The Efficacy and Safety of Insulin Degludec Given in Variable Once-Daily Dosing Intervals Compared With Insulin Glargine and Insulin Degludec Dosed at the Same Time Daily

A 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes

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OBJECTIVE—The requirement to inject current basal insulin analogs at a fixed time each day may complicate adherence and compromise glycemic control. This trial evaluated the efficacy and safety of varying the daily injection time of insulin degludec (IDeg), an ultra-long-acting basal insulin.

RESEARCH DESIGN AND METHODS—This 26-week, open-label, treat-to-target trial enrolled adults (≥18 years) with type 2 diabetes who were either insulin naïve and receiving oral antidiabetic drugs (OADs) (HbA_{1c} = 7–11%) or previously on basal insulin ± OAD(s) (HbA_{1c} = 7–10%). Participants were randomized to *1*) once-daily (OD) IDeg in a prespecified dosing schedule, creating 8–40-h intervals between injections (IDeg OD Flex; *n* = 229); *2*) once-daily IDeg at the main evening meal (IDeg OD; *n* = 228); or 3) once-daily insulin glargine at the same time each day (IGlar OD; *n* = 230). The primary outcome was noninferiority of IDeg OD Flex to IGlar OD in HbA_{1c} reduction after 26 weeks.

RESULTS—After 26 weeks, IDeg OD Flex, IDeg OD, and IGlar OD improved HbA_{1c} by 1.28, 1.07, and 1.26% points, respectively (estimated treatment difference [IDeg OD Flex − IGlar OD]: 0.04% points [–0.12 to 0.20], confirming noninferiority). No statistically significant differences in overall or nocturnal hypoglycemia were found between IDeg OD Flex and IGlar OD. Comparable glycemic control and rates of hypoglycemia were seen with IDeg OD Flex and IDeg OD. Adverse event profiles were similar across groups.

CONCLUSIONS—The use of extreme dosing intervals of 8–40 h demonstrates that the daily injection time of IDeg can be varied without compromising glycemic control or safety.

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The International Diabetes Federation estimates that 366 million people have diabetes worldwide, with type 2 diabetes accounting for >90% of all cases (1). Insulin therapy remains the most efficacious glucose-lowering treatment option for type 2 diabetes (2) when lifestyle modifications and metformin fail to achieve recommended glycemic targets (3,4).

Based on their pharmacodynamic action profiles, NPH insulin and current basal insulin analogs are injected at the same time each day to ensure optimal biological action and consistent glycemic response (5,6). Strict dosing schedules required for current insulin products might be difficult to maintain, which may affect glycemic control (7–9). On average, adherence to insulin therapy in patients with type 2 diabetes is low (~70%) (8,10,11). Although this is a clearly recognized issue for patients using prandial insulin coverage, it is also a relevant issue for those administering basal insulin. A recent study showed that ~50% of patients with type 2 diabetes had intentionally missed a basal insulin injection, with 22% reporting that they had missed a dose in the previous 30 days (mean of three doses) and 24% reporting that they had mistimed an injection by >2 h (mean of 4.2 occasions) in the last month (12). One reason for insulin omission/nonadherence cited frequently by patients is that injections interfere with daily activities (13–15). Accordingly, an insulin preparation that allows a more flexible dosing schedule, while maintaining consistent glycemic effects, might benefit patients requiring exogenous insulin replacement.

Insulin degludec (IDeg) is an ultra-long-acting basal insulin analog that forms a soluble depot of multihexamers

after subcutaneous injection, with subsequent slow release of monomers into the circulation. It has a long half-life (~25 h) and a consistent glucose-lowering effect of >42 h at steady state (16–19). Given these attributes, we reasoned that it should be possible to vary the time of day at which once-daily injections of IDeg are given without impacting glycemic control or safety, thereby allowing for greater flexibility in the timing of injections.

The principal aim of this 26-week, phase 3 trial was to compare the efficacy and safety of once-daily IDeg given in a prespecified, "forced," rotating morning-and-evening dosing regimen to create 8–40-h intervals between injections, with that of insulin glargine (IGlar) dosed at the same time each day (i.e., according to label) as well as IDeg given at the same time each day. Dosing intervals of 8–40 h were chosen for IDeg because these were considered to reflect the potential extreme ranges in once-daily basal insulin dosing that patients might encounter when routines are disrupted by everyday life.

RESEARCH DESIGN AND METHODS

Study design and participants

This phase 3, 26-week, randomized, controlled, open-label, three-arm, parallel-group trial was conducted at 69 sites in 14 countries (Supplementary Table 1) between November 2009 and September 2010. The trial protocol was approved by independent ethics committees or institutional review boards (with written informed consent obtained before patients entered the trial) and conducted according to the Declaration of Helsinki and Good Clinical Practice (20,21).

Adults (≥18 years of age) diagnosed with type 2 diabetes for at least 6 months, a BMI of ≤40 kg/m^2, and previously treated with either oral antidiabetic drugs (OADs) (baseline HbA_{1c} = 7.0–11.0%, inclusive) or any basal insulin ± OADs (baseline HbA_{1c} = 7.0–10.0%, inclusive) were eligible for enrollment in the trial. Patients were excluded if they were using glucagon-like peptide-1 receptor agonists, rosiglitazone, dipeptidyl peptidase-4 inhibitors, or α-glucosidase inhibitors within 3 months of screening. See Supplementary Tables 2 and 3 for all inclusion and exclusion criteria.

Randomization and masking

Randomization was performed using an interactive voice/web system; participants were stratified into three groups according to prestudy treatment and randomly assigned in a 1:1:1 ratio to receive IDeg in a flexible once-daily (OD) dosing regimen (IDeg OD Flex, a prespecified, rotating morning and evening dosing schedule, creating 8–40-h intervals between doses) (Fig. 1), IDeg dosed once daily at the main evening meal (IDeg OD), or IGlar given once daily (IGlar OD) at any time during the day (but at the same time each day) according to approved product labeling (5) (the time of dosing was not recorded in this study). Treatment group assignment was masked for individuals involved with titration surveillance, safety committee members, and personnel involved in defining analysis sets until data were locked for statistical analysis.

Procedures

IDeg (100 units/mL, 3 mL FlexPen; Novo Nordisk, Bagsværd, Denmark) and IGlar (100 units/mL, 3 mL SoloSTAR; Sanofi, Paris, France) were administered subcutaneously in the thigh, deltoid area, or abdomen. Participants previously treated with OADs continued their prestudy OAD treatment without any change in dose or regimen. The starting dose of IDeg or IGlar for insulin-naïve participants was 10 units. Participants receiving once-daily basal insulin prior to the study were switched to IGlar or IDeg on a unit-for-unit dose basis, whereas participants on a prestudy twice-daily basal insulin regimen were switched to lower starting doses of IGlar and IDeg. For IGlar, the starting dose was 20–30% lower than the prestudy total daily insulin dose according to approved product labeling; for IDeg, the starting dose was determined by the investigator on an individual subject basis. On the basis of self-measured plasma glucose (SMPG) concentrations before breakfast (mean value from three consecutive days), insulin doses were titrated individually once a week throughout the trial, aiming at a prebreakfast SMPG target of 3.9 to <5.0 mmol/L (Supplementary Table 4).

Outcome measures

The primary end point was change from baseline (week 0) in HbA_{1c} concentration after 26 weeks of treatment. Secondary efficacy end points included patients achieving an HbA_{1c} concentration of <7%, changes in laboratory-measured fasting plasma glucose (FPG), insulin dose, and 9-point SMPG profiles. Safety assessments included adverse events (AEs), hypoglycemic episodes, injection site reactions, body weight, laboratory analyses (hematology, biochemistry, and antibodies), physical examination, vital signs, fundoscopy, and electrocardiogram. Laboratory analyses were performed by Quintiles Central Laboratories (Livingston, Scotland; Mumbai, India; Singapore; Marietta, GA; and Irene, South Africa), and CentraLab (Buenos Aires, Argentina). Antibodies specific to IDeg and cross-reacting between IDeg and human insulin were analyzed by Celerion (Fehraltorf, Switzerland) using a validated subtraction radioimmunoassay method (22,23). Confirmed hypoglycemia comprised episodes with a plasma glucose value <3.1 mmol/L (regardless of symptoms) and severe episodes requiring assistance (Supplementary Fig. 1). Confirmed hypoglycemic episodes with an onset between 00:01 h and 05:59 h (inclusive) were classified as nocturnal.

Statistical analyses

The primary objective of this trial was to confirm the noninferiority of IDeg OD

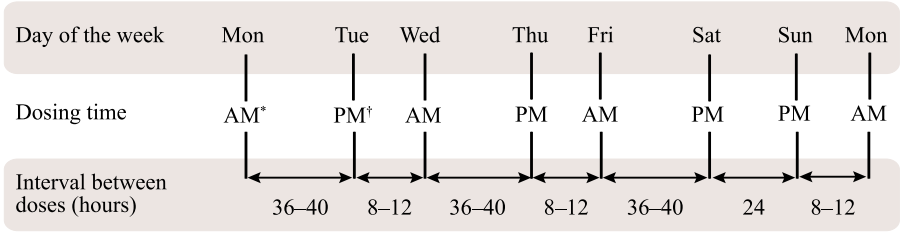

Figure 1—*Dosing schedule for IDeg OD Flex treatment group. *, defined as the period from waking up until first meal of the day; †, defined as the period from start of evening meal until bedtime. A 24-h interval was introduced between Saturday and Sunday evening doses to ensure an equal number of short (8–12 h) and long (36–40 h) intervals during the week.*

Flex to IGlar OD, as assessed by the change in HbA_{1c} concentration from baseline after 26 weeks, with a noninferiority limit of 0.4% for the treatment difference.

Sample size was determined using a one-sided Student *t* test with $\alpha = 0.025$, assuming a zero mean treatment difference, and an SD of 1.3% for HbA_{1c}. Assuming a 15% dropout rate, 675 participants were to be randomized for at least 85% power in the per-protocol analysis set.

Statistical analyses of HbA_{1c}, FPG, and hypoglycemia included all randomized participants (full analysis set), according to the intention-to-treat principle. Safety end points were evaluated in participants exposed to treatment. Missing values were imputed using the last observation carried forward based on Food and Drug Administration guidance (24).

Treatment differences in changes from baseline in HbA_{1c} after 26 weeks were assessed using an ANOVA model, with treatment, antidiabetic therapy at screening, sex, and region as fixed factors and age and baseline value as covariates. Noninferiority was confirmed if the upper limit of the 95% CI for the treatment difference was 0.4% or less (24).

Details of sensitivity analyses of the primary end point (per protocol population, simple model with only baseline HbA_{1c} concentration as covariate, and a repeated measurement model) are provided in Supplementary Table 5. Changes from baseline in FPG and body weight after 26 weeks were analyzed using the same ANOVA model as for the primary end point. The proportion of patients attaining an HbA_{1c} of <7.0% was analyzed using a logistic regression model, with treatment, antidiabetic therapy at screening, sex, and region as fixed factors and age and baseline HbA_{1c} as covariates.

Rate ratio estimates of hypoglycemic episodes were made using a negative binomial regression model, including treatment, antidiabetic therapy at screening, sex, and region as fixed factors and age as covariate. The time to first achieve prebreakfast SMPG of 3.9 to <5 mmol/L was analyzed in a Cox proportional hazards model. Data were reported using 95% CI and *P* values for two-sided testing at $\alpha = 0.05$.

A secondary objective of the trial was to compare IDeg OD Flex with IDeg OD with respect to the same end points analyzed for the primary comparison (IDeg OD Flex vs. IGlar OD); no comparisons were prespecified or performed for IDeg OD versus IGlar OD.

RESULTS—Of 946 patients screened, 687 were randomly assigned and 610 completed the trial (Table 1 and Supplementary Fig. 2). Baseline and demographic characteristics were comparable between treatment groups, except for modest differences in the male-to-female ratio (Table 1). A similar proportion (11–12%) of participants withdrew from each treatment group during the trial (Table 1 and Supplementary Fig. 2).

Mean HbA_{1c} concentration–time profiles were similar between treatment groups, as were observed mean decreases in HbA_{1c} from baseline to end of trial (Fig. 2*A*): –1.28% points for IDeg OD Flex, –1.07% points for IDeg OD, and –1.26% points for IGlar OD. The estimated mean treatment difference (ETD) between IDeg OD Flex and IGlar OD was 0.04% points (–0.12 to 0.20), demonstrating that IDeg OD Flex was noninferior to IGlar OD in lowering HbA_{1c}. The results of the primary analysis were supported by the results of the per-protocol analysis and two other sensitivity analyses (Supplementary Table 5).

No statistically significant difference in HbA_{1c} was found between the IDeg OD

Table 1—*Baseline characteristics of randomized population and subject disposition*

	IDeg OD Flex	IDeg OD	IGlar OD	Overall population
Female	94 (41%)	104 (46%)	119 (52%)	317 (46%)
Race (% white/black/Asian/other)	66/1/31/2	67/4/29/0	67/3/30/0	67/2/30/1
Age (years)	56.2 (10.3)	56.5 (9.6)	56.7 (8.8)	56.4 (9.6)
Body weight (kg)	81.3 (16.3)	81.8 (17.1)	82.1 (16.6)	81.8 (16.6)
BMI (kg/m^2)	29.3 (4.6)	29.4 (4.9)	30.0 (4.7)	29.6 (4.7)
Duration of diabetes (years)	10.8 (6.9)	10.3 (6.7)	10.8 (6.4)	10.6 (6.7)
HbA_{1c} (%)	8.5 (1.0)	8.4 (0.9)	8.4 (0.9)	8.4 (0.9)
HbA_{1c} (mmol/mol)*	69	68	68	68
FPG (mmol/L)	9 (2.6)	8.8 (2.8)	9 (2.8)	8.9 (2.7)
Participants randomized	229	228	230	687
Participants exposed	230	226	229	685
Participants completing trial	203	204	203	610
Withdrawals	26	24	27	77
AEs	2	1	2	5
Noncompliance	3	3	3	9
Ineffective therapy	2	2	1	5
Withdrawal criteria	5	4	4	13
Other	14	14	17	45
Prestudy treatment				
OADs only	133 (58.1%)	131 (57.5%)	134 (58.3%)	398 (57.9%)
Basal insulin only	7 (3.1%)	8 (3.5%)	6 (2.6%)	21 (3.1%)
Basal insulin + at least one OAD	89 (38.9%)	88 (38.6%)	89 (38.7%)	266 (38.7%)
Other†	0	1 (0.4%)	1 (0.4%)	2 (0.3%)
Of subjects on prestudy OADs				
Metformin	207 (90.4%)	205 (89.9%)	211 (91.7%)	623 (90.7%)
DPP-4 inhibitor	0	0	1 (0.4%)	1 (0.1%)‡
Glinide	10 (4.4%)	14 (6.1%)	8 (3.5%)	32 (4.7%)
Sulphonylurea	160 (69.9%)	138 (60.5%)	157 (68.3%)	455 (66.2%)
Thiazolidinedione	13 (5.7%)	17 (7.5%)	17 (7.4%)	47 (6.8%)

Data are *n*, *n* (%), or mean (SD). Of the 687 randomized participants, two withdrew their consent before exposure to trial product (one subject in each of the IDeg OD Flex and IGlar OD groups). These subjects are included in the full analysis set for their respective treatment groups. Two subjects were randomized to IDeg OD but were treated according to the IDeg OD Flex regimen by mistake. Because the full analysis set was defined as all patients randomized to a particular treatment group (according to the intention-to-treat principle), these two subjects were included in the IDeg OD full analysis set. However, as subjects were to contribute to the statistical evaluation of safety "as treated," they were included in the safety analysis set for the IDeg OD Flex group. DPP-4, dipeptidyl peptidase-4. *Calculated using the following formula: HbA_{1c} (mmol/mol) = [HbA_{1c} (%) – 2.15] × 10.929. †Other = treatment with premix insulin or basal-bolus insulin therapy. ‡This patient was included in the trial by mistake; the patient fulfilled exclusion criteria 1 (Supplementary Table 3).

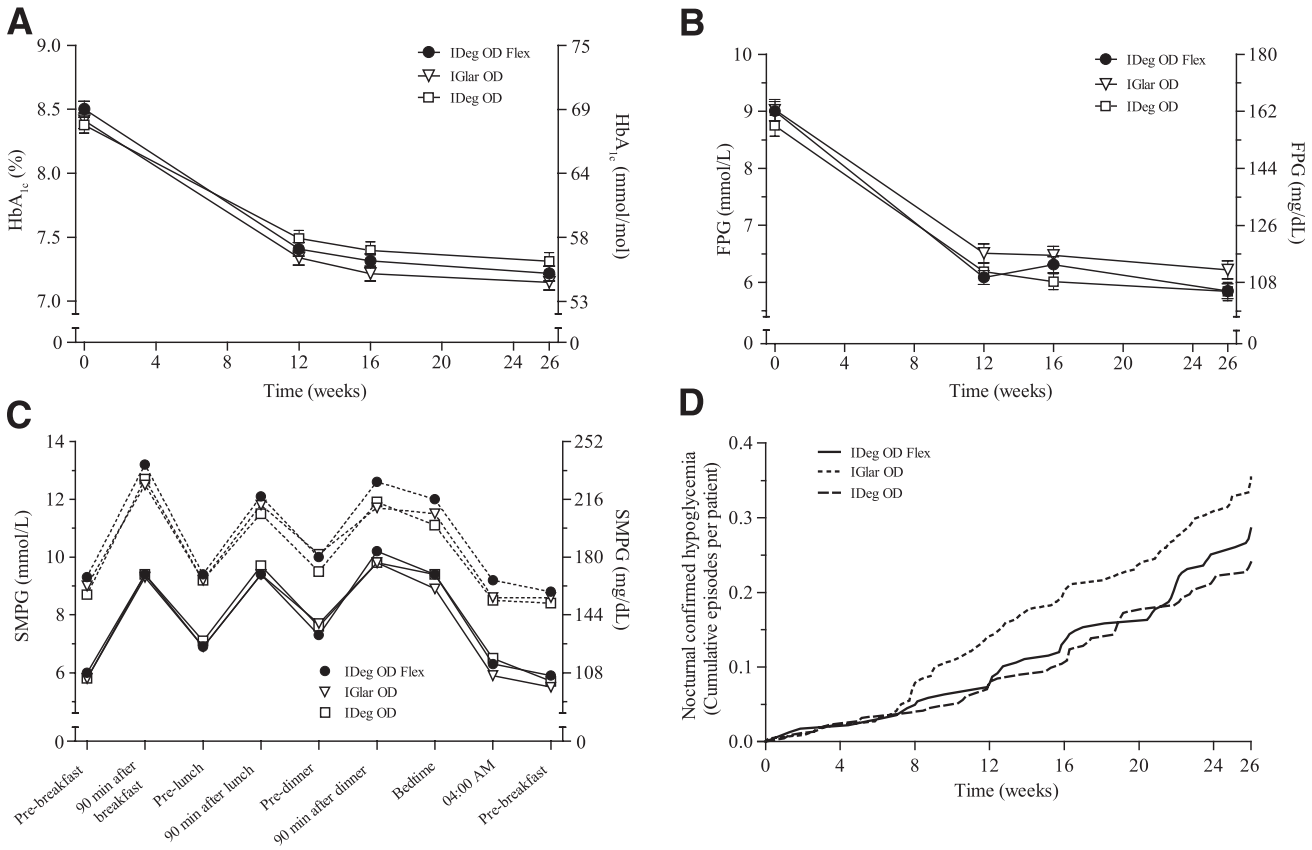

Figure 2—*Glycemic efficacy and cumulative nocturnal hypoglycemia.* A*: Mean HbA$_{1c}$ (±SEM) over time.* B*: Mean FPG (±SEM) over time.* C*: Mean 9-point SMPG profiles at baseline (dashed lines) and week 26 (full lines).* D*: Cumulative mean number of nocturnal hypoglycemic episodes per participant. For* A *and* B*, data are observed mean values for all randomized participants (last observation carried forward is used for each postbaseline time point). Plasma-calibrated values are shown in* C*. Nocturnal confirmed hypoglycemia, confirmed hypoglycemia with an onset between 00:01 h and 05:59 h (inclusive).*

Flex and IDeg OD treatment groups (ETD –0.13% points [–0.29 to 0.03]).

After 26 weeks of treatment, similar proportions of participants had achieved an HbA$_{1c}$ of <7.0% with IDeg OD Flex and IGlar OD (38.9 vs. 43.9%, *P* = 0.34); likewise, no statistically significant difference in HbA$_{1c}$ was found between the IDeg OD Flex and IDeg OD groups (38.9 vs. 40.8%, *P* = 0.99).

Mean laboratory-measured FPG values decreased in all treatment groups (Fig. 2*B*); at the end of the trial, the observed mean FPG concentration was 5.8 mmol/L for IDeg OD Flex and IDeg OD and 6.2 mmol/L for IGlar OD. IDeg OD Flex was associated with a significantly greater reduction in FPG than IGlar OD after 26 weeks of treatment (ETD –0.42 mmol/L [–0.82 to –0.02], *P* = 0.04); no significant difference was found between IDeg OD Flex and IDeg OD (ETD –0.05 mmol/L [–0.45 to 0.35], *P* = NS).

After 26 weeks, mean 9-point SMPG profiles were similar for the three treatment groups and decreased compared with corresponding mean profiles at baseline (Fig. 2*C*).

Insulin doses were adjusted during the trial to achieve the specified prebreakfast SMPG target. The rate at which the insulin dose was increased during the trial was similar across treatment groups, with the largest dose increases occurring in the first 8 weeks of treatment (Supplementary Fig. 3). At the end of the trial, mean daily insulin doses were similar for IDeg OD Flex, IDeg OD, and IGlar OD, both for participants receiving insulin treatment prior to the trial (0.6, 0.6, and 0.6 units/kg) and those who had previously been insulin naïve (0.5, 0.5, and 0.5 units/kg). The median time taken to first achieve the prebreakfast SMPG target of 3.9 to <5 mmol/L for IDeg OD Flex, IDeg OD, and IGlar OD was 8, 6, and 7 weeks, respectively. The time to first achieving the titration target did not differ significantly between IDeg OD Flex and IGlar OD (estimated hazard ratio 0.91 [0.74–1.11], *P* = NS) or IDeg OD Flex and IDeg OD (estimated hazard ratio 0.82 [0.67–1.00], *P* = NS).

No statistically significant difference in mean weight gain (baseline to end of trial) was found between IDeg OD Flex and IGlar OD (1.5 vs. 1.3 kg; ETD 0.27 kg [–0.25 to 0.79], *P* = NS) or IDeg OD Flex and IDeg OD (1.5 vs. 1.6 kg, ETD 0.00 kg [–0.53 to 0.52], *P* = NS).

A similar proportion of participants (44–51%) reported confirmed hypoglycemia in the three treatment groups (Table 2). Severe hypoglycemia was rare (two episodes in each treatment group). No significant differences were found between IDeg OD Flex and IGlar OD with respect to the rates of overall confirmed hypoglycemia (rate ratio [RR] IDeg OD Flex/IGlar OD 1.03 [0.75–1.40], *P* = NS) and nocturnal confirmed hypoglycemia (RR 0.77 [0.44–1.35], *P* = NS) (Fig. 2*D*). Rates of nocturnal confirmed hypoglycemia were similar for IDeg OD Flex and IGlar OD, regardless of whether IDeg was dosed in the morning or evening (Supplementary Table 6). Hypoglycemia rates were also comparable for IDeg OD Flex and IDeg OD, both in terms of

Table 2—*Summary of hypoglycemic episodes*

	IDeg OD Flex (n = 230)			IDeg OD (n = 226)			IGlar OD (n = 229)		
	n (%)	E	Rate	n (%)	E	Rate	n (%)	E	Rate
Confirmed	117 (51)	388	3.6	99 (44)	378	3.6	113 (49)	368	3.5
Nocturnal confirmed	31 (13)	67	0.6	24 (11)	58	0.6	49 (21)	79	0.8

Hypoglycemic episodes occurring on or after the first day of exposure to treatment and no later than 7 days after the last day of treatment. Nocturnal confirmed, confirmed hypoglycemia with an onset between 00:01 h and 05:59 h (inclusive). E, number of events; rate, unadjusted event rate (episodes/patient-year of exposure).

overall confirmed hypoglycemia (IDeg OD Flex/IDeg OD RR 1.10 [0.79–1.52], P = NS) and nocturnal confirmed hypoglycemia (RR 1.18 [0.66–2.12], P = NS) (Fig. 2*D*).

No obvious differences were observed between treatment groups in physical examination findings, vital signs, standard laboratory analysis (hematology and biochemistry), fundoscopy, or electrocardiogram.

Overall AE rates were similar across treatment groups, as were rates of AEs considered by the investigator to be possibly or probably related to investigational product (see Supplementary Table 7 for a summary of AE and serious AE [SAE] rates). The majority of AEs (>95%) were mild or moderate in severity, and no apparent treatment group–specific patterns or clustering were observed (see Supplementary Table 8 for most frequent AEs). Two participants died during the trial: one in the IDeg OD group (anemia and myelodysplastic syndrome) and one in the IGlar OD group (cause of death unknown; no autopsy was permitted by relatives). Both deaths were considered by the investigator to be unlikely related to the investigational product.

A low proportion of participants reported injection site reactions in the IDeg OD Flex (1.3%), IDeg OD (3.5%), and IGlar OD (1.7%) treatment groups.

Levels of IDeg- and IGlar-specific antibodies remained close to zero during the trial. No clinically relevant increases (from baseline to week 27) in the concentration of antibodies cross-reacting between IDeg and human insulin were observed for participants receiving insulin treatment prestudy (Supplementary Table 9) or who were previously insulin naïve (Supplementary Table 10). Overall, a similar number of participants in each treatment group had a change in cross-reacting antibody levels of ≥10% bound/total during the trial (9, 8, and 16 participants in the IDeg OD Flex, IDeg OD, and IGlar OD groups, respectively). There was no apparent association between the development of cross-reacting antibodies and hypoglycemia, HbA_{1c}, or insulin dose in any of the treatment groups (data not shown).

CONCLUSIONS—This 26-week, phase 3, treat-to-target trial in individuals with type 2 diabetes was designed to test extreme intervals for basal insulin administration with once-daily doses of IDeg, using a forced dosing schedule that created alternating short (8–12 h) and long (36–40 h) intervals between doses. This rotating dosing regimen (IDeg OD Flex) is clearly not intended for clinical practice; rather, it was used to explore (from an efficacy and safety perspective) the impact of variable timing of basal insulin administration that might be encountered by patients with changing schedules. The trial population encompassed a broad range of individuals who were likely to benefit from either insulin initiation or intensification.

Overall, variable dosing intervals for insulin degludec (IDeg OD Flex) resulted in similar glycemic control, hypoglycemia risk, and weight gain to fixed dosing intervals for either IGlar (IGlar OD) or itself (IDeg OD). The lower FPG level found for IDeg OD Flex compared with IGlar OD did not come at the expense of a higher incidence of nocturnal hypoglycemia. Indeed, IDeg OD Flex was associated with a nonsignificant 23% numerically lower rate of nocturnal hypoglycemia than IGlar OD, consistent with findings from other studies (25–28). Because rates of nocturnal confirmed hypoglycemia were similar for IDeg OD Flex and IGlar OD, regardless of whether IDeg was dosed in the morning or evening, the lower overall rate of nocturnal hypoglycemia associated with IDeg Flex is thought to be due to the more consistent pharmacokinetic profile of IDeg relative to IGlar, as well as lower day-to-day and hour-to-hour pharmacodynamic variability (16,17).

The overall safety profiles of the IDeg OD Flex, IGlar OD, and IDeg OD groups were comparable; no clinically relevant differences were found with respect to standard safety assessments, and there were no apparent group-specific patterns or clustering of AEs. Notably, no AEs of hyperglycemia, a possible consequence of insufficient insulin coverage, were reported for IDeg when administered at intervals of up to 40 h.

Given the use of different insulin delivery systems and the complexity of the IDeg OD Flex dosing regimen, a blinded, double-dummy trial design was impractical. Consequently, it cannot be ruled out that the open-label design used in this study may have influenced efforts by participants and investigators to attain the target blood glucose level and, possibly, influenced the reporting of hypoglycemia and AEs, although presumably less so between the two IDeg arms. To minimize potential reporting bias for hypoglycemia, we used confirmed hypoglycemia (plasma glucose <3.1 mmol/L or severe episodes requiring assistance) instead of symptoms alone to compare rates between treatment groups. As in any open-label trial, there may have been greater caution in adjusting doses of the new drug (IDeg), but this was not reflected by median times taken to first achieve the prebreakfast SMPG titration target or the proportion of patients reaching HbA_{1c} goals at the end of the trial when compared with IGlar. It could be argued that the trial should have included a fourth treatment arm where IGlar was tested in the same rotating dosing regimen as the IDeg OD Flex arm. However, because IGlar is only approved for dosing at the same time each day, we considered such off-label use inappropriate and unlikely to be approved by local ethics committees and institutional review boards.

In conclusion, the results from this trial in individuals with type 2 diabetes demonstrate that it is possible to vary the time of day at which once-daily injections of the ultra-long-acting basal insulin IDeg are given from one day to the next without compromising glycemic control or increasing the risk of hypoglycemia. It is recommended that, when possible, IDeg should be administered at a similar time each day. However, on those occasions when consistent timing of insulin administration is not possible or is impractical,

the flexibility afforded by IDeg will still allow for appropriate basal insulin coverage, without negatively impacting blood glucose control, further facilitating insulin administration and potentially improving treatment compliance.

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L.M., I.R., and K.B. analyzed and interpreted data. S.L.A. analyzed and collected data. S.C.L.G. and L.B. interpreted data. M.S. collected data. S.B. collected and interpreted data. T.J. contributed to study design and collected and interpreted data. K.I.B. collected and interpreted data and discussed results. All authors participated in the writing and reviewing of the manuscript, approved the final version for submission, and take full responsibility for the contents. K.I.B. 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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