL cholesterol (mmol/L)	1.15 ± 0.33	1.12 ± 0.28
LDL cholesterol (mmol/L)	2.44 ± 0.93	2.42 ± 0.91
Total cholesterol (mmol/L)	4.50 ± 1.10	4.49 ± 1.09
Triglycerides (mmol/L)	2.08 ± 1.58	2.19 ± 1.91
Antidiabetic treatment at screening		
OAD regimen		
Metformin monotherapy¶	212 (27.4)	88 (34.2)
Metformin ± (sulfonylurea or glinides) ± α-glucosidase inhibitor#	428 (55.4)	122 (47.5)
Metformin + DPP-4 inhibitor ± (sulfonylurea or glinides) ± α-glucosidase inhibitor	133 (17.2)	47 (18.3)
OADs at screening		
Metformin	771 (99.7)	257 (100.0)
Sulfonylurea	471 (60.9)	139 (54.1)
DPP-4 inhibitor	133 (17.2)	47 (18.3)
Sitagliptin	122 (15.8)	42 (16.3)
Vildagliptin	11 (1.4)	5 (1.9)
Glinide	29 (3.8)	10 (3.9)
α-Glucosidase inhibitor	7 (0.9)	3 (1.2)
Thiazolidinedione	5 (0.6)**	—
Number of OADs at screening		
1	213 (27.6)	88 (34.2)
2	478 (61.8)	141 (54.9)
>2	82 (10.6)	28 (10.9)
Diabetes complications at screening	105 (13.6)	22 (8.6)
Diabetic neuropathy	67 (8.7)	12 (4.7)
Diabetic retinopathy	23 (3.0)	5 (1.9)
Diabetic nephropathy	11 (1.4)	5 (1.9)

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assumption of a one-sided *t* test of size 2.5%, a zero mean treatment difference, and a 1.3% SD for A1C. In total, 984 participants were to be randomized for ≥95% power in the per protocol analysis set.

In line with the intention-to-treat principle, statistical analyses of all efficacy end points, hypoglycemia, and body weight included the full analysis set, comprising all randomized participants. Safety end points were evaluated with the safety analysis set, comprising all participants exposed to treatment. Missing values were imputed with the last observation carried forward method. The last observation carried forward approach was selected for the primary analysis on the basis of U.S. Food and Drug Administration guidance (22), and its robustness was ensured by excluding early withdrawals, as in the per protocol analysis (including only participants treated for ≥12 weeks), and by sensitivity analyses (described in Supplementary Data online).

Treatment differences in A1C, FPG, SMBG, functional health status, insulin dose (post hoc), and body weight after 52 weeks were analyzed with ANOVA, with treatment, antidiabetic therapy at screening, sex, and region (European Union or North America) as fixed factors and age and baseline value as covariates. The numbers of treatment-emergent confirmed hypoglycemic episodes per patient-year of exposure (PYE) were analyzed with a negative binomial regression model that included treatment, antidiabetic therapy at screening, sex, and region as fixed factors and age as covariate for all reported treatment-emergent episodes. A similar model was used for post hoc analysis of episodes in the maintenance period (weeks 16−52), when stable insulin dose and glycemic control were achieved for most participants. For severe hypoglycemia, the negative binomial model could not be fitted to the sparse data, and a simpler Poisson regression model was used with the same covariates as originally intended. The 9-point SMBG profile was analyzed with a repeated-measures ANOVA model (Supplementary Data online).

RESULTS—Of 1,597 participants assessed for entry into the trial, 567 participants were excluded, and 1,030 participants were randomized. The majority of excluded participants (92%) did not meet the inclusion criteria or fulfilled

Table 1—*Continued*

	IDeg od	IGlar od
Microalbuminuria	8 (1.0)	3 (1.2)
Vascular disorders	577 (74.6)	186 (72.4)
Hypertension	561 (72.6)	182 (70.8)
Arteriosclerosis	9 (1.2)	3 (1.2)

Data are presented as *n*, *n* (%), or mean ± SD. All data are for the full analysis set, with the exception of lipids and blood pressure, which are for the safety analysis set. Per-protocol analysis set comprised participants with exposure to treatment for at least 12 weeks with a valid A1C assessment at baseline and ≥12 weeks and without any violations of inclusion or exclusion criteria. Ideg, insulin degludec; Iglar, insulin glargine; od, once daily. Blood pressure data were reported at screening (week −1), and FPG, A1C, and lipids were measured at randomization (week 0). *Reasons for withdrawal that occurred before treatment included randomization by mistake (*n* = 3), withdrawal or refusal of informed consent (*n* = 3), and investigator discretion (*n* = 1). †AEs leading to withdrawal are described in the Supplementary Data online. ‡Participants withdrawn for ineffective therapy are described in the Supplementary Data online. §Other reasons leading to withdrawal are described in the Supplementary Data online. ¤Calculated as follows: A1C (in mmol/mol) = [A1C (in %) − 2.15] × 10.929. ¶Includes 1 participant receiving unknown monotherapy. #Includes 1 participant receiving glimepiride monotherapy who was withdrawn. **All participants were withdrawn according to the criterion for exclusion of patients receiving thiazolidinediones at screening.

exclusion criteria. According to the 3:1 randomization, 773 and 257 participants were assigned to treatment with degludec and glargine, respectively; all but seven degludec participants were exposed to treatment (Table 1). Similar proportions of participants exposed to treatment withdrew (Supplementary Fig. 2), with 79% and 77% of participants completing the trial for degludec and glargine, respectively.

Overall, the treatment groups were well matched at baseline. Participants had been diagnosed with type 2 diabetes for 9 years on average and had a mean A1C of 8.2%. Mean age was 59 years (28% being >65 years of age), and 62% were male. All participants were insulin naive and treated with OADs at baseline, with most taking two OADs (Table 1).

Consistent with the treat-to-target design, reduction of A1C from baseline to end of trial was similar between treatments (Fig. 1*A* and Supplementary Fig. 3*A*); mean A1C decreased by 1.06 to 7.1% with degludec and by 1.19 to 7.0% with glargine. The estimated treatment difference (ETD) between degludec and glargine of 0.09% (95% CI −0.04 to 0.22) for all randomized participants confirms the noninferiority of degludec to glargine in A1C reduction. It is noteworthy that these results were consistent with the efficacy analyses in the per protocol population (ETD between degludec and glargine of 0.13 [−0.01 to 0.26]) and with the sensitivity analyses results (Supplementary Table 1*A*). Similar proportions of participants achieved A1C levels of <7% at the end of the trial with degludec (52%, 400/773) and glargine (54%, 139/257; *P* = 0.40) (Supplementary Table 1*B*). Similar proportions of participants achieved A1C levels of <7% without confirmed hypoglycemia (degludec 42%, 296/703; glargine 46%, 106/232; *P* = 0.34) and without nocturnal confirmed hypoglycemia (degludec 53%, 373/703; glargine 54%, 126/232; *P* = 0.68) in the last 12 weeks of treatment (Supplementary Table 1*B*).

Central laboratory–measured FPG decreased from baseline to the end of the trial in both groups, with the most pronounced decline occurring during the first 12 weeks (Fig. 1*B* and Supplementary Fig. 3*B*). Mean FPG levels decreased by 3.8 and 3.3 mmol/L to 5.9 and 6.4 mmol/L with degludec and glargine, respectively. FPG reduction was significantly greater with degludec (ETD between degludec and glargine of −0.43 mmol/L [95% CI −0.74 to −0.13]; *P* = 0.005). The 9-point SMBG profiles appeared similar at baseline and decreased in both groups at the end of the trial (Fig. 1*C*).

Mean insulin doses at week 1 were similar (degludec 0.12 units/kg and glargine 0.11 units/kg) and were titrated upward throughout the trial, increasing most rapidly in the first 16 weeks of treatment. Doses were similar at the end of the treatment (0.59 units/kg for degludec and 0.60 units/kg for glargine; see Supplementary Table 2).

Participants treated with degludec reported greater improvements in "overall physical" and "physical functioning" scores in the SF-36 questionnaire assessing functional health status (ETD between degludec and glargine of 1.0 [95% CI 0.1–2.0]; *P* = 0.033 for "overall physical" and 1.4 [0.3–2.4]; *P* = 0.016 for "physical functioning"). No significant differences were observed between treatments in other domains.

Rates of overall confirmed hypoglycemic episodes were similar (*P* = 0.106) between treatments (Fig. 2*A* and Table 2). The rate of nocturnal confirmed hypoglycemic episodes was significantly lower (by 36%) with degludec; the estimated rate ratio of degludec to glargine was 0.64 (95% CI 0.42–0.98; *P* = 0.038) (Fig. 2*B* and Table 2). In specific analyses of the maintenance period (weeks 16–52), overall confirmed hypoglycemia rates were similar between treatments (*P* = 0.067); again, however, the rate of nocturnal confirmed hypoglycemia was significantly lower (49%) with degludec (*P* = 0.004) (Table 2). Few severe hypoglycemic episodes were reported in either group, but the rate was significantly lower (*P* = 0.017) with degludec (0.003 vs. 0.023 episodes/PYE with glargine) (Table 2).

Observed mean weight gain at the end of the trial was similar between degludec and glargine groups (2.4 and 2.1 kg; *P* = 0.28) (Supplementary Table 1*A*). No clinically meaningful differences were noted in plasma lipids, cardiovascular risk markers, or cardiac repolarization (Supplementary Table 1*C*). No differences were observed between treatments in laboratory measurements, physical examination, vital signs, ECGs, or fundoscopy.

Approximately 75% of degludec-treated participants and 71% of glargine-treated participants reported AEs (Supplementary Table 3). Most AEs (96%, 3,397/3,525) were mild or moderate, and 7% (236/3,525) were considered by the investigator to be possibly or probably related to basal insulin. The most frequently reported AEs in both groups were nasopharyngitis, headache, and diarrhea. Twenty-five participants were withdrawn for AEs (Supplementary Data online). Injection site reaction rates were rare, with rates of 0.10 (degludec) and 0.13 (glargine) events per PYE, and none were severe.

Serious AEs were reported by 8.1% (62/766) of degludec-treated participants and 10.1% (26/257) of glargine-treated participants and were distributed similarly between groups (Supplementary Table 3 and Supplementary Fig. 4). The most frequently reported insulin-related serious AEs were three hypoglycemic episodes (Supplementary Table 4). Eleven

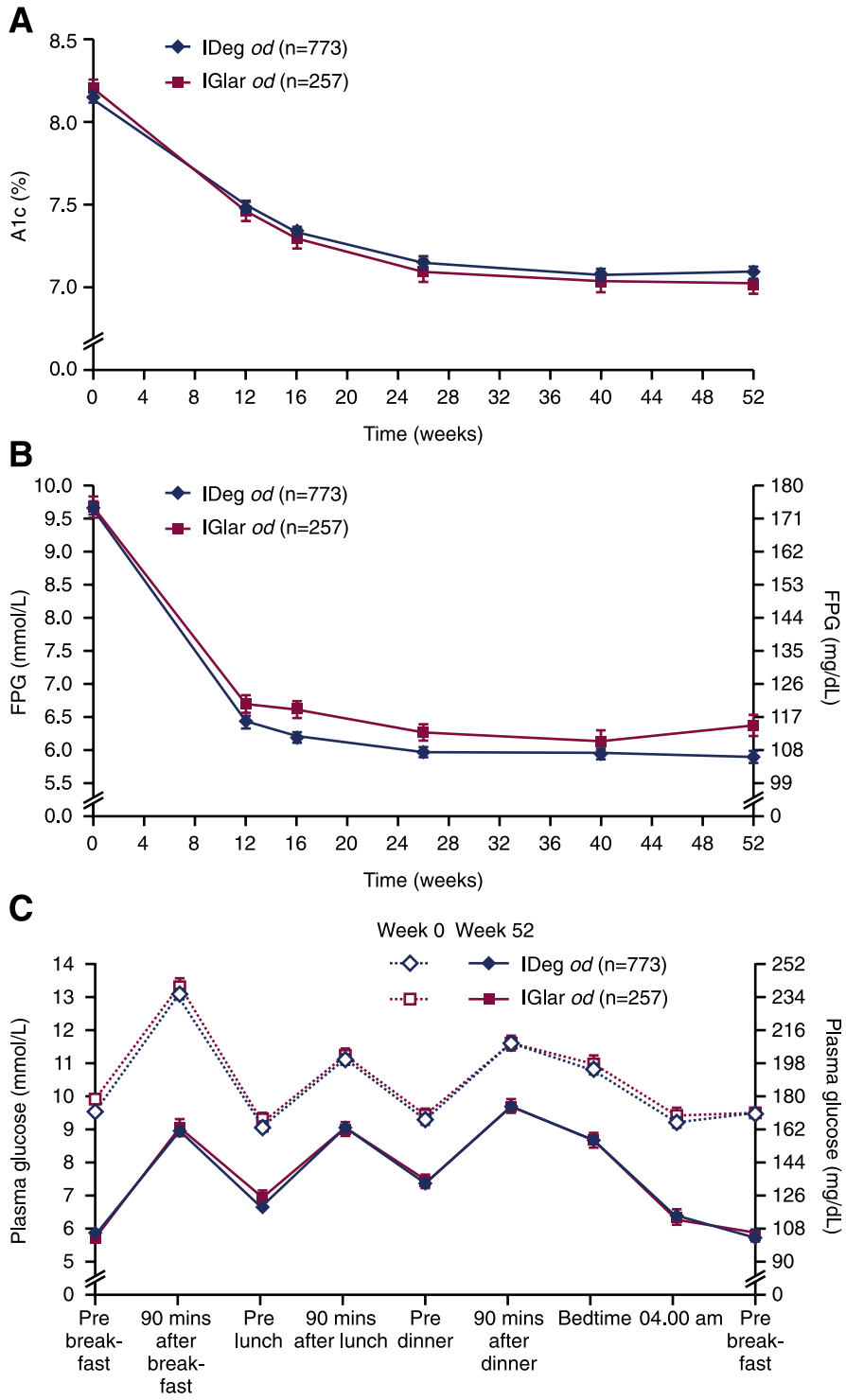

Figure 1—*Glycemic efficacy. A: Mean A1C with time. B: Mean fasting PG with time. C: Nine-point profiles of SMBG at baseline (week 0) and after 52 weeks. Data for the first seven points are obtained on one day and data for the remaining two points are drawn from the next day. Data are reported as the mean ± SEM. Missing data after baseline were imputed with the last observation carried forward approach. Ideg, insulin degludec; IGlar, insulin glargine; od, once daily.*

confirmed cases of malignant neoplasms were reported by equal proportions of participants in the two groups (degludec 8/766, 1%, and glargine 2/257, 1%). None were considered treatment related by investigators. In the insulin degludec group, the malignant neoplasms included two nonserious cases of squamous cell carcinoma, one nonserious case of lung neoplasm and six serious cases, including prostate cancer stage I, basal cell carcinoma, colon cancer, bladder adenocarcinoma of unspecified stage, and thyroid cancer. In the insulin glargine group, two serious cases of breast and thyroid cancers were reported. A total of 89 cardiac disorder events were reported in equal rates in the two treatment groups: 70 events in 766 participants receiving degludec (0.1 events per PYE) and 19 events in 257 participants receiving glargine (0.09 events per PYE). A total of 76 vascular disorder events were reported in this study: 63 events in 766 participants in the degludec group (0.09 events per PYE) and 13 events in 257 participants in the glargine group (0.06 events per PYE). The majority were hypertensive or hypotensive events (degludec 36 events in 766 patients [0.05 events per PYE] and glargine 6 events in 257 patients [0.03 events per PYE]). Of the two study deaths (both considered unrelated to treatment by investigators), one was reported as treatment emergent related to urosepsis in a glargine-treated male participant. The other, a nontreatment emergent sudden cardiac death, occurred in a degludec-treated male participant 11 days after stopping treatment.

Immunogenicity of insulin degludec, as assayed by degludec-specific antibodies and antibodies cross-reacting between degludec and human insulin, was negligible (Supplementary Table 5).

CONCLUSIONS—This study was designed as a treat-to-target trial to allow efficacy and safety comparisons of the new basal insulin degludec with the most frequently prescribed basal insulin, glargine. Not surprisingly, this treat-to-target design resulted in similar A1C levels at 1 year, thereby facilitating direct safety comparisons without confounding differences in A1C, in accordance with the U.S. Food and Drug Administration's regulatory guidance (22).

A major concern of patients and clinicians when initiating basal insulin as an add-on to OADs is hypoglycemia, particularly nocturnal hypoglycemia (25,26). Therefore, the most important finding of this study is that insulin degludec achieved overall glycemic control similar to that of glargine but with lower nocturnal hypoglycemia rates. Although the rate of nocturnal hypoglycemia per patient-year was already low, it was reduced by 36% with degludec relative to glargine when considering the entire study period. During the maintenance

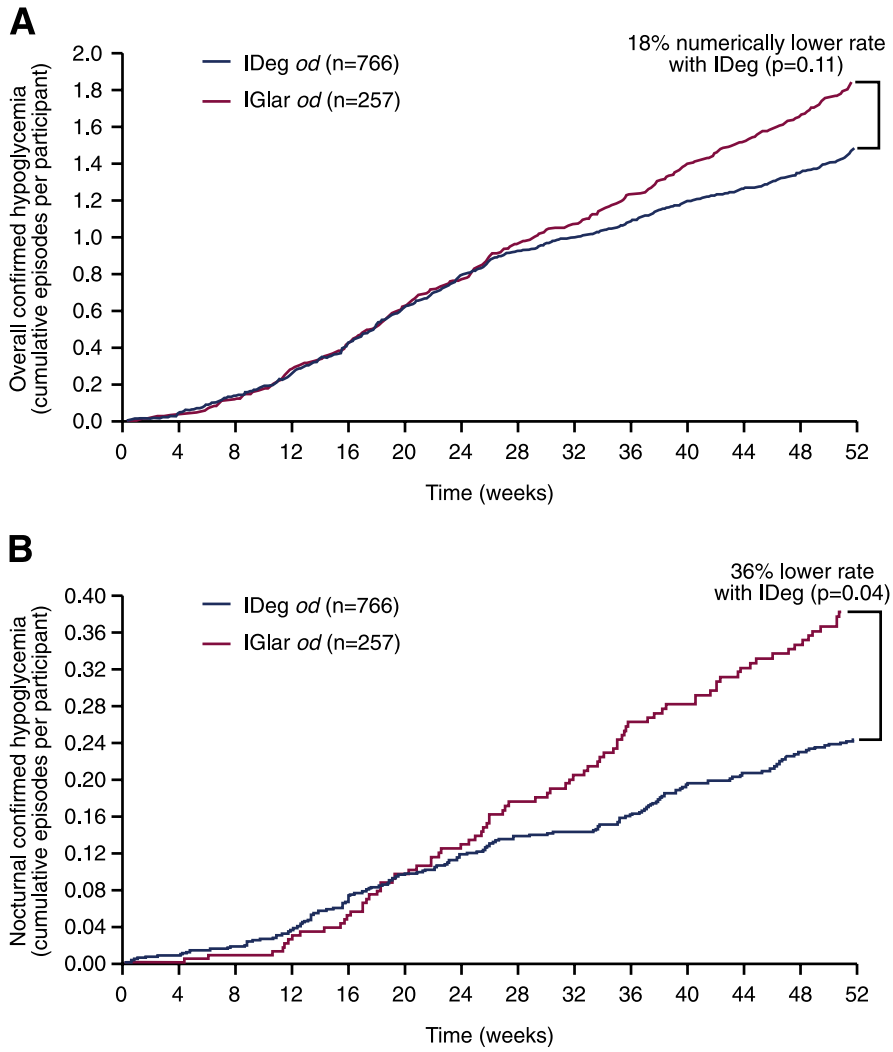

Figure 2—*Confirmed hypoglycemic episodes.* A*: Overall confirmed hypoglycemic episodes.* B*: Nocturnal confirmed hypoglycemic episodes. See methodology for plotting graph in the Supplementary Data online. IDeg, insulin degludec; IGlar, insulin glargine; od, once daily.*

period, after insulin dose titration had stabilized, the nocturnal hypoglycemia rate was reduced by 49% relative to glargine.

The reduction in nocturnal hypoglycemia may be attributable to the more consistent pharmacokinetic profile of degludec observed in the 24 h after once daily dosing; it is unlike glargine, with which 60% of insulin exposure occurs in the first 12 h (15). It is likely that the reduced day-to-day and hour-to-hour pharmacodynamic variability in insulin action observed with degludec relative to glargine also contributed to the lower rate of hypoglycemia in the maintenance phase (27).

Hypoglycemic risk reduction is likely to lower barriers for both physicians and patients to initiating insulin to achieve glycemic control (6,8). The reduction in nocturnal hypoglycemia observed here is noteworthy, because nocturnal hypoglycemia is often asymptomatic and can lead to significant consequences (28,29). Furthermore, nocturnal hypoglycemia can negatively affect patient productivity and quality of life (30).

Of interest, the potential advance in insulin therapy with insulin degludec versus glargine demonstrated in this study is comparable to that seen with insulins glargine and detemir versus NPH insulin in earlier treat-to-target studies, in which glargine and detemir achieved similar reductions in A1C as NPH insulin with significantly lower risk for nocturnal hypoglycemia (10,12).

When designing this study within the context of the overall phase 3 program for degludec, a narrow and nondiabetic pre-breakfast SMBG titration target of PG 3.9−4.9 mmol/L was chosen. This target choice was supported by the finding of Blonde et al. (31) that superior glycemic control can be safely achieved when aiming for the more normoglycemic target compared with the FPG target of 4.4−6.1 mmol/L when using detemir, another basal insulin analog. Thus, a lower titration target approximating normal glycemia was considered appropriate and appeared to be safely implemented here, especially with degludec. Although only 38% of all participants achieved the titration target of <5 mmol/L at end of study, approximately 90% reached the target at least once during the trial (Supplementary Fig. 5), demonstrating that normal FPG is an achievable goal with careful titration. This of course must be balanced against the risk of hypoglycemia and the consequences of hypoglycemia in the individual patient.

The open-label trial design poses a risk for reporting bias (particularly for end points involving patient or investigator judgment), but it was unavoidable because of lack of available appropriate placebo-containing injection devices. Because quantification of hypoglycemic episodes was critical, we sought to minimize the reporting bias for hypoglycemia by choosing confirmed hypoglycemia (PG <3.1 mmol/L or severe episodes requiring assistance) as a safety end point rather than hypoglycemic symptoms alone. Biochemical confirmation of hypoglycemic episodes occurred by protocol-specified SMBG monitoring or was prompted by hypoglycemic symptoms. Thus, the true hypoglycemia rates, particularly the nocturnal rates, may be underreported in this study. There was, however, no indication of a preferential ascertainment bias across the treatments. The divergence in the rates of hypoglycemia between the two treatments was observed after insulin dose titrations. Patient-reported outcomes (e.g., functional health status) are also often considered subject to bias in an open-label study. The 52-week duration of the study, however, was considered sufficient to ensure that any expectations related to the initiation of insulin therapy would have "washed out" by the end of the trial. In addition, the baseline values were likely to be unaffected by brand-specific bias because the study population was insulin naive and completion of the baseline SF-36 questionnaire happened before randomization. Finally, glargine was prescribed at the same time once daily in accordance with the prescribing

Table 2—*Hypoglycemic episodes*

	IDeg od			IGlar od			Estimated rate ratio	
	Participants	Episodes	Rate	Participants	Episodes	Rate	IDeg/IGlar (95% CI)	*P* value
Severe in SAS	2 (0.3%)	2	0.003	5 (1.9%)	5	0.023	0.14 (0.03–0.70)	0.017
Overall confirmed in SAS	356 (46.5%)	1,014	1.52	119 (46.3%)	403	1.85	0.82 (0.64–1.04)	0.106
Nocturnal confirmed in SAS	106 (13.8%)	169	0.25	39 (15.2%)	84	0.39	0.64 (0.42–0.98)	0.038
Overall confirmed in maintenance period	282 (41.2%)	710	1.60	97 (42.9%)	301	2.09	0.77 (0.59–1.02)	0.067
Nocturnal confirmed in maintenance period	84 (12.3%)	118	0.27	32 (14.2%)	72	0.50	0.51 (0.32–0.81)	0.004

Participants were randomized 3:1 to receive insulin degludec or insulin glargine. Numbers of participants contributing to analyses were 766 for the insulin degludec safety analysis set, 257 for the insulin glargine safety analysis set, 685 for the insulin degludec maintenance period, and 226 for the insulin glargine maintenance period. Hypoglycemic episodes (severe, confirmed, diurnal confirmed, nocturnal confirmed) 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 or insulin glargine. Maintenance period includes confirmed hypoglycemic episodes occurring between weeks 16 and 52. Interpretation of *n* must take into consideration the 3:1 ratio of insulin degludec to insulin glargine in the randomization. Rate represents the rate of hypoglycemia in episodes per patient-year of exposure. IDeg, insulin degludec; IGlar, insulin glargine; od, once daily; SAS, safety analysis set.

information, whereas degludec was administered with the main evening meal in this study. Thus, glargine could be prescribed once daily at any time of day (but at same time every day), as considered appropriate by the investigator.

Importantly, the findings of this large, 1-year treat-to-target study are consistent with those of a phase 2 study in which a reduction of nocturnal hypoglycemia of similar magnitude was observed in insulin-naive patients with type 2 diabetes who received insulin degludec once daily compared with insulin glargine (17).

In conclusion, this study demonstrates that initiating insulin therapy with either insulin degludec or insulin glargine administered once daily provides similar improvements in long-term glycemic control for patients with type 2 diabetes that is insufficiently controlled by OADs. Although nocturnal and severe hypoglycemia were infrequent in this patient population with type 2 diabetes, the rates were lower with insulin degludec than with insulin glargine. These findings illustrate the beneficial profile of this new basal insulin in the treatment arsenal for patients with type 2 diabetes.

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B.Z., A.P.-T., T.J., and C.M. contributed to study design. B.Z., A.P.-T., B.C., Y.H., H.W.R., and C.M. were trial investigators and helped obtain data. B.Z. and C.M. prepared the first draft of the manuscript (with medical writing assistance provided by Novo Nordisk, Inc., Princeton, NJ) after an authors' meeting. T.J. was the International Medical Director and responsible for medical oversight during the trial. L.E. was responsible for the statistical considerations in the analysis and trial design. All authors participated in reviewing and interpreting the data, in generating post hoc analyses, and in providing further comments and revisions to the manuscript. All authors are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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